New α-Substituted Succinate-Based Hydroxamic Acids as TNFα Convertase Inhibitors

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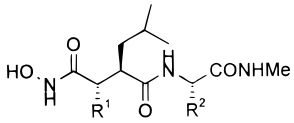
Tumor necrosis factor α convertase (TACE), the enzyme responsible for the processing of pro-TNFα to TNFα, has been reported to be a metalloproteinase closely related to matrix metalloproteinases (MMPs). Current inhibitors of TACE such as succinate-based hydroxamic acids exemplified by Marimastat (TACE IC_{50}: 3.8 nM; blood IC_{50}: 7 μM) and BB1101 (TACE IC_{50}: 0.2 nM; blood IC_{50}: 2.3 μM) suffer from modest potency in blood and poor in vivo properties. The introduction of new bulky α-substituents into these succinate-based hydroxamic acids was studied. Substituents such as thioethers, sulfonamides, and ethers showed improved potency against TACE when compared with Marimastat. Although this improvement did not translate into better blood potency for thioether or ether substituents, the sulfonamide series exhibited improved potency both against TACE and in blood when compared with Marimastat. Optimization of this sulfonamide series has culminated in the identification of heterocyclic bicyclic sulfonamides such as **3t** (TACE IC_{50}: 0.57 nM; blood IC_{50}: 0.28 μM).

Introduction

Matrix metalloproteases (MMPs) are a family of tightly regulated zinc-containing proteinases involved in tissue remodeling. They are capable of degrading all major extracellular matrix components under both physiological and pathological conditions.[1] While their role in normal and pathological turnover of these tissues still remains unclear, elevated levels of these enzymes have been implicated in various diseases such as cancer,[2] arthritis,[3] and periodontal and ocular disease. Therefore, there have been considerable efforts in the design and synthesis of MMP inhibitors: several of them have advanced into human clinical trials for the treatment of cancer, arthritis, and corneal ulceration. This field has been extensively reviewed.[4]

Tumor necrosis factor α[5] (TNFα), a cytokine produced mainly by activated macrophages/monocytes, is a major mediator of inflammatory and immune responses and a strong inducer of other proinflammatory cytokines such as IL-1β, IL-6, and IL-8. Elevated TNFα levels occur in diseases[6] such as rheumatoid arthritis (RA), septic shock, inflammatory bowel disease (IBD), graft vs host disease (GvHD), cachexia, and adult respiratory distress syndrom (ARDS). Agents which inhibit TNFα production[7] could be effective in the treatment of such diseases, as illustrated by advanced clinical trials underway with TNF soluble receptors (Enbrel)[8] or TNF antibodies such as cA2.[9]

TNFα is produced as a proform, 26 kDa membrane-bound pro-TNF, the activity of which is still unclear.[10] Processing of this 26 kDa precursor into the 17 kDa mature form is performed by specific proteolytic cleavage between Ala-76 and Val-77 of pro-TNF. The potential utility of MMP inhibitors as therapeutic agents has further expanded with the recent recognition that TNFα converting enzyme (TACE), probably the major enzyme responsible for this conversion, belongs to a family closely related to the MMPs[11] and that a subset of MMP inhibitors blocks TNF production in vitro and in vivo.[12]



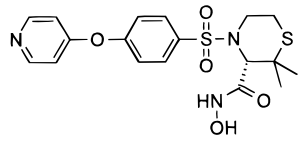
Marimastat (R^1= OH; R^2= tBu)

1 (R^1= cyclopentyl; R^2= tBu)

GW9471 (R^1= CH_2SPh; R^2= CH_2Ph)

BB1101 (R^1= allyl; R^2= CH_2Ph)

Ro31-9790 (R^1= H; R^2= tBu)



AG3340

Figure 1. MMP inhibitors.

The most widely pursued approach toward MMP inhibition has been the design of molecules that bind to the catalytic site of the enzymes. Peptidomimetics or pseudopeptidic structures that incorporate a zinc ligand and a P1′ side chain are the most common class of MMP inhibitors, although sulfonamide- and biphenyl ketone-based inhibitors have been reported.[4] The vast majority of MMP inhibitors incorporate an hydroxamic acid group as the zinc binding ligand whereas other ligands such carboxylic acids, thiols, phosphinates, and phosphonates have been studied less thoroughly and appear

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to be less potent.[4] This approach has culminated in the design of Marimastat, which is a potent MMP inhibitor and which also inhibits TNF release from cells.[4d] However, the MMP inhibitors disclosed to date, such as Marimastat, GW9471,[12b] BB1101,[13] **1**,[14] or AG 3340[15] (Figure 1) have shown only moderate inhibition of TNF production in our tests (IC_{50}: 2−15 μM in human whole blood assay, Table 1). Moreover, several reports[14,16] have highlighted their poor in vivo properties, i.e., poor pharmacokinetics, possibly due to metabolism of the hydroxamic acid group,[17] and poor bioavailability.

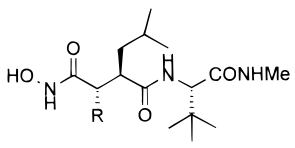
Table 1. Activity of Disclosed MMPIs in Our Tests (IC_{50})[a]

compd	TACE (nM)	MMP-1 (nm) published results[b]		MMP-8 (nm) published results[b]		blood (μM)
GW 9471	1.8					5.3
Marimastat	3.8 ± 1.7 (7)	2.1	5		2	7 ± 3 (77)
BB1101	0.2		10		3	2.3
Ro31-9790	20 ± 3 (3)	3.5	10[c]			>50
AG3340	5.5 ± 0.1 (2)	16	8.2	0.2		16.6 ± 6.1 (2)
1	1 ± 0.05 (2)		4		20	8.8

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than one value has been determined, IC_{50}s are shown ± SD (number of determinations). [b] Data from ref 4d. [c] Data from ref 4b.

In an attempt to find more potent TNFα convertase inhibitors, with modified physicochemical properties and potentially better pharmacokinetic profile, we have investigated the wide derivatization of the position α to the hydroxamic acid. The modifications could indeed help us to identify new interactions with the enzyme, thus increasing in vitro potency of these succinate-based hydroxamic acids. Moreover, the introduction of bulky substituents has been investigated as a means of preventing metabolism, and possibly improving absorption, which could result in overall improved pharmacokinetics. This hypothesis was supported by in-house molecular dynamics simulations performed on various bulky α-substituted succinates. This study showed that such a substitution could significantly reduce the conformational flexibility of compounds and favor conformations where the α-substituent is placed in the vicinity of the hydroxamate group,[18] providing potential protection against metabolic enzymes.

We disclose here several series with new α-substituents (Figure 2) and discuss the SAR of these inhibitors for TACE and TNF production in human blood.



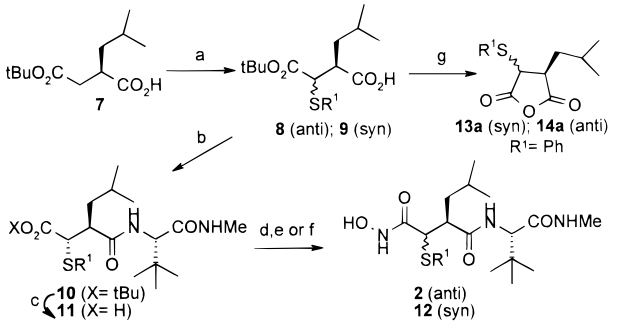
2 R= SR^1
3 R= $NHSO_2R^1$
4 R= $NHCOR^1$
5 R= NR^1R^2
6 R= OR^1

Figure 2.

Chemistry

The inhibitors of the present study were prepared using the following sequences. Synthesis of the thioether-based inhibitors **2** started from succinate **7** (Scheme 1).[19] The dianion of **7** was reacted with disulfides to give thioethers **8** and **9** as a mixture of two diastereoisomers,[20] which were separated at this stage. The anti-isomer **8** was coupled with L-*tert*-leucine methylamide under classical HOBT/EDCI conditions. Deprotection of the *tert*-butyl ester **10** with TFA and subsequent conversion of acid **11** to the hydroxamic acid by coupling of hydroxylamine or protected hydroxylamines such as Me_3SiONH_2, $tBuMe_2SiONH_2$, and *O*-(2,4-dimethoxybenzyl)hydroxylamine[21] with EDCI afforded the desired inhibitors **2**,[22] after removal of the protecting group when necessary.

Scheme 1[a]

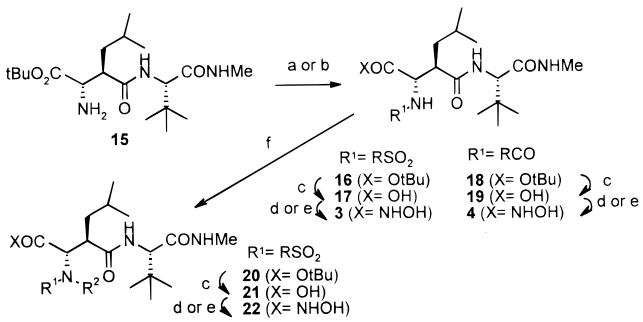


[a] (a) 2 LDA, THF, R^1SSR^1, −78 °C; (b) L-*tert*-leucine methylamide, EDCI, HOBT, DMF; (c) TFA/CH_2Cl_2 (1:1); (d) **11**, NH_2OH·HCl, lutidine, EDCI, DMF; (e) **11**, NH_2OTMS, lutidine, EDCI, DMF; (f) **11**, NH_2ODMB, EDCI, DMF; 5% TFA, CH_2Cl_2; (g) $(COCl)_2$, cat. DMF.

In a few cases when **8** and **9** were not easily separable, the same sequence was carried out on the diastereomeric mixture, and the two diastereoisomers **2** and **12** were separated at the final stage. Proof of the stereochemistry[23] of the α-thioether substituent in **2a** (R^1 = Ph) was established by preparing the anhydrides **13a** and **14a** from **8a** and **9a**, respectively, with oxalyl chloride.

The route to sulfonamides **3** and amides **4** started from intermediate **15**[24] (Scheme 2): sulfonamide/amide coupling, followed by conversion of the *tert*-butyl ester into the hydroxamic acid according to the same methods used for the thioether series, gave the expected sulfonamides **3** and amides **4**. Sulfonamides **3** and amides **4** could equally be obtained from **23** by sulfonamide/amide coupling followed by acidic deprotection of the 2,4-dimethoxybenzyl group (optionally on solid phase[24]).

Scheme 2[a]

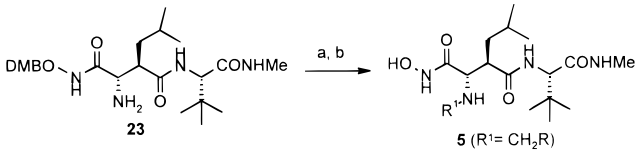


[a] (a) R^1=RSO_2: RSO_2Cl, py, cat. DMAP, CH_2Cl_2; (b) R^1=RCO: RCO_2H, EDCI, DMAP; (c) TFA/CH_2Cl_2 (1:1); (d) EDCI, $TMSONH_2$, DMF; (e) EDCI, NH_2ODMB; 5% TFA, CH_2Cl_2; (f) **16**, R^2-halide, K_2CO_3, DMF.

N-Alkylated sulfonamides **22** were obtained by alkylation of the corresponding sulfonamides **16** with the corresponding halide and subsequent conversion of the *tert*-butyl ester into the hydroxamic acid by methods already described.

Amines **5a** and **5b** were obtained from **15** and **23**, respectively, by alkylation of the amino group with 2-iodoethyl ether and 1,4-diiodobutane and subsequent transformation of the *tert*-butyl ester or the protected hydroxamate into the hydroxamic acid by methods already described. Reductive amination of aldehydes with **23**[24] followed by 2,4-dimethoxybenzyl deprotection (optionally on solid phase[24]) in 5% TFA/CH_2Cl_2 afforded the corresponding amines **5c**−**g** (Scheme 3).

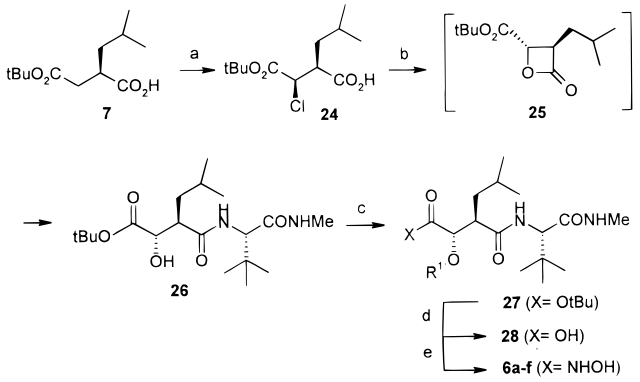
Scheme 3[a]



[a] (a) RCHO, $NaBH_3CN$, 1% AcOH, MeOH; (b) 5% TFA, CH_2Cl_2.

The synthesis of the ether-based inhibitors **6a**−**k** also began from succinate **7** (Scheme 4). Reaction of the dianion of **7** with carbon tetrachloride as a source of chlorine afforded the syn chloro derivative **24**, which reacted with L-*tert*-leucine methylamide to give **26** via the intermediate lactone **25**. This lactone can be isolated by treatment of **24** with ether/aqueous sodium bicarbonate. Alkylation of **26** and subsequent conversion of the *tert*-butyl esters into the hydroxamic acids afforded the expected ethers **6a**−**f**.

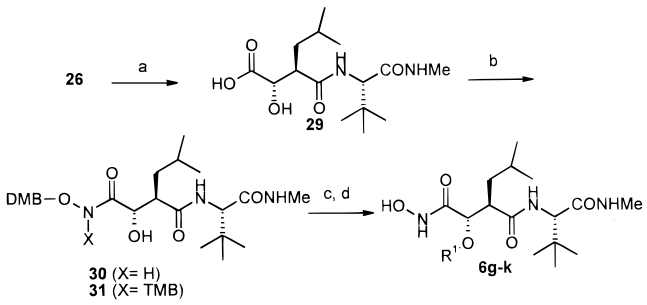
Scheme 4[a]



[a] (a) 2 LDA, THF, CCl_4, −78 °C; (b) L-*tert*-leucine methylamide, MeCN; (c) R^1-halide, NaH, NaI, THF; (d) TFA/CH_2Cl_2 (1:1); (e) NH_2OTMS, lutidine, EDCI, DMF.

Access to ethers **6g**−**k** is depicted in Scheme 5. Deprotection of **26** with TFA/CH_2Cl_2 (1:1) afforded the known acid **29**,[25] which was either converted to the O-protected hydroxamate **30** or the N,O-diprotected hydroxamate **31** by coupling with *O*-(2,4-dimethoxybenzyl)hydroxylamine[21] (DMBONH_2) or *O*-(2,4-dimethoxybenzyl)-*N*-(2,4,6-trimethoxybenzyl)hydroxylamine[21] (DMBONHTMB), respectively. Alkylation of **30** or **31** with various halides, followed by deprotection of the hydroxamate with 10% TFA/CH_2Cl_2, gave the expected ethers **6.** This is exemplified in the experimental data for **6g** and **6j** from **30** and **6h, 6i**, and **6k** from **31**.

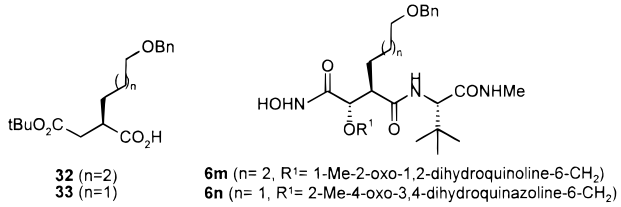
Scheme 5[a]



[a] (a) TFA/CH_2Cl_2 (1:1); (b) H_2NODMB (for **30**) or TMBNHODMB (for **31**), EDCI, DMF; (c) R^1-halide, NaI, NaH, 15-crown-5, THF; (d) 10% TFA, CH_2Cl_2.

Hydroxamates **6l**−**m** were made from succinates **32**[26] and **33**[26] (readily accessible by Evans' oxazolidinone chemistry) according to the same methodology (Scheme 6).

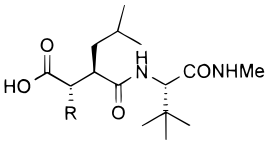
Scheme 6



Discussion

The inhibitory potency of the aforementioned inhibitors was determined against a partially purified TACE preparation using a fluorogenic substrate. TNF inhibition in cells was determined in LPS-stimulated human whole blood. The results are summarized in Tables 1 and 2. Selected inhibitors were also tested against MMP-1 and MMP-8 for selectivity evaluation (Table 3).

As previously noted with MMPs, succinate-based hydroxamic acids lead to potent TACE inhibitors. The hydroxamate zinc ligand is essential for TACE inhibition: its replacement by other zinc binding ligands such as a carboxylic acid, for example, leads to inactive compounds (Figure 3) as illustrated by **11a** (TACE IC_{50} > 100 nM) and **17a** (TACE IC_{50} > 10 μM).

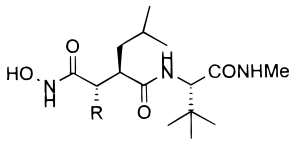


11a: R= SPh
17a: R=$NHSO_2Ph$

Figure 3.

α-Substitution of succinate-based hydroxamic acids improves both activity against the TACE isolated enzyme and inhibition of TNF production in human whole blood as demonstrated by Marimastat, GW9471, BB1101, **2a**, **3a**, and **6a** compared with Ro31-9790. Moreover, the correct stereochemistry of this α-substituent is critical for TACE inhibition as illustrated by **2a** vs **12a** (TACE IC_{50}: 1 nM vs 188 nM); this observation is in accordance with the published SAR[27,28] for MMPs.

Table 2. Inhibition of TACE and TNF Production in Blood by α-Substituted Hydroxamates (IC_{50})[a]



compd	R	TACE (nM)	blood (μM)	compd	R	TACE (nM)	blood (μM)
2a	(*S*)-PhS	1 (2)		**3v**	(*E*)-PhCH=CHSO$_2$NH	0.54 ± 0.35 (2)	0.77 ± 0.25 (2)
12a	(*R*)-PhS	188 ± 71 (2)		**3w**	MeSO$_2$NH	2.2	1.6 ± 0.05 (2)
2b	3,4-(MeO)$_2$C$_6$H$_3$S	1.2 ± 0.4 (2)		**22a**	PhSO$_2$(Me)N	0.61 ± 0.26 (2)	3 ± 0.05 (2)
2c	1-(Me)-2-(oxo)-1,2,3,4-tetrahydroquinoline-6-S	1.4 ± 0.4 (2)	6.6	**22b**	quinoline-8-SO$_2$(Me)N	4.4	4.5
				22c	quinoline-8-SO$_2$(n-Pr)N	10	
2d	4-(CN)C$_6$H$_4$S	0.63 ± 0.15 (2)	3.3 ± 1.4 (2)	**22d**	quinoline-8-SO$_2$(PhCH$_2$)N	85 ± 33 (2)	
2e	4-(MeO$_2$S)C$_6$H$_4$S	1.25 ± 0.55 (2)	2.1	**4a**	quinoline-8-CONH	2 ± 0.9 (3)	8 ± 3 (2)
2f	3,5-Cl$_2$C$_6$H$_3$S	0.42 ± 0.18 (2)	4.9 ± 1.3 (2)	**4b**	quinoline-6-CONH	9.5	
2g	2-Cl-4-FC$_6$H$_3$S	1.1	11	**4c**	pyridine-3-CONH	22	
2h	(8-quinoline)CH$_2$S	0.8	6.2 ± 2.8 (3)	**4d**	PhCONH	9	
2i	3-(NC(Me)$_2$C)C$_6$H$_4$S	1.6	2.8 ± 1 (2)	**4e**	naphthalene-2-CONH	3.3	>20
2j	MeS	1.6	2.3 ± 0.9 (3)	**4f**	AcNH	13	
2k	EtS	1.5 ± 0.5 (2)	5.6 ± 1.7 (6)	**5a**	O(CH$_2$CH$_2$)$_2$N	3.4 ± 1.5 (2)	3 ± 0.8 (5)
3a	PhSO$_2$NH	1.5 ± 0.1 (2)	1.3 ± 0.6 (6)	**5b**	(CH$_2$)$_4$N	2.8	6.1
3b	4-(AcNH)C$_6$H$_4$SO$_2$NH	1.3 ± 0.5 (2)	1.2	**5c**	quinoline-8-CH$_2$NH	0.23 ± 0.14 (3)	3.4 ± 0.5 (2)
3c	3,5-Cl$_2$C$_6$H$_3$SO$_2$NH$^-$	1	11.3	**5d**	PhCH$_2$NH	2.8	6.1
3d	2-(CN)C$_6$H$_4$SO$_2$NH	17 ± 7 (2)		**5e**	naphthalene-2-CH$_2$NH	0.57	6.7
3e	2-Cl-4-FC$_6$H$_3$SO$_2$NH	9.7		**5f**	quinoline-2-CH$_2$NH	1	5.7
3f	2,4,6-(^{i}Pr)$_3$C$_6$H$_2$SO$_2$NH	13		**5g**	MeS(CH$_2$)$_3$NH	1.3	4.6
3g	3-Me(imidazole)-5-SO$_2$NH	9 ± 2 (2)		**6a**	1-Me-2-oxo-1,2-dihydro-quinoline-6-CH$_2$O	1 ± 0.7 (3)	1.44 ± 0.45 (3)
3h	thiophene-2-SO$_2$NH	1.5	2.8				
3i	pyridine-3-SO$_2$NH	2.1	3.8	**6b**	1-Me-2-oxo-1,2-dihydro-quinoline-3-CH$_2$O	0.44 ± 0.02 (2)	2.35 ± 0.15 (2)
3j	4-(HO$_2$C)C$_6$H$_4$SO$_2$NH	3.2	4.4	**6c**	quinoline-8-CH$_2$O	0.4 ± 0.06 (2)	8.2 ± 1.2 (2)
3k	4-BrC$_6$H$_4$SO$_2$NH	1.4	4.4	**6d**	MeO	1.5	5 ± 1 (2)
3l	naphthalene-2-SO$_2$NH	0.66 ± 0.1 (2)	1.2 ± 0.5 (4)	**6e**	2-Me-4-oxo-3,4-dihydro-quinazoline-6-CH$_2$O	0.43	2.4 ± 1.1 (4)
3m	naphthalene-1-SO$_2$NH	1.2 ± 0.4 (2)	3.1 ± 0.9 (2)				
3n	quinoline-8-SO$_2$NH	4.2 ± 0.5 (2)	8.1 ± 3.4 (3)	**6f**	2-Me-4-oxo-3,4-dihydro-7-Br-quinazoline-6-CH$_2$O	0.33 ± 0.05 (2)	4.3 ± 1.3 (2)
3o	isoquinoline-5-SO$_2$NH	3.1	1.1 ± 0.1 (2)				
3p	4-(oxo)-3,4 dihydroquin-azoline-8-SO$_2$NH	3.4 ± 0.15 (2)	4.9 ± 3.3 (2)	**6g**	naphthalene-1-CH$_2$O	0.33 ± 0.11 (2)	7.6 ± 1.2 (2)
				6h	coumarine-6-CH$_2$O	0.79 ± 0.21 (2)	3.6
3q	1-(Me)-2-(oxo)-1,2,3,4-tetra-hydroquinoline-6-SO$_2$NH	2.9	3 ± 1.7 (2)	**6i**	quinoxaline-5-CH$_2$O	1.1	7.6
				6j	naphthalene-2-CH$_2$O	0.6 ± 0.24 (2)	7.3
3r	2-oxindole-5-SO$_2$NH	2.8	1.5 ± 0.5 (2)	**6k**	2-(Me)benzothiazole-5-CH$_2$O	0.21	3.5
3s	quinoline-6-SO$_2$NH	1.6	0.44 ± 0.08 (3)	**6l**		0.8	6.5 ± 3 (2)
3t	4-(oxo)-3,4 dihydroquin-azoline-6-SO$_2$NH	0.57 ± 0.17 (3)	0.28 ± 0.07 (5)	**6m**		12 ± 0.5 (2)	
3u	4-(pyridine)CH$_2$CH$_2$SO$_2$NH	1.3 ± 0.8 (4)	0.7 ± 0.3 (3)				

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than one value has been determined, IC_{50}s are shown ± SD (number of determinations).

Table 3. Inhibition of MMPs by Selected α-Substituted Hydroxamates (IC_{50})[a]

compd	MMP-1 (nM)	MMP-8 (nM)	compd	MMP-1 (nM)	MMP-8 (nM)
2h	2.8		**4a**	2.2 ± 0.6 (2)	
3n	1.1		**5a**	2.2	
3o	2.6		**5c**	1.7	0.2
3s	1.2		**6a**	0.88	
3t	1.3	3.7	**6l**	730 ± 253 (2)	
22a	1.5		**6m**	330 ± 5 (2)	
22b	2.4				

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than one value has been determined, IC_{50}s are shown ± SD (number of determinations).

A wide range of α-substituents in these series is allowed; whether bulky or small, electron donating or withdrawing, many substituents give subnanomolar TACE inhibition (0.2−5 nM range). However, highly polar substituents appear less suitable for TACE activity (e.g., imidazole **3g**: TACE IC_{50}: 9 nM), probably due to the high hydrophobicity of the enzyme S region[29] occupied by the α-substituent.

Some compounds in these series show improvement against the enzyme compared with Marimastat. In particular, the oxygen series gives exquisitely potent TACE inhibitors (**6k**: 0.21 nM; **6g**: 0.33 nM). Nevertheless, potent TACE inhibitors were also found in the thioether (**2f**: 0.42 nM; **2h**: 0.8 nM), sulfonamide (**3v**: 0.54 nM), and amine (**5c**: 0.23 nM) series. Only carboxamides (**4a**: 2 nM) are significantly less active than the previous series.

Inhibition of TNF production in whole blood is in the 2−10 μM range in the thioether and oxygen series: thus we observe a 2000−20000 drop between the enzyme and blood potencies. This is similar to that found for Marimastat, BB1101, and GW9471 in terms of intrinsic activity and ratio between enzyme potency and whole blood activity. More generally, in all series, the lipophilicity of compounds (i.e., **2f** vs **2j**; **6g** vs **6a**) broadly correlates with the loss in potency from enzyme to cell. Although factors such as serum protein binding[30] or penetration into cells may be implicated, another explanation for this general drop of potency could be an entropic effect due to the localization of both the enzyme and the pro-TNF substrate on the membrane.

Globally, in the sulfonamide series, as illustrated by **3a** (TACE IC_{50}: 1.5 nM; blood IC_{50}: 1.3 μM), this ratio is smaller (ca. 300−3000-fold), although highly lipophilic compounds such as **3c** also show a much higher ratio. This result prompted us to explore more widely substi-

tution in the sulfonamide series: *N*-methyl substitution on the sulfonamide is allowed but does not significantly increase the potency against TACE (**22a**: 0.61 nM/**3a**: 1.5 nM or **22b**: 4.4 nM/**3n**: 4.2 nM) whereas larger N-substituents show loss of activity (propyl (**22c**): 10 nM; benzyl (**22d**): 85 nM). Ortho-substitution on the phenyl decreases the activity (**3d**: 17 nM; **3e**: 9.7 nM; **3f**: 13 nM vs **3a**: 1.5 nM) while this is allowed in the oxygen (**6f**: 0.33 nM) and thioether series (**2g**: 1.1 nM).

Wide modifications of the phenyl substituent led to β-substituted bicyclic rings (**3l**: TACE IC_{50}: 0.66 nM, blood IC_{50}: 1.2 μM), whereas α-substituted bicyclic rings (such as **3m**: TACE IC_{50}: 1.2 nM, blood IC_{50}: 3.1 μM) are slightly less potent either against TACE or in blood. Our next goal was to reduce the lipophilicity of these compounds: introduction of heterocycles such as **3s** gave similar TACE potency, but increased blood activity (TACE IC_{50}: 1.6 nM, blood IC_{50}: 0.44 μM). Finally, based on a homology model of TACE,[31] we exploited potential new hydrogen bonding interactions between quinazolinones and the enzyme backbone in its S region: **3t** (TACE IC_{50}: 0.57 nM, blood IC_{50}: 0.28 μM) gave a significant increase (about 10-fold) in potency in blood compared with Marimastat and BB1101. Similar substitution in the carboxamide or amine series did not show the improvement seen with the sulfonamides.

These compounds are also MMP-1 and MMP-8 inhibitors as illustrated by **3t** (MMP-1 IC_{50}: 1.3 nM; MMP-8 IC_{50}: 3.7 nM). The necessity for selectivity for TACE against other MMPs remains to be seen, although it is known from early clinical trials that broad MMP inhibitors such as Marimastat or AG3340 show side effects such as tendonitis and musculoskeletal pain.[32] The precise cause of joint pain with these compounds is still unknown; different explanations have emerged such as the implication of MMP-1.

Other groups have previously shown that MMP-1 cannot accommodate large groups in its S1′ pocket.[26] Variation of the isobutyl P1′ substitution has led to more selective compounds as exemplified by **6l** (TACE: 0.8 nM, MMP-1: 730 nM, blood: 6.5 μM) or **6m** (TACE: 12 nM, MMP-1: 330 nM) bearing benzyloxybutyl and benzyloxypropyl P1′ chains, respectively.

The pharmacokinetics of these compounds have been evaluated in rat and marmoset: for example, after p.o. administration at 25 mg/kg to the marmoset, **3t** and **5a** gave lower blood levels than Marimastat (respectively, 310 ng/mL and 520 ng/mL vs 870 ng/mL for Marimastat after 0.5 h; 36 ng/mL and 36 ng/mL vs 190 ng/mL after 8 h). These blood levels are much lower than the concentrations required for inhibition of TNF production in whole blood and probably remain inadequate for TNF inhibition in vivo, although BB1101 despite its poor in vivo properties has been shown to inhibit TNF production in vivo.[13] The influence of these bulky α-substituents on in vitro metabolism of the hydroxamate group needs to be further investigated. The fate of these compounds in vivo will help in the search of new potent TACE inhibitors with adequate in vivo properties.

Conclusion

Detailed variation of the α-substitution on succinate-based hydroxamic acids has led to improved potency in the sulfonamide series both against TACE and in blood compared with Marimastat. Whereas thioether- and oxygen-based inhibitors also showed increased TACE potency, this improvement did not translate into better blood potency. This approach has culminated in the identification of heterocyclic bicyclic sulfonamides such as **3t** (TACE: 0.57 nM; blood: 0.28 μM) with improved potencies in blood compared with BB1101. Despite this, the in vivo properties of these products are still inadequate. It is expected that the availability of these highly potent TACE inhibitors will aid in the elucidation of the role of TACE in disease states.

Experimental Section

TACE Assay. Partially purified TACE enzyme was obtained from the membranes of THP-1.[33] This enzyme preparation cleaves 21 kDa soluble pro-TNFα at the correct cleavage site (Ala-Val), and enzyme activity is inhibited by matrix metalloprotease inhibitors.[34] 4′,5′-Dimethoxyfluoresceinyl·Ser·Pro·Leu·Ala·Gln·Ala·Val·Arg·Ser·Ser·Ser·Arg·Cys(4-(3-succinimid-1-yl)fluorescein)-NH_2 was used as the substrate to measure TACE activity.

Test compounds were solubilized in DMSO prior to serial dilutions in assay buffer (50 mM Tris-HCl, pH 7.4, containing 0.1% (w/v) Triton X-100 and 2 mM $CaCl_2$). Fifty microliters of each concentration was added to appropriate wells of a 96-well plate (Labsystems, catalog no. 9502817). Assay buffer (50 μL) was added to control wells. TACE enzyme (25 μL, 0.264 units/mL in assay buffer) was added (25 μL assay buffer was added to "substrate alone" control wells). Plates were incubated for 15 min at 26 °C, prior to addition of 25 μL of substrate (40 μM stock solution in assay buffer). Plates were read at time 0 to obtain background values (Fluoroskan II fluorometer) and after incubation at 26 °C for 18 h. IC_{50} values were calculated using a Microcal Origin package.

MMP Assays. The purified enzymes (purchased from Pr G. Murphy University of East Anglia, Norwich) can be used to monitor inhibitors of activity as follows: purified pro-MMPs were activated using 1 mM aminophenylmercuric acid (APMA), 20 h at 21 °C; they (11.25 ng per assay) were incubated for 4−5 h at 35 °C in assay buffer (0.1 M Tris-HCl, pH 7.5, containing 0.1 M NaCl, 20 mM $CaCl_2$, 0.02 mM $ZnCl_2$, and 0.05% (w/v) Brij 35) using (7-methoxycoumarin-4-yl)acetyl·Pro·Leu·Gly·Leu·*N*-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl·Ala·Arg·NH_2 as the substrate in the presence or absence of inhibitors. Activity was determined by measuring the fluorescence at 328 and 393 nm. IC_{50}s were calculated on a Microcal Origin package. This protocol[35] was adjusted for each MMP using substrates and buffers conditions optimal for the particular MMP.

Human Whole Blood Assay. Human whole blood assay was performed using a modification of the procedure[36] reported by Desch: Compounds were solubilized in DMSO at 50 mM, diluted 1:100 dilution in RPMI 1640 medium (GibcoBRL 31870-025), prior to serial dilutions in RPMI 1640 medium containing 1% DMSO (DMSO final concentration in all wells was 0.1%). Heparinized (10 units/mL) human blood (160 μL) obtained from healthy volunteers was incubated with 20 μL of test compound (triplicate cultures) for 30 min at 37 °C in a humidified (5% CO_2/95% air) incubator, prior to addition of 20 μL of LPS (*E. coli* 0111:B4, Sigma L-4130, final concentration 10 μg/mL). The 96-well round-bottom plates (Costar 4799) were then incubated for 6 h at 37 °C (humidified incubator), centrifuged (2000 rpm for 10 min; 4 °C), plasma harvested (50−100 μL), and stored in 96-well plates at −70 °C. TNFα content in plasma samples was determined by ELISA (R&D MAB610 & BAF210 anti-human TNFα antibodies).

Pharmacokinetics. Groups of marmosets ($n = 3$) were dosed orally with the test compound, and serial blood samples were removed. TACE inhibition activity was extracted and assayed against TACE; alternatively, the test compound was quantified by HPLC/MS. Concentration was calculated against a standard curve.

Chemistry. All experiments were carried out under an inert atmosphere unless otherwise stated. Flash chromatography was carried out on Merck Kieselgel 60 (Art. 9385). TLCs were performed on precoated silica gel plates (Merck Art. 5715). Melting points were determined on a Kofler Block or with a Büchi melting point apparatus and are uncorrected. Proton and ^{13}C NMR spectra were recorded on a JEOL JMM-EX400 spectrometer at 400 and 100 MHz, respectively, with TMS as an internal standard. Chemical shifts are expressed in units of δ (ppm), and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; s br, broad singlet; m, multiplet. Mass spectra were obtained on a Finnigan SSQ7000 mass spectrometer by electronic impact (EI) or electrospray (ESI) ionization techniques. Elemental analyses were performed on a Carlo Erba EA1108 instrument. Unless otherwise stated, HPLC retention times were measured on a 125/4.6 mm Kromasil C_{18}, 5 μm HPLC column; eluant: methanol and water/1% AcOH, linear gradient from 30:70 to 90:10 for 10 min then 100:0 for 5 min, flow rate 1.5 mL/min; UV detection 254 nm and light scattering.

2*S*-Isobutyl-3*S*-phenylthiobutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8a) and 2*S*-isobutyl-3*R*-phenylthiobutan-1,4-dioic Acid 4-*tert*-Butyl Ester (9a). To a stirred solution of LDA [32.8 mmol; prepared by addition of 1.6 M nBuLi (20.5 mL, 32.8 mmol) in hexane to a solution of diisopropylamine (4.4 mL, 33.75 mmol) in THF (20 mL) at −78 °C] cooled at −78 °C was added **7** (3.45 g, 15 mmol) in THF (15 mL) dropwise. The mixture was stirred for 90 min at −78 °C, and a solution of diphenyl disulfide (4.2 g, 19 mmol) in THF (15 mL) was added. The mixture was stirred for 30 min at −78 °C, warmed to room temperature and stirred for 2 h at room temperature. The solution was cooled to −78 °C and quenched by addition of methanol (6 mL). The solution was warmed to room temperature, and the solvents were evaporated in vacuo. Ice was added to the residue, and the mixture was acidified with 2 N HCl to pH 4. The solution was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using petroleum ether−EtOAc (gradient from 8/2 to 0/10) as eluant to give a 1:1 mixture of **8a** and **9a** (4.77 g). Preparative normal phase HPLC purification using EtOAc−cyclohexane (5:95) as eluant gave first **8a** (2.3 g, 45%): ^1H NMR ($CDCl_3$) 7.50 (m, 2H), 7.28 (m, 3H), 3.68 (d, 1H, J = 10.3 Hz), 2.98 (m, 1H), 1.72 (m, 1H), 1.63 (m, 1H), 1.39 (s, 9H), 1.26 (m, 1H), 0.85 (d, 3H, J = 7 Hz), 0.83 (d, 3H, J = 7.3 Hz). Further elution gave **9a** (2.2 g, 43%): ^1H NMR ($CDCl_3$) 7.49 (m, 2H), 7.30 (m, 3H), 3.62 (d, 1H, J = 10.3 Hz), 2.81 (m, 1H), 1.86 (m, 1H), 1.6−1.75 (m, 2H), 1.35 (s, 9H), 0.93 (d, 6H, J = 6.2 Hz).

3*S*-(3,4-Dimethoxyphenylthio)-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8b). From di-(3,4-dimethoxyphenyl)disulfide were similarly obtained **8b** (1.05 g, 60%) and **9b** (550 mg, 31%). **8b**: ^1H NMR ($CDCl_3$) 7.1 (m, 2H), 6.78 (d, 1H, J = 8.1 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.54 (d, 1H, J = 10.3 Hz), 2.96 (m, 1H), 1.75−1.55 (m, 2H), 1.42 (s, 9H), 1.26 (m, 1H), 0.91 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz). **9b**: ^1H NMR ($CDCl_3$) 7.09 (dd, 1H, J = 8.1 Hz, J' = 2.2 Hz), 7.02 (d, 1H, J = 2.2 Hz), 6.80 (d, 1H, J = 8.1 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (d, 1H, J = 10.3 Hz), 2.78 (m, 1H), 1.86 (m, 1H), 1.75−1.55 (m, 2H), 1.38 (s, 9H), 0.94 (d, 6H, J = 6.6 Hz).

2*S*-Isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)butan-1,4-dioic Acid 4-*tert*-Butyl Ester (8c). From di-(1-methyl-2-oxo-1,2,3,4−tetrahydroquinolin-6-yl) disulfide[37] were similarly obtained **8c** (950 mg, 40%) and **9c** (603 mg, 25%) after purification on C18 preparative HPLC eluting with 0.2% aqueous ammonium carbonate−acetonitrile (gradient from 100:0 to 72.5:27.5). **8c**: ^1H NMR ($CDCl_3$) 7.41 (d br, 1H, J = 8.4 Hz), 7.33 (s br, 1H), 6.90 (d, 1H, J = 8.4 Hz), 3.56 (d, 1H, J = 10.6 Hz), 3.33 (s, 3H), 2.95 (m, 1H), 2.88 (t, 2H, J = 7.3 Hz), 2.65 (t, 2H, J = 7.3 Hz), 1.8−1.5 (m, 2H), 1.43 (s, 9H), 1.26 (s, 1H), 0.92 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); MS (ESI) 444 (MNa^+). **9c**: ^1H NMR ($CDCl_3$) 7.39 (d br, 1H, J = 8.4 Hz), 7.32 (s br, 1H), 6.91 (d, 1H, J = 8.4 Hz), 3.52 (d, 1H, J = 10.3 Hz), 3.34 (s, 3H), 2.88 (t, 2H, J = 7.3 Hz), 2.76 (m, 1H), 2.65 (t, 2H, J = 7.3 Hz), 1.89 (m, 1H), 1.8−1.6 (m, 2H), 1.39 (s, 9H), 0.95 (d, 6H, J = 6.6 Hz); MS (ESI) 444 (MNa^+).

3*S*-(4-Cyanophenylthio)-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8d). From di-(4-cyanophenyl) disulfide[38] were similarly obtained **8d** (1.2 g, 50%) and **9d** (300 mg, 13%). **8d**: ^1H NMR ($CDCl_3$) 7.56 (m, 4H), 3.82 (d, 1H, J = 9.9 Hz), 2.99 (m, 1H), 1.8−1.55 (m, 2H), 1.41 (s, 9H), 1.28 (m, 1H), 0.92 (m, 6H). **9d**: ^1H NMR ($CDCl_3$) 7.57 (m, 4H), 3.82 (d, 1H, J = 10.2 Hz), 2.89 (m, 1H), 1.8−1.5 (m, 3H), 1.37 (s, 9H), 0.92 (d, 6H, J = 5.9 Hz).

2*S*-Isobutyl-3*S*-(4-(methylsulfonyl)phenylthio)butan-1,4-dioic Acid 4-*tert*-Butyl Ester (8e). From di-(4-(methylsulfonyl)phenyl) disulfide[39] (dissolved in DMF instead of THF) was similarly obtained a 1:1 mixture of **8e** and **9e** (800 mg, 34%): ^1H NMR ($CDCl_3$) 7.86 (m, 2H), 7.63 (m, 2H), 3.85 (d, 1H, J = 10.2 Hz), 3.05 (s, 3H), 3.01 and 2.89 (m, 1H), 1.8−1.3 (m, 3H), 1.42 and 1.38 (s, 9H), 0.94 (m, 6H).

3*S*-(3,5-Dichlorophenylthio)-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8f). From di-(3,5-dichlorophenyl) disulfide were similarly obtained **8f** (1.0 g, 36%) and **9f** (300 mg, 11%). **8f**: ^1H NMR ($CDCl_3$) 7.38 (d, 2H, J = 1.8 Hz), 7.26 (1H), 3.70 (d, 1H, J = 10.3 Hz), 2.97 (m, 1H), 1.8−1.5 (m, 2H), 1.43 (s, 9H), 1.25 (m, 1H), 0.94 (d, 3H, J = 6.6 Hz), 0.92 (d, 3H, J = 6.6 Hz). **9f**: ^1H NMR ($CDCl_3$) 7.39 (d, 2H, J = 1.8 Hz), 7.28 (t, 1H, J = 1.8 Hz), 3.69 (d, 1H, J = 10.2 Hz), 2.83 (m, 1H), 1.8−1.5 (m, 3H), 1.40 (s, 9H), 0.94 (m, 6H).

3*S*-(2-Chloro-4-fluorophenylthio)-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8g). From di-(2-chloro-4-fluorophenyl) disulfide were similarly obtained **8g** (2.5 g, 54%) and **9g**. **8g**: ^1H NMR ($CDCl_3$) 7.61 (dd, 1H, J = 8.8 Hz, J' = 5.8 Hz), 7.17 (dd, 1H, J = 8.8 Hz, J' = 2.5 Hz), 6.96 (m, 1H), 3.76 (d, 1H, J = 9.9 Hz), 2.98 (m, 1H), 1.75 (m, 1H), 1.62 (m, 1H), 1.39 (s, 9H), 1.30 (m, 1H), 0.93 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); MS (ESI) 415 ($M\{^{37}Cl\}Na^+$), 413 ($M\{^{35}Cl\}Na^+$). **9g:** ^1H NMR ($CDCl_3$) 7.61 (dd, 1H, J = 8.8 Hz, J' = 5.8 Hz), 7.20 (dd, 1H, J = 8.8 Hz, J' = 2.5 Hz), 6.96 (m, 1H), 3.76 (d, 1H, J = 9.2 Hz), 2.88 (m, 1H), 1.9−1.6 (m, 3H), 1.32 (s, 9H), 0.96 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 6.6 Hz).

2*S*-Isobutyl-3*S*-(quinolin-8-ylmethylthio)butan-1,4-dioic Acid 4-*tert*-Butyl Ester (8h). From di-(quinolin-8-ylmethyl) disulfide[40] was obtained a 1:1 mixture of **8h** and **9h** (487 mg from 1.74 mmol of **7**) contaminated with ca. 20% of **7**: ^1H NMR ($CDCl_3$) 8.96 (m, 1H), 8.15 (m, 1H), 7.75 (m, 2H), 7.48 (m, 1H), 7.40 (m, 1H), 4.70−4.50 (m, 2H), 3.40 and 3.37 (d, 1H, J = 10.3 Hz), 3.02 and 2.79 (m, 1H), 1.8−1.2 (m, 3H), 1.49 and 1.46 (s, 9H), 0.95−0.7 (m, 6H); MS (ESI) 404 (MH^+).

3*S*-[3-(1-Cyano-1-methylethyl)phenylthio]-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8i). From di-[3-(1-cyano-1-methylethyl)phenyl] disulfide were similarly obtained **8i** (565 mg, 36%) and **9i** (not isolated). **8i**: ^1H NMR ($CDCl_3$) 7.61 (s br, 1H), 7.45 (m, 2H), 7.34 (m, 1H), 3.67 (d, 3H, J = 10.2 Hz), 2.97 (m, 1H), 1.8−1.55 (m, 2H), 1.72 (s, 6H), 1.40 (s, 9H), 1.25 (m, 1H), 0.91 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz); MS (ESI) 428 (MNa^+).

Di-[3-(1-cyano-1-methylethyl)phenyl] disulfide was prepared as follows: alkylation of (3-bromophenyl)acetonitrile with excess sodium hydride/methyl iodide in THF gave 2-(3-bromophenyl)-2-methylpropionitrile (100%): ^1H NMR ($CDCl_3$) 7.60 (s br, 1H), 7.45 (m, 2H), 7.25 (m, 1H), 1.72 (s, 6H). This compound gave 2-(3-(*tert*-butylthio)phenyl)-2-methylpropionitrile (37%) by reaction with tBuSH (1.3 equiv) and tBuOK (1.35 equiv) in DMSO at 80 °C in the presence of $Pd(PPh_3)_4$ (0.05 equiv): ^1H NMR ($CDCl_3$) 7.62 (s br, 1H), 7.49 (m, 2H), 7.36 (m, 1H), 1.74 (s, 6H), 1.29 (s, 9H). This was converted to 2-(3-mercaptophenyl)-2-methylpropionitrile (82%) by reaction with TFA (1.7 equiv) and CF_3SO_3H (1 equiv) in thioanisole at room temperature: ^1H NMR ($CDCl_3$) 7.6−7.2 (m, 4H), 3.53 (s, 1H), 1.71 (s, 6H). Oxidation of this thiol in DMSO gave the desired disulfide (73%): ^1H NMR ($CDCl_3$) 7.60 (s br, 2H), 7.45 (m, 2H), 7.33 (m, 4H), 1.69 (m, 12H).

2*S*-Isobutyl-3*S*-methylthiobutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8j). From dimethyl disulfide was similarly obtained a 1:3 mixture of **8j** and **9j** (1.06 g, 89%): ^{1}H NMR ($CDCl_3$) 3.20 (d, J = 10.6 Hz, **9j**) and 3.17 (d, J = 11.3 Hz, **8j**) (1H), 2.97 (m, **8j**) and 2.77 (m, **9j**) (1H), 2.18 (s, **8j**) and 2.13 (s, **9j**) (3H), 1.8−1.3 (m, 3H), 1.49 (s, **8j**) and 1.46 (s, **9j**) (9H), 0.94 (m, 6H).

3*S*-Ethylthio-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (8k). From diethyl disulfide was similarly obtained a 3:2 mixture of **8k** and **9k** (380 mg, 61%): ^{1}H NMR ($CDCl_3$) 3.26 (d, J = 10.3 Hz, **9k**) and 3.23 (d, J = 11 Hz, **8k**) (1H), 2.95 (m, **8k**) and 2.77 (m, **9k**) (1H), 2.70−2.60 (m, 2H), 1.8−1.3 (m, 3H), 1.49 (s, **8k**) and 1.46 (s, **9k**) (9H), 1.29−1.22 (m, 3H), 0.96−0.90 (m, 6H).

***N*^{2}-[4-*tert*-Butyloxy-2*S*-isobutyl-3*S*-phenylthiosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10a).** To a solution of **8a** (2.75 g, 8.1 mmol) in DMF (16 mL) at 0 °C were added successively HOBT (1.32 g, 9.8 mmol) and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.87 g, 9.8 mmol). After 15 min, L-*tert*-leucine methylamide (1.41 g, 9.8 mmol) and DMAP (195 mg, 1.6 mmol) were added. The mixture was stirred at room temperature for 3 h. The mixture was poured into cold water and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvents were evaporated in vacuo, and the residue was purified by flash chromatography on silica using EtOAc−petroleum ether (3:7) as eluant to give **10a** (3.0 g, 79%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.47 (m, 2H), 7.27 (m, 3H), 6.45 (d, 1H, J = 9.2 Hz), 5.95 (m, 1H), 4.27 (d, 1H, J = 9.2 Hz), 3.71 (d, 1H, J = 11 Hz), 2.80 (d, 3H, J = 4.8 Hz), 2.67 (m, 1H), 1.74 (m, 1H), 1.45 (m, 1H), 1.34 (s, 9H), 1.17 (m, 1H), 1.06 (s, 9H), 0.90 (d, 3H, J = 6.2 Hz), 0.84 (d, 3H, J = 6.6 Hz); MS (ESI) 487 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-3*S*-(3,4-dimethoxyphenylthio)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10b).** Similarly **10b** was obtained (1.1 g, 84%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.05 (m, 2H), 6.77 (d, 1H, J = 8.8 Hz), 6.44 (d br, 1H, J = 9.2 Hz), 5.76 (m, 1H), 4.25 (d, 1H, J = 9.2 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.61 (d, 1H, J = 10.6 Hz), 2.81 (d, 3H, J = 4.4 Hz), 2.66 (m, 1H), 1.73 (m, 1H), 1.45 (m, 1H), 1.39 (s, 9H), 1.12 (m, 1H), 1.06 (s, 9H), 0.89 (d, 3H, J = 6.6 Hz), 0.84 (d, 3H, J = 6.6 Hz); MS (ESI) 547 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-2*S*-isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10c).** Similarly was obtained **10c** (250 mg, 50%) as a white foam after C18 preparative HPLC eluting with 0.2% aqueous ammonium carbonate−acetonitrile (gradient from 90:10 to 50:50): ^{1}H NMR ($CDCl_3$) 7.37 (dd, 1H, J = 8.4 Hz, J' = 2.2 Hz), 7.30 (d, 1H, J = 2.2 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.44 (d br, 1H J = 9.2 Hz), 5.77 (m, 1H), 4.25 (d, 1H, J = 9.2 Hz), 3.62 (d, 1H, J = 10.6 Hz), 3.33 (s, 3H), 2.87 (m, 2H), 2.82 (d, 3H, J = 4.8 Hz), 2.65 (m, 3H), 1.75 (m, 1H), 1.43 (m, 1H), 1.39 (s, 9H), 1.14 (m, 1H), 1.07 (s, 9H), 0.90 (d, 3H, J = 6.2 Hz), 0.84 (d, 3H, J = 6.2 Hz); MS (ESI) 570 (MNa^+). Anal. ($C_{29}H_{45}N_3O_5S$) C H calcd 8.28 found 8.85, N S.

***N*^{2}-[4-*tert*-Butyloxy-3*S*-(4-cyanophenylthio)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10d).** Similarly **10d** was obtained (1.09 g, 74%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.52 (s, 4H), 6.44 (d br, 1H, J = 9.2 Hz), 5.68 (m, 1H), 4.18 (d, 1H, J = 9.2 Hz), 3.84 (d, 1H, J = 10.8 Hz), 2.81 (d, 3H, J = 4.6 Hz), 2.71 (m, 1H), 1.76 (m, 1H), 1.45 (m, 1H), 1.39 (s, 9H), 1.18 (m, 1H), 1.00 (s, 9H), 0.91 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz); MS (ESI) 512 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-2*S*-isobutyl-3*S*-(4-(methylsulfonyl)-phenylthio)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10e).** Similarly, from a 1:1 mixture of **8e** and **9e** (800 mg) was obtained a mixture of **10e** and its epimer (800 mg, 78%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.83 (m, 2H), 7.62 (m, 2H), 6.47 (m, 1H), 5.70 (m, 1H), 4.20 and 4.14 (d, 1H, J = 9.2 Hz), 3.94 (d, J = 9.9 Hz) and 3.87 (d, J = 11.2 Hz) (1H), 3.05 and 3.03 (s, 3H), 2.81 (m, 3H), 2.72 (m, 1H), 1.8−1.1 (m, 3H), 1.41 and 1.34 (s, 9H), 1.01 and 0.99 (s, 9H), 0.92−0.85 (m, 6H); MS (ESI) 565 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-3*S*-(3,5-dichlorophenylthio)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10f).** Similarly **10f** was obtained (1.0 g, 77%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.34 (d, 2H, J = 1.8 Hz), 7.22 (t, 1H, J = 1.8 Hz), 6.44 (d, 1H, J = 9.2 Hz), 5.77 (m, 1H), 4.22 (d, 1H, J = 9.2 Hz), 3.75 (d, 1H, J = 11 Hz), 2.81 (d, 3H, J = 5.1 Hz), 2.68 (m, 1H), 1.74 (m, 1H), 1.47 (m, 1H), 1.41 (s, 9H), 1.17 (m, 1H), 1.04 (s, 9H), 0.91 (d, 3H, J = 6.2 Hz), 0.85 (d, 3H, J = 6.2 Hz); MS (ESI) 559 (M{^{37}Cl,^{37}Cl}Na^+), 557 (M{^{35}Cl,^{37}Cl}Na^+), 555 (M{^{35}Cl,^{35}Cl}Na^+). Anal. ($C_{25}H_{38}Cl_2N_2O_4S$) C H N S.

***N*^{2}-[4-*tert*-Butyloxy-3*S*-(2-chloro-4-fluorophenylthio)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10g).** Similarly **10g** was obtained (2.38 g, 72%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.59 (dd, 1H, J = 8.8 Hz, J' = 5.8 Hz), 7.14 (dd, 1H, J = 8.8 Hz, J' = 2.6 Hz), 6.94 (m, 1H), 6.49 (d br, 1H, J = 9.2 Hz), 6.04 (m., 1H), 4.28 (d, 1H, J = 9.2 Hz), 3.81 (d, 1H, J = 10.6 Hz), 2.81 (d, 3H, J = 4.8 Hz), 2.71 (m, 1H), 1.76 (m, 1H), 1.46 (m, 1H), 1.35 (s, 9H), 1.19 (m, 1H), 1.05 (s, 9H), 0.90 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.6 Hz); MS (ESI) 541 (M{^{37}Cl}Na^+), 539 (M{^{35}Cl}Na^+).

***N*^{2}-[4-*tert*-Butyloxy-2*S*-isobutyl-3*S*-(quinolin-8-ylmethylthio)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10h).** Similarly, from a mixture of **8h** and **9h** (450 mg, 1.12 mmol, contaminated with **7**) was obtained **10h** and its epimer (451 mg, 1:1): ^{1}H NMR ($CDCl_3$) 8.95 (m, 1H), 8.13 (m, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.41 (m, 1H), 6.65 and 6.45 (m, 1H), 6.0−5.9 (m, 1H), 4.65 and 4.62 (AB system, 1H, J = 13.2 Hz), 4.46 and 4.43 (AB system, 1H, J = 9.9 Hz), 4.19 and 4.12 (d, 1H, J = 9.2 Hz), 3.44 (d, J = 9.9 Hz) and 3.40 (d, J = 10.7 Hz) (1H), 2.75 (m, 4H), 1.46 and 1.42 (s, 9H), 1.6−1.2 (m, 3H), 1.0−0.7 (m, 15H).

***N*^{2}-[4-*tert*-Butyloxy-3*S*-[3-(1-cyano-1-methylethyl)-phenylthio]-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10i).** Similarly, **10i** was obtained (495 mg, 67%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.54 (s br, 1H), 7.40 (m, 2H), 7.31 (m, 1H), 6.46 (d br, 1H, J = 9.2 Hz), 5.79 (m, 1H), 4.24 (d, 1H, J = 9.2 Hz), 3.72 (d, 1H, J = 11 Hz), 2.81 (d, 3H, J = 4.8 Hz), 2.68 (m, 1H), 1.75 (m, 1H), 1.71 (s, 6H), 1.46 (m, 1H), 1.36 (s, 9H), 1.15 (m, 1H), 1.05 (s, 9H), 0.90 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.6 Hz); MS (ESI) 554 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-2*S*-isobutyl-3*S*-methylthiosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10j).** Similarly, from a 1:3 mixture of **8j** and **9j** was obtained **10j** and its epimer (913 mg, 79%, 1:3). **10j**: ^{1}H NMR ($CDCl_3$) 6.38 (m, 1H), 5.90 (m, 1H), 4.22 (d, 1H, J = 9.2 Hz), 3.22 (d, 1H, J = 11 Hz), 2.80 (d, 3H, J = 4.6 Hz), 2.62 (m, 1H), 2.17 (s, 3H), 1.49 (s, 9H), 1.8−1.3 (m, 3H), 1.04 (s, 9H), 0.89 (d, 3H, J = 6.6 Hz), 0.84 (d, 3H, J = 6.6 Hz). Epimer: ^{1}H NMR ($CDCl_3$) 6.54 (m, 1H), 5.90 (m, 1H), 4.16 (d, 1H, J = 9.2 Hz), 3.28 (d, 1H, J = 10.2 Hz), 2.79 (d, 3H, J = 4.6 Hz), 2.62 (m, 1H), 2.11 (s, 3H), 1.45 (s, 9H), 1.8−1.3 (m, 3H), 0.99 (s, 9H), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz); MS (ESI) 425 (MNa^+).

***N*^{2}-[4-*tert*-Butyloxy-3*S*-ethylthio-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (10k).** Similarly, from a 3:2 mixture of **8k** and **9k** was obtained **10k** and its epimer (200 mg, 56%, 3:2): ^{1}H NMR ($CDCl_3$) 6.65 and 6.35 (m, 1H), 5.80 (m, 1H), 4.20 and 4.13 (d, 1H, J = 9.2 Hz), 3.32 and 3.26 (d, 1H, J = 9.9 Hz), 2.80 and 2.79 (d, 3H, J = 4.8 Hz), 2.62 (m, 3H), 1.8−1.2 (m, 3H), 1.49 and 1.46 (s, 9H), 1.27 and 1.22 (t, 3H, J = 7.3 Hz), 1.04 and 1.00 (s, 9H), 0.92 and 0.84 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz); MS (ESI) 439 (MNa^+).

***N*^{2}-[4-Hydroxy-2*S*-isobutyl-3*S*-phenylthiosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (11a).** TFA (8.3 mL) was added to a solution of **10a** (3.0 g, 6.05 mmol) in dry CH_2Cl_2 (19 mL). The solution was stirred at 0 °C for 18 h. The solvents were evaporated in vacuo. The residue was taken up in toluene, and the solvent was removed in vacuo (3×) to give white crystals which were washed with pentane and dried in vacuo. **11a**: (2.56 g, 97%) mp = 226−228 °C; ^{1}H NMR (DMSO-d_6) 8.13 (d br, 1H, J = 9.2 Hz), 7.86 (q, 1H, J = 4.4 Hz), 7.43−7.24 (m, 5H), 4.26 (d, 1H, J = 9.2 Hz), 3.62 (d, 1H, J = 11 Hz), 3.03 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.56 (m, 1H), 1.40 (m, 1H), 1.06 (m, 1H), 0.96 (s, 9H), 0.87 (d, 1H, J = 6.6 Hz), 0.79

(d, 1H, $J = 6.6$ Hz); MS (ESI) 409 (MH^+). Anal. ($C_{21}H_{32}N_2O_4S \cdot 0.38H_2O$) C H N S.

Acids **11b**−**k** were obtained from **10b**−**k** using the method described above for **11a**.

***N*²-[3*S*-(3,4-Dimethoxyphenylthio)-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11b):** (795 mg, 100%) white solid; ^{1}H NMR (DMSO-d_6) 8.10 (m, 1H), 7.88 (m, 1H), 7.03−6.89 (m, 3H), 4.30 (d, 1H, $J = 9.5$ Hz), 3.76 (s, 3H), 3.75 (s, 3H), 3.49 (d, 1H, $J = 11$ Hz), 2.99 (m, 1H), 2.58 (d, 3H, $J = 4.4$ Hz), 1.53 (m, 1H), 1.40 (m, 1H), 1.05 (m, 1H), 0.98 (s, 9H), 0.87 (d, 3H, $J = 6.2$ Hz), 0.78 (d, 3H, $J = 6.2$ Hz); MS (ESI) 491 (MNa^+), 469 (MH^+).

***N*²-[4-Hydroxy-2*S*-isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (11c):** (370 mg, 100%) white solid; ^{1}H NMR ($CDCl_3$) 7.7 (s br, 1H), 7.40 (dd, 1H, $J = 8.4$ Hz, $J' = 2.2$ Hz), 7.29 (d, 1H, $J = 2.2$ Hz), 6.38 (d, 1H, $J = 8.4$ Hz), 4.37 (d, 1H, $J = 9.6$ Hz), 3.81 (d, 1H, $J = 9.2$ Hz), 3.36 (s, 3H), 2.93 (m, 1H), 2.86 (m, 2H), 2.82 (d, 3H, $J = 4.7$ Hz), 2.63 (m, 2H), 1.70 (m, 1H), 1.46 (m, 1H), 1.34 (m, 1H), 1.03 (s, 9H), 0.88 (d, 3H, $J = 6.3$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz).

***N*²-[3*S*-(4-Cyanophenylthio)-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11d):** (737 mg, 77%) white solid: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 7.53 (s, 4H), 7.1−7.0 (m, 2H), 4.29 (d, 1H, $J = 6.9$ Hz), 3.91 (d, 1H, $J = 10.6$ Hz), 2.90 (m, 1H), 2.74 (d, 3H, $J = 4.4$ Hz), 1.75 (m, 1H), 1.45 (m, 1H), 1.24 (m, 1H), 0.99 (s, 9H), 0.91 (d, 3H, $J = 6.6$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz); MS (ESI) 456 (MNa^+), 434 (MH^+).

***N*²-[4-Hydroxy-2*S*-isobutyl-3*S*-(4-(methylsulfonyl)-phenylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (11e).** From a mixture of **10e** and its epimer was similarly obtained a mixture of **11e** and its epimer (500 mg, 73%) as a white solid. ^{1}H NMR (DMSO-d_6) 8.20 (m, 1H), 7.90 (m, 1H), 7.86 (m, 2H), 7.68 and 7.60 (d, 2H, $J = 8.8$ Hz), 4.22 and 4.19 (d, 1H, $J = 9.2$ Hz), 3.97 (d, $J = 10$ Hz) and 3.85 (d, $J = 11$ Hz) (1H), 3.23 and 3.22 (s, 3H), 3.13 and 3.02 (m, 1H), 2.57 (m, 3H), 1.65−1.35 (m, 2H), 1.12 (m, 1H), 0.93 and 0.90 (s, 9H), 0.90−0.78 (m, 6H); MS (ESI) 509 (MNa^+).

***N*²-[3*S*-(3,5-Dichlorophenylthio)-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11f):** (775 mg, 87%) white solid; ^{1}H NMR (DMSO-d_6) 8.21 (d br, 1H, $J = 9.6$ Hz), 7.90 (q, 1H, $J = 4.4$ Hz), 7.52 (s, 1H), 7.45 (s, 2H), 4.26 (d, 1H, $J = 9.6$ Hz), 3.72 (d, 1H, $J = 10.6$ Hz), 3.09 (m, 1H), 2.56 (d, 3H, $J = 4.4$ Hz), 1.57 (m, 1H), 1.40 (m, 1H), 1.1 (m, 1H), 0.93 (s, 9H), 0.87 (d, 3H, $J = 6.2$ Hz), 0.80 (d, 3H, $J = 6.6$ Hz).

***N*²-[3*S*-(2-Chloro-4-fluorophenylthio)-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11g):** (2.0 g, 97%) white solid; ^{1}H NMR (DMSO-d_6) 8.15 (m, 1H), 7.85 (m, 1H), 7.60 (dd, 1H, $J = 8.8$ Hz, $J' = 5.8$ Hz), 7.49 (dd, 1H, $J = 8.8$ Hz, $J' = 2.6$ Hz), 7.27 (m, 1H), 4.20 (d, 1H, $J = 9.2$ Hz), 3.71 (d, 1H, $J = 10.6$ Hz), 3.07 (m, 1H), 2.55 (d, 3H, $J = 4.4$ Hz), 1.57 (m, 1H), 1.39 (m, 1H), 1.09 (m, 1H), 0.93 (s, 9H), 0.86 (d, 3H, $J = 6.6$ Hz), 0.78 (d, 3H, $J = 6.6$ Hz); MS (ESI) 485 (M{^{37}Cl}Na^+), 483 (M{^{35}Cl}Na^+).

***N*²-[4-Hydroxy-2*S*-isobutyl-3*S*-(quinolin-8-ylmethylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (11h).** From a mixture of **10h** and its epimer was similarly obtained a mixture of **11h** and its epimer as the trifluoroacetate salt. MS (EI): 474 (MH^+); C18 HPLC (50% MeOH, 1% AcOH−water) t_R 5.4 and 9 min.

***N*²-[3*S*-[3-(1-Cyano-1-methylethyl)phenylthio]-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11i):** (440 mg, 99%) white solid; ^{1}H NMR (DMSO-d_6) 8.14 (d br, 1H, $J = 9.6$ Hz), 7.88 (m, 1H), 7.52 (s, 1H), 7.40 (m, 3H), 4.27 (d, 1H, $J = 9.6$ Hz), 3.66 (d, 1H, $J = 11.4$ Hz), 3.07 (m, 1H), 2.57 (d, 3H, $J = 4.4$ Hz), 1.68 (s, 6H), 1.56 (m, 1H), 1.41 (m, 1H), 1.07 (m, 1H), 0.96 (s, 9H), 0.88 (d, 3H, $J = 6.6$ Hz), 0.79 (d, 3H, $J = 6.6$ Hz); MS (ESI) 498 (MNa^+).

***N*²-[4-Hydroxy-2*S*-isobutyl-3*S*-methylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11j).** From a mixture of **10j** and its epimer was similarly obtained a 1:3 mixture of **11j** and its epimer (1.7 g, 99%) as a white solid. **11j**: ^{1}H NMR ($CDCl_3$) 7.85 (m, 1H), 6.80 (m, 1H), 4.53 (d, 1H, $J = 9.9$ Hz), 3.36 (d, 1H, $J = 11$ Hz), 2.85 (m, 4H), 2.22 (s, 3H), 1.7−1.4 (m, 3H), 1.03 (s, 9H), 0.84 (d, 3H, $J = 6.6$ Hz), 0.82 (d, 3H, $J = 6.6$ Hz). Epimer ^{1}H NMR ($CDCl_3$) 7.7 (m, 1H), 6.60 (m, 1H), 4.41 (d, 1H, $J = 9.9$ Hz), 3.44 (d, 1H, $J = 7.3$ Hz), 2.90 (m, 1H), 2.85 (d, 3H, $J = 5.1$ Hz), 2.24 (s, 3H), 1.7−1.4 (m, 3H), 1.01 (s, 9H), 0.89 (d, 3H, $J = 6.2$ Hz), 0.87 (d, 3H, $J = 6.2$ Hz); MS (ESI) 369 (MNa^+), 347 (MH^+).

***N*²-[3*S*-Ethylthio-4-hydroxy-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (11k).** From a mixture of **10k** and its epimer was similarly obtained a 3:2 mixture of **11k** and its epimer (199 mg, 100%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.4 (m, 1H), 6.3 and 5.9 (m, 1H), 4.40 and 4.26 (d, 1H, $J = 9.5$ Hz), 3.55 (d, $J = 6.6$ Hz) and 3.45 (d, $J = 10.3$ Hz) (1H), 2.86 and 2.83 (d, 3H, $J = 4.7$ Hz), 2.80−2.71 (m, 3H), 1.8−1.3 (m, 3H), 1.22 (m, 3H), 1.03 (s, 9H), 0.98−0.82 (m, 6H); MS (ESI) 383 (MNa^+), 361 (MH^+).

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*S*-phenylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2a).** To acid **11a** (2.15 g, 5.1 mmol) in DMF (15 mL) was added HOBT (770 mg, 5.7 mmol), followed by EDCI (1.09 g, 5.7 mmol). The mixture was stirred at room temperature for 1 h. $NH_2OH \cdot HCl$ (529 mg, 7.6 mmol) was added immediately followed by 2,6-lutidine (830 μL, 7.6 mmol) and DMAP (62 mg, 0.51 mmol). The resulting solution was stirred at room temperature for 3 h. The resulting mixture was purified by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 20:80 to 60:40) to give **2a** (520 mg, 24%): mp = 198−200 °C; ^{1}H NMR (DMSO-d_6) 10.75 (m, 1H), 9.0 (s br, 1H), 8.00 (d, 1H, $J = 9.5$ Hz), 7.79 (q, 1H, $J = 4.8$ Hz), 7.4−7.15 (m, 5H), 4.22 (d, 1H, $J = 9.5$ Hz), 3.56 (d, 1H, $J = 11.3$ Hz), 3.00 (m, 1H), 2.55 (d, 3H, $J = 4.8$ Hz), 1.5−1.3 (m, 2H), 1.0−0.9 (m, 1H), 0.93 (s, 9H), 0.84 (d, 3H, $J = 6.6$ Hz), 0.76 (d, 3H, $J = 6.6$ Hz); MS (ESI) 446 (MNa^+). Anal. ($C_{21}H_{33}N_3O_4S$) C H N.

***N*²-[3*S*-(3,4-Dimethoxyphenylthio)-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2b).** Similarly, **2b** was obtained (170 mg, 37%) as a white solid: mp = 218−220 °C; ^{1}H NMR (DMSO-d_6) 10.53 (s br, 1H), 8.98 (s br, 1H), 7.99 (d, 1H, $J = 9.5$ Hz), 7.81 (q, 1H, $J = 4.4$ Hz), 6.99 (s, 1H), 6.88 (m, 2H), 4.29 (d, 1H, $J = 9.5$ Hz), 3.76 (s, 3H), 3.75 (s, 3H), 3.37 (d, 1H, $J = 11.4$ Hz), 2.98 (m, 1H), 2.58 (d, 3H, $J = 4.4$ Hz), 1.40 (m, 2H), 1.0 (m, 1H), 0.98 (s, 9H), 0.85 (d, 3H, $J = 6.2$ Hz), 0.77 (d, 3H, $J = 6.2$ Hz); MS (ESI) 506 (MNa^+). Anal. ($C_{23}H_{37}N_3O_6S$) C H calcd 7.66 found 8.13, N S.

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (2c).** Similarly, **2c** was obtained (75 mg, 20%) as a white solid: mp = 235 °C (decomposition); ^{1}H NMR (DMSO-d_6) 10.8−10.5 (m, 1H), 9.1−8.9 (m, 1H), 8.00 (d, 1H, $J = 9.2$ Hz), 7.85−7.8 (m, 1H), 7.26 (d, 1H, $J = 8.5$ Hz), 7.2 (s, 1H), 7.02 (d, 1H, $J = 8.5$ Hz), 4.26 (d, 1H, $J = 9.2$ Hz), 3.46 (d, 1H, $J = 11.3$ Hz), 3.24 (s, 3H), 3.00 (m, 1H), 2.83 (m, 2H), 2.6−2.5 (m, 2H), 2.57 (d, 3H, $J = 4.8$ Hz), 1.5−1.3 (m, 2H), 1.05−0.95 (m, 1H), 0.97 (s, 9H), 0.85 (d, 3H, $J = 6.6$ Hz), 0.76 (d, 3H, $J = 6.6$ Hz); MS (ESI) 529 (MNa^+). Anal. ($C_{25}H_{38}N_4O_5S \cdot 1H_2O$) C H N S.

***N*²-[3*S*-(4-Cyanophenylthio)-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2d).** From **11d** were similarly obtained **2d** (68 mg, 22%, eluting first) as a white solid: mp = 238−241 °C; ^{1}H NMR (DMSO-d_6) 10.90−10.75 (m, 1H), 9.15−9.05 (m, 1H), 8.09 (d, 1H, $J = 9.2$ Hz), 7.83−7.75 (m, 1H), 7.73 (d, 2H, $J = 8.8$ Hz), 7.51 (d, 2H, $J = 8.8$ Hz), 4.17 (d, 1H, $J = 9.2$ Hz), 3.80 (d, 1H, $J = 11$ Hz), 3.15−3.06 (m, 1H), 2.55 (d, 3H, $J = 4.8$ Hz), 1.53−1.3 (m, 2H), 1.08−0.97 (m, 1H), 0.88 (s, 9H), 0.86 (d, 3H, $J = 6.6$ Hz), 0.78 (d, 3H, $J = 6.6$ Hz); MS (ESI) 471 (MNa^+). Anal. ($C_{22}H_{32}N_4O_4S \cdot 1.7H_2O$) C H N S. Compound **12d** (20 mg) was also obtained as a white solid formed by epimerization during the reaction: ^{1}H NMR (DMSO-d_6) 10.85 (s, 1H), 8.94 (s, 1H), 7.85−7.75 (m, 2H), 7.80 (d, 2H, $J = 8.4$ Hz), 7.60 (d, 2H, $J = 8.4$ Hz), 4.15 (d, 1H, $J = 9.5$ Hz), 3.88 (d, 1H, $J = 9.5$ Hz), 3.04−2.97 (m, 1H), 2.56 (d, 3H, $J = 4.4$ Hz), 1.6−1.38 (m, 3H), 0.88 (s, 9H), 0.80 (d, 3H, $J = 6$ Hz), 0.76 (d, 3H, $J = 6$ Hz).

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*S*-(4-(methylsulfonyl)phenylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (2e).** Similarly, except that $TMSONH_2$ was used instead of $NH_2OH{\cdot}HCl$, from the 1:1 mixture of **11e** and its epimer was obtained **2e** (105 mg, 22%, eluting first) as a white solid after purification of the crude mixture by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 0:100 to 45:55): mp = 222−224 °C; ^{1}H NMR (DMSO-d_6) 10.85 (s br, 1H), 9.15 (s, 1H), 8.1 (d, 1H, J = 9.2 Hz), 7.83 (m, 3H), 7.61 (d, 2H, J = 8.8 Hz), 4.23 (d, 1H, J = 9.2 Hz), 3.86 (d, 1H, J = 11.3 Hz), 3.26 (s, 3H), 3.15 (m, 1H), 2.60 (d, 3H, J = 4.8 Hz), 1.55 (m, 1H), 1.44 (m, 1H), 1.08 (m, 1H), 0.94 (s, 9H), 0.91 (d, 3H, J = 6.2 Hz), 0.83 (d, 3H, J = 6.6 Hz); MS (ESI) 524 (MNa^+). Anal. ($C_{22}H_{35}N_3O_6S_2{\cdot}0.5H_2O$) C, H calcd 7.11 found 7.65, N calcd 8.23 found 8.83. Further elution gave **12e** (77 mg, 16%) as a white solid: ^{1}H NMR (DMSO-d_6) 10.9 (s br, 1H), 8.97 (s, 1H), 7.89 (m, 4H), 7.71 (d, 2H, J = 8.4 Hz), 4.21 (d, 1H, J = 9.2 Hz), 3.41 (d, 1H, J = 9.2 Hz), 3.27 (s, 3H), 3.03 (m, 1H), 2.62 (d, 3H, J = 4.4 Hz), 1.48 (m, 3H), 0.93 (s, 9H), 0.85 (d, 3H, J = 6.6 Hz), 0.82 (d, 3H, J = 6.6 Hz); MS (ESI) 524 (MNa^+).

***N*²-[3*S*-(3,5-Dichlorophenylthio)-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2f).** Similarly was obtained **2f** (80 mg, 11%) as a white solid: mp = 199−202 °C; ^{1}H NMR (DMSO-d_6) 10.6 (m, 1H), 9.1 (s br, 1H), 8.13 (d, 1H, J = 9.5 Hz), 7.85 (q, 1H, J = 4.4 Hz), 7.46 (t, 1H, J = 1.8 Hz), 7.42 (d, 2H, J = 1.8 Hz), 4.24 (d, 1H, J = 9.5 Hz), 3.68 (d, 1H, J = 11 Hz), 3.10 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.37 (m, 2H), 1.01 (m, 1H), 0.91 (s, 9H), 0.86 (d, 3H, J = 6.2 Hz), 0.78 (d, 3H, J = 6.2 Hz); MS (ESI) 518 (M{^{37}Cl,^{37}Cl}-Na^+), 516 (M{^{35}Cl,^{37}Cl}Na^+), 514 (M{^{35}Cl,^{35}Cl}Na^+). Anal. ($C_{21}H_{31}Cl_2N_3O_4S{\cdot}0.7H_2O$) C H N.

***N*²-[3*S*-(2-Chloro-4-fluorophenylthio)-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2g).** Similarly, except that $tBuMe_2SiONH_2$ (1.1 equiv) was used instead of $NH_2OH{\cdot}HCl$, there was obtained **2g** (451 mg, 45%) as a white solid after purification of the crude mixture by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 20:80 to 65:35): mp = 231−233 °C; ^{1}H NMR (DMSO-d_6) 10.72 (s, 1H), 9.03 (s, 1H), 8.07 (d, 1H, J = 9.5 Hz), 7.80 (m, 1H), 7.60 (dd, 1H, J = 8.8 Hz, J' = 5.8 Hz), 7.46 (dd, 1H, J = 8.8 Hz, J' = 2.9 Hz), 7.23 (td, 1H, J_t = 8.8 Hz, J_d = 2.9 Hz), 4.20 (d, 1H, J = 9.5 Hz), 3.69 (d, 1H, J = 11 Hz), 3.05 (m, 1H), 2.56 (d, 3H, J = 4.8 Hz), 1.49 (m, 1H), 1.37 (m, 1H), 1.03 (m, 1H), 0.92 (s, 9H), 0.86 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz); MS (ESI) 500 (M{^{37}-Cl}Na^+), 498 (M{^{35}Cl}Na^+). Anal. ($C_{21}H_{31}ClFN_3O_4S{\cdot}0.2H_2O$) C H N calcd 8.76 found 8.25, S. Compound **12g** was not isolated.

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*S*-(quinolin-8-ylmethylthio)succinyl]-L-*tert*-leucine-*N*¹-methylamide (2h).** To a solution of **11h** and its epimer (460 mg, 1:1, 0.97 mmol) in DMF (5 mL) cooled at 0 °C were added HOBT (270 mg, 2 mmol), *N*-methylmorpholine (400 μL), O-(2,4-dimethoxybenzyl)hydroxylamine[21] (366 mg, 2 mmol), and EDCI (382 mg, 2 mmol). The mixture was stirred at room temperature for 18 h. The mixture was partitioned between water and EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The solvents were evaporated in vacuo to give the O-protected hydroxamate. To this crude material in CH_2Cl_2 (10 mL) was added TFA (0.7 mL). The mixture was stirred at room temperature for 15 min. The solvents were evaporated in vacuo. Methanol was added (20 mL); the solids were filtered. The filtrate was concentrated and purified by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 0:100 to 50:50) to give **2h** (76 mg, 36% based on **11h,** eluting first): mp = 205−215 °C; ^{1}H NMR (DMSO-d_6) 10.75 (s, 1H), 9.04 (s, 1H), 8.93 (m, 1H), 8.36 (m, 1H), 7.89 (m, 2H), 7.80 (m, 2H), 7.55 (m, 2H), 4.54 (d, 1H, J = 12.5 Hz), 4.43 (d, 1H, J = 12.5 Hz), 4.20 (d, 1H, J = 9.2 Hz), 3.28 (d, 1H, J = 11 Hz), 3.08 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.5−1.3 (m, 2H), 1.04 (m, 1H), 0.86 (m, 12H), 0.78 (d, 3H, J = 6.6 Hz); MS (EI) 488 ($M^{+\bullet}$). Anal. ($C_{25}H_{36}N_4O_4S{\cdot}1.25H_2O{\cdot}0.05AcOH{\cdot}0.45CF_3CO_2H$) C calcd 55.22 found 54.80, H N S. Compound **12h** was not isolated.

***N*²-[3*S*-(3-(1-Cyano-1-methylethyl)phenylthio)-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2i).** Similarly to **2g**, from **11i** was obtained **2i** (170 mg, 40%) as a white solid after treatment of the crude reaction mixture with HCl (2 N, 3 mL) and purification by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 20:80 to 65:35): mp = 202−206 °C; ^{1}H NMR (DMSO-d_6) 10.72 (s, 1H), 9.05 (s, 1H), 8.04 (d, 1H, J = 9.2 Hz), 7.81 (m, 1H), 7.44−7.35 (m, 4H), 4.25 (d, 1H, J = 9.2 Hz), 3.62 (d, 1H, J = 11.4 Hz), 3.04 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.69 (s, 6H), 1.47 (m, 1H), 1.37 (m, 1H), 1.01 (m, 1H), 0.94 (s, 9H), 0.86 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz); MS (ESI) 513 (MNa^+). Anal. ($C_{25}H_{38}N_4O_4S{\cdot}1.3H_2O$) C H calcd 7.96 found 8.45, N S. Compound **12i** was not isolated.

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*S*-methylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2j).** Similarly to **2g**, from **11j** and its epimer was obtained, after treatment of the crude reaction mixture with HCl (2 N, 3 mL) and purification by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 40:60 to 60:40), **2j** (150 mg, 9%) as a white solid: mp = 214−218 °C; ^{1}H NMR (DMSO-d_6) 10.58 (s, 1H), 9.0 (m, 1H), 7.95 (d, 1H, J = 9.2 Hz), 7.81 (q, 1H, J = 4.4 Hz), 4.23 (d, 1H, J = 9.2 Hz), 3.01 (m, 2H), 2.54 (d, 3H, J = 4.4 Hz), 2.11 (s, 3H), 1.45−1.25 (m, 2H), 1.0−0.85 (m, 1H), 0.96 (s, 9H), 0.84 (d, 3H, J = 6.2 Hz), 0.75 (d, 3H, J = 6.2 Hz); MS (ESI) 384 (MNa^+). Anal. ($C_{16}H_{31}N_3O_4S{\cdot}1.5H_2O{\cdot}$0.1AcOH) C H N S. Further elution afforded **12j** (560 mg, 32%): mp = 125−128 °C; ^{1}H NMR (DMSO-d_6) 10.7 (m, 1H), 8.8 (s, 1H), 7.8 (q, 1H, J = 4.4 Hz), 7.57 (d, 1H, J = 9.5 Hz), 4.14 (d, 1H, J = 9.5 Hz), 3.08 (d, 1H, J = 10 Hz), 2.89−2.84 (m, 1H), 2.54 (d, 3H, J = 4.4 Hz), 2.11 (s, 3H), 1.57−1.43 (m, 2H), 1.0−0.8 (m, 1H), 0.91 (s, 9H), 0.89 (d, 3H, J = 6.2 Hz), 0.84 (d, 3H, J = 6.2 Hz); MS (ESI) 384 (MNa^+).

***N*²-[3*S*-Ethylthio-4-(*N*-hydroxyamino)-2*S*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (2k).** Similarly to **2h**, from **11k** and its epimer was obtained, after purification by C18 preparative HPLC using as eluant methanol and water/1% AcOH (45:55), **2k** (190 mg, 37%) as a white solid: mp = 190−196 °C; ^{1}H NMR (DMSO-d_6) 10.6 (s br, 1H), 8.95 (s br, 1H), 7.89 (d, 1H, J = 9.2 Hz), 7.78 (q, 1H, J = 4.4 Hz), 4.23 (d, 1H, J = 9.2 Hz), 3.06 (d, 1H, J = 11.3 Hz), 2.96 (m, 1H), 2.64 (m, 2H), 2.56 (d, 3H, J = 4.4 Hz), 1.5−1.3 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz), 1.0−0.9 (m, 1H), 0.96 (s, 9H), 0.84 (d, 3H, J = 6.2 Hz), 0.76 (d, 3H, J = 6.2 Hz); MS (ESI) 376 (MH^+). Anal. ($C_{17}H_{33}N_3O_4S$) C H N. Further elution afforded a mixture of **2k** and **12k** (130 mg).

***N*²-[4-(*N*-Hydroxyamino)-2*S*-isobutyl-3*R*-phenylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (12a).** Similarly to **10a**, *N*²-[4-*tert*-butyloxy-2*S*-isobutyl-3*R*-phenylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (540 mg, 78%) was obtained from **9a** as a white foam: ^{1}H NMR ($CDCl_3$) 7.49 (m, 2H), 7.30 (m, 3H), 6.56 (d, 1H, J = 9.2 Hz), 5.88 (q, 1H, J = 5.1 Hz), 4.14 (d, 1H, J = 9.2 Hz), 3.73 (d, 1H, J = 9.9 Hz), 2.78 (d, 3H, J = 5.1 Hz), 2.64 (m, 1H), 1.79 (m, 1H), 1.64 (m, 1H), 1.51 (m, 1H), 1.33 (s, 9H), 0.99 (s, 9H), 0.88 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.6 Hz). Similarly to **11a**, this compound was converted to *N*²-[4-hydroxy-2*S*-isobutyl-3*R*-phenylthiosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (460 mg, 100%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.7 (m, 1H), 7.50 (m, 2H), 7.32 (m, 3H), 6.28 (s br, 1H), 4.38 (d, 1H, J = 9.5 Hz), 3.84 (d, 1H, J = 6.6 Hz), 2.97 (m, 1H), 2.86 (d, 3H, J = 5.1 Hz), 1.80−1.55 (m, 3H), 1.06 (s, 9H), 0.87 (d, 3H, J = 6.2 Hz), 0.84 (d, 3H, J = 6.2 Hz); MS (ESI) 409 (MH^+). Similarly to **2a** (except that lutidine was replaced by *N*-methylmorpholine), this acid (170 mg, 0.41 mmol) was converted to **2a** (55 mg, 32%, eluting first) and **12a** (49 mg, 29%) after purification by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 20:80 to 60:40). **12a**: mp = 194−198 °C; ^{1}H NMR (DMSO-d_6) 10.75 (m, 1H), 8.86 (s, 1H), 7.78 (q, 1H, J = 4.8 Hz), 7.69 (d, 1H, J = 9.5 Hz), 7.5−7.2 (m, 5H), 4.12 (d, 1H, J = 9.5 Hz), 3.62 (d, 1H, J = 9.5 Hz), 2.88 (m, 1H), 2.55 (d, 3H, J = 4.8 Hz), 1.6−1.3 (m, 3H), 0.87 (s, 9H), 0.79 (d, 3H, J = 6.6 Hz), 0.75 (d, 3H,

J = 6.6 Hz); MS (ESI) 446 (MNa^+). Anal. ($C_{21}H_{33}N_3O_4S$) C H calcd 7.85 found 8.33, N S.

Anhydride 13a. To a solution of **8a** (130 mg, 0.38 mmol) in CH_2Cl_2 was added oxalyl chloride (76 μL, 0.88 mmol) and DMF (1 drop). The mixture was stirred at room temperature for 2 h. Evaporation of the solvents afforded **13a** (quantitative yield): ^{1}H NMR ($CDCl_3$) 7.55 (m, 2H), 7.39 (m, 3H), 4.20 (d, 1H, J = 8.4 Hz), 3.37 (ddd, 1H, $J = J' = 8.4$ Hz, J'' = 5.5 Hz), 1.9 (m, 3H), 1.04 (d, 3H, J = 5.9 Hz), 1.00 (d, 3H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$) 168.6, 134.6, 130.2, 129.9, 50.1, 43.3, 34.1, 26.0, 22.6, 21.7; MS (EI) 264 ($M^{+\bullet}$).

Anhydride 14a. Similarly, from **9a** (300 mg, 0.89 mmol) was obtained **14a** (quantitative yield): ^{1}H NMR ($CDCl_3$) 7.55 (m, 2H), 7.40 (m, 3H), 3.80 (d, 1H, J = 5.5 Hz), 2.96 (ddd, 1H, J = 8.8 Hz, J' = 6.2 Hz, J'' = 5.5 Hz), 1.9−1.75 (m, 2H), 1.60 (m, 1H), 0.98 (d, 3H, J = 6.2 Hz), 0.97 (d, 3H, J = 6.2 Hz); MS (EI) 264 ($M^{+\bullet}$).

***N*²-[3*S*-Benzenesulfonylamino-4-*tert*-butyloxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (16a).** To a solution of **15** (740 mg, 1.98 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added successively pyridine (500 μL, 6.18 mmol), benzenesulfonyl chloride (310 μL, 2.43 mmol), and DMAP (a few crystals). The mixture was stirred at room temperature for 18 h. The reaction mixture was poured into 2 N HCl (50 mL) and extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were evaporated in vacuo, and the residue was purified by flash chromatography on silica using EtOAc−petroleum ether (1:1) as eluant to give **16a** (849 mg, 84%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.86 (d, 2H, J = 7 Hz), 7.55−7.45 (m, 3H), 6.37 (d br, 1H, J = 9.9 Hz), 6.26 (d br, 1H, J = 9.1 Hz), 5.75 (s br, 1H), 4.08 (d, 1H, J = 9.1 Hz), 3.98 (dd, 1H, J = 9.9 Hz, J = 3.3 Hz), 2.82 (d, 3H, J = 4.7 Hz), 1.65−1.40 (m, 3H), 1.23 (s, 9H), 0.96 (s, 9H), 0.89 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz).

***N*²-[3*S*-(4-Acetamidobenzenesulfonylamino)-4-*tert*-butyloxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (16b).** Similarly from 4-acetamidobenzenesulfonyl chloride was obtained **16b** (790 mg, 87%) as a white foam: ^{1}H NMR (DMSO-d_6) 7.91 (m, 1H), 7.75−7.65 (m, 5H), 7.50 (d br, 1H, J = 9.2 Hz), 4.15 (d, 1H, J = 9.2 Hz), 3.66 (m, 1H), 2.81 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 2.10 (s, 3H), 1.5−1.2 (m, 2H), 1.22 (s, 9H), 0.98 (m, 1H), 0.90 (s, 9H), 0.77 (m, 6H); MS (ESI) 591 (MNa^+).

***N*²-[4-*tert*-Butyloxy-3*S*-(3,5-dichlorobenzene-1-sulfonylamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (16c).** Similarly from 3,5-dichlorobenzenesulfonyl chloride was obtained **16c** (629 mg, 81%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.74 (d, 2H, J = 1.8 Hz), 7.50 (t, 1H, J = 1.8 Hz), 6.74 (m, 1H), 6.26 (m, 1H), 5.62 (m, 1H), 4.05 (d, 1H, J = 9.2 Hz), 4.00 (m, 1H), 2.89 (m, 1H), 2.84 (d, 3H, J = 4.8 Hz), 1.7−1.4 (m, 3H), 1.28 (s, 9H), 0.96 (s, 9H), 0.92 (d, 6H, J = 6.2 Hz); MS (ESI) 604 (M{^{37}Cl,^{35}Cl}Na^+), 602 (M-{^{35}Cl,^{35}Cl}Na^+).

***N*²-[4-*tert*-Butyloxy-3*S*-(2-cyanobenzene-1-sulfonylamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (16d).** Similarly from 2-cyanobenzenesulfonyl chloride was obtained **16d** (507 mg, 71%) as a white foam: ^{1}H NMR ($CDCl_3$) 8.01 (d, 1H, J = 7.7 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.65−7.52 (m, 2H), 6.92 (m, 1H), 6.21 (d br, 1H, J = 9.2 Hz), 5.59 (m, 1H), 4.11−4.02 (m, 2H), 2.86 (m, 1H), 2.76 (d, 3H, J = 5.2 Hz), 1.7−1.1 (m, 3H), 1.19 (s, 9H), 0.88 (s, 9H), 0.83 (d, 3H, J = 6.6 Hz), 0.81 (d, 3H, J = 6.6 Hz); MS (ESI) 559 (MNa^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(1-methylimidazole-4-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16g).** Similarly, except that the crude reaction mixture after evaporation of the solvents was directly purified by flash chromatography on silica using CH_2Cl_2−methanol (95:5) as eluant, from 1-methyl-imidazole-4-sulfonyl chloride was obtained **16g** (953 mg, 98%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.45 (s, 1H), 7.42 (s, 1H), 6.50 (d br, 1H, J = 9.5 Hz), 6.12 (m, 1H), 5.83 (m, 1H), 4.26 (m, 1H), 4.11 (d, 1H, J = 9.2 Hz), 3.72 (s, 3H), 2.85 (m, 1H), 2.81 (d, 3H, J = 4.8 Hz), 1.7−1.0 (m, 3H), 1.37 (s, 9H), 0.98 (s, 9H), 0.89 (d, 3H, J = 6.2 Hz), 0.88 (d, 3H, J = 6.2 Hz); MS (ESI) 516 (MH^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(thiophene-2-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16h).** Similarly from thiophene-2-sulfonyl chloride was obtained **16h** (567 mg, 82%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.58 (d, 1H, J = 3.7 Hz), 7.54 (d, 1H, J = 5.1 Hz), 7.05 (dd, 1H, J = 5.1 Hz, J' = 3.7 Hz), 6.48 (m, 1H), 6.26 (m, 1H), 5.68 (m, 1H), 4.07 (d, 1H, J = 9.2 Hz), 4.04 (m, 1H), 2.86 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.7−1.0 (m, 3H), 1.29 (s, 9H), 0.96 (s, 9H), 0.91 (d, 6H, J = 6.2 Hz); MS (ESI) 540 (MNa^+).

***N*²-[4-*tert*-butyloxy-2*R*-isobutyl-3*S*-(3-pyridinesulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16i).** Similarly from 3-pyridinesulfonyl chloride (360 mg) was obtained **16i** (500 mg, 73%) as a white foam: ^{1}H NMR ($CDCl_3$) 9.06 (s br, 1H), 8.75 (m, 1H), 8.16 (m, 1H), 7.40 (m, 1H), 6.73 (d br, 1H, J = 9.9 Hz), 6.27 (d br, 1H, J = 9.2 Hz), 5.63 (m, 1H), 4.05 (d, 1H, J = 9.2 Hz), 4.04 (m, 1H), 2.87 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.7−1.3 (m, 3H), 1.24 (s, 9H), 0.95 (s, 9H), 0.92 (d, 6H, J = 6.6 Hz); MS (ESI) 535 (MNa^+), 513 (MH^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(naphthalene-2-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16l).** Similarly from naphthalene-2-sulfonyl chloride was obtained **16l** (690 mg, 77%) as a white foam: ^{1}H NMR (DMSO-d_6) 8.39 (s, 1H), 8.18−8.00 (m, 3H), 7.92 (m, 1H), 7.80−7.60 (m, 5H), 4.15 (d, 1H, J = 9.4 Hz), 3.75 (m, 1H), 2.83 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.45−1.20 (m, 2H), 1.02 (s, 9H), 0.95 (m, 1H), 0.89 (s, 9H), 0.74 (d, 3H, J = 6.6 Hz), 0.71 (d, 3H, J = 6.6 Hz); MS (ESI) 584 (MNa^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(naphthalene-1-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide(16m).** Similarly from naphthalene-1-sulfonyl chloride (403 mg) was obtained **16m** (620 mg, 69%) as a white foam: ^{1}H NMR (DMSO-d_6) 8.55 (d, 1H, J = 8.4 Hz), 8.24 (d, 1H, J = 8.4 Hz), 8.10 (m, 2H), 7.97 (m, 2H), 7.80−7.60 (m, 4H), 4.20 (d, 1H, J = 9.2 Hz), 3.67 (t, 1H, J = 8.8 Hz), 2.80 (m, 1H), 2.58 (d, 3H, J = 4.8 Hz), 1.30 (m, 1H), 1.10 (m, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.74 (m, 1H), 0.67 (d, 3H, J = 6.6 Hz), 0.59 (d, 3H, J = 6.6 Hz); MS (ESI) 584 (MNa^+).

***N*²-[4-*tert*-butyloxy-2*R*-isobutyl-3*S*-(quinoline-8-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16n).** Similarly from 8-quinolinesulfonyl chloride was obtained **16n** (375 mg, 50%) as a white foam: ^{1}H NMR ($CDCl_3$) 9.09 (m, 1H), 8.36 (d br, 1H, J = 7.3 Hz), 8.23 (d br, 1H, J = 8.4 Hz), 8.01 (d br, 1H, J = 8.4 Hz), 7.61 (dd, 1H, J = 8.4 Hz, J' = 7.3 Hz), 7.53 (dd, 1H, J = 8.4 Hz, J' = 4 Hz), 7.32 (d br, 1H, J = 9.2 Hz), 6.29 (d br, 1H, J = 9.2 Hz), 5.85 (m, 1H), 4.34 (dd, 1H, J = 9.2 Hz, J' = 4.7 Hz), 4.14 (d, 1H, J = 9.2 Hz), 2.83 (m, 1H), 2.82 (d, 3H, J = 4.4 Hz), 1.7−1.3 (m, 3H), 0.98 (s, 9H), 0.93 (s, 9H), 0.85 (d, 3H, J = 6.6 Hz), 0.81 (d, 3H, J = 6.6 Hz); MS (ESI) 563 (MH^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(isoquinoline-5-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16o).** Similarly from isoquinoline-5-sulfonyl chloride was obtained **16o** (580 mg, 77%) as a white foam: ^{1}H NMR ($CDCl_3$) 9.32 (s, 1H), 8.72 (d, 1H, J = 6.2 Hz), 8.53 (d, 1H, J = 6.2 Hz), 8.41 (d, 1H, J = 8 Hz), 8.17 (d, 1H, J = 8 Hz), 7.66 (t, 1H, J = 8 Hz), 6.98 (d br, 1H, J = 9.5 Hz), 6.25 (d br, 1H, J = 9.2 Hz), 5.58 (m, 1H), 4.05 (d, 1H, J = 9.2 Hz), 3.94 (dd, 1H, J = 9.5 Hz, J' = 3.3 Hz), 2.83 (d, 3H, J = 4.8 Hz), 2.79 (m, 1H), 1.5−1.2 (m, 2H), 1.06 (s, 9H), 1.00 (m, 1H), 0.96 (s, 9H), 0.79 (d, 3H, J = 6.2 Hz), 0.72 (d, 3H, J = 6.2 Hz); MS (ESI) 585 (MNa^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16p) and *N*²-[4-*tert*-butyloxy-2*R*-isobutyl-3*S*-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (16t).** Similarly, from a mixture of 4-oxo-3,4-dihydroquinazoline-6-sulfonyl chloride and 4-oxo-3,4-dihydroquinazoline-8-sulfonyl chloride [1.5 g, 1:1, prepared by heating of 3,4-dihydroquinazolin-4-one with excess of chlorosulfonic acid at 140 °C: ^{1}H NMR (DMSO-d_6) 9.03 and 8.92 (s, 1H), 8.34 (d, 0.5H, J = 1.8 Hz), 8.25 (m, 1H), 8.11 (dd, 0.5H, J = 8.4 Hz, J' = 1.8 Hz), 7.75 (m, 1H); MS (EI): 244

(M{^{35}Cl}$^{+\bullet}$)], there was obtained **16p** (332 mg, 29%) as a foam and **16t** (428 mg, 37%) after purification on HPLC using EtOAc as eluant. **16p**: ^{1}H NMR ($CDCl_3$) 8.49 (dd, 1H, J = 8.1 Hz, J' = 1.5 Hz), 8.46 (d, 1H, J = 3.3 Hz), 8.36 (dd, 1H, J = 8.1 Hz, J' = 1.5 Hz), 7.53 (t, 1H, J = 8.1 Hz), 7.15 (m, 1H), 7.07 (d, 1H, J = 9.9 Hz), 6.77 (d br, 1H, J = 9.5 Hz), 4.55 (d, 1H, J = 9.9 Hz), 4.24 (dd, 1H, J = 9.9 Hz, J' = 3.7 Hz), 3.00 (m, 1H), 2.84 (d, 3H, J = 4.8 Hz), 1.8 (m, 2H), 1.45 (m, 1H), 1.10 (s, 9H), 0.94−0.90 (m, 15H); MS (ESI) 602 (MNa$^+$). **16t**: ^{1}H NMR ($CDCl_3$) 8.84 (d, 1H, J = 1.8 Hz), 8.21 (dd, 1H, J = 8.8 Hz, J' = 1.8 Hz), 8.11 (d, 1H, J = 1.8 Hz), 7.83 (d, 1H, J = 8.8 Hz), 6.86 (m, 2H), 6.05 (m, 1H), 4.20 (d, 1H, J = 9.2 Hz), 4.06 (dd, 1H, J = 10.3 Hz, J' = 4.4 Hz), 2.95 (m, 1H), 2.84 (d, 3H, J = 4.8 Hz), 1.7−1.4 (m, 3H), 1.21 (s, 9H), 0.98 (s, 9H), 0.87 (d, 3H, J = 6.2 Hz), 0.85 (d, 3H, J = 6.2 Hz); MS (ESI) 602 (MNa$^+$).

***N*^{2}-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (16q).** Similarly from 1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride[39] was obtained **16q** (679 mg, 85%) as a white foam: ^{1}H NMR ($CDCl_3$) 7.76 (dd, 1H, J = 8.8 Hz, J' = 2.2 Hz), 7.66 (d, 1H, J = 2.2 Hz), 7.02 (d, 1H, J = 8.8 Hz), 6.37 (d br, 1H, J = 9.9 Hz), 6.26 (d, 1H, J = 9.2 Hz), 5.66 (m, 1H), 4.06 (d, 1H, J = 9.2 Hz), 3.97 (dd, 1H, J = 9.9 Hz, J' = 3.6 Hz), 3.36 (s, 3H), 2.95 (m, 2H), 2.83 (d, 3H, J = 4.8 Hz), 2.66 (m, 2H), 1.7−1.1 (m, 3H), 1.25 (s, 9H), 0.96 (s, 9H), 0.90 (d, 6H, J = 6.6 Hz); MS (ESI) 617 (MNa$^+$).

***N*^{2}-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(oxindole-5-sulfonylamino)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (16r).** Similarly from oxindole-5-sulfonyl chloride (prepared by reaction of oxindole with chlorosulfonic acid) was obtained **16r** (660 mg, 87%) as a white foam: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 10.23 (s, 1H), 7.70 (d, 1H, J = 8.1 Hz), 7.65 (s, 1H), 6.90 (m, 2H), 6.73 (m, 2H), 4.15 (d, 1H, J = 9.2 Hz), 3.85 (dd, 1H, J = 9.9 Hz, J' = 5.1 Hz), 3.49 (s, 2H), 2.81 (m, 1H), 2.76 (d, 3H, J = 4.8 Hz), 1.6−1.2 (m, 3H), 1.28 (s, 9H), 0.96 (s, 9H), 0.86 (d, 3H, J = 6.2 Hz), 0.85 (d, 3H, J = 6.2 Hz); MS (ESI) 589 (MNa$^+$).

***N*^{2}-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(quinoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (16s).** Similarly from quinoline-6-sulfonyl chloride[41] was obtained **16s** (510 mg, 67%) as a white foam: ^{1}H NMR ($CDCl_3$) 9.03 (dd, 1H, J = 4.4 Hz, J' = 1.8 Hz), 8.41 (d, 1H, J = 1.8 Hz), 8.26 (dd, 1H, J = 8.4 Hz, J' = 1.8 Hz), 8.20 (d, 1H, J = 8.4 Hz), 8.10 (dd, 1H, J = 8.4 Hz, J' = 1.8 Hz), 7.52 (dd, 1H, J = 8.4 Hz, J' = 4.4 Hz), 6.62 (d br, 1H, J = 9.2 Hz), 6.27 (d br, 1H, J = 9.2 Hz), 5.63 (m, 1H), 4.06 (m, 2H), 2.85 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.7−1.4 (m, 3H), 1.10 (s, 9H), 0.95 (s, 9H), 0.88 (d, 3H, J = 6.2 Hz), 0.85 (d, 3H, J = 6.2 Hz); MS (ESI) 563 (MH$^+$).

***N*^{2}-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-methanesulfonylaminosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (16w).** Similarly from methanesulfonyl chloride was obtained **16w** (372 mg, 62%) as a white foam: ^{1}H NMR ($CDCl_3$) 6.31 (d br, 1H, J = 9.2 Hz), 6.23 (d br, 1H, J = 9.5 Hz), 5.63 (m, 1H), 4.07 (m, 2H), 3.01 (s, 3H), 2.95 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.8−1.4 (m, 3H), 1.47 (s, 9H), 0.97 (s, 9H), 0.96 (d, 3H, J = 6.2 Hz), 0.93 (d, 3H, J = 6.2 Hz); MS (ESI) 472 (MNa$^+$).

***N*^{2}-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(4-pyridineethanesulfonylamino)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (16u).** To **15** (1 g, 2.69 mmol) in CH_2Cl_2 were added NEt_3 (3 mL) and 4-pyridineethanesulfonyl chloride hydrochloride[42] (1.8 g, 7.4 mmol) in small portions over 2 h. The residue was partitioned between EtOAc and water. The organic layer was dried on $MgSO_4$ to give **16u** (1.38 g, 95%) after evaporation of the solvents: ^{1}H NMR ($CDCl_3$) 8.54 (m, 2H), 7.18 (m, 2H), 6.45 (m, 1H), 6.33 (m, 1H), 5.75 (m, 1H), 4.10 (m, 2H), 3.31 (m, 3H), 3.12 (m, 1H), 2.95 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.75−0.9 (m, 3H), 1.45 (s, 9H), 0.98 (s, 9H), 0.97 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 6.6 Hz); MS (ESI) 541 (MH$^+$).

***N*^{2}-[3*S*-Benzenesulfonylamino-4-hydroxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (17a).** Using the procedure described for **11a**, from **16a** was obtained **17a** (676 mg, 98%): mp = 120−130 °C; ^{1}H NMR (DMSO-d_6) 7.88 (m, 1H), 7.75 (m, 2H), 7.65−7.5 (m, 5H), 4.12 (d, 1H, J = 9.2 Hz), 3.74 (dd, 1H, J = 9.5 Hz, J = 7.7 Hz), 2.83 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.5−1.2 (m, 2H), 0.97 (m, 1H), 0.88 (m, 1H), 0.76 (d, 3H, J = 6.2 Hz), 0.74 (d, 3H, J = 6.2 Hz); MS (ESI) 478 (MNa$^+$), 456 (MH$^+$). Anal. ($C_{21}H_{33}N_3O_6S\cdot0.3H_2O$) C calcd 54.72 found 55.17, H calcd 7.35 found 7.87, N S calcd 6.96 found 6.50.

The following compounds were obtained similarly.

17b: (656 mg, 97%) white solid; ^{1}H NMR (DMSO-d_6) 7.89 (m, 1H), 7.72 (d, 2H, J = 8.8 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.60 (d br, 1H, J = 9.2 Hz), 7.38 (d br, 1H, J = 9.2 Hz), 4.12 (d, 1H, J = 9.2 Hz), 3.70 (t, 1H, J = 8.1 Hz), 2.81 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 2.10 (s, 3H), 1.45−1.20 (m, 2H), 0.95 (m, 1H), 0.89 (s, 9H), 0.76 (d, 3H, J = 6.6 Hz), 0.74 (d, 3H, J = 6.6 Hz); MS (ESI) 535 (MNa$^+$), 513 (MH$^+$).

17c: (480 mg, 92%) white solid; ^{1}H NMR ($CDCl_3$) 7.74 (s br, 2H), 7.53 (s br, 1H), 7.25 (m, 1H), 6.60 (m, 1H), 5.90 (m, 1H), 4.19 (d, 1H, J = 9.5 Hz), 3.99 (m, 1H), 3.13 (m, 1H), 2.82 (d, 3H, J = 4.8 Hz), 1.6−1.2 (m, 3H), 0.96 (s, 9H), 0.90 (d, 6H, J = 6.2 Hz); MS (ESI) 548 (M{^{37}Cl,^{35}Cl}Na$^+$), 546 (M{^{35}Cl,^{35}Cl}-Na$^+$).

17d: (400 mg, 93%) white solid; ^{1}H NMR ($CDCl_3$) 8.07 (d, 1H, J = 7.7 Hz), 7.86 (d, 1H, J = 7.7 Hz), 7.75−7.63 (m, 2H), 7.21 (m, 1H), 6.89 (m, 1H), 6.04 (m, 1H), 4.21 (d, 2H, J = 9.5 Hz), 3.14 (m, 1H), 2.80 (d, 3H, J = 4.8 Hz), 1.55−1.2 (m, 3H), 0.92 (s, 9H), 0.87 (d, 3H, J = 5.8 Hz), 0.83 (d, 3H, J = 5.8 Hz); MS (ESI) 503 (MNa$^+$), 481 (MH$^+$).

17g: trifluoroacetate salt (819 mg, 82%) white solid; ^{1}H NMR (DMSO-d_6) 7.90 (m, 1H), 7.77 (m, 2H), 7.68 (s, 1H), 7.16 (d, 1H, J = 9.5 Hz), 4.14 (d, 1H, J = 9.2 Hz), 3.77 (m, 1H), 3.69 (s, 3H), 2.88 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.31 (m, 2H), 1.01 (m, 1H), 0.89 (s, 9H), 0.78 (d, 3H, J = 6.2 Hz), 0.74 (d, 3H, J = 6.2 Hz); MS (ESI) 460 (MH$^+$).

17h: (518 mg, 96%) white solid; ^{1}H NMR ($CDCl_3$) 7.60 (m, 2H), 7.09−7.00 (m, 2H), 6.22 (m, 1H), 5.68 (m, 1H), 4.17 (d, 1H, J = 9.5 Hz), 3.96 (m, 1H), 3.11 (m, 1H), 2.85 (d, 3H, J = 4.8 Hz), 1.5−1.2 (m, 3H), 1.02 (s, 9H), 0.92 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz); MS (ESI) 484 (MNa$^+$), 462 (MH$^+$).

17i: (340 mg, 81%) white solid; ^{1}H NMR (DMSO-d_6 + CF_3CO_2D) 9.07 (s br, 1H), 8.90 (d, 1H, J = 4.8 Hz), 8.40 (d, 1H, J = 8.1 Hz), 7.79 (dd, 1H, J = 8.1 Hz, J' = 4.8 Hz), 4.11 (s, 1H), 3.91 (d, 1H, J = 7.3 Hz), 2.90 (m, 1H), 2.56 (s, 3H), 1.43 (m, 2H), 1.09 (m, 1H), 0.87 (s, 9H), 0.79 (d, 3H, J = 6.2 Hz), 0.78 (d, 3H, J = 6.2 Hz); MS (ESI) 479 (MNa$^+$), 457 (MH$^+$).

17l: (540 mg, 93%) white solid; ^{1}H NMR (DMSO-d_6) 8.36 (s, 1H), 8.12−8.00 (m, 3H), 7.85 (m, 1H), 7.75−7.55 (m, 5H), 4.08 (d, 1H, J = 9.5 Hz), 3.76 (dd, 1H, J = 10.5 Hz, J' = 8 Hz), 2.80 (m, 1H), 2.53 (d, 3H, J = 4.4 Hz), 1.4−1.2 (m, 2H), 0.94 (m, 1H), 0.83 (s, 9H), 0.68 (d, 3H, J = 6.2 Hz), 0.64 (d, 3H, J = 6.2 Hz); MS (ESI) 528 (MNa$^+$), 506 (MH$^+$). Anal. ($C_{25}H_{35}N_3O_6S$) C H N.

17m: (518 mg, 96%) white solid; ^{1}H NMR (DMSO-d_6) 8.56 (d, 1H, J = 8.4 Hz), 8.24 (d, 1H, J = 8.4 Hz), 8.11 (m, 2H), 7.92 (m, 1H), 7.80−7.60 (m, 5H), 4.14 (d, 1H, J = 9.2 Hz), 3.68 (dd, 1H, J = 9.2 Hz, J' = 6.6 Hz), 2.85 (m, 1H), 1.15 (m, 1H), 0.97 (m, 1H), 0.89 (s, 9H), 0.71 (m, 1H), 0.59 (d, 3H, J = 6.6 Hz), 0.45 (d, 3H, J = 6.6 Hz); MS (ESI) 528 (MNa$^+$), 506 (MH$^+$).

17n: (315 mg, 100%) white solid; ^{1}H NMR (DMSO-d_6) 9.03 (m, 1H), 8.53 (d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 7 Hz), 7.92 (m, 2H), 7.72−7.62 (m, 3H), 4.13 (d, 1H, J = 9.2 Hz), 3.96 (dd, 1H, J = 8.8 Hz, J' = 5.1 Hz), 3.01 (m, 1H), 2.54 (d, 3H, J = 4.4 Hz), 1.3−1.1 (m, 2H), 0.82 (s, 9H), 0.80 (m, 1H), 0.64 (d, 3H, J = 6.6 Hz), 0.49 (d, 3H, J = 6.6 Hz); MS (ESI) 507 (MH$^+$).

17o: (450 mg, 91%) white solid; ^{1}H NMR (DMSO-d_6) 9.47 (s, 1H), 8.72 (d, 1H, J = 6.2 Hz), 8.43 (d, 1H, J = 8 Hz), 8.31 (m, 2H), 7.92 (m, 2H), 7.79 (t, 1H, J = 8 Hz), 7.69 (d br, 1H, J = 9.2 Hz), 4.12 (d, 1H, J = 9.2 Hz), 3.69 (m, 1H), 2.80 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.25 (m, 1H), 1.10 (m, 1H), 0.86 (s, 9H), 0.75 (m, 1H), 0.63 (d, 3H, J = 6.6 Hz), 0.53 (d, 3H, J = 6.6 Hz); MS (ESI) 507 (MH$^+$).

17p: (260 mg, 97%) solid; ^{1}H NMR (DMSO-d_6) 8.32 (dd, 1H, J = 8.1 Hz, J' = 1.5 Hz), 8.22 (d, 1H, J = 3.3 Hz), 8.17 (dd,

1H, $J = 8.1$ Hz, $J' = 1.5$ Hz), 7.91 (m, 2H), 7.60 (t, 1H, $J = 8.1$ Hz), 7.42 (d, 1H, $J = 9.5$ Hz), 4.13 (d, 1H, $J = 9.5$ Hz), 3.90 (m, 1H), 3.01 (m, 1H), 2.55 (d, 3H, $J = 4.8$ Hz), 1.30 (m, 2H), 0.87 (m, 1H), 0.84 (s, 9H), 0.72 (d, 3H, $J = 5.9$ Hz), 0.65 (d, 3H, $J = 5.9$ Hz); MS (ESI) 524 (MH^+).

17q: (520 mg, 88%) white solid; ^{1}H NMR (DMSO-d_6) 7.89 (m, 1H), 7.61 (m, 3H), 7.42 (d, 1H, $J = 9.9$ Hz), 7.22 (d, 1H, $J = 8.4$ Hz), 4.12 (d, 1H, $J = 9.5$ Hz), 3.71 (dd, 1H, $J = 9.9$ Hz, $J' = 8.1$ Hz), 3.29 (s, 3H), 2.94 (m, 2H), 2.83 (m, 1H), 2.59 (m, 2H), 2.57 (d, 3H, $J = 4.8$ Hz), 1.50−1.25 (m, 2H), 0.99 (m, 1H), 0.89 (s, 9H), 0.76 (d, 3H, $J = 6.9$ Hz), 0.75 (d, 3H, $J = 6.9$ Hz); MS (ESI) 561 (MNa^+), 539 (MH^+).

17r: (496 mg, 87%) solid; ^{1}H NMR (DMSO-d_6) 10.7 (s, 1H), 7.86 (m, 1H), 7.60−7.50 (m, 3H), 7.31 (d, 1H, $J = 9.9$ Hz), 6.89 (d, 1H, $J = 8$ Hz), 4.09 (d, 1H, $J = 9.5$ Hz), 3.64 (m, 1H), 3.53 (s, 2H), 2.79 (m, 1H), 2.55 (d, 3H, $J = 4.4$ Hz), 1.42−1.25 (m, 2H), 0.96 (m, 1H), 0.87 (s, 9H), 0.74 (d, 3H, $J = 6.9$ Hz), 0.72 (d, 3H, $J = 6.9$ Hz); MS (ESI) 533 (MNa^+).

17s: (530 mg, 100%) white solid; ^{1}H NMR (DMSO-d_6 + CF_3CO_2D) 9.31 (d br, 1H, $J = 4.8$ Hz), 9.07 (d, 1H, $J = 8.1$ Hz), 8.71 (s br, 1H), 8.31 (d, 1H, $J = 8.1$ Hz), 8.25 (d, 1H, $J = 8.1$ Hz), 8.01 (dd, 1H, $J = 8.1$ Hz, $J' = 4.8$ Hz), 7.65 (d, 1H, $J = 9.2$ Hz, NH not exchanged), 4.12 (d, 1H, $J = 9.2$ Hz), 3.86 (d, 1H, $J = 7.5$ Hz), 2.88 (m, 1H), 2.56 (s, 3H), 1.5−1.3 (m, 1H), 1.01 (m, 1H), 0.86 (s, 9H), 0.74 (d, 3H, $J = 6.6$ Hz), 0.71 (d, 3H, $J = 6.6$ Hz); MS (ESI) 507 (MH^+).

17t: (360 mg, 100%) solid; ^{1}H NMR (DMSO-d_6) 8.42 (d, 1H, $J = 2.2$ Hz), 8.24 (s, 1H), 8.07 (dd, 1H, $J = 8.5$ Hz, $J' = 2.2$ Hz), 7.9−7.75 (m, 3H), 7.56 (d br, 1H, $J = 9.2$ Hz), 4.11 (d, 1H, $J = 9.2$ Hz), 3.75 (t, 1H, $J = 8.8$ Hz), 2.79 (m, 1H), 2.55 (d, 3H, $J = 4.4$ Hz), 1.42 (m, 1H), 1.31 (m, 1H), 0.96 (m, 1H), 0.86 (s, 9H), 0.74 (d, 3H, $J = 6.6$ Hz), 0.72 (d, 3H, $J = 6.6$ Hz); MS (ESI) 524 (MH^+).

17u: trifluoroacetate salt (194 mg, 91%) solid; ^{1}H NMR (DMSO-d_6) 8.73 (m, 2H), 7.90 (m, 1H), 7.73 (m, 3H), 7.28 (d br, 1H, $J = 9.5$ Hz), 4.16 (d, 1H, $J = 9.5$ Hz), 3.90 (m, 1H), 3.50−3.13 (m, 4H), 2.98 (m, 1H), 2.58 (d, 3H, $J = 4$ Hz), 1.50 (m, 2H), 1.26 (m, 1H), 0.91 (s, 9H), 0.86 (d, 3H, $J = 5.8$ Hz), 0.84 (d, 3H, $J = 5.8$ Hz); MS (ESI) 485 (MH^+). Anal. ($C_{22}H_{36}N_4O_6S \cdot 0.22AcOH \cdot 2H_2O$) C H calcd 7.72 found 7.29, N S. (An analytical sample of **17u** was obtained by purification on C18 HPLC eluting with MeOH/1% AcOH−water.)

17w: (292 mg, 98%) white solid; ^{1}H NMR (DMSO-d_6) 7.91 (m, 1H), 7.70 (d, 1H, $J = 9.5$ Hz), 7.04 (d, 1H, $J = 9.5$ Hz), 4.16 (d, 1H, $J = 9.2$ Hz), 3.84 (dd, 1H, $J = 9.1$ Hz, $J' = 7.3$ Hz), 2.92 (m, 1H), 2.88 (s, 3H), 2.57 (d, 3H, $J = 4.4$ Hz), 1.5−1.1 (m, 3H), 0.91 (s, 9H), 0.85 (d, 3H, $J = 6.2$ Hz), 0.83 (d, 3H, $J = 6.2$ Hz).

***N*²-[3*S*-Benzenesulfonylamino-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3a).** To **17a** (600 mg, 1.32 mmol) in DMF (10 mL) were added sucessively HOBT (231 mg, 1.7 mmol), EDCI (324 mg, 1.7 mmol), and 2,6-lutidine (181 μL, 1.6 mmol). The mixture was stirred at room temperature for 1 h. A solution of $NH_2OH \cdot HCl$ (270 mg, 3.9 mmol) and 2,6-lutidine (453 μL, 3.9 mmol) in DMF (1 mL) was added. The resulting solution was stirred at room temperature for 18 h. The resulting mixture was purified by C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 0:100 to 45:55) to give **3a** (228 mg, 37%): mp = 220−222 °C; ^{1}H NMR (DMSO-d_6) 10.74 (s, 1H), 8.82 (s, 1H), 7.89 (m, 1H), 7.75 (d, 2H, $J = 7.7$ Hz), 7.67−7.52 (m, 4H), 7.27 (m, 1H), 4.12 (d, 1H, $J = 9.2$ Hz), 3.70 (t br, 1H, $J = 9.2$ Hz), 2.73 (m, 1H), 2.59 (d, 3H, $J = 4.4$ Hz), 1.47 (m, 1H), 1.31 (m, 1H), 0.92 (m, 1H), 0.91 (s, 9H), 0.79 (d, 3H, $J = 5.9$ Hz), 0.77 (d, 3H, $J = 5.9$ Hz); MS (ESI) 493 (MNa^+). Anal. ($C_{21}H_{34}N_4O_6S$) C H calcd 7.28 found 7.80, N S.

***N*²-[3*S*-(4-Pyridinethanesulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3u).** Similarly to **3a,** from **17t** was obtained **3t** (55 mg, 14%) as a white solid: mp = 194−195 °C; ^{1}H NMR (DMSO-d_6 + CD_3CO_2D) 8.48 (m, 2H), 7.34 (m, 2H), 4.15 (m, 1H), 3.64 (d, 1H, $J = 10.3$ Hz), 3.21 (m, 1H), 3.03 (m, 2H), 2.91 (m, 1H), 2.75 (m, 1H), 2.56 (s, 3H), 1.54 (m, 1H), 1.34 (m, 1H), 0.91 (s, 9H), 0.90 (m, 1H), 0.78 (d, 6H, $J = 6.6$ Hz); MS (ESI) 522 (MNa^+), 500 (MH^+). Anal. ($C_{22}H_{37}N_5O_6S \cdot 1H_2O$) C H N.

***N*²-[3*S*-(4-Acetamidobenzenesulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3b).** To **17b** (512 mg, 1 mmol) in DMF (8 mL) were added EDCI (230 mg, 1.2 mmol), 2,6-lutidine (128 μL, 1.1 mmol), and $tBuMe_2SiONH_2$ (191 mg, 1.3 mmol). The mixture was stirred at room temperature for 2 h. Addition of 1 N HCl (1 mL) to the crude mixture at the end of the reaction and purification on C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 0:100 to 40:60) afforded **3b** (335 mg, 63%) as a white solid: mp = 272−274 °C; ^{1}H NMR (DMSO-d_6) 10.73 (s, 1H), 10.31 (s, 1H), 8.83 (s, 1H), 7.90 (m, 1H), 7.73 (d, 2H, $J = 8.8$ Hz), 7.67 (d, 2H, $J = 8.8$ Hz), 7.47 (m, 1H), 7.28 (d, 1H, $J = 9.5$ Hz), 4.16 (d, 1H, $J = 9.2$ Hz), 3.67 (m, 1H), 2.72 (m, 1H), 2.61 (d, 3H, $J = 4.4$ Hz), 2.15 (s, 3H), 1.49 (m, 1H), 1.32 (m, 1H), 0.96 (m, 1H), 0.95 (s, 9H), 0.80 (d, 3H, $J = 6.2$ Hz), 0.79 (d, 3H, $J = 6.2$ Hz); MS (ESI) 550 (MNa^+). Anal. ($C_{23}H_{37}N_5O_7S \cdot 0.3H_2O$) C H N S.

Hydroxamic acids **3c**, **3g**−**i**, **3l**−**t**, and **3w** were obtained using the protocole described above for **3b**.

***N*²-[3*S*-(3,5-Dichlorobenzene-1-sulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3c):** (310 mg, 68%) white solid; mp = 239−242 °C; ^{1}H NMR (DMSO-d_6) 10.79 (s, 1H), 8.86 (s, 1H), 8.12 (d, 1H, $J = 9.5$ Hz), 7.88 (m, 2H), 7.67 (s, 2H), 7.17 (d, 1H, $J = 9.5$ Hz), 4.12 (d, 1H, $J = 9.5$ Hz), 3.65 (t, 1H, $J = 9.5$ Hz), 2.67 (m, 1H), 2.56 (d, 3H, $J = 4.4$ Hz), 1.43 (m, 1H), 1.29 (m, 1H), 0.95 (m, 1H), 0.89 (s, 9H), 0.76 (d, 3H, $J = 6.6$ Hz), 0.75 (d, 3H, $J = 6.6$ Hz); MS (ESI) 563 (M{^{35}Cl,^{37}Cl}Na^+), 561 (M-{^{35}Cl,^{35}Cl}Na^+). Anal. ($C_{21}H_{32}Cl_2N_4O_6S$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(1-methylimidazole-4-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3g):** (265 mg, 46%) white solid. Obtained after addition of water (2 mL) and acetic acid (1 mL) to the crude mixture at the end of the reaction and purification on C18 preparative HPLC using as eluant methanol and water/1% AcOH (gradient from 0:100 to 40:60): mp = 222−224 °C; ^{1}H NMR (DMSO-d_6) 10.59 (s, 1H), 8.74 (s, 1H), 7.84 (m, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.41 (d, 1H, $J = 9.2$ Hz), 7.17 (d, 1H, $J = 9.1$ Hz), 4.14 (d, 1H, $J = 9.1$ Hz), 3.67 (s, 3H), 3.62 (t, 1H, $J = 8.8$ Hz), 2.75 (m, 1H), 2.56 (d, 3H, $J = 4.4$ Hz), 1.41 (m, 1H), 1.29 (m, 1H), 0.92 (s, 9H), 0.90 (m, 1H), 0.76 (d, 3H, $J = 6.2$ Hz), 0.75 (d, 3H, $J = 6.2$ Hz); MS (ESI) 497 (MNa^+). Anal. ($C_{19}H_{34}N_6O_6S$) C H calcd 7.22 found 7.65, N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(thiophene-2-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3h):** (245 mg, 60%) white solid; mp = 195−197 °C; ^{1}H NMR (DMSO-d_6) 10.75 (s, 1H), 8.84 (s, 1H), 7.86 (m, 2H), 7.79 (m, 1H), 7.47 (d, 1H, $J = 4.0$ Hz), 7.23 (m, 1H), 7.10 (t, 1H, $J = 4.0$ Hz), 4.12 (d, 1H, $J = 9.1$ Hz), 3.69 (d br, 1H, $J = 9.9$ Hz), 2.71 (m, 1H), 2.56 (d, 3H, $J = 4.4$ Hz), 1.46 (m, 1H), 1.29 (m, 1H), 0.93 (m, 1H), 0.91 (s, 9H), 0.76 (d, 3H, $J = 6.2$ Hz), 0.75 (d, 3H, $J = 6.2$ Hz); MS (ESI) 499 (MNa^+). Anal. ($C_{19}H_{32}N_4O_6S_2$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(3-pyridinesulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3i):** (315 mg, 94%) white solid; mp = 228−231 °C; ^{1}H NMR (DMSO-d_6) 10.75 (m, 1H), 8.86 (s, 1H), 8.81 (m, 1H), 8.76 (d, 1H, $J = 4.8$ Hz), 8.04 (d, 1H, $J = 8$ Hz), 7.96 (m, 1H), 7.87 (m, 1H), 7.56 (dd, 1H, $J = 8$ Hz, $J' = 4.8$ Hz), 7.20 (m, 1H), 4.10 (d, 1H, $J = 9.5$ Hz), 3.69 (d br, 1H, $J = 9.9$ Hz), 2.68 (m, 1H), 2.56 (d, 3H, $J = 4.8$ Hz), 1.44 (m, 1H), 1.29 (m, 1H), 0.90 (m, 1H), 0.88 (s, 9H), 0.76 (d, 3H, $J = 6.6$ Hz), 0.75 (d, 3H, $J = 6.6$ Hz); MS (ESI) 494 (MNa^+). Anal. ($C_{20}H_{33}N_5O_6S \cdot 0.5AcOH \cdot 0.7H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(naphthalene-2-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3l):** (362 mg, 73%) white solid; mp = 214−216 °C; ^{1}H NMR (DMSO-d_6) 10.79 (s, 1H), 8.79 (s, 1H), 8.39 (s, 1H), 8.14−8.06 (m, 3H), 7.89 (m, 1H), 7.78−7.68 (m, 4H), 7.27 (m, 1H), 4.13 (d, 1H, $J = 9.2$ Hz), 3.76 (m, 1H), 2.75 (m, 1H), 2.60 (d, 3H, $J = 4.4$ Hz), 1.46 (m, 1H), 1.30 (m, 1H), 0.92 (m, 1H), 0.90

(s, 9H), 0.77 (d, 3H, J = 7 Hz), 0.75 (d, 3H, J = 7 Hz); MS (ESI) 543 (MNa^+). Anal. ($C_{25}H_{36}N_4O_6S$) C H calcd 6.97 found 7.44, N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(naphthalene-1-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3m):** (342 mg, 62%) white solid; mp = 162−170 °C; ^{1}H NMR (DMSO-d_6) 10.79 (s, 1H), 8.67−8.57 (m, 2H), 8.25−8.05 (m, 3H), 7.92 (s br, 1H), 7.80−7.55 (m, 4H), 7.45 (m, 1H), 4.16 (d, 1H, J = 9.2 Hz), 3.72 (d br, 1H, J = 8.8 Hz), 2.75 (m, 1H), 2.60 (d, 3H, J = 4.4 Hz), 1.35 (m, 1H), 1.20 (m, 1H), 0.92 (s, 9H), 0.91 (m, 1H), 0.70 (d, 3H, J = 6.2 Hz), 0.65 (d, 3H, J = 5.9 Hz); MS (ESI) 543 (MNa^+). Anal. ($C_{25}H_{36}N_4O_6S$) C H N calcd 10.76 found 10.27, S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(quinoline-8-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3n):** (190 mg, 59%) white solid; mp = 178−181 °C; ^{1}H NMR (DMSO-d_6) 10.47 (m, 1H), 9.06 (m, 1H), 8.53−8.44 (m, 2H), 8.25−8.19 (m, 2H), 7.83−7.68 (m, 4H), 7.39 (m, 1H), 4.15 (d, 1H, J = 9.2 Hz), 3.84 (m, 1H), 2.83 (m, 1H), 2.56 (d, 3H, J = 4.8 Hz), 1.3−1.0 (m, 2H), 0.86 (s, 9H), 0.82 (m, 1H), 0.65 (d, 3H, J = 6.6 Hz), 0.62 (d, 3H, J = 6.6 Hz); MS (ESI) 544 (MNa^+), 522 (MH^+). Anal. ($C_{24}H_{35}N_5O_6S\cdot0.25H_2O$) C H N.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(isoquinoline-5-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3o):** (204 mg, 46%) white solid; mp = 208−210 °C; ^{1}H NMR (DMSO-d_6) 10.60 (s, 1H), 9.45 (s, 1H), 8.71 (d, 1H, J = 6.3 Hz), 8.57 (s, 1H), 8.39 (d, 1H, J = 7.7 Hz), 8.33 (d, 1H, J = 6.3 Hz), 8.27 (d, 1H, J = 7.7 Hz), 7.99 (d, 1H, J = 8.8 Hz), 7.90 (m, 1H), 7.76 (t, 1H, J = 7.7 Hz), 7.35 (d, 1H, J = 9.1 Hz), 4.14 (d, 1H, J = 9.1 Hz), 3.69 (m, 1H), 2.70 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.41 (m, 1H), 1.23 (m, 1H), 0.90 (m, 1H), 0.89 (s, 9H), 0.71 (d, 3H, J = 6.6 Hz), 0.67 (d, 3H, J = 6.6 Hz); MS (ESI) 522 (MH^+). Anal. ($C_{24}H_{35}N_5O_6S\cdot0.3H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3p):** (158 mg, 64%) solid; mp = 212−214 °C; ^{1}H NMR (DMSO-d_6) 10.44 (s, 1H), 8.48 (s, 1H), 8.31 (d, 1H, J = 7.9 Hz), 8.24 (s, 1H), 8.16 (d, 1H, J = 7.9 Hz), 7.84 (m, 1H), 7.76 (d, 1H, J = 9.5 Hz), 7.59 (t, 1H, J = 7.9 Hz), 7.14 (d, 1H, J = 9.9 Hz), 4.17 (d, 1H, J = 9.2 Hz), 3.76 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.35 (m, 1H), 1.25 (m, 1H), 0.90 (m, 1H), 0.89 (s, 9H), 0.71 (m, 6H); MS (ESI) 539 (MH^+). Anal. ($C_{23}H_{34}N_6O_7S\cdot0.3H_2O$) C H N calcd 15.45 found 15.02.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3q):** (322 mg, 63%) white solid; mp = 260−262 °C; ^{1}H NMR (DMSO-d_6) 10.72 (s, 1H), 8.76 (s, 1H), 7.85 (m, 1H), 7.57 (m, 2H), 7.42 (m, 1H), 7.25 (d, 1H, J = 8.8 Hz), 7.17 (d, 1H, J = 8.4 Hz), 4.12 (d, 1H, J = 9.1 Hz), 3.63 (m, 1H), 3.29 (s, 3H), 2.92 (m, 2H), 2.69 (m, 1H), 2.59 (m, 2H), 2.56 (d, 3H, J = 4.4 Hz), 1.44 (m, 1H), 1.28 (m, 1H), 0.91 (s, 9H), 0.90 (m, 1H), 0.76 (d, 3H, J = 6.6 Hz), 0.74 (d, 3H, J = 6.6 Hz); MS (ESI) 576 (MNa^+). Anal. ($C_{25}H_{39}N_5O_7S\cdot0.3H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(oxindole-5-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3r):** (228 mg, 47%) white solid; mp = 232−234 °C; ^{1}H NMR (DMSO-d_6) 10.75 (s, 1H), 10.69 (s, 1H), 8.76 (s, 1H), 7.85 (m, 1H), 7.55 (d, 1H, J = 8 Hz), 7.52 (s, 1H), 7.32 (m, 1H), 7.25 (m, 1H), 6.86 (d, 1H, J = 8 Hz), 4.11 (d, 1H, J = 9.1 Hz), 3.59 (m, 1H), 3.53 (s, 2H), 2.68 (m, 1H), 2.56 (d, 3H, J = 4.8 Hz), 1.41 (m, 1H), 1.27 (m, 1H), 0.90 (s, 9H), 0.85 (m, 1H), 0.74 (d, 3H, J = 6.6 Hz), 0.73 (d, 3H, J = 6.6 Hz); MS (ESI) 548 (MNa^+). Anal. ($C_{23}H_{35}N_5O_7S\cdot0.6H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(quinoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3s):** (204 mg, 40%) white solid; mp = 248−250 °C; ^{1}H NMR (DMSO-d_6) 10.76 (s, 1H), 9.05 (m, 1H), 8.74 (s, 1H), 8.54 (d, 1H, J = 9.1 Hz), 8.43 (s, 1H), 8.12 (d, 1H, J = 9.1 Hz), 7.97 (d, 1H, J = 9.1 Hz), 7.83 (m, 2H), 7.68 (m, 1H), 7.22 (d, 1H, J = 9.1 Hz), 4.11 (d, 1H, J = 9.1 Hz), 3.73 (m, 1H), 2.70 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.45 (m, 1H), 1.27 (m, 1H), 0.89 (m, 1H), 0.85 (s, 9H), 0.74 (d, 3H, J = 7 Hz), 0.72 (d, 3H, J = 7 Hz); MS (ESI) 522 (MH^+). Anal. ($C_{24}H_{35}N_5O_6S\cdot0.3H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3t):** (195 mg, 56%) solid; mp = 248−250 °C; ^{1}H NMR (DMSO-d_6) 10.74 (s, 1H), 8.70 (m, 1H), 8.44 (s, 1H), 8.24 (s, 1H), 8.02 (dd, 1H, J = 8.5 Hz, J' = 2.2 Hz), 7.85 (m, 2H), 7.75 (d, 1H, J = 8.5 Hz), 7.21 (d, 1H, J = 9.5 Hz), 4.11 (d, 1H, J = 9.2 Hz), 3.67 (m, 1H), 2.67 (m, 1H), 2.56 (d, 1H, J = 4.4 Hz), 1.43 (m, 1H), 1.27 (m, 1H), 0.90 (m, 1H), 0.88 (s, 9H), 0.73 (m, 6H); MS (ESI) 539 (MH^+). Anal. ($C_{23}H_{34}N_6O_7S\cdot0.5H_2O$) C H N S calcd 5.85 found 5.29.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methanesulfonylaminosuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3w):** (230 mg, 83%) solid; mp = 169−171 °C; ^{1}H NMR (DMSO-d_6) 10.9 (m, 1H), 9.09 (m, 1H), 7.88 (m, 1H), 7.30 (d, 1H, J = 9.2 Hz), 7.15 (m, 1H), 4.16 (d, 1H, J = 9.2 Hz), 3.61 (d, 1H, J = 9.9 Hz), 2.77 (s, 3H), 2.73 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.50 (m, 1H), 1.33 (m, 1H), 0.93 (s, 9H), 0.90 (m, 1H), 0.79 (d, 6H, J = 6.6 Hz); MS (ESI) 431 (MNa^+). Anal. ($C_{16}H_{32}N_4O_6S$) C H N calcd 13.71 found 13.30, S calcd 7.85 found 7.40.

***N*²-[3*S*-(2-Cyanobenzene-1-sulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3d).** Acid **17d** (380 mg, 0.79 mmol), $tBuMe_2SiONH_2$ (175 mg, 1.19 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (254 mg, 1.03 mmol) in $CHCl_3$ (5 mL) were stirred for 18 h. Evaporation of the solvents, partitioning between Et_2O and water, and filtration of the resulting solid afforded **3d** (202 mg, 52%) as a white solid: mp = 200−205 °C; ^{1}H NMR (DMSO-d_6) 10.57 (s, 1H), 8.67 (s, 1H), 8.04−7.76 (m, 6H), 7.56 (d, 1H, J = 9.2 Hz), 4.18 (d, 1H, J = 9.2 Hz), 3.67 (t, 1H, J = 9.6 Hz), 2.84 (m, 1H), 2.58 (d, 3H, J = 4.4 Hz), 1.46 (m, 1H), 1.30 (m, 1H), 0.93 (s, 9H), 0.91 (m, 1H), 0.77 (d, 3H, J = 6 Hz), 0.75 (d, 3H, J = 6 Hz); MS (ESI) 518 (MNa^+). Anal. ($C_{22}H_{33}N_5O_6S$) C H N.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(E-*β*-styrenesulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3v).** To amine **23** (450 mg, 0.93 mmol) in CH_2Cl_2 (15 mL) were added pyridine (2 mL) and E-*β*-styrenesulfonyl chloride (285 mg, 1.4 mmol). The mixture was stirred at room temperature for 18 h. The mixture was diluted with EtOAc, washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents, trituration of the residue with Et_2O afforded the protected hydroxamate (421 mg, 70%) as a yellowish solid: MS (ESI) 647 (MH^+). This compound in 5% TFA/CH_2Cl_2 (15 mL) was stirred for 15 min. After evaporation of the solvent, the residue was triturated with methanol (15 mL) and filtered. Purification of the filtrates on a C18 silica cartridge (methanol/water 1:1) afforded **3v** (217 mg, 74%) as a solid: mp = 242−243 °C (decomposition); ^{1}H NMR (DMSO-d_6) 10.82 (s, 1H), 9.01 (s br, 1H), 7.88 (m, 1H), 7.60 (m, 2H), 7.50−7.30 (m, 6H), 6.83 (d, 1H, J = 15.3 Hz), 4.18 (d, 1H, J = 9.6 Hz), 3.61 (t, 1H, J = 9.6 Hz), 2.76 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.50 (m, 1H), 1.32 (m, 1H), 0.93 (m, 1H), 0.92 (s, 9H), 0.79 (m, 6H); MS (ESI) 497 (MH^+). Anal. ($C_{23}H_{36}N_4O_6S\cdot0.8H_2O$) C H N.

Sulfonamides **3e**−**f** and **3j**−**k** were obtained by solid phase synthesis.[24]

***N*²-[3*S*-(2-Chloro-4-fluorobenzene-1-sulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3e):** 15 mg; MS (ESI) 525 ($M\{^{37}Cl\}H^+$), 523 ($M\{^{35}Cl\}H^+$); HPLC t_R 8.0 min.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(2,4,6-triisopropylbenzene-1-sulfonylamino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (3f):** 22.3 mg; MS (ESI) 597 (MH^+); HPLC t_R 12.6 min.

***N*²-[3*S*-(4-Carboxybenzene-1-sulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (3j):** 13.5 mg; MS (ESI) 515 (MH^+); HPLC t_R 6.6 min.

***N*²-[3*S*-(4-Bromobenzene-1-sulfonylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-

methylamide (3k): 11.8 mg; MS (ESI) 551 ($M\{^{81}Br\}H^+$), 549 ($M\{^{79}Br\}H^+$); HPLC t_R 8.8 min.

***N*²-[3*S*-(*N*-Benzenesulfonyl-*N*-methylamino)-4-*tert*-butyloxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (20a).** To **16a** (511 mg, 1 mmol) in acetone (10 mL) were added K_2CO_3 (207 mg, 1.5 mmol) and MeI (1 mL, 15 mmol). The mixture was stirred at room temperature for 18 h, diluted with EtOAc, and washed with water and brine. The organic layers were dried over $MgSO_4$, and the solvents were removed in vacuo to give **20a** (460 mg, 88%) as a yellowish solid: ^{1}H NMR ($CDCl_3$) 7.83 (d, 2H, J = 7.4 Hz), 7.6−7.45 (m, 3H), 6.25 (d br, 1H, J = 8.8 Hz), 6.00 (m, 1H), 4.62 (d, 1H, J = 9.6 Hz), 4.17 (d, 1H, J = 8.8 Hz), 2.93 (s, 3H), 2.91 (m, 1H), 2.80 (d, 3H, J = 4.8 Hz), 1.75−1.5 (m, 2H), 1.23 (s, 9H), 1.1 (m, 1H), 1.01 (s, 9H), 0.90 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz); MS (ESI) 548 (MNa^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(*N*-methyl-*N*-(quinoline-8-sulfonyl)amino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (20b).** Similarly from **16n** was obtained **20b** (429 mg, 93%) as a yellowish solid: ^{1}H NMR ($CDCl_3$) 9.03 (m, 1H), 8.51 (d br, 1H, J = 7.3 Hz), 8.22 (d br, 1H, J = 8.4 Hz), 8.03 (d br, 1H, J = 8.4 Hz), 7.63 (dd, 1H, J = 8.4 Hz, J' = 7.3 Hz), 7.50 (dd, 1H, J = 8.4 Hz, J' = 4 Hz), 6.39 (d br, 1H, J = 8.4 Hz), 6.19 (m, 1H), 4.86 (d, 1H, J = 9.5 Hz), 4.16 (d, 1H, J = 8.4 Hz), 3.32 (s, 3H), 3.07 (m, 1H), 2.83 (d, 3H, J = 4.8 Hz), 1.75−1.5 (m, 2H), 1.2 (m, 1H), 1.07 (s, 9H), 0.90 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz), 0.81 (s, 9H); MS (ESI) 599 (MNa^+).

***N*²-[4-*tert*-Butyloxy-2*R*-isobutyl-3*S*-(*N*-propyl-*N*-(quinoline-8-sulfonyl)amino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (20c).** Similarly, except that the reaction mixture was heated at 40 °C for 72 h, KI (1 equiv) was added, and acetone was replaced by DMF, from **16n** and propyl bromide was obtained **20c** (200 mg, 42%): ^{1}H NMR ($CDCl_3$) 9.02 (m, 1H), 8.52 (d br, 1H, J = 7.3 Hz), 8.22 (d br, 1H, J = 8.4 Hz), 8.03 (d br, 1H, J = 8.4 Hz), 7.64 (dd, 1H, J = 8.4 Hz, J' = 7.3 Hz), 7.50 (dd, 1H, J = 8.4 Hz, J' = 4 Hz), 6.65 (m, 1H), 6.27 (m, 1H), 4.92 (d br, 1H, J = 9.5 Hz), 4.17 (d, 1H, J = 9.2 Hz), 3.93 (m, 1H), 3.52 (m, 1H), 3.13 (m, 1H), 2.82 (d, 3H, J = 4.8 Hz), 1.8−0.8 (m, 14H), 1.08 (s, 9H), 0.89 (s, 9H); MS (ESI) 605 (MH^+).

***N*²-[3*S*-(*N*-Benzyl-*N*-(quinoline-8-sulfonyl)amino)-4-*tert*-butyloxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (20d).** Similarly, except that KI (1 equiv) was added and the reaction was refluxed for 2 h, from **16n** and benzyl bromide was obtained **20d** (353 mg, 62%): ^{1}H NMR ($CDCl_3$) 9.01 (m, 1H), 8.20 (d br, 1H, J = 8 Hz), 8.13 (d, 1H, J = 8 Hz), 7.94 (d, 1H, J = 8 Hz), 7.50 (dd, 1H, J = 8 Hz, J' = 4.6 Hz), 7.42 (t, 1H, J = 8 Hz), 7.30−7.05 (m, 5H), 6.50 (m, 1H), 6.05 (m, 1H), 5.42 (d, 1H, J = 15.8 Hz), 5.22 (d, 1H, J = 7.4 Hz), 4.73 (d, 1H, J = 15.8 Hz), 4.11 (d, 1H, J = 9.2 Hz), 2.98 (m, 1H), 2.78 (d, 3H, J = 4.7 Hz), 1.65 (m, 1H), 1.43 (m, 1H), 1.15 (m, 1H), 1.07 (s, 18H), 0.80 (d, 3H, J = 6.6 Hz), 0.76 (d, 3H, J = 6.6 Hz); MS (ESI) 653 (MH^+).

***N*²-[3*S*-(*N*-Benzenesulfonyl-*N*-methylamino)-4-hydroxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (21a).** According to the method described for **17a**, from **20a** was obtained **21a** (676 mg, 98%): ^{1}H NMR (DMSO-d_6) 7.99 (d, 1H, J = 9.2 Hz), 7.89 (m, 1H), 7.71 (d, 2H, J = 8.1 Hz), 7.65−7.50 (m, 3H), 4.46 (d, 1H, J = 11 Hz), 4.15 (d, 1H, J = 9.2 Hz), 3.08 (m, 1H), 2.88 (s, 3H), 2.56 (d, 3H, J = 4.4 Hz), 1.50 (m, 1H), 1.35 (m, 1H), 0.85 (s, 9H), 0.84 (m, 4H), 0.77 (d, 3H, J = 6.6 Hz); MS (ESI) 492 (MNa^+), 470 (MH^+).

Similarly, the following compounds were obtained.

21b: (427 mg, 99%) white solid; ^{1}H NMR (DMSO-d_6) 8.98 (m, 1H), 8.50 (d br, 1H, J = 8.4 Hz), 8.32 (d br, 1H, J = 8.4 Hz), 8.26 (d br, 1H, J = 8.4 Hz), 7.90 (m, 1H), 7.81 (d br, 1H, J = 9.2 Hz), 7.74−7.65 (m, 2H), 4.78 (d, 1H, J = 9.9 Hz), 4.18 (d, 1H, J = 9.2 Hz), 3.14 (s, 3H), 3.10 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.57 (m, 1H), 1.38 (m, 1H), 1.02 (m, 1H), 0.91 (s, 9H), 0.85 (d, 3H, J = 6.2 Hz), 0.79 (d, 3H, J = 6.2 Hz); MS (ESI) 521 (MH^+).

21c: (121 mg, 79%) white solid; ^{1}H NMR (DMSO-d_6) 8.94 (m, 1H), 8.49 (d br, 1H, J = 8.4 Hz), 8.34 (d br, 1H, J = 8.4 Hz), 8.24 (d br, 1H, J = 8.4 Hz), 7.90 (m, 1H), 7.70 (m, 2H), 7.55 (m, 1H), 5.13 (d, 1H, J = 7.7 Hz), 4.11 (d, 1H, J = 9.2 Hz), 3.4−3.3 (m, 2H), 3.10 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.7−1.4 (m, 4H), 1.17 (m, 1H), 0.87 (s, 9H), 0.86 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz), 0.68 (t, 3H, J = 7.3 Hz); MS (ESI) 549 (MH^+).

21d: (286 mg, 98%) white solid; ^{1}H NMR (DMSO-d_6) 8.94 (m, 1H), 8.44 (d, 1H, J = 8.2 Hz), 8.07 (d, 1H, J = 8.2 Hz), 7.93 (m, 1H), 7.76 (d br, 1H, J = 9.2 Hz), 7.64 (m, 2H), 7.32 (t, 1H, J = 8.2 Hz), 7.06−6.80 (m, 5H), 5.43 (d, 1H, J = 7.4 Hz), 5.00 (d, 1H, J = 15.4 Hz), 4.59 (d, 1H, J = 15.4 Hz), 4.16 (d, 1H, J = 9.2 Hz), 3.17 (m, 1H), 2.57 (d, 3H, J = 4.4 Hz), 1.64 (m, 1H), 1.37 (m, 1H), 1.16 (m, 1H), 0.97 (s, 9H), 0.77 (d, 3H, J = 6.6 Hz), 0.73 (d, 3H, J = 6.6 Hz); MS (ESI) 597 (MH^+).

***N*²-[3*S*-(*N*-Benzenesulfonyl-*N*-methylamino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (22a).** According to the procedure described for **3d**, from **21a** was obtained **22a** (202 mg; 58%) as a white solid: mp = 209−211 °C; ^{1}H NMR (DMSO-d_6) 10.88 (s, 1H), 8.84 (s, 1H), 7.94 (d, 1H, J = 9.2 Hz), 7.85 (m, 1H), 7.75 (d, 2H, J = 8 Hz), 7.64 (m, 1H), 7.55 (m, 2H), 4.35 (d, 1H, J = 11 Hz), 4.14 (d, 1H, J = 9.2 Hz), 3.16 (m, 1H), 2.91 (s, 3H), 2.57 (d, 3H, J = 4.4 Hz), 1.47 (m, 1H), 1.38 (m, 1H), 0.85 (m, 13H), 0.79 (d, 3H, J = 6.6 Hz); MS (ESI) 507 (MNa^+). Anal. ($C_{22}H_{36}N_4O_6S\cdot 1H_2O$) C H N.

According to the protocol described for **3b**, **21b**−**d** were converted to hydroxamic acids **22b**−**d**.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(*N*-methyl-*N*-(quinoline-8-sulfonyl)amino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (22b):** (250 mg, 61%) mp = 166−168 °C; ^{1}H NMR (DMSO-d_6) 10.54 (s, 1H), 9.03 (m, 1H), 8.48 (m, 1H), 8.29 (d, 1H, J = 7.3 Hz), 8.22 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 9.2 Hz), 7.82 (m, 1H), 7.66 (m, 3H), 4.40 (d, 1H, J = 10.7 Hz), 4.14 (d, 1H, J = 9.1 Hz), 3.32 (s, 3H), 3.18 (m, 1H), 2.56 (d, 3H, J = 4 Hz), 1.45 (m, 1H), 1.36 (m, 1H), 0.90 (m, 1H), 0.88 (s, 9H), 0.84 (d, 3H, J = 6.6 Hz), 0.77 (d, 3H, J = 6.6 Hz); MS (ESI) 558 (MNa^+). Anal. ($C_{25}H_{37}N_5O_6S\cdot 0.2H_2O$) C H N S.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(*N*-propyl-*N*-(quinoline-8-sulfonyl)amino)succinyl]-L-*tert*-leucine-*N*¹-methylamide (22c):** (42 mg, 41%) white solid; mp = 148−150 °C; ^{1}H NMR (DMSO-d_6) 10.6 (s, 1H), 9.01 (m, 1H), 8.72 (m, 1H), 8.48 (m, 1H), 8.31 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.1 Hz), 7.67 (m, 4H), 4.53 (d, 1H, J = 10.2 Hz), 3.99 (d, 1H, J = 8.8 Hz), 3.72 (m, 1H), 3.59 (m, 1H), 3.15 (m, 1H), 2.56 (d, 3H, J = 4.8 Hz), 1.65−1.3 (m, 4H), 0.87−0.70 (m, 19H); MS (ESI) 564 (MH^+). Anal. ($C_{27}H_{41}N_5O_6S\cdot 0.55H_2O$) C H N S.

***N*²-[3*S*-(*N*-Benzyl-*N*-(quinoline-8-sulfonyl)amino)-4-(*N*-hydroxyamino)-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*¹-methylamide (22d):** (76 mg, 28%) white solid; mp = 149−154 °C; ^{1}H NMR (DMSO-d_6) 11.03 (s, 1H), 9.04 (m, 1H), 8.39 (m, 1H), 7.97 (d, 1H, J = 8.4 Hz), 7.84 (m, 1H), 7.65−7.5 (m, 4H), 7.20 (m, 1H), 6.9−6.6 (m, 5H), 5.28 (d, 1H, J = 14.3 Hz), 4.96 (d, 1H, J = 9.5 Hz), 4.65 (d, 1H, J = 14.3 Hz), 4.13 (d, 1H, J = 8.5 Hz), 3.26 (m, 1H), 2.57 (d, 3H, J = 4 Hz), 1.62 (m, 1H), 1.41 (m, 1H), 1.05 (s, 9H), 1.0 (m, 1H), 0.86 (d, 3H, J = 6.6 Hz), 0.82 (d, 3H, J = 6.6 Hz); MS (ESI) 634 (MNa^+). Anal. ($C_{31}H_{41}N_5O_6S\cdot 1.3H_2O$) C H N.

***N*²-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(8-quinolinecarboxamido)succinyl]-L-*tert*-leucine-*N*¹-methylamide (4a).** A solution of **15** (428 mg, 1.16 mmol), 8-quinoline carboxylic acid (261 mg, 1.5 mmol), HOBT (216 mg, 1.6 mmol), *N*-methyl morpholine (300 μL, 2.7 mmol), and EDCI (305 mg, 1.6 mmol) in DMF (8 mL) was stirred for 18 h. The mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ and brine, and dried over $MgSO_4$. Chromatography on silica gel (eluant: EtOAc/petroleum ether 7:3) gave **18a** (562 mg, 92%) as a white foam: ^{1}H NMR ($CDCl_3$) 9.00 (m, 1H), 8.82 (d br, 1H, J = 8 Hz), 8.26 (d br, 1H, J = 8 Hz), 7.97 (d br, 1H, J = 8 Hz), 7.67 (t, 1H, J = 8 Hz), 7.47 (dd, 1H, J = 8 Hz, J' = 4 Hz), 6.57 (m, 1H), 5.93 (m, 1H), 5.10 (dd, 1H, J = 8.1 Hz, J' = 4.4 Hz), 4.22 (d, 1H, J = 9.2 Hz), 3.07 (m, 1H), 2.73 (d, 3H, J = 4.8 Hz), 1.8−1.4 (m, 3H), 1.48 (s, 9H), 0.96 (s, 9H), 0.88 (d, 3H, J = 6.2 Hz), 0.87 (d, 3H, J = 6.2 Hz); MS (ESI) 527 (MH^+). **18a** was converted to acid **19a** (487 mg, 97%) using the same method

described for **17a**. **19a**: ^{1}H NMR ($CDCl_3$) 9.10 (m, 1H), 8.68 (d, 1H, J = 7.3 Hz), 8.40 (d, 1H, J = 8.7 Hz), 8.07 (d, 1H, J = 8 Hz), 7.74 (dd, 1H, J = 8 Hz, J' = 7.3 Hz), 7.61 (dd, 1H, J = 8.7 Hz, J' = 4.4 Hz), 7.30 (m, 1H), 5.97 (m, 1H), 5.00 (m, 1H), 4.28 (d, 1H, J = 9.5 Hz), 3.35 (m, 1H), 2.84 (d, 3H, J = 4.8 Hz), 1.75−1.45 (m, 3H), 1.01 (s, 9H), 0.86 (d, 3H, J = 5.8 Hz), 0.85 (d, 3H, J = 5.8 Hz); MS (ESI) 471 (MH^+). Anal. ($C_{25}H_{34}N_4O_5 \cdot 0.3H_2O \cdot 0.9CF_3CO_2H$) C H N. Using the procedure described for **2h**, from **19a** was obtained **4a** (173 mg, 75%) as a white solid: mp = 147−155 °C; ^{1}H NMR (DMSO-d_6) 9.14 (m, 1H), 8.56 (m, 2H), 8.20 (d, 1H, J = 7 Hz), 7.91 (d, 1H, J = 9.5 Hz), 7.80−7.65 (m, 3H), 4.65 (t, 1H, J = 9.2 Hz), 4.08 (d, 1H, J = 9.5 Hz), 3.19 (m, 1H), 1.57 (m, 1H), 1.41 (m, 1H), 1.11 (m, 1H), 0.90 (d, 3H, J = 6.6 Hz), 0.83 (d, 3H, J = 6.6 Hz), 0.46 (s, 9H); MS (EI) 485 ($M^{+\bullet}$). Anal. ($C_{25}H_{35}N_5O_5 \cdot 1H_2O \cdot 1CF_3CO_2H$) C H N.

Amides **4b**−**f** were obtained by solid phase synthesis.[24]

4b: 27 mg; MS (ESI) 486 (MH^+); HPLC t_R 6.7 min.

4c: 21 mg; MS (ESI) 436 (MH^+); HPLC t_R 5.8 min.

4d: 14.7 mg; MS (ESI) 435 (MH^+); HPLC t_R 7.7 min.

4e: 22.6 mg; MS (ESI) 485 (MH^+); HPLC t_R 9.5 min.

4f: 18.2 mg; MS (ESI) 373 (MH^+); HPLC t_R 5.1 min.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-morpholinosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (5a).** A solution of **15** (500 mg, 1.35 mmol), 2-iodoethyl ether (1.76 g, 5.4 mmol), and iPr_2EtN (700 μL, 4.1 mmol) in DMF (5 mL) was stirred at room temperature in the dark for 8 days. The mixture was diluted with EtOAc, washed with water, and dried over $MgSO_4$. Purification on silica gel (EtOAc/CH_2Cl_2 3:1) afforded the corresponding morpholine contaminated with traces of 2-iodoethyl ether (500 mg, 84%): ^{1}H NMR ($CDCl_3$) 6.63 (d br, 1H, J = 9.2 Hz), 5.80 (m, 1H), 4.23 (d, 1H, J = 9.2 Hz), 3.64 (m, 4H), 3.25 (d, 1H, J = 11.7 Hz), 2.81 (d, 3H, J = 4.8 Hz), 2.78−2.70 (m, 3H), 2.55−2.50 (m, 2H), 1.7−1.4 (m, 2H), 1.50 (s, 9H), 1.06 (m, 1H), 1.03 (s, 9H), 0.89 (d, 3H, J = 6.2 Hz), 0.85 (d, 3H, J = 6.2 Hz). According to the procedure described for **16a**, this compound was converted to the carboxylic acid: ^{1}H NMR (DMSO-d_6 + CF_3CO_2D) 8.29 (d br, 1H, J = 9.2 Hz, NH not exchanged), 4.20 (d, 1H, J = 9.2 Hz), 3.99 (m, 1H), 3.84 (m, 4H), 3.25 (m, 5H), 2.56 (s, 3H), 1.65 (m, 1H), 1.39 (m, 1H), 1.15 (m, 1H), 0.93 (s, 9H), 0.84 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.4 Hz); MS (ESI) 386 (MH^+). Anal. ($C_{19}H_{35}N_3O_5 \cdot 0.8H_2O$) C H N. According to the method described for **3a**, this acid was converted to hydroxamic acid **5a** (120 mg, 22%): mp = 195−200 °C; ^{1}H NMR (DMSO-d_6) 10.52 (s, 1H), 8.85 (s, 1H), 7.88 (q, 1H, J = 4.4 Hz), 7.83 (d, 1H, J = 9.2 Hz), 4.26 (d, 1H, J = 9.2 Hz), 3.48 (m, 4H), 3.0 (m, 2H), 2.8−2.77 (m, 2H), 2.56 (d, 3H, J = 4.4 Hz), 2.37−2.34 (m, 2H), 1.40−1.25 (m, 2H), 0.96 (s, 9H), 0.89 (m, 1H), 0.82 (d, 3H, J = 6.2 Hz), 0.75 (d, 3H, J = 6.2 Hz); MS (ESI) 401 (MH^+). Anal. ($C_{19}H_{36}N_4O_5 \cdot 0.8H_2O \cdot 0.11AcOH$) C H N.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-pyrrolidinosuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (5b).** A solution of **23** (400 mg, 0.83 mmol), 1,4-diiodobutane (438 μL, 3.3 mmol), and iPr_2EtN (434 μL, 2.49 mmol) in DMF (10 mL) was stirred at room temperature in the dark for 3 days. Aqueous workup and purification on silica gel (eluant: EtOAc) afforded the protected hydroxamate (170 mg, 38%): ^{1}H NMR (DMSO-d_6) 10.95 (s, 1H), 7.80 (m, 2H), 7.20 (d, 1H, J = 8.4 Hz), 6.56 (s br, 1H), 6.51 (d br, 1H, J = 8.4 Hz), 4.72 (s, 2H), 4.23 (d, 1H, J = 9.5 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 3.16 (d, 1H, J = 11 Hz), 2.93 (m, 1H), 2.69 (m, 2H), 2.55 (d, 3H, J = 4.4 Hz), 2.53 (m, 2H), 1.6−1.2 (m, 7H), 0.88 (s, 9H), 0.83 (d, 3H, J = 6.2 Hz), 0.75 (d, 3H, J = 6.2 Hz); MS (ESI) 535 (MH^+), which was deprotected using the method described for **3v** to give **5b** (100 mg, 87%) as a solid: mp = 138−144 °C; ^{1}H NMR (DMSO-d_6 + CF_3CO_2D) 4.17 (s, 1H), 3.92 (d, 1H, J = 7.8 Hz), 3.45−3.15 (m, 5H), 2.59 (s, 3H), 1.96 (m, 4H), 1.6−1.4 (m, 2H), 1.2 (m, 1H), 0.97 (s, 9H), 0.94 (d, 3H, J = 6.2 Hz), 0.91 (d, 3H, J = 6.2 Hz); MS (ESI) 385 (MH^+). Anal. ($C_{19}H_{36}N_4O_4 \cdot 1H_2O \cdot 1CF_3COOH$) C H N.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(8-quinolinemethylamino)succinyl]-L-*tert*-leucine-*N*^{1}-methylamide (5c).** To a solution of **23** (250 mg, 0.52 mmol) and quinoline 8-carboxaldehyde (100 mg, 0.64 mmol) in methanol (10 mL) was added $NaBH_3CN$ (14 mg, 0.22 mmol) and AcOH (2 drops). The mixture was stirred for 30 min, diluted with EtOAc, washed with 5% $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent gave the corresponding amine (330 mg, 100%): ^{1}H NMR (DMSO-d_6) 11.21 (s br, 1H), 8.88 (m, 1H), 8.34 (d br, 1H, J = 8 Hz), 7.80 (m, 3H), 7.66 (d br, 1H, J = 9.5 Hz), 7.51 (m, 2H), 7.24 (d, 1H, J = 8 Hz), 6.56 (s br, 1H), 6.40 (d br, 1H, J = 8 Hz), 4.75 (s, 2H), 4.34 (m, 1H), 4.19 (d, 1H, J = 9.5 Hz), 4.04 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.08 (m, 1H), 2.76 (m, 1H), 2.55 (d, 3H, J = 4.8 Hz), 1.49 (m, 1H), 1.35 (m, 1H), 0.9−0.8 (m, 4H), 0.81 (s, 9H), 0.77 (d, 3H, J = 6.9 Hz). This amine was deprotected using the method described for **3v** to give **5c** (118 mg, 48%) after purification on C18 preparative HPLC (eluant MeOH/0.2% aqueous ammonium carbonate from 0:100 to 60:40): mp = 176−178 °C; ^{1}H NMR (DMSO-d_6) 10.75 (s, 1H), 8.99 (s, 1H), 8.89 (m, 1H), 8.36 (d br, 1H, J = 8.4 Hz), 7.82 (m, 3H), 7.67 (d br, 1H, J = 9.6 Hz), 7.60−7.5 (m, 2H), 4.36 (m, 1H), 4.21 (d, 1H, J = 9.6 Hz), 3.99 (m, 1H), 3.13 (m, 1H), 2.80 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.50 (m, 1H), 1.34 (m, 1H), 0.95 (m, 1H), 0.83 (m, 15H); MS (ESI) 472 (MH^+). Anal. ($C_{25}H_{37}N_5O_4$ $0.7H_2O$) C H N.

Compounds **5d**−**g** were made on solid phase.[24]

5d: 10 mg, 48%; MS (ESI) 421 (MH^+); HPLC t_R 6.4 min.

5e: 23 mg, 98%; MS (ESI) 471 (MH^+); HPLC t_R 9.2 min.

5f: 25 mg, 106%; MS (ESI) 472 (MH^+); HPLC t_R 5.8 min.

5g: 22.4 mg, 107%; MS (ESI) 419 (MH^+); HPLC t_R 4.0 min.

3*R*-Chloro-2*S*-isobutylbutan-1,4-dioic Acid 4-*tert*-Butyl Ester (24). To a stirred solution of LDA [45.5 mmol; prepared by addition of 2.5 M *n*-butyllithium (18.2 mL, 45.5 mmol) in hexane to a solution of diisopropylamine (6.3 mL, 48.3 mmol) in dry THF (20 mL) at −78 °C] cooled to −78 °C was added dropwise a solution of **7** (5.0 g, 21.7 mmol) in dry THF (15 mL). The mixture was stirred for 45 min at −78 °C, and a solution of carbon tetrachloride (2.3 mL, 23.9 mmol) in dry THF (3 mL) was added slowly, dropwise over ca. 8 min avoiding that the internal temperature rises above −65 °C. The mixture was allowed to stir at −78 °C for 30 min, warmed to room temperature, and stirred for 1 h at room temperature. The solution was cooled to −78 °C and quenched by addition of HCl (2 N, 3.3 mL). The solution was warmed to room temperature and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed to give directly one crude single isomer. The residue was purified by flash chromatography on silica using acetonitrile as eluant to give **24** (5.6 g, 98%) as a pale brown oil: ^{1}H NMR ($CDCl_3$) 4.41 (d, 1H, J = 8.1 Hz), 3.1−3.05 (m, 1H), 1.8−1.65 (m, 2H), 1.55 (m, 1H), 1.48 (s, 9H), 0.95 (d, 3H, J = 4.8 Hz), 0.94 (d, 3H, J = 4.8 Hz); MS (EI) 266 ($M\{^{37}Cl\}H^+$), 264 ($M\{^{35}Cl\}H^+$).

***N*^{2}-[3*S*-Hydroxy-2*R*-isobutyl-4-*tert*-butyloxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (26).** To a stirred solution of **24** (4.0 g, 15 mmol) in acetonitrile (100 mL) was added L-*tert*-leucine *N*-methylamide (2.8 g, 19.4 mmol). The mixture was stirred at room temperature for 24 h. A further quantity of acetonitrile (25 mL) was added, and the mixture was stirred for 12 h. The solvents were evaporated in vacuo, and the residue was partitioned between water and EtOAc. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using MeCN/CH_2Cl_2 (gradient from 20:80 to 25:75) as eluant to give **26** (2.48 g, 45%) as a beige solid: ^{1}H NMR ($CDCl_3$) 6.68 (d, 1H, J = 9.1 Hz), 5.88 (m, 1H), 4.13 (d, 1H, J = 8.8 Hz), 4.1 (m, 1H), 3.73 (d, 1H, J = 5.9 Hz), 2.79 (d, 3H, J = 5.1 Hz), 2.75 (m, 1H), 1.75−1.55 (m, 3H), 1.47 (s, 9H), 0.99 (s, 9H), 0.96 (d, 3H, J = 6.2 Hz), 0.92 (d, 3H, J = 6.2 Hz); MS (EI) 373 (MH^+).

3*R*-Isobutyl-4-oxo-2*S*-oxetanecarboxylic Acid *tert*-Butyl Ester (25). To a stirred solution of **24** (2.3 g, 8.7 mmol) in Et_2O (50 mL) was added an aqueous solution (5%) of $NaHCO_3$ (45 mL), and the biphasic mixture was vigorously stirred at room temperature for 48 h. The layers were separated, the organic phase was washed with water, dried over $MgSO_4$, and filtered, and the solvents were removed to give directly **25**

(1.3 g, 68%) as a brown gum: ^{1}H NMR ($CDCl_3$) 4.47 (d, 1H, J = 4.03 Hz), 3.7 (m, 1H), 1.85−1.7 (m, 3H), 1.52 (s, 9H), 0.98 (d, 3H, J = 6.2 Hz), 0.94 (d, 3H, J = 6.2 Hz); MS (EI) 229 (MH^+).

Alternative Preparation of 26 from 25. To a stirred solution of **25** (1.2 g, 5.3 mmol) in acetonitrile (15 mL) was added L-*tert*-leucine *N*-methylamide (0.98 g, 6.8 mmol). The mixture was stirred at room temperature for 36 h. The solvents were evaporated in vacuo, and the residue was partitioned between water and Et_2O. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using MeCN/CH_2Cl_2 (gradient from 10:90 to 30:70) as eluant to give **26** (1.27 g, 66%) as a beige solid.

Preparation of 6a−f from 26: N^2-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl-)methoxysuccinyl]-L-*tert*-leucine-N^1-methylamide (6a). A solution of **26** (400 mg, 1.07 mmol) was prepared in THF (10 mL). Sodium hydride (50 mg, 60% in oil, 1.2 mmol) was added followed 3 min later by a solution of 6-bromomethyl-1-methyl-2-oxo-1,2-dihydroquinoline[43] (325 mg, 1.3 mmol) in THF (10 mL) and sodium iodide (161 mg, 1.07 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was treated with a saturated solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using MeCN/CH_2Cl_2 (gradient from 3/7 to 3/2) as eluant to give **27a** (469 mg, 81%) as a foam: ^{1}H NMR ($CDCl_3$) 7.67 (d, 1H, J = 9.52 Hz), 7.57 (m, 2H), 7.35 (d, 1H, J = 8.8 Hz), 6.83 (d, 1H, J = 8.8 Hz), 6.73 (d, 1H, J = 9.52 Hz), 6.22 (m, 1H), 4.76 (d, 1H, J = 10.62 Hz), 4.49 (d, 1H, J = 11 Hz), 4.07 (d, 1H, J = 9.16 Hz), 3.97 (d, 1H, J = 5.49 Hz), 3.72 (s, 3H), 2.79 (d, 3H, J = 4.77 Hz), 2.76 (m, 1H), 1.67 (m, 1H), 1.52 (m, 1H), 1.48 (s, 9H), 1.33 (m, 1H), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 0.85 (s, 9H); MS (ESI) 566 (MNa^+), 544 (MH^+). Trifluoroacetic acid (1.38 mL) was added dropwise to a solution of **27a** (489 mg, 0.9 mmol) in dry dichloromethane (2 mL). The solution was stirred at room temperature overnight. The solvents were evaporated in vacuo. The residue was taken up in toluene, and the solvent was removed in vacuo (three times). The residue was taken up in Et_2O, triturated, and filtered to give **28a** (440 mg, 100%): ^{1}H NMR (DMSO-d_6 + CD_3CO_2D) 7.48−7.84 (m, 5H), 6.63 (d, 1H, J = 9.52 Hz), 4.51 (dd, 2H), 4.2 (m, 1H), 3.95 (d, 1H, J = 8.8 Hz), 3.62 (s, 3H), 2.9 (m, 1H), 2.53 (d, 3H, J = 5 Hz), 1.5 (m, 1H), 1.4 (m, 1H), 1.05 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.83 (s, 9H), 0.79 (d, 3H, J = 6.6 Hz); MS (ESI) 510 (MNa^+), 488 (MH^+). A solution of **28a** (435 mg, 0.89 mmol) was prepared in DMF (8 mL). HOBT (180 mg, 1.35 mmol) was added, followed by EDCI (256 mg, 1.35 mmol), 2,6-lutidine (207 μL, 1.78 mmol), and *O*-(*tert*-butyldimethylsilyl)-hydroxylamine (180 mg, 1.16 mmol). The resulting solution was stirred at room temperature overnight. The crude reaction mixture was treated with HCl (2 N, 1.5 mL) and purified by C18 preparative HPLC using as eluant a mixture of acetonitrile and water/1% AcOH (gradient from 1/9 to 35/65). Elution yielded **6a** (200 mg, 45% yield) as a white solid: mp = 160−169 °C; ^{1}H NMR (DMSO-d_6) 10.87 (s, 1H), 9.11 (s, 1H), 7.82 (d, 1H, J = 9.5 Hz), 7.8−7.7 (m, 2H), 7.59 (s, 1H), 7.48 (m, 2H), 6.64 (d, 1H, J = 9.1 Hz), 4.51 (d, 1H, J = 11.7 Hz), 4.32 (d, 1H, J = 11.7 Hz), 4.20 (d, 1H, J = 9.1 Hz), 3.80 (d, 1H, J = 9.5 Hz), 3.62 (s, 3H), 2.95 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.49−1.32 (m, 2H), 0.91 (m, 1H), 0.85 (d, 3H, J = 6.2 Hz), 0.81 (s, 9H), 0.79 (d, 3H, J = 6.2 Hz); MS (ESI) 541 (MK^+), 525 (MNa^+). Anal. ($C_{26}H_{38}N_4O_6 \cdot 0.5H_2O$) C H N.

N^2-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methoxysuccinyl]-L-*tert*-leucine-N^1-methylamide (6b). From **26** and 3-bromomethyl-1-methyl-2-oxo-1,2-dihydroquinoline[44] was similarly obtained **27b** (383 mg, 88%) as a gum, **28b** (294 mg, 74%) as a solid, and **6b** (150 mg, 50%) as a white solid. **27b:** ^{1}H NMR ($CDCl_3$) 7.92 (s, 1H), 7.24−7.65 (m, 4H), 6.96 (d, 1H, J = 8.79 Hz), 6.38 (m, 1H), 4.71 (d, 1H, J = 13.56 Hz), 4.61 (d, 1H, J = 13.92 Hz), 4.16 (d, 1H, J = 9.16 Hz), 4.10 (d, 1H, J = 5.13 Hz), 3.74 (s, 3H), 2.83 (m, 1H), 2.77 (d, 3H, J = 4.76 Hz), 1.73 (m, 1H), 1.62 (m, 1H), 1.47 (s, 9H), 1.46 (m, 1H), 0.98 (s, 9H), 0.94 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); MS (ESI) 566 (MNa^+), 544 (MH^+). **28b:** ^{1}H NMR (DMSO-d_6) 7.3−7.92 (m, 7H), 4.37 (dd, 2H), 4.23 (d, 1H, J = 9.16 Hz), 4.03 (d, 1H, J = 8.8 Hz), 3.64 (s, 3H), 2.95 (m, 1H), 2.54 (d, 3H, J = 4.4 Hz), 1.52 (m, 1H), 1.4 (m, 1H), 1.05 (m, 1H), 0.86 (d, 3H, J = 6.6 Hz), 0.85 (s, 9H), 0.81 (d, 3H, J = 6.6 Hz); MS (ESI) 525 (MNa^+), 503 (MH^+). **6b:** mp = 158−161 °C; ^{1}H NMR (DMSO-d_6) 10.96 (s br, 1H), 9.12 (s br, 1H), 7.89 (m, 2H), 7.81 (m, 1H), 7.65−7.55 (m, 3H), 7.33 (m, 1H), 4.38 (d, 1H, J = 15.0 Hz), 4.23 (d, 1H, J = 9.1 Hz), 4.22 (d, 1H, J = 15.0 Hz), 3.87 (d, 1H, J = 9.5 Hz), 3.65 (s, 3H), 3.04 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.48−1.38 (m, 2H), 0.95 (m, 1H), 0.86 (d, 3H, J = 6.6 Hz), 0.85 (s, 9H), 0.80 (d, 3H, J = 6.6 Hz); MS (ESI) 525 (MNa^+), 503 (MH^+). Anal. ($C_{26}H_{38}N_4O_6 \cdot 0.3H_2O$) C H N.

N^2-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(quinolin-8-yl)methoxysuccinyl]-L-*tert*-leucine-N^1-methylamide (6c). From **26** and 8-iodomethylquinoline (prepared by treatment of commercially available 8-bromomethylquinoline with sodium iodide in acetone) was similarly obtained **27c** (540 mg, 79%) as a gum, **28c** (432 mg, 94.5%) as a white solid, and **6c** (280 mg, 65%) as a white solid. **27c:** ^{1}H NMR ($CDCl_3$) 8.91 (m, 1H), 8.18 (m, 1H), 7.4−7.9 (m, 4H), 7.06 (m, 1H), 6.6 (m, 1H), 5.34 (m, 2H), 4.15 (d, 1H, J = 4.03 Hz), 4.05 (d, 1H, J = 9.16 Hz), 2.8 (m, 1H), 2.75 (d, 3H, J = 4.76 Hz), 1.62 (m, 1H), 1.52 (m, 1H), 1.48 (s, 9H), 1.45 (m, 1H), 0.86 (s, 9H), 0.85 (m, 6H); MS (ESI) 536 (MNa^+), 514 (MH^+). **28c**: ^{1}H NMR (DMSO-d_6) 8.91 (m, 1H), 8.45 (m, 1H), 7.52−7.95 (m, 6H), 5.1 (dd, 2H), 4.25 (s br, 1H), 4.17 (d, 1H, J = 9.16 Hz), 4.11 (d, 1H, J = 8.79 Hz), 3.0 (s, 1H), 2.52 (d, 3H, J = 4.4 Hz), 1.55 (m, 1H), 1.4 (m, 1H), 1.1 (m, 1H), 0.85 (d, 3H, J = 6.6 Hz), 0.8 (d, 3H, J = 6.6 Hz), 0.79 (s, 9H); MS (ESI) 480 (MNa^+), 458 (MH^+). **6c**: mp = 118−121 °C; ^{1}H NMR (DMSO-d_6) 11.2 (s br, 1H), 9.1 (s br, 1H), 8.89 (m, 1H), 8.4 (m, 1H), 7.91−7.76 (m, 4H), 7.60−7.53 (m, 2H), 5.14 (d, 1H, J = 13.9 Hz), 4.93 (d, 1H, J = 13.9 Hz), 4.17 (d, 1H, J = 9.2 Hz), 3.97 (d, 1H, J = 9.2 Hz), 3.04 (m, 1H), 2.55 (d, 3H, J = 4.8 Hz), 1.37−1.52 (m, 2H), 1.0 (m, 1H), 0.87 (d, 3H, J = 6.2 Hz), 0.81 (d, 3H, J = 6.2 Hz), 0.80 (s, 9H); MS (ESI) 495 (MNa^+), 473 (MH^+). Anal. ($C_{25}H_{36}N_4O_5 \cdot 0.8H_2O$) C H N.

N^2-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-methoxysuccinyl]-L-*tert*-leucine-N^1-methylamide (6d). From **26** and methyl iodide was similarly obtained **27d** (180 mg, 93%) as a brown foam, **28d** (110 mg, 73%) as a white solid, and **6d** (280 mg, 65%) as a white solid. **27d**: ^{1}H NMR ($CDCl_3$) 6.83 (m, 1H), 6.4 (m, 1H), 4.11 (d, 1H, J = 8.79 Hz), 3.71 (d, 1H, J = 5.5 Hz), 3.43 (s, 3H), 2.78 (d, 3H, J = 4.76 Hz), 2.68 (m, 1H), 1.68 (m, 1H), 1.55 (m, 1H), 1.48 (s, 9H), 1.31 (m, 1H), 1.02 (s, 9H), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz); MS (ESI) 409 (MNa^+). **28d**: ^{1}H NMR (DMSO-d_6) 7.8 (m, 1H), 7.5 (m, 1H), 4.21 (d, 1H, J = 9.52 Hz), 3.62 (d, 1H, J = 8.8 Hz), 3.17 (s, 3H), 2.8 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 1.46 (m, 1H), 1.35 (m, 1H), 0.97 (m, 1H), 0.89 (s, 9H), 0.82 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz); MS (ESI) 353 (MNa^+). **6d**: mp = 127−130 °C; ^{1}H NMR (DMSO-d_6) 10.76 (s br, 1H), 9.01 (m, 1H), 7.78 (m, 1H), 7.71 (d, 1H, J = 9.5 Hz), 4.23 (d, 1H, J = 9.5 Hz), 3.48 (d, 1H, J = 9.9 Hz), 3.11 (s, 3H), 2.84 (m, 1H), 2.57 (d, 3H, J = 4.7 Hz), 1.41−1.31 (m, 2H), 0.92 (m, 1H), 0.92 (s, 9H), 0.83 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz); MS (ESI) 345 ($M^{+\bullet}$). Anal. ($C_{16}H_{31}N_3O_5 \cdot 0.3H_2O$) C H N.

N^2-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)methoxysuccinyl]-L-*tert*-leucine-N^1-methylamide (6e). From **26** and 6-bromomethyl-2-methyl-4-oxo-3,4-dihydroquinazoline,[45] except that 15-crown-5 (1 drop) was also added, was similarly obtained **27e** (530 mg, 57%) as a foam, **28e** (480 mg, 100%), and **6e** (152 mg, 32%) as a white solid. **27e**: ^{1}H NMR ($CDCl_3$) 8.18 (s, 1H), 7.73 (d, 1H, J = 8.43 Hz), 7.63 (d, 1H, J = 8.43 Hz), 6.84 (m, 1H), 6.81 (m, 1H), 4.81 (d, 1H, J = 11.36 Hz), 4.46 (d, 1H, J = 11.35 Hz), 4.28 (d, 1H, J = 9.15 Hz), 3.88 (d, 1H, J = 6.96 Hz), 2.79 (d, 3H, J = 4.77 Hz), 2.75 (m, 1H), 2.33 (s, 3H), 1.6 (m, 1H), 1.52 (s, 9H), 1.5 (m, 1H), 1.25 (m, 1H), 0.96 (s, 9H), 0.89 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz); MS (EI): 545 (MH^+). **28e**:

^{1}H NMR (DMSO-d_6) 8.01 (d, 1H, J = 1.84 Hz), 7.77−7.7 (m, 3H), 7.53 (d, 1H, J = 8.42 Hz), 4.53 (dd, 2H), 4.17 (d, 1H, J = 9.16 Hz), 3.94 (d, 1H, J = 9.16 Hz), 2.95 (m, 1H), 2.53 (d, 3H, J = 4.39 Hz), 2.4 (s, 3H), 1.5 (m, 1H), 1.4 (m, 1H), 1.02 (m, 1H), 0.83 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz), 0.78 (s, 9H); MS (ESI) 511 (MNa^+), 489 (MH^+). **6e**: mp = 180−187 °C; ^{1}H NMR (DMSO-d_6) 12.16 (br, 1H), 10.91 (s br, 1H), 9.12 (s br, 1H), 7.96 (d, 1H, J = 1.47 Hz), 7.74−7.68 (m, 2H), 7.63 (dd, 1H, J = 8.4 Hz, J' = 1.8 Hz), 7.49 (d, 1H, J = 8.4 Hz), 4.5 (d, 1H, J = 11.7 Hz), 4.34 (d, 1H, J = 11.7 Hz), 4.16 (d, 1H, J = 9.1 Hz), 3.81 (d, 1H, J = 9.5 Hz), 2.97 (m, 1H), 2.56 (d, 3H, J = 4.4 Hz), 2.35 (s, 3H), 1.45−1.3 (m, 2H), 0.89 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz), 0.76 (s, 9H); MS (ESI) 526 (MNa^+).

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(7-bromo-2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6f).** From **26** and 7-bromo-6-bromomethyl-2-methyl-4-oxo-3,4-dihydroquinazoline[46] was similarly obtained **27f** (500 mg, 64%) as a foam, **28f** (387 mg, 85%) as a white solid, and **6f** (140 mg, 40%) as a white powder. **27f**: ^{1}H NMR ($CDCl_3$) 8.24 (s, 1H), 7.89 (s, 1H), 6.89 (m, 1H), 6.84 (m, 1H), 4.86 (d, 1H, J = 11.73 Hz), 4.64 (d, 1H, J = 11.72 Hz), 4.26 (d, 1H, J = 8.79 Hz), 3.94 (d, 1H, J = 6.59 Hz), 2.8 (m, 1H), 2.78 (d, 3H, J = 4.76 Hz), 2.38 (s, 3H), 1.63 (m, 1H), 1.52 (s, 9H), 1.48 (m, 1H), 1.33 (m, 1H), 0.94 (s, 9H), 0.88 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz); MS (ESI) 647 (M-{^{81}Br}Na^+), 645 (M{^{79}Br}Na^+). **28f**: ^{1}H NMR (DMSO-d_6) 8.17 (s, 1H), 7.81 (m, 1H), 7.79 (s, 1H), 7.74 (m, 1H), 4.62 (d, 1H, J = 12.82 Hz), 4.52 (d, 1H, J = 12.82 Hz), 4.14 (d, 1H, J = 9.16 Hz), 4.03 (d, 1H, J = 8.79 Hz), 2.99 (m, 1H), 2.53 (d, 3H, J = 4.4 Hz), 1.5 (m, 1H), 1.4 (m, 1H), 1.05 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz), 0.76 (s, 9H); MS (ESI) 567 (M{^{79}Br}H^+), 569 (M{^{81}Br}H^+). **6f**: mp = 184−188 °C; ^{1}H NMR (DMSO-d_6) 12.3 (s br, 1H), 11.0 (s br, 1H), 9.15 (s br, 1H), 8.17 (s, 1H), 7.83 (d, 1H, J = 9.15 Hz), 7.78 (s, 1H), 7.7 (m, 1H), 4.53 (d, 1H, J = 13.2 Hz), 4.44 (d, 1H, J = 12.8 Hz), 4.14 (d, 1H, J = 9.5 Hz), 3.9 (d, 1H, J = 9.9 Hz), 3.12 (m, 1H), 2.55 (d, 3H, J = 4.4 Hz), 2.35 (s, 3H), 1.45−1.32 (m, 2H), 0.9 (m, 1H), 0.86 (d, 3H, J = 6.6 Hz), 0.8 (d, 3H, J = 6.6 Hz), 0.72 (s, 9H); MS (ESI) 584 (M{^{81}Br}H^+), 582 (M{^{79}Br}H^+). Anal. ($C_{25}H_{36}BrN_5O_6\cdot 0.55H_2O$) C H N.

***N*^{2}-[4-(*N*-2,4-Dimethoxybenzyloxyamino)-3*S*-hydroxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (30).** HOBT (512 mg, 3.8 mmol) was added to a solution of **29**[25] (800 mg, 2.5 mmol) in DMF (20 mL), followed by EDCI (725 mg, 3.8 mmol), 2,6-lutidine (55 μL, 0.5 mmol), and *O*-(2,4-dimethoxybenzyl)hydroxylamine[21] (420 mg, 2.78 mmol). The resulting solution was stirred at room temperature overnight. The crude reaction mixture was diluted with EtOAc, and washed with water, 2% $NaHCO_3$, and brine. Purification on silica gel (eluant MeCN/CH_2Cl_2 from 40:60 to 55:45) afforded **30** (710 mg, 60%): ^{1}H NMR ($CDCl_3$) 9.4 (s, 1H), 7.17 (m, 1H), 6.68 (m, 1H), 6.48−6.45 (m, 2H), 5.69 (m, 1H), 5.01 (m, 1H), 4.92 (m, 2H), 4.1 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.06 (m, 1H), 2.81 (d, 3H, J = 4.8 Hz), 1.8−1.5 (m, 3H), 0.98 (s, 9H), 0.94 (d, 3H, J = 6.2 Hz), 0.90 (d, 3H, J = 6.2 Hz); MS (ESI) 504 (MNa^+), 482 (MH^+).

Preparation of 6g and 6j from 30. *N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(naphthalen-1-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6g). Sodium hydride (63 mg, 60% in oil, 1.6 mmol) was added to a solution of **30** (350 mg, 0.72 mmol) in THF (20 mL), followed 5 min later by 1-(bromomethyl)naphthalene (176 mg, 0.8 mmol), 15-crown-5 (1 drop), and sodium iodide (108 mg, 0.72 mmol). The resulting mixture was stirred at room temperature for 2 h. The mixture was treated with a saturated solution of NH_4Cl, the pH reduced to 3−4 with 2 N HCl, and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using MeCN/CH_2Cl_2 (gradient from 20:80 to 60:40) as eluant to give a foam (373 mg, 83%): MS (ESI) 644 (MNa^+), 622 (MH^+). This intermediate was immediately dissolved in CH_2Cl_2, and a 10% solution of TFA in CH_2Cl_2 (10 mL) was added dropwise at 3−4 °C. The solution was stirred at room temperature for 35 min. The solvents were evaporated in vacuo. The residue was taken up in toluene, and the solvent was removed in vacuo (three times). The residue was passed through a short column of C18 using MeOH as eluant, the MeOH evaporated, and the residue was triturated with Et_2O and filtered to give **6g** (191 mg, 68%) as a white solid: mp = 128−132 °C; ^{1}H NMR (DMSO-d_6) 10.96 (s, 1H), 9.16 (s, 1H), 8.0−7.4 (m, 9H), 4.88 (d, 1H), 4.62 (d, 1H), 4.06 (d, 1H, J = 9.2 Hz), 3.91 (d, 1H, J = 9.5 Hz), 2.95 (m, 1H), 2.5 (d, 3H, J = 4.4 Hz), 1.34−1.47 (m, 2H), 0.9 (m, 1H), 0.82 (d, 3H, J = 6.6 Hz), 0.77 (d, 3H, J = 6.6 Hz), 0.6 (s, 9H); MS (ESI) 494 (MNa^+), 472 (MH^+).

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(naphthalen-2-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6j).** From **30** and 2-(bromomethyl)naphthalene was similarly obtained **6j** (94 mg, 86%) as a white solid: mp = 148−152 °C; ^{1}H NMR (DMSO-d_6) 10.88 (s, 1H), 9.1 (s, 1H), 7.9−7.4 (m, 9H), 4.59 (d, 1H), 4.41 (d, 1H), 4.19 (d, 1H, J = 9.5 Hz), 3.85 (d, 1H, J = 9.5 Hz), 2.98 (m, 1H), 2.54 (d, 3H, J = 4.8 Hz), 1.45−1.34 (m, 2H), 0.9 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.8 (s, 9H), 0.78 (d, 3H, J = 6.6 Hz); MS (ESI) 494 (MNa^+), 472 (MH^+).

***N*^{2}-[4-(*N*-2,4-Dimethoxybenzyloxy-*N*-2,4,6-trimethoxybenzylamino)-3*S*-hydroxy-2*R*-isobutylsuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (31).** HOBT (5.1 g, 37.9 mmol) was added to a solution of **29** (8.0 g, 25.3 mmol) in DMF (150 mL), followed by EDCI (7.2 g, 37.9 mmol), 2,6-lutidine (588 μL, 5 mmol), and *O*-2,4-dimethoxybenzyl-*N*-2,4,6-trimethoxybenzyl hydroxylamine[21] (10.1 g, 27.8 mmol). The resulting solution was stirred at room temperature overnight. The crude reaction mixture was concentrated and partitioned between water and EtOAc. The combined organic extracts were washed with HCl (1 N) and brine, dried over $MgSO_4$, and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using acetonitrile−dichloromethane (2/3) as eluant to give **31** (8.8 g, 53% yield) as a white solid: ^{1}H NMR ($CDCl_3$) 7.0−6.85 (m, 3H), 6.4 (m, 2H), 6.14 (s, 2H), 5.14 (d, 1H, J = 14.2 Hz), 4.89 (d, 1H, J = 13.9 Hz), 4.81 (m, 2H), 4.52 (m, 1H), 4.12 (d, 1H, J = 8.4 Hz), 3.83 (s, 3H), 3.79 (s, 6H), 3.76 (s, 6H), 3.37 (d, 1H, J = 4.0 Hz), 2.79 (d, 3H, J = 4.8 Hz), 2.69 (m, 1H), 1.64−1.37 (m, 3H), 1.04 (s, 9H), 0.81 (d, 3H, J = 6.2 Hz), 0.7 (d, 3H, J = 6.2 Hz).

Preparation of 6h, 6i, and 6k from 31. *N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(coumarin-6-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6h). Sodium hydride (18 mg, 60% in oil, 0.43 mmol) was added to a solution of **31** (250 mg, 0.37 mmol) in THF (8 mL), followed 5 min later by 2-(bromomethyl)coumarin (99 mg, 0.41 mmol) and 15-crown-5 (1 drop). The resulting mixture was stirred at room temperature for 3 h. The mixture was treated with a saturated solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, and filtered, and the solvents were removed. The residue was purified by flash chromatography on silica using MeCN/CH_2Cl_2 (gradient from 20:80 to 60:40) as eluant to give a foam (248 mg, 84%): MS (ESI) 842 (MNa^+), 820 (MH^+). This intermediate was immediately dissolved in the minimum CH_2Cl_2, and a 10% solution of TFA in CH_2Cl_2 (12 mL) was added dropwise at 3−4 °C. The solution was stirred at room temperature for 2 h, toluene was added, and the solvent was removed in vacuo (three times). The residue was passed through a short column of C18 using MeOH/water (70:30) as eluant, the solvent evaporated, and the residue was triturated with Et_2O and filtered to give **6h** (103 mg, 73%): ^{1}H NMR (DMSO-d_6) 10.86 (s, 1H), 9.1 (s, 1H), 7.98 (d, 1H, J = 9.5 Hz), 7.76−7.7 (m, 2H), 7.57 (s, 1H), 7.48 (d, 1H, J = 8.4 Hz), 7.4 (d, 1H, J = 8.4 Hz), 6.51 (d, 1H, J = 9.5 Hz), 4.47 (d, 1H), 4.29 (d, 1H), 4.17 (d, 1H, J = 9.5 Hz), 3.79 (d, 1H, J = 9.9 Hz), 2.94 (m, 1H), 2.54 (d, 3H, J = 4.4 Hz), 1.43−1.35 (m, 2H), 0.9 (m, 1H), 0.83 (d, 3H, J = 6.6 Hz), 0.78 (s, 9H), 0.77 (d, 3H, J = 6.6 Hz); MS (ESI) 512 (MNa^+), 490 (MH^+).

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(quinoxalin-5-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6i).** From **31** and 5-bromomethylquinoxaline[47] was similarly ob-

tained **6i** (82 mg, 43%) as a white solid: mp = 170−174 °C; ^{1}H NMR (DMSO-d_6) 10.98 (s, 1H), 9.12 (s, 1H), 8.97 (d, 1H, *J* = 1.8 Hz), 8.92 (d, 1H, *J* = 1.8 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 7.9 (d, 1H, *J* = 7.3 Hz), 7.81−7.75 (m, 3H), 5.1 (d, 1H), 4.96 (d, 1H), 4.14 (d, 1H, *J* = 9.5 Hz), 3.94 (d, 1H, *J* = 9.9 Hz), 3.03 (m, 1H), 2.53 (d, 3H, *J* = 4.4 Hz), 1.5−1.35 (m, 2H), 0.93 (m, 1H), 0.85 (d, 3H, *J* = 6.2 Hz), 0.79 (d, 3H, *J* = 6.2 Hz), 0.75 (s, 9H); MS (ESI) 496 (MNa^+), 474 (MH^+). Anal. ($C_{24}H_{35}N_5O_5 \cdot 0.6H_2O$) C H N.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-isobutyl-3*S*-(2-methylbenzothiazol-5-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6k).** From **31** and 5-bromomethyl-2-methylbenzothiazole[48] was similarly obtained **6k** (110 mg, 40%) as a white solid: mp = 133−136 °C; ^{1}H NMR (DMSO-d_6) 10.86 (s, 1H), 9.1 (s, 1H), 7.93 (d, 1H, *J* = 8.1 Hz), 7.65−7.8 (m, 3H), 7.27 (d, 1H, *J* = 8.4 Hz), 4.55 (d, 1H), 4.37 (d, 1H), 4.18 (d, 1H, *J* = 9.2 Hz), 3.8 (d, 1H, *J* = 9.5 Hz), 2.95 (m, 1H), 2.79 (s, 3H), 2.54 (d, 3H, *J* = 4.4 Hz), 1.5−1.35 (m, 2H), 0.88 (m, 1H), 0.83 (d, 3H, *J* = 6.6 Hz), 0.8 (s, 9H), 0.77 (d, 3H, *J* = 6.6 Hz); MS (ESI) 515 (MNa^+), 493 (MH^+). Anal. ($C_{24}H_{36}N_4O_5S \cdot 1.2H_2O$) C H N S.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-(4-benzyloxy)butyl-3*S*-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6l).** In a manner analogous to that described for examples **6a**−**f**, from **32** and 6-bromomethyl-1-methyl-2-oxo-1,2-dihydroquinoline[43] was obtained **6l** (145 mg, 47%) as a white solid: mp = 188−190 °C; ^{1}H NMR ($CDCl_3$) 9.6 (s br, 2H), 7.69 (d, 1H, *J* = 1.5 Hz), 7.65 (d, 1H, *J* = 9.5 Hz), 7.61 (dd, 1H, *J* = 8.4 Hz, *J*′ = 1.8 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 7.38−7.25 (m, 6H), 7.0−6.95 (m, 1H), 6.72 (d, 1H, *J* = 9.5 Hz), 4.96 (d, 1H, *J* = 11.0 Hz), 4.5 (d, 1H, *J* = 11.0 Hz), 4.45 (d, 2H, *J* = 1.5 Hz), 4.1 (d, 1H, *J* = 3.3 Hz), 3.94 (d, 1H, *J* = 9.2 Hz), 3.7 (s, 3H), 3.41 (t, 2H, *J* = 6.23 Hz), 3.05−3.1 (m, 1H), 2.89 (d, 3H, *J* = 4.39 Hz), 1.8−1.5 (m, 4H), 1.45−1.39 (m, 2H), 0.86 (s, 9H); MS (ESI) 631 (MNa^+), 609 (MH^+). Anal. ($C_{33}H_{44}N_4O_7 \cdot 1.1H_2O$) C H N.

***N*^{2}-[4-(*N*-Hydroxyamino)-2*R*-(3-benzyloxy)propyl-3*S*-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)methoxysuccinyl]-L-*tert*-leucine-*N*^{1}-methylamide (6m).** From **33** and 6-bromomethyl-2-methyl-4-oxo-3,4-dihydroquinazoline[45] was similarly obtained **6m** (430 mg, 41%) as a white solid: mp = 189−194 °C; ^{1}H NMR (DMSO-d_6) 14.2 (s, 1H), 10.9 (s, 1H), 9.1 (s, 1H), 7.93 (s, 1H), 7.79 (m, 2H), 7.61 (d, 1H, *J* = 8.1 Hz), 7.47 (d, 1H, *J* = 8.4 Hz), 7.36−7.25 (m, 5H), 4.5 (d, 1H), 4.40 (s, 2H), 4.34 (d, 1H), 4.17 (d, 1H, *J* = 9.2 Hz), 3.86 (d, 1H, *J* = 9.9 Hz), 3.32 (m, 2H), 2.93 (m, 1H), 2.53 (d, 3H, *J* = 4.4 Hz), 2.33 (s, 3H), 1.5−1.2 (m, 4H), 0.77 (s, 9H); MS (ESI) 618 (MNa^+), 596 (MH^+). Anal. ($C_{31}H_{41}N_5O_7 \cdot 1.2H_2O$) C H N.

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