Novel Sulfonamide Derivatives as Inhibitors of Histone Deacetylase

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

Inhibition of the enzyme histone deacetylase (HDAC) is emerging as a novel approach to the treatment of cancer. A series of novel sulfonamide derivatives were synthesized and evaluated for their ability to inhibit human HDAC. Compounds were identified which are potent enzyme inhibitors, with IC_{50} values in the low nanomolar range against enzyme obtained from HeLa cell extracts, and with antiproliferative effects in cell culture. Extensive characterization of the structure–activity relationships of this series identified key requirements for activity. These include the direction of the sulfonamide bond and substitution patterns on the central phenyl ring. The alkyl spacer between the aromatic head group and the sulfonamide functionality also influenced the HDAC inhibitory activity. One of these compounds, ***m*11.1**, also designated PXD101, has entered clinical trials for solid tumors and haematological malignancies.

1. Introduction. – DNA in eukaryotic cells is tightly complexed with histone proteins to form chromatin. Histones are small proteins which are rich in basic amino acids. They are positively charged at physiological pH and contact the negatively charged phosphate groups of DNA. There are five main classes of histones: H1, H2A, H2B, H3, and H4. The amino acid sequences show remarkable conservation between species, with H1 varying somewhat, and in some cases being replaced by another histone, *e.g.*, H5. Four pairs of each of H2A, H2B, H3, and H4 together form a disk-shaped octomeric protein core, around which DNA (*ca.* 140 base pairs) is wound to form a nucleosome. Individual nucleosomes are connected by short stretches of linker DNA associated with another histone molecule (*e.g.*, H1, or in certain cases, H5) to form a structure resembling a beaded string, which is itself arranged in a helical stack, known as a solenoid. Within minutes of its synthesis, new DNA becomes associated with histones in nucleosomal structures.

Histones undergo a variety of post-translational modifications: in particular methylation, acetylation, or phosphorylation. These modifications predominantly occur in the N-terminal sequences of histones which extend from the nucleosomal core, and affect chromatin structure and gene expression [1].

Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation and/or differentiation, and the correlation between the

acetylation status of histones and the transcription of genes has been known for over 30 years [2]. The enzymes that catalyze and regulate the acetylation state of histones are the histone acetyltransferases (HATs) and deacetylases (HDACs). They have been identified in many organisms and have been implicated in the regulation of numerous genes, confirming the link between acetylation and transcription [3]. In general, histone acetylation correlates with transcriptional activation, whereas histone deacetylation is associated with gene repression. HDACs function as part of large multiprotein complexes, which are tethered to the promoter and repress transcription. Well-characterized transcriptional repressors such as Mad [4], pRb [5], nuclear receptors [6], and YY1 [7] associate with HDAC complexes to exert their repressor function. Interestingly, the regulation of the function of transcription factors is also mediated through acetylation. Further background on histone deacetylation can be found in recent reviews [8][9].

The study of inhibitors of histone deacetylases also indicates that these enzymes play an important role in cell proliferation and differentiation. The natural product inhibitor trichostatin A (TSA; **1**) [10] (see *Figure*) causes cell-cycle arrest at both the G1 and G2 phases of the cell cycle [11], reverts the transformed phenotype of different cell lines, and induces differentiation of *Friend* leukaemia cells and others [12]. TSA and the synthetic suberoylanilide hydroxamic acid (SAHA = *N*-hydroxy-*N*′-phenyl-octanediamide; **2**) have been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice [13][14]. Other synthetic HDAC inhibitors such as LAQ-824 (**3**) have also been reported as possessing antitumor activity in animal models [15]. Whilst many of the small-molecule HDAC inhibitors reported are hydroxamic acids (= *N*-hydroxyamides), other chemical classes have been reported, such as MS-275 (**4**), an example of the benzamide-class of inhibitor [16].

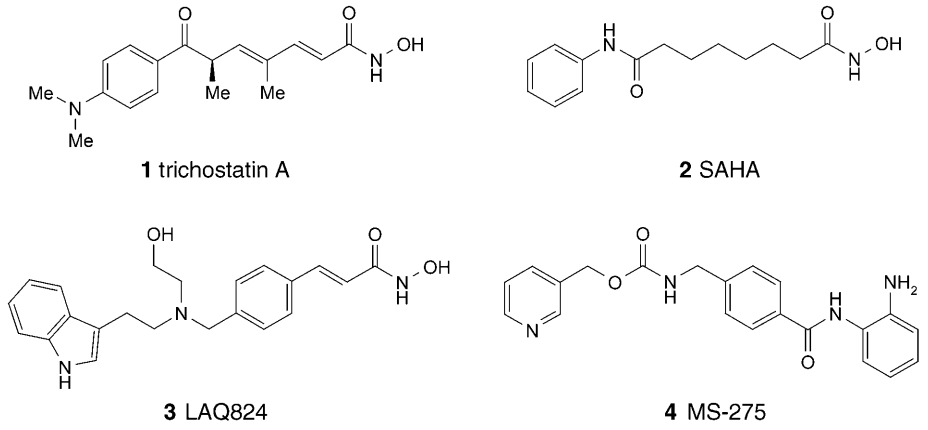


Figure. *Natural product and synthetic inhibitors of histone deacetylase* (HDAC)

Cell-cycle arrest by TSA correlates with increased expression of gelsolin [17], an actin-regulatory protein that is down-regulated in malignant breast cancer [18]. Similar effects on cell cycle and differentiation have been observed with a number of

deacetylase inhibitors [19]. Trichostatin A has also been reported to be useful in the treatment of fibrosis, *e.g.*, liver fibrosis and liver cirrhosis [20].

The modulation of HDAC enzyme activity, therefore, represents a novel approach for intervening in cell-cycle regulation, with potential therapeutic application in cancer and other proliferative diseases [21].

The classical pharmacophoric description of small-molecule HDAC inhibitors consists of three linearly connected groups, A–B–C. A represents an aryl group which provides potency and selectivity; B is a predominantly hydrophobic linking group, and C represents a moiety which interacts with the catalytic Zn-atom at the HDAC active site. This general arrangement can be clearly seen in compounds **1**–**3**.

We decided to base our design on the structures of hydroxamic acid containing inhibitors of histone-deacetylase known at the initiation of this work, particularly TSA. We designed templates which we believed would contain the appropriate motifs to provide potent enzyme inhibition whilst simultaneously being compatible with drug development. In this work, we describe the design, characterization, and structure–activity relationships of one of these templates, a series of novel sulfonamide derivatives, as histone-deacetylase inhibitors. One of these, PXD101, compound *m***11.1**, is currently under clinical investigation in cancer against both solid tumors and haematological disease.

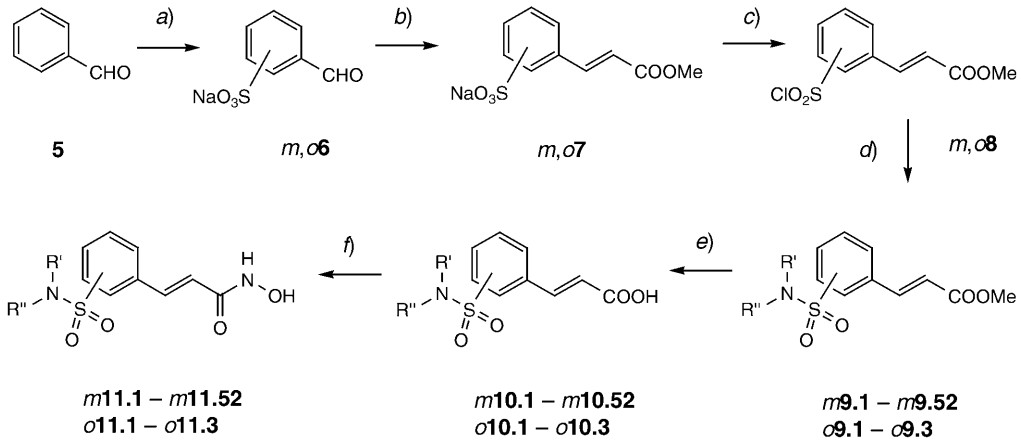
2. Syntheses. – The general synthetic strategies shown in *Schemes 1*–*9* were employed for the preparation of sulfonamide derivatives as HDAC inhibitors. One of the structural features that emerged as of most interest was the direction of attachment of the linking sulfonamide moiety. When present in the structure in such a way that the N-atom of the sulfonamide is nearer to the hydroxamic acid moiety, we designate this as the 'forward' sulfonamide direction. When the linkage is in the opposite direction, we designate it as 'reverse'.

The 'reverse' arylsulfonamides ($NHSO_2$ linkage direction) **11** with *ortho* or *meta* substitutions were prepared by sulfonylation of benzaldehyde (**5**) with oleum followed by coupling of the obtained 3-formyl derivative *m***6** with methyl(dimethoxyphosphinyl)acetate to give an intermediate *m***7** (*Scheme 1*). Similarly, commercial *o***6** was converted to *o***7**. Sulfonyl chlorides *m,o***8** were obtained by reacting *m,o***7** with excess of $SOCl_2$. Compounds *m***10.1**–*m***10.52** and *o***10.1**–*o***10.3** were prepared by coupling appropriately substituted aromatic amines with appropriate *m,o***8** followed by basic hydrolysis. The desired 'reverse' sulfonamides *m***11.1**–*m***11.52** and *o***11.1**–*o***11.3** were obtained *via* the corresponding acid chlorides by treating compounds **10** with oxalyl chloride followed by excess of hydroxylamine.

The 'reverse' sulfonamides **15** with *para* substitution were prepared from cinnamic acid (**12**) by chlorosulfonylation to yield the *para* derivative **13** (*Scheme 2*). Sulfonamides **14.1**–**14.7** were obtained by condensing **13** with appropriately substituted aromatic amines. The desired hydroxamic acids **15.1**–**15.7** were obtained *via* acid chlorides as in *Scheme 1*.

The 'forward' sulfonamides (SO_2NH linkage direction) **20** were prepared from nitro-substituted cinnamyl esters *m,p***16** by reaction with $SnCl_2$ and then with substituted aromatic sulfonyl chlorides in dioxane (*Scheme 3*). Subsequent ester hydrolysis gave compounds *m***19.1**–*m***19.6** and *p***19.2**–*p***19.4**. The corresponding

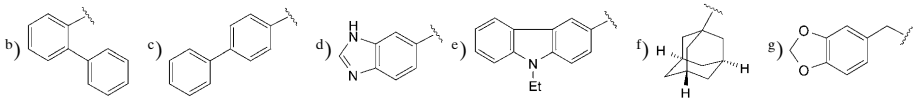
Scheme 1



m = *meta* substitution; *o* = *ortho* substitution

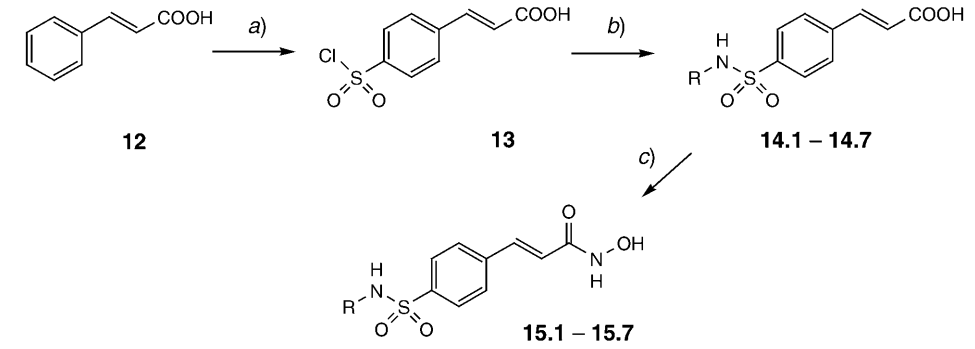
	R′[a])	R″[a])		R′[a])	R″[a])
***m*11.1**	Ph	H	***m*11.29**	$PhCH_2$	H
***m*11.2**	4-Me–C_6H_4	H	***m*11.30**	(1,3-benzodioxol-5-yl)CH_2[g])	H
***m*11.3**	4-Br–C_6H_4	H	***m*11.31**	(pyridin-3-yl)CH_2	H
***m*11.4**	4-Cl–C_6H_4	H	***m*11.32**	(3,4,5-trimethoxyphenyl)CH_2	H
***m*11.5**	2-MeO–C_6H_4	H	***m*11.33**	(naphthalen-2-yl)CH_2	H
***m*11.6**	3-MeO–C_6H_4	H	***m*11.34**	(3,5-dimethoxyphenyl)CH_2	H
***m*11.7**	3-Br–C_6H_4	H	***m*11.35**	(furan-2-yl)CH_2	H
***m*11.8**	4-CF_3O–C_6H_4	H	***m*11.36**	$PhCH_2CH_2$	H
***m*11.9**	2-F–C_6H_4	H	***m*11.37**	(3,4-dimethoxyphenyl)CH_2CH_2	H
***m*11.10**	3-F–C_6H_4	H	***m*11.38**	$PhCH_2CH_2CH_2$	H
***m*11.11**	4-CHF_2O–C_6H_4	H	***m*11.39**	$PhOCH_2CH_2$	H
***m*11.12**	2,6-difluorophenyl	H	***m*11.40**	$PhCH_2CH_2CH_2CH_2$	H
***m*11.13**	2-methoxy-5-(trifluoromethyl)phenyl	H	***m*11.41**	Ph_2CH	H
***m*11.14**	4-CF_3–C_6H_4	H	***m*11.42**	$PhCH_2CH$(Ph)	H
***m*11.15**	3-CF_3S–C_6H_4	H	***m*11.43**	$PhCH_2CH$(Et)	H
***m*11.16**	4-CF_3S–C_6H_4	H	***m*11.44**	PhCH(OH)CH_2	H
***m*11.17**	2,6-dimethylphenyl	H	***m*11.45**	$Ph_2CHCH_2CH_2$	H
***m*11.18**	3,5-difluorophenyl	H	***m*11.46**	Ph	Me
***m*11.19**	3,5-bis(trifluoromethyl)phenyl	H	***m*11.47**	Ph	Me_2CHCH_2
***m*11.20**	4-MeO–C_6H_4	H	***m*11.48**	$PhCH_2$	(pyridin-3-yl)CH_2
***m*11.21**	3,4-dimethoxyphenyl	H	***m*11.49**	(pyridin-3-yl)CH_2	(1,3-benzodioxol-5-yl)CH_2[g])
***m*11.22**	naphthalen-1-yl	H	***m*11.50**	(3,4-dimethoxyphenyl)CH_2CH_2	4-MeO–$C_6H_4CH_2$
***m*11.23**	naphthalen-2-yl	H	***m*11.51**	$PhCH_2CH_2CH_2$	(3,4-dimethoxyphenyl)CH_2CH_2
***m*11.24**	[1,1′-biphenyl]-2-yl[b])	H	***m*11.52**	$PhCH_2CH_2CH_2$	$PhCH_2CH_2CH_2$
***m*11.25**	[1,1′-biphenyl]-4-yl[c])	H	***o*11.1**	Ph	H
***m*11.26**	1*H*-benzimidazol-6-yl[d])	H	***o*11.2**	naphthalen-2-yl	H
***m*11.27**	9-ethyl-9*H*-carbazol-3-yl[e])	H	***o*11.3**	Ph	Me
***m*11.28**	adamantan-1-yl[f])	H			

[a]) The same substituents R′ and R″ are applicable to the corresponding intermediates.



a) Oleum; 51%. *b*) $(MeO)_2P(O)CH_2COOMe$, K_2CO_3, H_2O. *c*) $SOCl_2$, cat. DMF, benzene. *d*) R′R″NH, dioxane, aq. $NaHCO_3$ soln. *e*) aq. NaOH soln., MeOH. *f*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. $NH_2OH \cdot HCl$, THF, aq. $NaHCO_3$ soln.

Scheme 2

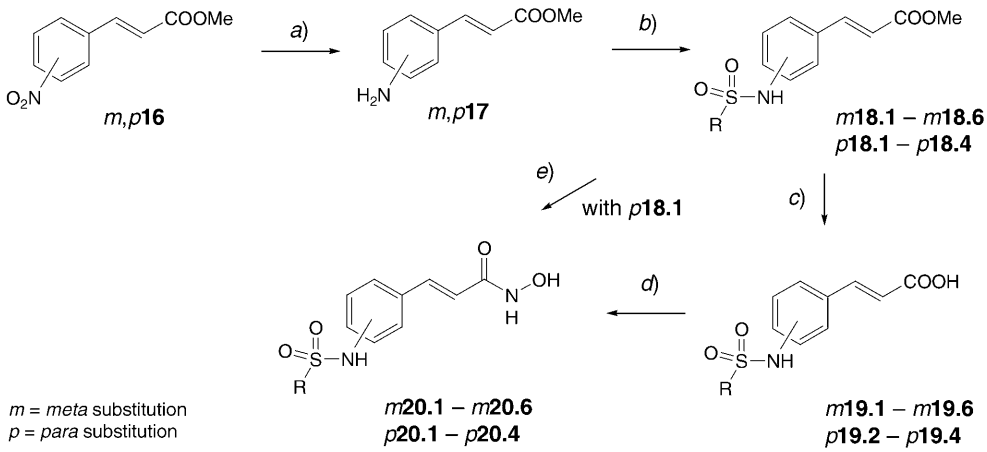


	R[a])		R[a])		R[a])
15.1	Ph	**15.4**	[1,1′-biphenyl]-4-yl[b])	**15.6**	9-ethyl-9*H*-carbazol-3-yl[c])
15.2	4-Br–C_6H_4	**15.5**	naphthalen-2-yl	**15.7**	$PhCH_2$
15.3	4-Cl–C_6H_4				

[a]) The same substituent R is applicable to the corresponding intermediates. [b]) See *Footnote c* in *Scheme 1*. [c]) See *Footnote e* in *Scheme 1*.

a) HSO_3Cl; 34%. *b*) RNH_2, CH_2Cl_2, pyridine. *c*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. $NH_2OH \cdot HCl$, THF, aq. $NaHCO_3$ soln.

Scheme 3



	R[a])		R[a])		R[a])
***m*20.1**	Ph	***m*20.5**	$PhCH_2$	***p*20.2**	[1,1′-biphenyl]-4-yl[b])
***m*20.2**	4-Me–C_6H_4	***m*20.6**	(*E*)-PhCH=CH	***p*20.3**	3,4-dimethoxyphenyl
***m*20.3**	3,4-dimethoxyphenyl	***p*20.1**	Ph	***p*20.4**	(*E*)-PhCH=CH
***m*20.4**	[1,1′-biphenyl]-4-yl[b])				

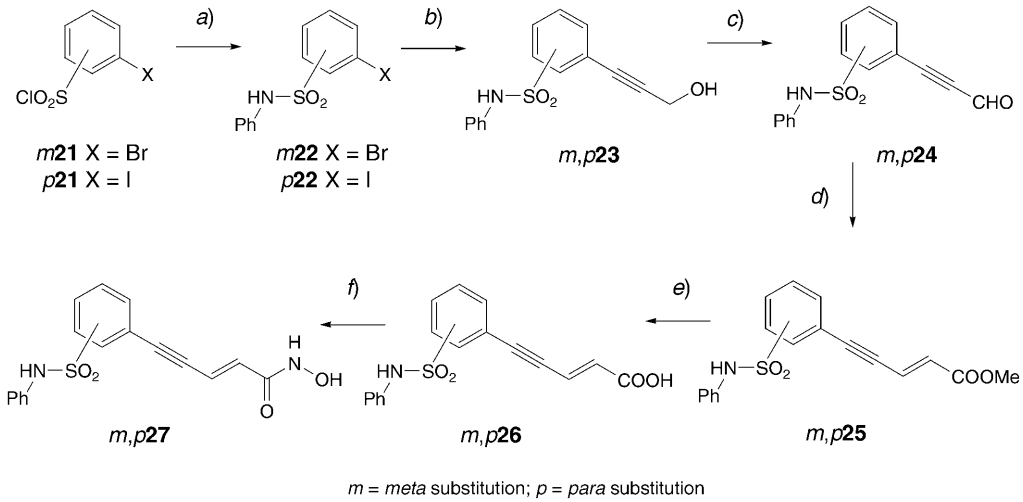
[a]) The same substituent R is applicable to the corresponding intermediates. [b]) See *Footnote c* in *Scheme 1*.

a) $SnCl_2$, EtOH, 80°. *b*) RSO_2Cl, dioxane, aq. $NaHCO_3$ soln. *c*) aq. NaOH soln., MeOH. *d*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. $NH_2OH \cdot HCl$, THF, aq. $NaHCO_3$ soln. *e*) $NH_2OH \cdot HCl$, MeOH, THF, H_2O, KOH.

sulfonamides **20** were obtained by treating compounds **19** with oxalyl chloride followed by hydroxylamine, except for *p***20.1**, which was directly prepared from ester *p***18.1** with hydroxylamine in the presence of base.

The alkyne analogues *m,p***27** of 'reverse' sulfonamides were prepared from appropriately substituted halobenzenesulfonyl chlorides *m,p***21** by condensation with aniline (→ *m,p***22**) and subsequent Pd/Cu-catalyzed coupling with propargyl alcohol (= prop-2-yn-1-ol) to yield *m,p***23** (*Scheme 4*). The primary alcohols *m,p***23** were oxidized to aldehydes *m,p***24** by a *Dess–Martin* periodinane protocol. Unsaturated esters *m,p***25** were prepared by treating *m,p***24** with methyl(dimethoxyphosphinyl) acetate. The hydroxamic acids *m,p***27** were obtained by hydrolysis of *m,p***25** and subsequent treatment of the acids *m,p***26** with oxalyl chloride followed by hydroxylamine.

Scheme 4

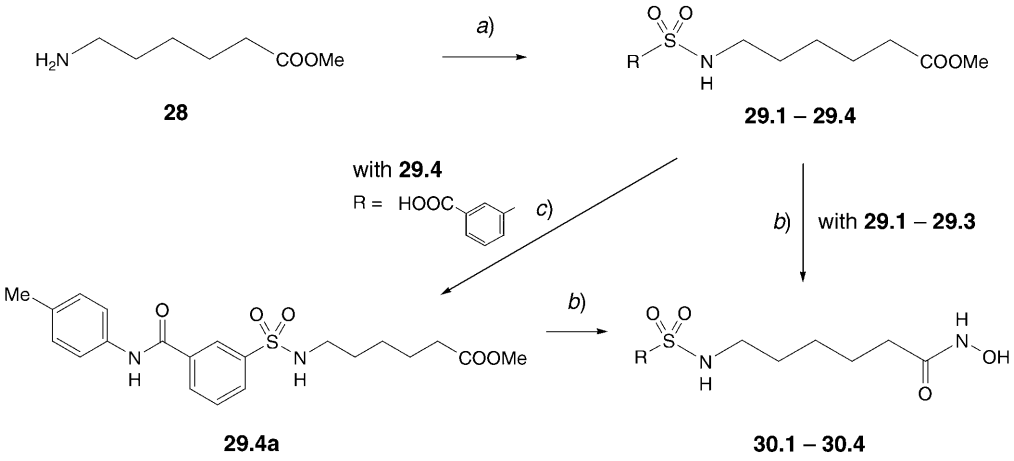


a) $PhNH_2$, MeCN, Na_2CO_3. *b*) $HC{\equiv}CCH_2OH$, $[Pd(Ph_3P)_4]$, CuI, Et_3N, benzene, reflux. *c*) *Dess–Martin* protocol, CH_2Cl_2. *d*) $(MeO)_2P(O)CH_2COOMe$, NaH, THF. *e*) aq. NaOH soln., MeOH. *f*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. $NH_2OH \cdot HCl$, THF, aq. $NaHCO_3$ soln.

The 'forward' sulfonamides **30** containing an aliphatic linkage between the sulfonamide and hydroxamic acid fragments were synthesized from methyl 6-aminohexanoate (**28**) by condensation with the appropriate sulfonyl chloride (→ **29**) and the sodium methoxide/hydroxylamine procedure (→ hydroxamic acids **30.1**–**30.4**; *Scheme 5*). The COOH-containing intermediate **29.4** was converted to the arylamide intermediate **29.4a** before conversion to the hydroxamic acid **30.4**.

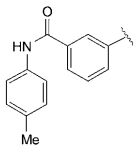
The 'reversed' sulfonamides containing an aliphatic linkage between the sulfonamide and hydroxamic acid fragments were synthesized from appropriate ω-bromocarboxylates **31** *via* the sodium sulfonates **32** which were treated with PCl_5 followed by the appropriate aromatic amine (*Scheme 6*). The obtained esters **33.1**–**33.6** were converted to the hydroxamic acids **34.1**–**34.6** by the sodium methoxide/hydroxylamine procedure.

Scheme 5



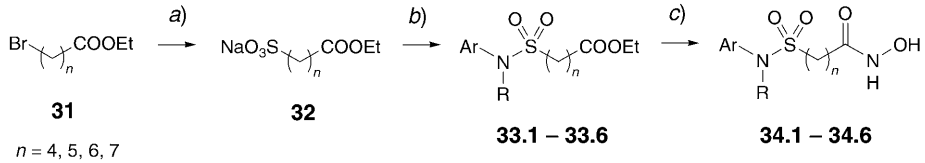
	R[a])		R[a])		R[a])
30.1	Ph	**30.3**	(*E*)-PhCH=CH	**30.4**	3-{[(4-methylphenyl)amino]carbonyl}phenyl[b])
30.2	$MeSO_2-C_6H_4$				

[a]) The same substituent R is applicable to the corresponding intermediates, except for **29.4**. [b])



a) RSO_2Cl, MeCN, Na_2CO_3. *b*) $NH_2OH \cdot HCl$, MeONa, MeOH. *c*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. 4-methylaniline, MeCN.

Scheme 6



	Ar[a])	R[a])	*n*[a])		Ar[a])	R[a])	*n*[a])
34.1	Ph	H	5	**34.4**	Ph	H	6
34.2	Ph	H	4	**34.5**	Ph	H	7
34.3	naphthalen-2-yl	H	4	**34.6**	Ph	Me	7

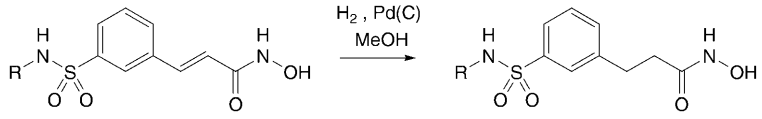
[a]) The same substituents Ar and R, and the same *n* are applicable to the corresponding intermediates.

a) Na_2SO_3, EtOH, H_2O. *b*) 1. PCl_5; 2. $ArNH_2$ or PhNHMe, benzene. *c*) $NH_2OH \cdot HCl$, MeONa, MeOH.

To investigate the structure–activity relationship (SAR) of the cinnamoyl moiety of the inhibitors, saturated analogues of some of the 'reversed' sulfonamido-substituted hydroxamic acids were prepared. The appropriate starting material was

hydrogenated over Pd-catalyst to give the corresponding saturated analogues **35.1**–**35.6** (*Scheme 7*).

Scheme 7



*m***11.1**, *m***11.2**, *m***11.5**, *m***11.20**, *m***11.25**, *m***11.38** → **35.1** – **35.6**

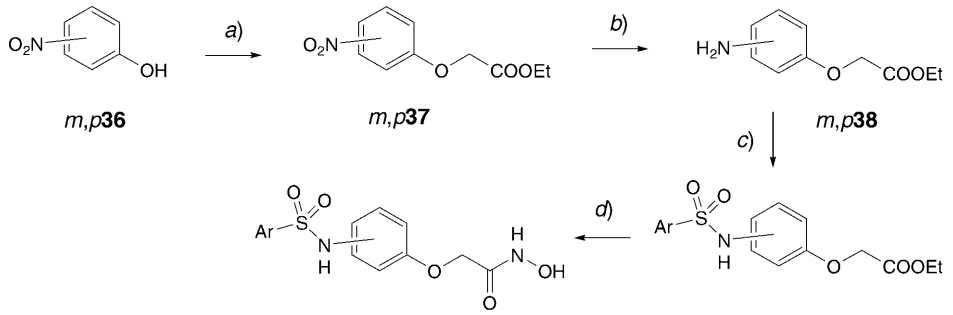
	R[a])		R[a])		R[a])
35.1	Ph	**35.3**	2-MeO–C_6H_4	**35.5**	[1,1′-biphenyl]-4-yl[b])
35.2	4-Me–C_6H_4	**35.4**	4-MeO–C_6H_4	**35.6**	$PhCH_2CH_2CH_2$

[a]) The same substituent R is applicable to the corresponding *m***11**. [b]) See *Footnote c* in *Scheme 1*.

To further investigate the SAR of this part of the molecule, compounds **40** with 'forward' sulfonamide and oxymethyl fragments were prepared from appropriate nitrophenols *m,p***36** by *O*-alkylation with ethyl bromoacetate (→ *m,p***37**) and reduction to anilines *m,p***38** (*Scheme 8*). The anilines *m,p***38**, were treated with appropriate aromatic sulfonyl chlorides followed by hydroxylamine in the presence of base to afford hydroxamic acids *m***40.1**, *m***40.2**, and *p***40**.

Also 'reversed' sulfonamide derivatives **45** and **48** with extended and shortened arylalkyl linker parts were synthesized (*Scheme 9*). Thus, sodium 3-formylbenzenesul-

Scheme 8

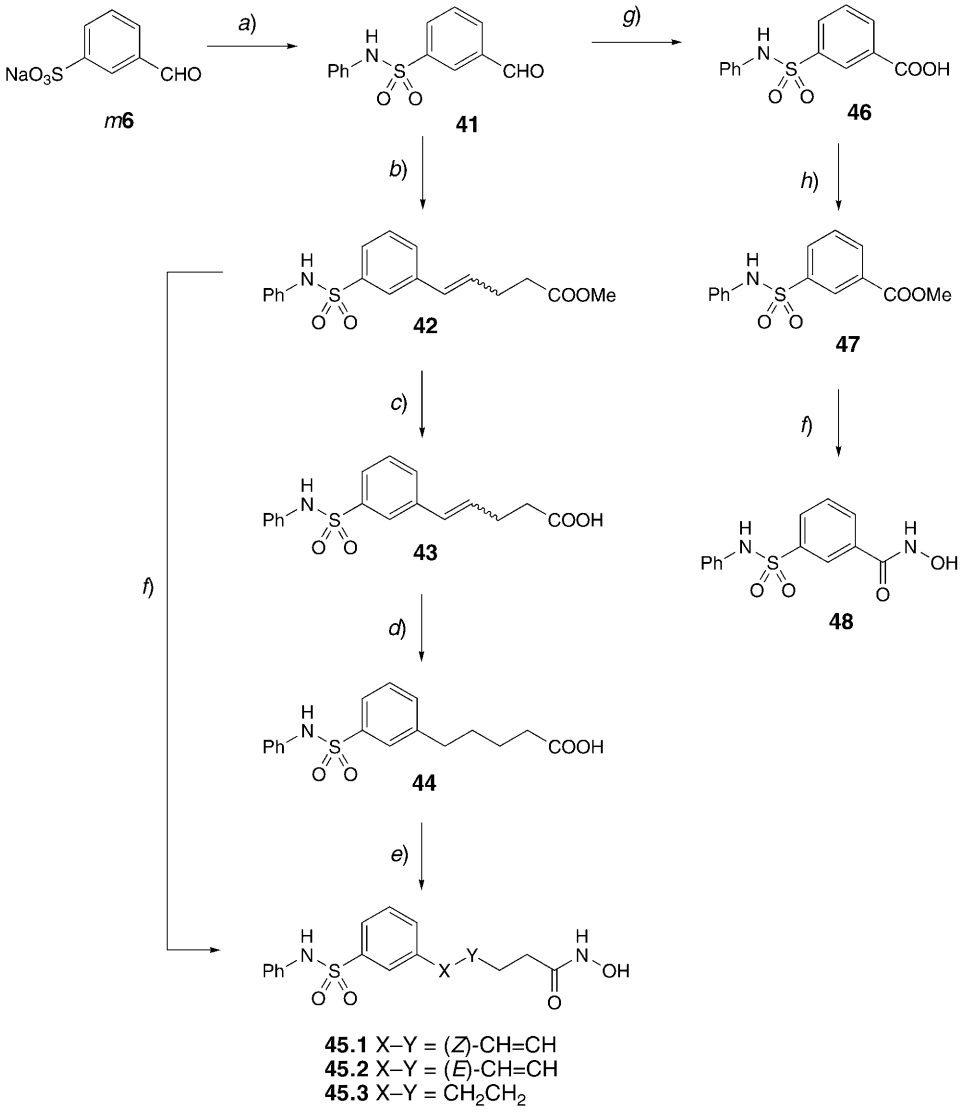


	Ar[a])		Ar[a])		Ar[a])
*p***40**	Ph	*m***40.1**	Ph	*m***40.2**	naphthalen-1-yl

[a]) The same substituent Ar is applicable to the corresponding intermediates.

a) $BrCH_2COOEt$, K_2CO_3, MeCN. *b*) H_2, 10% Pd/C, MeOH. *c*) $ArSO_2Cl$, $NaHCO_3$, acetone, H_2O. *d*) $NH_2OH \cdot HCl$, MeOH, THF, H_2O, KOH.

Scheme 9



a) 1. $SOCl_2$, cat. DMF, benzene; 2. $PhNH_2$, aq. $NaHCO_3$ soln.; 58%. *b*) $[Ph_3P(CH_2)_3COOMe]I$, NaH, THF; 31%. *c*) aq. NaOH soln., MeOH. *d*) H_2, 5% Pd/C, MeOH. *e*) 1. $(COCl)_2$, CH_2Cl_2, cat. DMF; 2. $NH_2OH \cdot HCl$, THF, aq. $NaHCO_3$ soln.; 66%. *f*) $NH_2OH \cdot HCl$, MeONa, MeOH. *g*) CrO_3, H_2SO_4, acetone; 98%. *h*) MeOH, HCl; 84%.

fonate *m***6** was condensed with aniline (→**41**) and treated with ylide to give (*Z*)/(*E*)-ester **42**. The mixture (*Z*)/(*E*)-**42** was separated into the isomers (*Z*)- and (*E*)-**42** by HPLC, and each was separately treated with hydroxylamine in the presence of base to give the (*Z*)- and (*E*)-isomers **45.1** and **45.2**, respectively. The hydroxamic acid with a

saturated side chain **45.3** was obtained from **42** by ester hydrolysis (→**43**), hydrogenation (→**44**), and the oxalyl chloride/hydroxylamine procedure. Alternatively, aldehyde **41** was oxidized to acid **46**. After esterification (→**47**), treatment with hydroxylamine in the presence of base gave hydroxamic acid **48**.

3. Biological Activity. – 3.1. *Preamble.* Compounds described in *Sect. 2* were profiled by using partially purified HDAC enzyme obtained from HeLa cell lysates. The HDAC inhibitory activity, measured as IC_{50} [nM] are shown in *Tables 1–6*, together with the antiproliferative activity of the compounds. In the vast majority of cases, enzyme activity was determined with a fluorometric assay format. In a few cases, a radiometric assay format was used – these are indicated by values in italics in the *Tables*. Extensive comparative studies showed that these assays yield equivalent results. Analysis of this data enables a number of observations and conclusions to be drawn from the SARs of this arylsulfonamido-substituted hydroxamic acid series of HDAC inhibitors.

3.2. *Direction of Sulfonamide Bond. Table 1* summarizes the data indicating that compounds having a 'reverse' sulfonamide functionality ($NHSO_2$) in the *meta* position, *i.e.*, *m***11.1**, *m***11.2**, *m***11.21**, *m***11.25**, and *m***11.29** show a small but consistently better HDAC-inhibitory activity compared to their counterparts with a 'forward' sulfonamide functionality (SO_2NH_2) in the *meta* position, *i.e.*, *m***20.1**, *m***20.2**, *m***20.3**, *m***20.4**, and *m***20.5**. At least in the one case examined, this is also the case when there is an intervening methylene between the aryl group and the sulfonamide moiety (*m***11.29** *vs.* *m***20.5**). There is no obvious equivalent trend when the substitution across the central aromatic ring is *para* although the number of compounds available for this comparison is relatively small (last four entries in *Table 1*).

Table 1. *Direction of Sulfonamide Bond* (n.t. = not tested)

Inhibitor	Sulfonamide direction	Position of attachment	Enzyme IC_{50} [nM]	WST1 [μM]	Inhibitor	Sulfonamide direction	Position of attachment	Enzyme IC_{50} [nM]	WST1 [μM]
*m***11.1**	$NHSO_2$	*meta*	28	1.27	*m***20.4**	SO_2NH	*meta*	106	3.35
*m***20.1**	SO_2NH	*meta*	188	8.85	*m***11.29**	$NHSO_2$	*meta*	34	3.79
*m***11.2**	$NHSO_2$	*meta*	18	1.64	*m***20.5**	SO_2NH	*meta*	*23%@1000*	n.t.
*m***20.2**	SO_2NH	*meta*	123	4.10	**15.1**	$NHSO_2$	*para*	29	1.13
*m***11.21**	$NHSO_2$	*meta*	23	2.90	*p***20.1**	SO_2NH	*para*	59	3.75
*m***20.3**	SO_2NH	*meta*	137	16.75	**15.4**	$NHSO_2$	*para*	66	1.40
*m***11.25**	$NHSO_2$	*meta*	54	1.41	*p***20.2**	SO_2NH	*para*	30	1.58

3.3. *Position of Substitution.* Both *meta*- and *para*-substitution patterns across the central aromatic ring lead to highly potent compounds (*Table 2*). Either pattern leads to approximately equal activity, but a slight preference may be discernable for greater activity with the *para*-substitution pattern in the case of the 'forward' sulfonamides, and equal or slightly greater activity for the 'reverse' sulfonamides when substituted *meta*. Although the differences are small, it is interesting to observe that for the 'reverse' sulfonamides, *meta* substitution seems to be preferred when substituted with bulky aromatic groups, but that in both cases where substitution is with a simple halo-substituted aromatic group, the *para* compounds are more potent (*m***11.3** *vs.* **15.2** and

Table 2. *Position of Substitution*

Inhibitor	Sulfonamide direction	Position of attachment	Enzyme IC_{50} [nM]	WST1 [μM]	Inhibitor	Sulfonamide direction	Position of attachment	Enzyme IC_{50} [nM]	WST1 [μM]
*m***11.1**	$NHSO_2$	*meta*	28	1.27	**15.5**	$NHSO_2$	*para*	44	0.38
15.1	$NHSO_2$	*para*	29	1.13	*m***11.3**	$NHSO_2$	*meta*	54	2.01
*m***20.1**	SO_2NH	*meta*	188	8.85	**15.2**	$NHSO_2$	*para*	16	3.40
*p***20.1**	SO_2NH	*para*	59	3.75	*m***11.4**	$NHSO_2$-	*meta*	42	2.33
*m***20.3**	SO_2NH	*meta*	137	16.75	**15.3**	$NHSO_2$	*para*	27	1.71
*p***20.3**	SO_2NH	*para*	21	3.52	*m***11.27**	$NHSO_2$	*meta*	36	0.90
*m***11.25**	$NHSO_2$	*meta*	54	1.41	**15.6**	$NHSO_2$	*para*	163	2.35
15.4	$NHSO_2$	*para*	66	1.40	*m***20.6**	SO_2NH	*meta*	96	5.98
*m***20.4**	SO_2NH	*meta*	106	3.35	*p***20.4**	SO_2NH	*para*	203	1.35
*p***20.2**	SO_2NH	*para*	30	1.58	*o***11.1**	$NHSO_2$	*ortho*	inact.	106.00
*m***11.29**	$NHSO_2$	*meta*	34	3.79	*o***11.2**	$NHSO_2$	*ortho*	inact.	78.00
15.7	$NHSO_2$	*para*	97	5.45	*o***11.3**	$NHSO_2$	*ortho*	inact.	89.00
*m***11.23**	$NHSO_2$	*meta*	42	1.42					

*m***11.4** *vs.* **15.3**). The *ortho*-substitution invariably leads to inactive compounds (*o***11.1**–*o***11.3**).

3.4. *Influence of the Aromatic Head Group.* HDAC-Inhibitory activity is also modulated by the substitution patterns and size of the aromatic head group R′ (*Table 3*). In general, substitution of the aromatic ring with small groups leads to compounds of approximately equal potency, irrespective of the electronic properties of the group or its position of attachment, especially when this substitution is *meta* or *para*. There is a suggestion that *ortho* substitution is somewhat disfavored, as indicated by the weaker activity of compounds *m***11.24**, *m***11.12**, *m***11.13**, *m***11.5**, and *m***11.17**. Compound *m***11.9**, where the *ortho* substitutent is the small F-atom, retains activity. Some clear SAR trends are shown among various bulky head groups tried. In the light of the *ortho*-substitution findings just noted, it is perhaps surprising that there is only a twofold potency difference between the naphthalen-1-yl and naphthalen-2-yl derivatives *m***11.22** and *m***11.23**, respectively. However, consistent with this SAR, the more-extended [1,1′-biphenyl]-4-yl derivative *m***11.25** is more potent than the [1,1′-biphenyl]-2-yl analog *m***11.24**. Planar bicyclic or tricyclic substituents R′ such as the 1*H*-benzimidazol-6-yl (*m***11.26**), and 9-ethyl-9*H*-carbazol-3-yl group (*m***11.27**) produced good activity, which was not preserved with the nonplanar adamantan-1-yl derivative *m***11.28**.

3.5. *Influence of the Alkyl Spacer Group.* A homologous series of compounds was created by inserting a straight alkyl chain of increasing length in R′ between the Ph groups and the sulfonamide moiety. This does not affect the activity of the compounds, except for a very modest decrease in activity for the longer homologues, despite adding considerable incremental rotational freedom to the molecules (*Table 4*; see *m***11.1**, *m***11.29**, *m***11.36**, *m***11.38**, and *m***11.40**). Presumably, the entropic penalty on binding is compensated by an equivalent gain in enthalpy of binding. The incorporation of heteroatoms into the linking group is also allowed without loss of activity (see *m***11.39**). Some aromatic systems other than Ph are also tolerated in R′ when there is a methylene or ethylene spacer (see *m***11.30** and *m***11.34**), but not universally (see *m***11.31**, *m***11.32**, and *m***11.33**). The weak activity of the naphthalen-2-yl derivative *m***11.33** in particular contrasts with its potent activity when directly attached (see *m***11.23** in *Table 3*).

Table 3. *Influence of Aryl Group* (n.t. = not tested)

Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]	Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]
***m*11.1**	28	1.27	***m*11.15**	34	6.27
***m*11.2**	18	1.64	***m*11.16**	76	15.60
***m*11.3**	54	2.01	***m*11.17**	113	4.33
***m*11.4**	42	2.33	***m*11.18**	18	5.10
***m*11.5**	81	1.63	***m*11.19**	13	11.78
***m*11.6**	22	4.07	***m*11.20**	13	0.48
***m*11.7**	31	1.59	***m*11.21**	23	2.90
***m*11.8**	*16*	1.87	***m*11.22**	71	0.76
***m*11.9**	32	2.60	***m*11.23**	42	1.42
***m*11.10**	20	2.00	***m*11.24**	311	5.06
***m*11.11**	10	1.22	***m*11.25**	54	1.41
***m*11.12**	92	12.51	***m*11.26**	9	n.t.
***m*11.13**	74	3.55	***m*11.27**	36	0.90
***m*11.14**	41	8.53	***m*11.28**	120	0.68

Introducing additional aryl substituents into the linking chain of R′ is poorly tolerated (see ***m*11.41**, ***m*11-42**, and ***m*11.45**), but small alkyl or OH substituents can be introduced to good effect (see ***m*11.43** and ***m*11.44**). Few compounds with a 'forward' sulfonamide were synthesized, but it is interesting to observe that a single methylene linker yields an inactive compound, whereas an ethenyl linker provides an inhibitor with modest activity (but only when substituted in the *meta* position; see ***m*20.5**, ***m*20.6**, and ***p*20.4**).

Table 4. *Influence of Alkyl Spacer* (n.t. = not tested)

Inhibitor	Enzyme FDL IC_{50} [nM]	WST1 [μM]	Inhibitor	Enzyme FDL IC_{50} [nM]	WST1 [μM]
***m*11.1**	28	1.27	***m*11.35**	89	4.14
***m*11.29**	34	3.79	***m*11.37**	122	9.55
***m*11.36**	27	1.88	***m*11.41**	268	5.69
***m*11.38**	58	3.50	***m*11.42**	182	5.96
***m*11.40**	76	4.80	***m*11.43**	50	1.85
***m*11.39**	32	1.47	***m*11.44**	39	2.20
***m*11.30**	36	9.67	***m*11.45**	408	6.60
***m*11.31**	163	3.79	***m*20.5**	*23%@1000*	n.t.
***m*11.32**	389	86.50	***m*20.6**	96	5.98
***m*11.33**	*640*	9.67	***p*20.4**	203	1.35
***m*11.34**	25	3.37			

3.6. *Substitution of the Sulfonamide Moiety.* Compounds in which the sulfonamide N-atom was substituted (R″ ≠ H) are shown in *Table 5*. Substitution of the amide proton at the 'reverse' sulfonamide functionality with an alkyl group decreased the HDAC inhibitory activity (see ***m*11.46** and ***m*11.47**). Similarly, arylalkyl substitution yields compounds with reduced activity (see ***m*11.48**–***m*11.52**).

Table 5. *Influence of Sulfonamide Substitution*

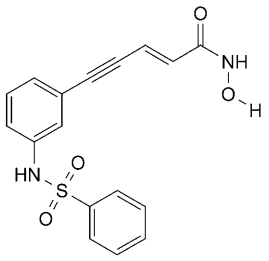
Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]	Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]
***m*11.46**	476	7.29	***m*11.50**	368	1.35
***m*11.47**	510	17.93	***m*11.51**	434	3.07
***m*11.48**	174	3.54	***m*11.52**	566	6.03
***m*11.49**	164	6.60			

3.7. *Compounds Not Based on Cinnamic Acid.* Saturation of the C=C bond of the cinnamic acid moiety leads to compounds with significantly reduced enzyme-inhibition activity and weak antiproliferative activity (see **35.1**–**35.6**, *Table 6*) when compared to their cinnamic acid counterparts. Extending the length of the alkyl linker, either unsaturated or saturated, yields compounds with a similar profile (see **45.1**–**45.3**). Complete removal of the C=C bond yields a completely inactive compound (see **48**). Replacing one of the C-atoms with an O-atom is also not tolerated (see *m***40.2**, *m***40.1**, and *p***40**).

Table 6. *Compounds Not Based on Cinnamic Acid* (n.t. = not tested)

Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]	Inhibitor	Enzyme IC_{50} [nM]	WST1 [μM]
35.1	346	21.45	**49**	47	1.10
35.2	207	17.60	*m***27**	*14*	0.78
35.3	616	70%@90	*p***27**	*45*	5.70
35.4	122	3.24	**30.1**	795	16.73
35.6	165	13.95	**30.2**	892	72.00
35.5	148	29.45	**30.3**	142	4.20
45.1	*20%@100*	n.t.	**30.4**	69	2.85
45.2	*29%@100*	n.t.	**34.1**	246	6.82
45.3	135	11.90	**34.2**	2030	96.20
48	inact.	inact.	**34.3**	145	n.t.
*m***40.2**	inact.	31.30	**34.4**	379	18.35
*m***40.1**	inact.	39.80	**34.5**	181	10.67
*p***40**	136	11.65	**34.6**	565	n.t.

Other unsaturated systems are also compatible with good activity, *e.g.*, in compounds structurally related to oxamflatin (**49**) [22] (see *m***27** and *p***27**). There is an interesting contrast between the sulfonamide-containing HDAC inhibitors reported here and the compounds reported in the scientific and patent literature which employ a carboxamide linking group, such as SAHA (**2**). These molecules typically employ a straight-chain saturated alkyl group between the hydroxamic acid and carboxamide linkage, yielding highly potent enzyme inhibitors. However, this SAR does not translate when a sulfonamide linkage is used, as compounds of this type are generally weak inhibitors (see **30.1**–**30.3** and **34.1**–**34.5**). As with the carboxamides, short chains give inactive compounds, but the inhibitors remain weak even as the length of the chain increases. Moderately potent compounds can be obtained, however, by appropriate manipulation of the group on the distal side of the sulfonamide from the hydroxamic



49 oxamflatin

acid (see **30.4**). In common with the cinnamic acid series, methylation of the sulfonamide N-atom yields a less active compound, **34.6**.

3.8. *Antiproliferative Activity.* There is no very strong correlation between enzyme inhibition and antiproliferative activity as measured by the WST-1 assay. This is perhaps not surprising given the quite large structural diversity of the inhibitors. The concomitant differences in polarity, hydrophobicity, and other factors that affect cellular uptake and stability will impact on this correlation. Another possibly confounding factor is the existence of multiple enzyme isoforms (see below). Nonetheless chemical series that generally make weak inhibitors of the enzyme tend also to be poor antiproliferatives, such as the alkyl-linker class and when the cinammic acid C=C bond is saturated. In fact, all compounds which are inactive in the biochemical assay, or have inhibitory activity that is weak (close to μM), are also weak antiproliferatives. Analyzing the set of compounds for which numerical data is available in both assays gives a rank correlation coefficient of *ca.* 0.6, which is quite reasonable given the considerations outlined above. It is also interesting to note that compounds which have good cellular activity relative to their enzyme-inhibitory potency tend to be more hydrophobic than the average (see *m***11.28**, *m***11.50**, *p***20.4**, and **15.5**), and that those where the translation is less good often have halogen or other heteroatom substitution (see *m***11.18**, *m***11.19**, *m***11.30**, and **15.2**).

The most-potent antiproliferative compounds are from the cinnamic acid series, and with the aryl group directly connected to the sulfonamide. Planar aromatic groups, such as phenyl, naphthalenyl, and carbazolyl groups have the best activity.

4. Conclusion. – An extensive survey of the SARs of a novel sulfonamide-containing class of histone-deacetylase inhibitors was performed. This has identified sulfonamides based on cinnamic acid as a template for the generation of potent HDAC inhibitors, with enzyme inhibition in the low nanomolar range. Appropriately aryl-substituted compounds with low micromolar or submicromolar antiproliferative activity were also obtained. These molecules are also active in both syngeneic (data to be presented elsewhere) and xenograft animal models of cancer [23]. Based in part on the data presented here, a molecule, *m***11.1**, also designated PXD101, was selected for clinical investigation and is currently in phase-I and phase-II trials for cancer.

The area of HDAC inhibitors remains one with great potential for drug discovery. A growing number of histone-deacetylase-family members have been identified [24], and may be drug targets. The first deacetylase, HDAC1, was identified in 1996 [25]. Subsequently, two other nuclear mammalian deacetylases were found, HDAC2 and HDAC3 [26–30]. To date, eleven human HDACs have been cloned, falling into two distinct classes, with HDACs 1–3 and 8 belonging to class I, and HDACs 4–7 and 9–11 to class II. In the work reported here, a HeLa cell extract was used as source of histone-deacetylase activity. This source of enzyme, therefore, represents a mixture of at least some of these isoforms. A continuing focus of our own work, and that of others, is the elucidation of the role of the different HDAC family members in disease and the identification of family-member-specific inhibitors as pharmacological tools and potential therapeutic compounds with exciting opportunities in cancer and other areas of high unmet medical need.

Experimental Part

1. *Biology.* 1.1. *Histone Deacetylase Assays.* Candidate compounds were assessed for their ability to inhibit deacetylase activity (biochemical assays) and to inhibit cell proliferation (cell-based antiproliferation assays), as described below.

1.2. *Primary Assay 1* (*P.A.1*): *Deacetylase Activity. Radiometric Assay.* Briefly, this assay relies on the release of radioactive acetate from a radioactively labelled histone fragment by the action of HDAC enzyme. Test compounds, which inhibit HDAC, reduce the yield of radioactive acetate. Signal (*e.g.*, scintillation counts) measured in the presence and absence of a test compound provide an indication of that compound's ability to inhibit HDAC activity. Decreased activity indicates increased inhibition by the test compound.

The histone fragment was an N-terminal sequence from histone H4, and it was labelled with radioactively labelled acetyl groups by using tritiated acetylcoenzyme A (Ac-CoA) in conjunction with an enzyme which is the histone acetyltransferase domain of the transcriptional coactivator p300. Peptide H4 (= the N-terminal 20 amino acids of histone H4, synthesized by conventional methods; 0.33 mg) was incubated with His6-tagged p300 histone acetyltransferase domain (amino acids 1195–1673, expressed in *E. coli* strain BLR(DE3)pLysS (*Novagen*, Cat. No. 69451-3) and ^{3}H-acetyl-CoA (10 µl of 3.95 Ci/mmol; from *Amersham*) in a total volume of 300 µl of HAT buffer (50 mM *Tris*·HCl (pH 8), 5% glycerol, 50 mM KCl, 0.1 mM ethylenediaminetetraacetic acid (edta), 1 mM dithiothreitol (DTT), and 1 mM 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF). The mixture was incubated at 30° for 45 min after which the His-p300 was removed by using nickel/trinitriloacetic acid agarose (*Qiagen*, Cat No. 30210). The acetylated peptide was then separated from free Ac-CoA by size-exclusion chromatography (*Sephadex G-15* (*Sigma G-15-120*), dist. H_2O).

After purification of the radiolabelled histone fragment, it was incubated with a source of HDAC (an extract of HeLa cells), and any released acetate was extracted into an org. phase and quantitatively determined by scintillation counting. By including a test compound with the source of HDAC, that compound's ability to inhibit the HDAC was determined.

Assay Method: A source of HDAC (*e.g.*, 2 µl of crude HeLa extract; in elution buffer, as above) was incubated with 3 µl of radioactively labelled peptide along with appropriate dilutions of candidate compounds (1.5 µl) in a total volume of 150 µl of buffer (20 mM *Tris*·HCl (pH 7.4), 10% glycerol). The reaction was carried out at 37° for 1 h, after which the reaction was stopped by adding 20 µl of 1M HCl/0.4M NaOAc. Then, 750 µl of AcOEt was added, the samples were vortexed and, after centrifugation (14000 r.p.m., 5 min), 600 µl from the upper phase were transferred to a vial containing 3 ml of scintillation liquid (*UltimaGold*, *Packard*, Cat. No. 6013329). Radioactivity was measured with a *Tri-Carb-2100TR* liquid scintillation analyzer (*Packard*).

Percent activity (% activity) for each test compound was calculated as % activity = $\{(S^C - B)/(S^\circ - B)\} \cdot 100$, wherein S^C denotes the signal measured in the presence of enzyme and the compound being tested, S° denotes the signal measured in the presence of enzyme but in the absence of the compound being tested, and B denotes the background signal measured in the absence of both enzyme and compound being tested. The IC_{50} corresponds to the concentration which achieves 50% activity.

1.3. *Primary Assay 2* (*P.A.2*): *Deacetylase Activity: Fluorescent Assay.* Alternatively, the activity of the compounds as HDAC inhibitors was determined with a commercially available fluorescent assay kit: (*Fluor de Lys*™, *BioMol Research Labs*, *Inc.*, Plymouth Meeting, USA). HeLa Extract was incubated for 1 h at 37° in assay buffer (25 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, pH 8.0) with 15 µM acetylated substrate in the presence of test compound (HDAC inhibitor). The extent of deacetylation was determined by the addition of 50 µl of a 1-in-500 dilution of developer and measurement of the fluorescence (excitation 355 nm, emission 460 nm), according to the instructions provided with the kit. The IC_{50} corresponds to the concentration which achieves 50% activity. IC_{50} values were calculated with the software package Prism 3.0 (*GraphPad Software Inc.*, San Diego, CA), setting the top value at 100 and the bottom value at 0.

Extensive comparative studies showed that *P.A.1* and *P.A.2*, discussed above, yield equivalent results. Primary-assay results reported herein are *a*) exclusively from *P.A.1*, *b*) exclusively from *P.A.2*, or *c*) from both *P.A.1* and *2*.

1.4. *HeLa Cell Extracts.* HeLa cells (ATCC Ref. No. CCL-2) were cultured in DMEM containing 10% FCS, 100 U/ml of penicillin and 100 µg/ml of streptomycin. Subconfluent cells were harvested by trypsinization and washed twice in ice-cold PBS. The cells were resuspended in 2 volumes of buffer (60 mM *Tris*·HCl (pH 7.4), 30% glycerol, 450 mM NaCl) and lysed by three freeze and thaw cycles (dry ice/ – 30°). Cell debris was removed by centrifugation at 20817 *g* and the supernatant aliquoted and stored at – 80°.

1.5. *Secondary Assay: Cell Proliferation.* Compounds with HDAC-inhibition activity, as determined by the primary assay, were subsequently evaluated using secondary cell-based assays. HeLa Cells were cultured,

exposed to candidate compounds, and incubated for a time, and the number of viable cells was then assessed by using the cell proliferation reagent WST-1 from *Boehringer Mannheim* (Cat. No. 1644807), described below. Cells were plated in 96-well plates at $3-10\cdot10^3$ cells/well in 100 µl of culture medium. The following day, different concentrations of candidate compounds were added and the cells incubated at 37° for 48 h. Subsequently, 10 µl/well of WST-1 reagent was added, and the cells were reincubated for 1 h. After the incubation time, absorbance was measured.

WST-1 is a tetrazolium salt which is cleaved to a formazan dye by cellular enzymes. An expansion in the number of viable cells results in an increase in the overall activity of mitochondrial dehydrogenases in the sample. This augmentation in the enzyme activity leads to an increase in the amount of formazan dye formed, which directly correlates to the number of metabolically active cells in the culture. The formazan dye produced is quantified by a scanning multiwell spectrophotometer by measuring the absorbance of the dye soln. at 450 nm wavelength (reference wavelength 690 nm).

Percent activity (% activity) in reducing the number of viable cells was calculated for each test compound as: % activity $=\{(S^C-B)/(S^\circ-B)\}\cdot100$, wherein S^C denotes the signal measured in the presence of the compound being tested, S° the signal measured in the absence of the compound being tested, and B the background signal measured in blank wells containing medium only. The IC_{50} corresponds to the concentration which achieves 50% activity. IC_{50} Values were calculated with the software package Prism 3.0 (*GraphPad Software Inc.*, San Diego, CA), setting the top value at 100 and the bottom value at 0.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points was used to assess both cytotoxicity and the effect of the compound on cell proliferation.

2. *Syntheses. General.* All the solvents were purified before use by routine techniques. The reaction products were isolated by evaporating the solvent (vacuum rotary evaporator). Column chromatography (CC): silica gel 0.035–0.070 mm (*Acros*). Anal. HPLC (reversed phase): *Varian ProStar* HPLC system equipped with a spectrophotometer; check of the purity of synthesized compounds. M.p.: *Boëtius* or *Fisher* micro melting point apparatus; uncorrected. NMR Spectra: *Varian WH-90/DS-* or *Mercury-200* spectrometers; at r.t.; δ in ppm, J in Hz. Elemental analyses: *Carlo-Erba EA-1108* instrument.

Sodium 3-Formylbenzenesulfonate (*m***6**). While maintaining the temp. at 30°, **5** (2.00 g, 18.84 mmol) was added slowly to oleum (5 ml). The resultant soln. was stirred at 40° for 10 h and at r.t. overnight. The mixture was poured into ice and extracted with AcOEt. The aq. phase was treated with $CaCO_3$ until the evolution of CO_2 ceased (pH *ca.* 6–7), and the precipitated $CaSO_4$ was filtered off and washed with H_2O. The filtrate was treated with solid Na_2CO_3 until the pH of the medium increased to 8, obtained $CaCO_3$ was filtered off, and the soln. was evaporated. The residue was washed with MeOH, the washings were evaporated, and the obtained solid was dried in a desiccator (P_2O_5): *m***6** (2.00 g, 51%). ^{1}H-NMR (D_2O, 90 MHz): 7.56–8.40 (*m*, 4 H); 10.04 (*s*, 1 H).

*Sodium 3-[(1*E*)-3-Methoxy-3-oxoprop-1-enyl]benzenesulfonate* (*m***7**). A mixture of *m***6** (1.00 g, 4.80 mmol), K_2CO_3 (1.32 g, 9.56 mmol), methyl (dimethoxyphosphinyl) acetate (1.05 g, 5.77 mmol) and H_2O (2 ml) was stirred at r.t. for 30 min. Precipitated solid was filtered off and washed with MeOH. The filtrate was evaporated and dried: *m***7** (0.70 g, 55%). White solid. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 3.68 (*s*, 3 H); 6.51 (*d*, $J=16.0$, 1 H); 7.30–7.88 (*m*, 5 H).

*Methyl (2*E*)-3-[3-(Chlorosulfonyl)phenyl]prop-2-enoate* (*m***8**). To *m***7** (13.1 g, 49.5 mmol) in benzene (150 ml), $SOCl_2$ (10.6 ml, 146.1 mmol) and DMF (0.2 ml, 2.6 mmol) were added, and the resultant suspension was stirred under reflux until all the solid dissolved (*ca.* 4–5 H). The mixture was evaporated, the residue dissolved in benzene (100 ml), the soln. filtered, the filtrate evaporated, the residue dissolved in benzene (50 ml), and the soln. again evaporated. This procedure was repeated once more, and the obtained material was dried over P_2O_5 *in vacuo: m***8** (10.6 g, 82%). White solid. ^{1}H-NMR ($CDCl_3$, 90 MHz): 3.82 (*s*, 3 H); 6.57 (*d*, $J=16.1$, 1 H); 7.66 (*t*, $J=7.5$, 1 H); 7.70 (*d*, $J=16.1$, 1 H); 7.85 (*dt*, $J=1.5, 7.5$, 1 H); 8.03 (*dt*, $J=1.5, 7.5$, 1 H); 8.16 (*t*, $J=1.5$, 1 H).

*Methyl (2*E*)-3-[3-[(Phenylamino)sulfonyl]phenyl]prop-2-enoate* (*m***9.1**). A soln. of *m***8** (1.00 g, 3.83 mmol) in dioxane (12 ml) was added to a mixture of benzenamine (0.38 ml, 3.43 mmol) in dioxane (5 ml) and $NaHCO_3$ (0.64 g, 7.66 mmol) in H_2O (7.5 ml). The resultant mixture was stirred at r.t. for 1 h (TLC control), evaporated, and supplemented with H_2O (25 ml). The mixture was stirred at r.t. for 1 h, the precipitate filtered, washed with H_2O, and dried: 0.89 g (74%) of *m***9.1**. ^{1}H-NMR ($CDCl_3$, 90 MHz): 3.72 (*s*, 3 H); 6.34 (*d*, $J=16.0$, 1 H); 6.68 (br. *s*, 1 H); 6.92–7.89 (*m*, 10 H).

*(2*E*)-3-[3-[(Phenylamino)sulfonyl]phenyl]prop-2-enoic Acid* (*m***10.1**). *m***9.1** (4.10 g, 12.9 mmol) was dissolved in MeOH (50 ml), 1M NaOH (38.75 ml, 38.75 mmol) was added, and the soln. was stirred at r.t. overnight (TLC control). The mixture was partitioned between AcOEt and H_2O. The aq. layer was acidified with 2M HCl and stirred for 30 min. The precipitated solid was filtered, washed with H_2O, and dried in the

desiccator (P_2O_5): *m***10.1** (3.32 g, 85%). White solid. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.53 (*d*, *J* = 16.0, 1 H); 6.87–7.34 (*m*, 5 H); 7.52 (*t*, *J* = 7.6, 1 H); 7.56 (*d*, *J* = 16.0, 1 H); 7.73 (*d*, *J* = 8, 1 H); 7.89 (*d*, *J* = 8, 1 H); 7.96 (*s*, 1 H); 10.23 (br. *s*, 1 H); 12.53 (br. *s*, 1 H).

*(2*E*)-*N*-Hydroxy-3-{3-[(phenylamino)sulfonyl]phenyl}prop-2-enamide* (*m***11.1**). To a suspension of *m***10.1** (2.88 g, 9.49 mmol) in CH_2Cl_2 (35 ml), oxalyl chloride (2.7 ml, 30.84 mmol) and 1 drop of DMF were added. The mixture was stirred at reflux for 1 h and then evaporated and the residue dried *in vacuo* and dissolved in THF (30 ml). In another vessel, to a suspension of hydroxylamine hydrochloride (3.36 g, 48.69 mmol) in THF (55 ml), a sat. $NaHCO_3$ soln. (38 ml) was added, and the resultant mixture was stirred at r.t. for 10 min. The contents of both vessels were combined and stirred at r.t. for 1 h. The mixture was partitioned between AcOEt and 2M HCl. The org. phase was washed successively with H_2O and sat. NaCl soln. and evaporated, and the residue crystallized from AcOEt: *m***11.1** (2.57 g, 85%). White crystals. M.p. 172°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 7.18–8.05 (*m*, 10 H); 9.16 (br. *s*, 1 H); 10.34 (*s*, 1 H); 10.85 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{14}N_2O_4S$ (318.35): C 56.59, H 4.43, N 8.80; found: C 56.55, H 4.41, N 8.66.

3-[(Aminosulfonyl)phenyl]-N*-hydroxypropenamides m***11.2**–*m***11.52** *and o***11.1**–*o***11.3** were obtained as described for *m***11.1**.

*(2*E*)-*N*-Hydroxy-3-{3-[[(4-methylphenyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m***11.2**): M.p. 200°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 2.16 (*s*, 3 H); 6.47 (*d*, *J* = 16.0, 1 H); 6.98 (*s*, 4 H); 7.29–7.98 (*m*, 5 H); 9.09 (br. *s*, 1 H); 10.09 (*s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S$ (332.38): C 57.82, H 4.85, N 8.43; found: C 57.61, H 4.93, N 8.16.

*(2*E*)-3-{3-[[(4-Bromophenyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.3**): M.p. 204°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 7.05 (*d*, *J* = 9.0, 2 H); 7.34–7.98 (*m*, 7 H); 9.09 (br. *s*, 1 H); 10.47 (*s*, 1 H); (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}BrN_2O_4S$ (397.25): C 45.35, H 3.30, N 7.05; found: C 45.73, H 3.33, N 6.81.

*(2*E*)-3-{3-[[(4-Chlorophenyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.4**): M.p. 198°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 6.98–8.05 (*m*, 9 H); 9.16 (br. *s*, 1 H); 10.49 (*s*, 1 H); 10.85 (*s*, 1 H). Anal. calc. for $C_{15}H_{13}ClN_2O_4S$ (352.80): C 51.07, H 3.71, N 7.94, S 9.09; found: C 50.96, H 3.62, N 7.76, S 9.00.

*(2*E*)-*N*-Hydroxy-3-{3-[[(2-methoxyphenyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m***11.5**): M.p. 181°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 3.45 (*s*, 3 H); 6.49 (*d*, *J* = 16.0, 1 H); 6.76–7.96 (*m*, 9 H); 9.09 (br. *s*, 1 H); 9.54 (*s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_5S$ (348.38): C 55.16, H 4.63, N 8.04; found: C 55.14, H 4.52, N 7.99.

*(2*E*)-*N*-Hydroxy-3-{3-[[(3-methoxyphenyl)amino]sulfonyl]phenyl]prop-2-enamide* (*m***11.6**): M.p. 137°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 3.65 (*s*, 3 H); 6.38–6.78 (*m*, 4 H); 6.98–7.27 (*m*, 1 H); 7.34–8.03 (*m*, 5 H); 9.14 (br. *s*, 1 H); 10.30 (*s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_5S \cdot 0.2\ H_2O$ (351.98): C 54.60, H 4.70, N 7.96; found: C 54.61, H 4.58, N 7.96.

*(2*E*)-3-{3-[[(3-Bromophenyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.7**): M.p. 135.5–136.5°. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 6.53 (*d*, *J* = 15.6, 1 H); 7.07–7.28 (*m*, 4 H); 7.48 (*d*, *J* = 15.6, 1 H); 7.60 (*t*, *J* = 7.6, 1 H); 7.72 (*d*, *J* = 7.6, 1 H); 7.81 (*d*, *J* = 7.6, 1 H); 7.94 (*s*, 1 H); 9.15 (br. *s*, 1 H); 10.60 (br. *s*, 1 H); 10.84 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}BrN_2O_4S$ (397.25): C 45.35, H 3.30, N 7.05; found: C 45.38, H 3.03, N 6.96.

*(2*E*)-*N*-Hydroxy-3-{3-[[[4-(trifluoromethoxy)phenyl]amino}sulfonyl]phenyl]prop-2-enamide* (*m***11.8**): M.p. 131°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 7.03–8.05 (*m*, 9 H); 8.98 (br. *s*, 1 H); 10.54 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{13}F_3N_2O_5S$ (402.35): C 47.76, H 3.26, N 6.96; found: C 47.68, H 3.15, N 6.91.

*(2*E*)-3-{3-[[(2-Fluorophenyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.9**): M.p. 102–103°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.44 (*d*, *J* = 16.0, 1 H); 6.96–7.24 (*m*, 4 H); 7.43 (*d*, *J* = 16.0, 1 H); 7.49–7.91 (*m*, 4 H); 9.04 (br. *s*, 1 H); 10.13 (br. *s*, 1 H); 10.73 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}N_2O_4FS \cdot 0.9$ EtOH (377.80): C 53.41, H 4.91, N 7.41; found: C 53.79, H 4.62, N 7.13.

*(2*E*)-3-{3-[[(3-Fluorophenyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.10**): M.p. 130–133°. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 6.52 (*d*, *J* = 15.8, 1 H); 6.75–6.97 (*m*, 4 H); 7.17–7.32 (*m*, 1 H); 7.47 (*d*, *J* = 15.8, 1 H); 7.58 (*t*, *J* = 7.8, 1 H); 7.67–7.85 (*m*, 2 H); 7.94 (*s*, 1 H); 9.19 (br. *s*, 1 H); 10.89 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}N_2O_4FS \cdot 0.65$ EtOH (366.28): C 53.45, H 4.65, N 7.65, S 8.75; found: C 53.54, H 4.32, N 7.37, S 8.50.

*(2*E*)-3-{3-[[[4-(Difluoromethoxy]phenyl]amino}sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.11**): M.p. 91–93°. ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.47 (*d*, *J* = 16.0, 1 H); 6.96 (*s*, 4 H); 7.31–7.93 (*m*, 6 H). Anal. calc. for $C_{16}H_{14}N_2O_5F_2S \cdot 0.3\ H_2O \cdot 0.5$ EtOH (412.79): C 49.46, H 4.30, N 6.79, S 7.77; found: C 49.46, H 3.95, N 6.65, S 7.39.

*(2*E*)-3-{3-[[(2,6-Difluorophenyl)amino]sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.12**): M.p. 79–82°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.47 (*d*, *J* = 16.0, 1 H); 6.89–7.89 (*m*, 8 H); 9.07 (br. *s*, 1 H); 10.02 (br. *s*, 1 H); 10.73 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{12}N_2O_4F_2S \cdot 1.2$ EtOH (409.61): C 51.02, H 4.72, N 6.84, S 7.83; found: C 50.84, H 4.60, N 6.78, S 7.76.

*(2*E*)*-N-*Hydroxy-3-{3-[[[2-methoxy-5-(trifluoromethyl)phenyl]amino}sulfonyl]phenyl}prop-2-enamide* (*m***11.13**): M.p. 207° (dec.). ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.57 (*s*, 3 H); 6.52 (*d*, *J* = 15.8, 1 H); 7.12 (*d*, *J* = 8.4, 1 H); 7.36–8.09 (*m*, 7 H); 9.11 (br. *s*, 1 H); (*s*, 1 H); 10.82 (*s*, 1 H). Anal. calc. for $C_{17}H_{15}F_3N_2O_5S$ (416.38): C 49.04, H 3.63, N 6.78; found: C 49.39, H 3.41, N 6.66.

*(2*E*)*-N-*Hydroxy-3-{3-[[[4-(trifluoromethyl)phenyl]amino}sulfonyl]phenyl}prop-2-enamide* (*m***11.14**): M.p. 184–185°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.53 (*d*, *J* = 15.9, 1 H); 7.30 (*d*, *J* = 8.4, 2 H); 7.49 (*d*, *J* = 15.9, 1 H); 7.61 (*t*, *J* = 7.4, 1 H); 7.62 (*d*, *J* = 8.4, 2 H); 7.78 (*d*, *J* = 8.4, 1 H); 7.82 (*d*, *J* = 8.2, 1 H); 8.00 (*s*, 1 H); 9.17 (*s*, 1 H); 10.86 (*s*, 1 H); 10.97 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{13}F_3N_2O_4S$ (386.35): C 49.74, H 3.39, N 7.25, S 8.30; found: C 49.78, H 3.47, N 7.05, S 8.34.

*(2*E*)*-N-*Hydroxy-3-{3-[{[3-[(trifluoromethyl)thio]phenyl}amino}sulfonyl]phenyl}prop-2-enamide* (*m***11.15**): M.p. 139–140°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.51 (*d*, *J* = 15.8, 1 H); 7.26–7.53 (*m*, 5 H); 7.58 (*t*, *J* = 7.7, 1 H); 7.71 (*d*, *J* = 8.0, 1 H); 7.80 (*d*, *J* = 7.6, 1 H); 7.91 (*s*, 1 H); 9.14 (*s*, 1 H); 10.70 (*s*, 1 H); 10.84 (*s*, 1 H). Anal. calc. for $C_{16}H_{13}F_3N_2O_4S_2$ (418.42): C 45.93, H 3.13, N 6.70, S 15.33; found: C 46.04, H 3.02, N 6.74, S 15.31.

*(2*E*)*-N-*Hydroxy-3-{3-[{[4-[(trifluoromethyl)thio]phenyl}amino}sulfonyl]phenyl}prop-2-enamide* (*m***11.16**): M.p. 151° (dec.). ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.53 (*d*, *J* = 15.7, 1 H); 7.24 (*d*, *J* = 8.6, 2 H); 7.49 (*d*, *J* = 15.7, 1 H); 7.59 (*d*, *J* = 8.6, 2 H); 7.63 (*d*, *J* = 7.8, 1 H); 7.78 (*d*, *J* = 8.0, 1 H); 7.80 (*t*, *J* = 7.9, 1 H); 7.99 (*s*, 1 H); 9.16 (*s*, 1 H); 10.85 (*s*, 1 H); 10.91 (*s*, 1 H). Anal. calc. for $C_{16}H_{13}F_3N_2O_4S_2$ (418.42): C 45.93, H 3.13, N 6.70; found: C 45.99, H 2.96, N 6.61.

*(2*E*)-3-{3-[[(2,6-Dimethylphenyl)amino]sulfonyl]pheny}*-N-*hydroxyprop-2-enamide* (*m***11.17**): M.p. 163–165°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.96 (*s*, 6 H); 6.56 (*d*, *J* = 16.0, 1 H); 7.07 (*m*, 3 H); 7.56 (*d*, *J* = 16.0, 1 H);7.69–7.98 (*m*, 4 H); (br. *s*, 2 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_4S \cdot 1.4$ H_2O, (371.62): C 54.94, H 5.64, N 7.54; found: C 54.96, H 5.20, N 7.58.

*(2*E*)-3-{3-[[(3,5-Difluorophenyl)amino]sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.18**): M.p. 135°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.54 (*d*, *J* = 15.7, 1 H); 6.69–6.82 (*m*, 2 H); 6.90 (*tt*, *J* = 2.1, 9.4, 1 H); 7.52 (*d*, *J* = 15.7, 1 H); 7.61 (*t*, *J* = 7.9, 1 H); 7.78 (*d*, *J* = 7.9, 1 H); 7.84 (*d*, *J* = 7.9, 1 H); 7.99 (*s*, 1 H); 9.16 (*s*, 1 H); 10.86 (*s*, 2 H). Anal. calc. for $C_{15}H_{12}F_2N_2O_4S$ (354.33): C 50.85, H 3.41, N 7.91; found: C 50.71, H 3.22, N 7.99.

*(2*E*)-3-{3-[{[3,5-Bis(trifluoromethyl)phenyl]amino}sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.19**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.54 (*d*, *J* = 15.8, 1 H); 7.48 (*d*, *J* = 15.8, 1 H); 7.63 (*t*, *J* = 7.7, 1 H); 7.65 (*s*, 3 H); 7.73–7.81 (*m*, 2 H); 7.84 (*d*, *J* = 7.6, 1 H); 7.98 (*s*, 1 H); 9.14 (br. *s*, 1 H); (*s*, 1 H). Anal. calc. for $C_{17}H_{12}F_6N_2O_4S$ (454.35): C 44.96, H 2.63, N 6.17; found: C 44.94, H 2.66, N 6.17.

*(2*E*)*-N-*Hydroxy-3-{3-[[(4-methoxyphenyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m***11.20**): M.p. 186°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.67 (*s*, 3 H); 6.49 (*d*, *J* = 16.0, 1 H); 6.72–8.03 (*m*, 9 H); 9.14 (br. *s*, 1 H); 9.91 (*s*, 1 H); 10.85 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_5S$ (348.38): C 55.16, H 4.63, N 8.04, S 9.20; found: C 55.07, H 4.60, N 7.94, S 9.01.

*(2*E*)-3-{3-[[(3,4-Dimethoxyphenyl)amino]sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.21**): M.p. 191°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.60 (*s*, 3 H); 3.65 (*s*, 3 H); 6.34–6.87 (*m*, 4 H); 7.32–8.03 (*m*, 5 H); 9.09 (br. *s*, 1 H); 9.92 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_6S$ (378.41): C 53.96, H 4.79, N 7.40; found: C 53.84, H 4.78, N 7.25.

*(2*E*)*-N-*Hydroxy-3-{3-[(naphthalen-1-ylamino)sulfonyl]phenyl}prop-2-enamide* (*m***11.22**): M.p. 180°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.45 (*d*, *J* = 16.0, 1 H); 7.14 (*dd*, *J* = 1.4, 7.0, 1 H); 7.31–8.14 (*m*, 11 H); 9.09 (br. *s*, 1 H); 10.27 (*s*, 1 H); (br. *s*, 1 H). Anal. calc. for $C_{19}H_{16}N_2O_4S$ (368.41): C 61.94, H 4.38, N 7.60; found: C 61.18, H 4.32, N 7.54.

*(2*E*)*-N-*Hydroxy-3-{3-[(naphthalen-2-ylamino)sulfonyl]phenyl}prop-2-enamide* (*m***11.23**): M.p. 164°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 7.16–7.89 (*m*, 12 H); 7.98 (br. *s*, 1 H); (*s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{16}N_2O_4S$ (368.41): C 61.94, H 4.38, N 7.60; found: C 61.44, H 4.39, N 7.48.

*(2*E*)-3-{3-[([1,1′-Biphenyl]-2-ylamino)sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.24**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.43 (*d*, *J* = 16.0, 1 H); 6.94–7.85 (*m*, 14 H); 9.07 (br. *s*, 1 H); 9.58 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{18}N_2O_4S \cdot 0.5$ H_2O (403.45): C 62.52, H 4.75, N 6.94; found: C 62.58, H 4.66, N 6.65.

*(2*E*)-3-{3-[([1,1′-Biphenyl]-4-ylamino)sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (*m***11.25**): M.p. 188°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 7.07–8.07 (*m*, 14 H); 9.09 (br. *s*, 1 H); 10.35 (br. *s*, 1 H);

10.80 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{18}N_2O_4S \cdot 0.2\ H_2O$ (398.05): C 63.37, H 4.66, N 7.04; found: C 63.42, H 4.57, N 6.95.

*(2*E*)-3-{3-[(1*H*-Benzimidazol-6-ylamino)sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.26**): M.p. 197° (dec.). ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.49 (*d*, *J* = 16.0, 1 H); 6.94 (*dd*, *J* = 2.0, 8.8, 1 H); 7.22–8.07 (*m*, 7 H); 8.13 (*s*, 1 H); 9.11 (br. *s*, 1 H); 10.12 (*s*, 1 H); 10.80 (*s*, 1 H); 12.34 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{14}N_4O_4S \cdot 0.2\ AcOEt \cdot 0.4\ H_2O$ (383.20): C 52.66, H 4.31, N 14.62, S 8.37; found: C 52.50, H 3.82, N 14.57, S 8.45.

*(2*E*)-3-{3-[[(9-Ethyl-9*H*-carbazol-3-yl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.27**): M.p. 130–133°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.20 (*t*, *J* = 6.6, 3 H); 4.34 (*q*, *J* = 6.6, 2 H); 6.42 (*d*, *J* = 16.0, 1 H); 6.93–8.07 (*m*, 13 H); 9.07 (br. *s*, 1 H); 10.3 (br. *s*, 1 H). Anal. calc. for $C_{23}H_{21}N_3O_4S \cdot 0.8\ H_2O \cdot 0.4$ EtOH (468.34): C 60.91, H 5.11, N 9.27, S 7.07; found: C 61.01, H 5.15, N 8.75, S 6.65.

*(2*E*)-*N*-Hydroxy-3-{3-[(tricyclo[3.3.1.1.^{3,7}]dec-1-ylamino)sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.28**): M.p. 179°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.32–2.05 (*m*, 15 H); 6.52 (*d*, *J* = 16.0, 1 H); 7.29–7.87 (*m*, 5 H); 7.98 (br. *s*, 1 H); 9.09 (*s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{24}N_2O_4S$ (376.48): C 60.62, H 6.43, N 7.44; found: C 60.71, H 6.39, N 7.24.

*(2*E*)-3-{3-[(Benzylamino)sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.29**): M.p. 179°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.02 (*d*, *J* = 6.4, 2 H); 6.53 (*d*, *J* = 16.0, 1 H); 7.25 (*s*, 5 H); 7.39–8.03 (*m*, 5 H); 8.20 (*t*, *J* = 6.4, 1 H); 9.12 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S$ (332.38): C 57.82, H 4.85, N 8.43, S 9.60; found: C 57.59, H 4.82, N 8.14, S 9.65.

*(2*E*)-3-{3-[[(1,3-Benzodioxol-5-ylmethyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.30**): M.p. 163°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.92 (*d*, *J* = 6.4, 2 H); 5.92 (*s*, 2 H); 6.49 (*d*, *J* = 16.0, 1 H); 6.67 (*s*, 3 H); 7.34–7.89 (*m*, 5 H); 8.12 (*t*, *J* = 6.4, 1 H); 9.07 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{16}N_2O_6S$ (376.39): C 54.25, H 4.28, N 7.44; found: C 54.19, H 4.20, N 7.33.

*(2*E*)-*N*-Hydroxy-3-{3-[[(pyridin-3-ylmethyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.31**): M.p. 191°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.05 (*d*, *J* = 6.4, 2 H); 6.56 (*d*, *J* = 16.0, 1 H); 7.16–8.05 (*m*, 7 H); 8.16–8.49 (*m*, 3 H); 9.12 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{15}N_3O_4S$ (333.37): C 54.04, H 4.54, N 12.60; found: C 53.72, H 4.33, N 12.41.

*(2*E*)-*N*-Hydroxy-3-{3-[[(3,4,5-trimethoxybenzyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.32**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.54 (*s*, 3 H); 3.65 (*s*, 6 H); 3.98 (*m*, 2 H); 6.46 (*s*, 2 H); 6.56 (*d*, *J* = 15.0, 1 H); 7.32–7.98 (*m*, 5 H); 8.18 (br. *t*, *J* = 5.5, 1 H); 9.12 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_7S \cdot 0.5\ H_2O$ (431.46): C 52.89, H 5.37, N 6.49; found: C 53.13, H 5.31, N 6.02.

*(2*E*)-*N*-Hydroxy-3-{3-[[(naphthalen-1-ylmethyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.33**): M.p. 177°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.45 (*d*, *J* = 6.0, 2 H); 6.58 (*d*, *J* = 16.0, 1 H);7.29–8.38 (*m*, 13 H); 9.12 (br. *s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{18}N_2O_4S$ (382.44): C 62.54, H 4.70, N 7.21; found: C 62.81, H 4.74, N 7.32.

*(2*E*)-3-{3-[[(3,5-Dimethoxybenzyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.34**): M.p. 114°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 3.64 (*s*, 6 H); 3.98 (*d*, *J* = 5.0, 2 H); 6.28 (*t*, *J* = 2.2, 1 H); 6.35 (*d*, *J* = 2.2, 2 H); 6.53 (*d*, *J* = 15.8, 1 H); 7.47 (*d*, *J* = 15.8, 1 H); 7.57 (*t*, *J* = 7.9, 1 H); 7.70–7.80 (*m*, 2 H); 7.88 (*s*, 1 H); 8.15–8.26 (*m*, 1 H); 9.13 (br. *s*, 1 H); 10.81 (br. *s*, 1 H). Anal. calc. for $C_{18}H_{20}N_2O_6S$ (392.43): C 55.09, H 5.14, N 7.14; found: C 55.12, H 5.05, N 7.09.

*(2*E*)-3-{3-[[(2-Furan-2-ylmethyl)amino]sulfonyl]phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.35**): M.p. 165°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.03 (*d*, *J* = 6.4, 2 H); 6.23 (*m*, 2 H); 6.54 (*d*, *J* = 16.0, 1 H); 7.38–8.05 (*m*, 6 H); 8.20 (*t*, *J* = 6.4, 1 H); 9.09 (br. *s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{14}H_{14}N_2O_5S$ (322.34): C 52.17, H 4.38, N 8.69; found: C 51.87, H 4.39, N 8.41.

*(2*E*)-*N*-Hydroxy-3-{3-[[(2-phenylethyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.36**): M.p. 114°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.67 (*m*, 2 H); 3.00 (*m*, 2 H); 6.55 (*d*, *J* = 16.0, 1 H); 7.00–8.05 (*m*, 11 H); 9.12 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_4S$ (346.41): C 58.94, H 5.24, N 8.09, S 9.26; found: C 58.81, H 5.16, N 8.00, S 9.05.

*(2*E*)-3-{3-{[[2-(Dimethoxyphenyl)ethyl]amino}sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m*.p. **11.37**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.58 (*t*, *J* = 7.0, 2 H, overlapped with DMSO); 2.85–3.16 (*m*, 2 H); 3.67 (*s*, 6 H); 6.38–6.94 (*m*, 4 H); 7.38–8.05 (*m*, 6 H); 9.16 (br. *s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_6S \cdot H_2O$ (424.47): C 53.76, H 5.70, N 6.60; found: C 53.75, H 5.24, N 6.45.

*(2*E*)-*N*-Hydroxy-3-{3-[[(3-phenylpropyl)amino]sulfonyl]phenyl}prop-2-enamide* (*m*.p. **11.38**): M.p. 148°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.40–1.83 (*m*, 2 H); 2.27–2.94 (*m*, 4 H, overlapped with DMSO); 6.56 (*d*, *J* = 15.6, 1 H); 6.98–7.38 (*m*, 5 H); 7.38–8.09 (*m*, 6 H); 9.16 (br. *s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{18}H_{20}N_2O_4S$ (360.44): C 59.98, H 5.59, N 7.77; found: C 59.73, H 5.55, N 7.63.

*(2*E*)-*N*-Hydroxy-3-{3-{[(2-phenoxyethyl)amino]sulfonyl}phenyl}prop-2-enamide* (*m***11.39**): M.p. 151°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.00–3.54 (*m*, 2 H, overlapped with H_2O); 3.94 (*t*, *J* = 7.0, 2 H); 6.59 (*d*, *J* = 16.0, 1 H); 6.74–7.05 (*m*, 3 H); 7.12–8.12 (*m*, 8 H); 9.09 (br. *s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_5S$ (362.41): C 56.34, H 5.01, N 7.73; found: C 56.04, H 4.96, N 7.54.

*(2*E*)-*N*-Hydroxy-3-{3-{[(4-phenylbutyl)amino]sulfonyl}phenyl}prop-2-enamide* (*m***11.40**): M.p. 103°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.16–1.83 (*m*, 4 H); 2.27–3.58 (*m*, 4 H, overlapped with DMSO); 6.56 (*d*, *J* = 15.6, 1 H); 6.94–7.40 (*m*, 5 H); 7.41–8.12 (*m*, 6 H); 9.16 (*s*, 1 H); 10.83 (*s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_4S$ (374.46): C 60.94, H 5.92, N 7.48; found: C 60.76, H 5.86, N 7.41.

*(2*E*)-3-{3-{[(Diphenylmethyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.41**): M.p. 180°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 5.60 (*d*, *J* = 9.0, 1 H); 6.43 (*d*, *J* = 16.0, 1 H); 6.98–7.83 (*m*, 15 H); 8.85 (*d*, *J* = 9.0, 1 H); 9.14 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{22}H_{20}N_2O_4S$ (408.48): C 64.69, H 4.94, N 6.86; found: C 64.60, H 4.94, N 6.77.

*(2*E*)-3-{3-{[(1,2-Diphenylethyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.42**): M.p. 150°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.83 (*d*, *J* = 9.0, 2 H); 4.47 (*q*, *J* = 9.0, 1 H); 6.38 (*d*, *J* = 16.0, 1 H); 6.92–7.65 (*m*, 15 H); 8.38 (*d*, *J* = 9.0, 1 H); 9.12 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{23}H_{22}N_2O_4S$ (422.51): C 65.39, H 5.25, N 6.63; found: C 64.97, H 5.14, N 6.57.

*(2*E*)-3-{3-{[(1-Benzylpropyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.43**): M.p. 129–130°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 0.67 (*t*, *J* = 7.3, 3 H); 1.09–1.45 (*m*, 2 H); 2.40–2.66 (*m*, 2 H, overlapped with DMSO); 3.14–3.41 (*m*, 1 H, overlapped with H_2O); 6.55 (*d*, *J* = 15.8, 1 H); 6.97–7.23 (*m*, 5 H); 7.48 (*d*, *J* = 15.8, 1 H); 7.53 (*t*, *J* = 7.6, 1 H); 7.63–7.80 (*m*, 3 H); 7.86 (*s*, 1 H); 9.15 (*s*, 1 H); 10.84 (*s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_4S$ (374.46): C 60.94, H 5.92, N 7.48; found: C 60.88, H 5.92, N 7.39.

*(2*E*)-*N*-Hydroxy-3-{3-{[(2-hydroxy-2-phenylethyl)amino]sulfonyl}phenyl}prop-2-enamide* (*m***11.44**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.77–2.98 (*m*, 2 H); 4.49–4.61 (*m*, 1 H); 5.52 (*d*, *J* = 4.4, 1 H); 6.56 (*d*, *J* = 15.8, 1 H); 7.17–7.36 (*m*, 5 H); 7.51 (*d*, *J* = 15.8, 1 H); 7.59 (*t*, *J* = 8.0, 1 H); 7.70–7.84 (*m*, 3 H); 7.95 (*s*, 1 H); 9.14 (br. *s*, 1 H); 10.82 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_5S \cdot 0.5\ H_2O$ (371.41): C 54.98, H 5.16, N 7.54; found: C 54.90, H 4.91, N 7.18.

*(2*E*)-3-{3-{[(3,3-Diphenylpropyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.45**): M.p. 169°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.11 (*q*, *J* = 7.3, 2 H); 2.65 (*q*, *J* = 6.5, 2 H); 3.97 (*t*, *J* = 7.8, 1 H); 6.55 (*d*, *J* = 16.0, 1 H); 7.07–7.29 (*m*, 10 H); 7.51 (*d*, *J* = 16.0, 1 H); 7.60 (*t*, *J* = 7.6, 1 H); 7.70 (*d*, *J* = 7.6, 1 H); 7.75 (*t*, *J* = 5.6, 1 H); 7.80 (*d*, *J* = 7.6, 1 H); 7.88 (*s*, 1 H); 9.14 (*s*, 1 H); 10.02 (*s*, 1 H). Anal. calc. for $C_{24}H_{24}N_2O_4S$ (436.53): C 66.04, H 5.54, N 6.42; found: C 66.11, H 5.47, N 6.40.

*(2*E*)-*N*-Hydroxy-3-{3-{[methyl(phenyl)amino]sulfony}phenyl}prop-2-enamide* (*m***11.46**): M.p. 152°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.16 (*s*, 3 H); 6.47 (*d*, *J* = 16.0, 1 H); 7.03–7.96 (*m*, 10 H); 9.09 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S$ (332.38): C 57.82, H 4.85, N 8.43; found: C 57.82, H 4.83, N 8.35.

*(2*E*)-*N*-Hydroxy-3-{3-{[(2-methylpropyl)phenylamino]sulfonyl}phenyl}prop-2-enamide* (*m***11.47**): M.p. 154–155°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 0.85 (*d*, *J* = 6.6, 6 H); 1.43 (*m*, 1 H); 3.37 (*d*, *J* = 6.6, 2 H, overlapped with H_2O); 6.49 (*d*, *J* = 16.0, 1 H); 7.02–7.13 (*m*, 2 H); 7.27–7.42 (*m*, 3 H); 7.48 (*d*, *J* = 7.6, 1 H); 7.51 (*d*, *J* = 16.0, 1 H); 7.60 (*t*, *J* = 7.8, 1 H); 7.67 (*s*, 1 H); 7.86 (*d*, *J* = 7.6, 1 H); 9.15 (br. *s*, 1 H); 10.81 (*s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_4S$ (374.46): C 60.94, H 5.92, N 7.48, S 8.56; found: C 60.91, H 5.83, N 7.35, S 8.54.

*(2*E*)-3-{3-{[Benzyl(pyridin-3-ylmethyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.48**): M.p. 146°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.38 (*s*, 4 H); 6.60 (*d*, *J* = 16.0, 1 H); 7.00–7.38 (*m*, 6 H); 7.39–8.09 (*m*, 6 H); 8.20–8.54 (*m*, 2 H); 9.16 (br. *s*, 1 H); 10.80 (br. *s*, 1 H). Anal. calc. for $C_{22}H_{21}N_3O_4S$ (423.49): C 62.40, H 5.00, N 9.92; found: C 62.29, H 4.95, N 9.76.

*(2*E*)-3-{3-{[(1,3-Benzodioxol-5-ylmethyl)(pyridin-3-ylmethyl)amino]sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.49**): M.p. 85°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 4.23 (*s*, 2 H); 4.37 (*s*, 2 H); 5.93 (*s*, 2 H); 6.54–6.68 (*m*, 3 H); 6.72 (*d*, *J* = 8.4, 1 H); 7.22 (*dd*, *J* = 4.7, 7.7, 1 H); 7.48 (*dt*, *J* = 1.7, 7.7, 1 H); 7.54 (*d*, *J* = 16.0, 1 H); 7.65 (*t*, *J* = 7.8, 1 H); 7.80–7.93 (*m*, 2 H); 7.99 (*s*, 1 H); 8.27 (*d*, *J* = 1.8, 1 H); 8.36 (*dd*, *J* = 1.2, 4.7, 1 H); 9.15 (br. *s*, 1 H);10.81 (br. *s*, 1 H). Anal. calc. for $C_{23}H_{21}N_3O_6S \cdot 0.5\ H_2O \cdot 0.25\ Et_2O$ (495.03): C 58.23, H 4.99, N 8.49; found: C 58.28, H 4.95, N 8.13.

*(2*E*)-3-{3-{[[2-(3,4-Dimethoxyphenyl)ethyl](4-methoxybenzyl)amino}sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.50**): M.p. 114°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.23–2.69 (*m*, 2 H, overlapped with DMSO); 2.98–3.45 (*m*, 2 H, overlapped with H_2O); 3.60 (*s*, 6 H); 3.76 (*s*, 3 H); 4.27 (*s*, 2 H); 6.42–7.09 (*m*, 6 H); 7.15–7.43 (*m*, 2 H); 7.45–8.09 (*m*, 5 H); 9.09 (br. *s*, 1 H); 10.72 (br. *s*, 1 H). Anal. calc. for $C_{27}H_{30}N_2O_7S$ (526.61): C 61.58, H 5.74, N 5.32; found: C 61.36, H 5.66, N 5.27.

*(2*E*)-3-{3-{[[2-(3,4-Dimethoxyphenyl)ethyl](3-phenylpropyl)amino}sulfonyl}phenyl}-*N*-hydroxyprop-2-enamide* (*m***11.51**): M.p. 47°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.58–1.87 (*m*, 2 H); 2.42–2.59 (*m*, 2 H,

overlapped with DMSO); 2.59–2.81 (*m*, 2 H); 2.97–3.24 (*m*, 2 H); 3.24–3.47 (*m*, 2 H, overlapped with H_2O); 3.70 (*s*, 6 H); 6.49–6.91 (*m*, 4 H); 7.04–7.37 (*m*, 5 H); 7.46–8.03 (*m*, 5 H); 9.16 (br. *s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{28}H_{32}N_2O_6S \cdot 0.3\ H_2O$ (530.04): C 63.45, H 6.20, N 5.29; found: C 63.45, H 6.30, N 5.14.

*(2*E*)-3-{3-{[Bis(3-phenylpropyl)amino]sulfonyl}phenyl}*-N*-hydroxyprop-2-enamide* (*m***11.52**): M.p. 117°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.62–1.81 (*m*, 4 H); 2.43–2.61 (*m*, 4 H, overlapped with DMSO); 3.13 (*t*, *J* = 7.3, 4 H); 6.58 (*d*, *J* = 16.2, 1 H); 7.08–7.32 (*m*, 10 H); 7.47–7.75 (*m*, 3 H); 7.80–7.90 (*m*, 2 H); 9.44 (br. *s*, 1 H); 10.38 (br. *s*, 1 H). Anal. calc. for $C_{27}H_{30}N_2O_4S$ (478.62): C 67.76, H 6.32, N 5.85; found: C 67.54, H 6.30, N 5.88.

*(2*E*)*-N*-Hydroxy-3-{2-[(phenylamino)sulfonyl]phenyl}prop-2-enamide* (*o***11.1**): M.p. 205–206.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.37 (*d*, *J* = 16.0, 1 H); 6.99–8.04 (*m*, 10 H); 8.23 (*d*, *J* = 16.0, 1 H); 10.55 (*s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{14}N_2O_4S \cdot 0.1$ MeCN $\cdot 0.3\ H_2O$ (327.86): C 55.63, H 4.58, N 8.97; found: C 55.63, H 4.36, N 9.07.

*(2*E*)*-N*-Hydroxy-3-{2-[(naphthalen-1-ylamino)sulfonyl]phenyl}prop-2-enamide* (*o***11.2**): M.p. 186–187°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.29 (*d*, *J* = 15.0, 1 H); 7.17–8.16 (*m*, 11 H); 8.36 (*d*, *J* = 15.0, 1 H); 9.14 (br. *s*, 1 H); 10.57 (*s*, 1 H); 10.83 (*s*, 1 H). Anal. calc. for $C_{19}H_{16}N_2O_4S \cdot 0.5\ H_2O$ (377.41): C 60.47, H 4.54, N 7.42; found: C 60.46, H 4.35, N 7.69.

*(2*E*)*-N*-Hydroxy-3-{2-{[methyl(phenyl)amino]sulfonyl}phenyl}prop-2-enamide* (*o***11.3**): M.p. 144.5–145.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.16 (*s*, 3 H); 6.32 (*d*, *J* = 16.0, 1 H); 7.00–7.86 (*m*, 9 H); 8.09 (*d*, *J* = 16.0, 1 H); 9.12 (br. *s*, 1 H); 10.80 (*s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S \cdot 0.8\ H_2O$ (346.79): C 55.42, H 5.12, N 8.08; found: C 55.17, H 4.65, N 8.05.

*(2*E*)-3-[4-(Chlorosulfonyl)phenyl]prop-2-enoic Acid* (**13**). To neat chlorosulfonic acid (50.1 g, 0.43 mol) at 13–16°, cinnamic acid (**12**, 7.9 g, 0.054 mmol) was added in portions. The mixture was stirred at 10–12° for 26 h, at r.t. for 2 h, and at 46° for 1 h. The dark, viscous syrup was poured onto ice and the precipitate filtered, washed with H_2O, and dried *in vacuo* (P_2O_5) to afford a white solid (6.06 g). The solid was crystallized from dioxane: **13** (4.5 g, 34%). White crystals. M.p. 219°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.53 (*d*, *J* = 16.0, 1 H); 7.57 (*d*, *J* = 16.0, 1 H); 7.60 (*d*, *J* = 8.5, 2 H); 7.64 (*d*, *J* = 8.5, 2 H); 9.53 (br. *s*, 1 H and H_2O).

*(2*E*)-3-[4-[(Phenylamino)sulfonyl]phenyl]prop-2-enoic Acid* (**14**). To a mixture of benzenamine (0.35 g, 3.75 mmol) and pyridine (1 ml), a soln. of **13** (0.45 g, 1.82 mmol) in CH_2Cl_2 (3 ml) was added, and the resultant soln. was stirred at 40° for 1 h. The mixture was evaporated and the residue partitioned between AcOEt and 6M HCl. The org. layer was washed successively with H_2O, sat. NaCl soln., dried (Na_2SO_4), and evaporated: **14.1** (0.30 g, 54%). ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.60 (*d*, *J* = 16.0, 1 H); 6.93–7.43 (*m*, 5 H); 7.60 (*d*, *J* = 16.0, 1 H); 7.79 (*d*, *J* = 8.0, 2 H); 7.87 (*d*, *J* = 8.0, 2 H); 10.35 (*s*, 1 H).

*(2*E*)*-N*-Hydroxy-3-{4-[(phenylamino)sulfonyl]phenyl}prop-2-enamide* (**15.1**). As described for *m***11.1**, with **14**; washing with Et_2O: 39% of **15.1**. White crystals. M.p. 176–177.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.54 (*d*, *J* = 16.0, 1 H); 6.96–7.32 (*m*, 5 H); 7.47 (*d*, *J* = 16.0, 1 H); 7.76 (*s*, 4 H); 9.14 (br. *s*, 1 H); (br. *s*, 1 H); (*s*, 1 H). Anal. calc. for $C_{15}H_{14}N_2O_4S$ (318.35): C 56.59, H 4.43, N 8.80; found: 55.82, H 4.38, N 9.01.

3-[4-(Aminosulfonyl)phenyl]-N*-hydroxypropenamides* **15.2**–**15.7** were obtained as described for **15.1**.

*(2*E*)-3-{4-[(4-Bromophenyl)amino]sulfonyl}phenyl}*-N*-hydroxyprop-2-enamide* (**15.2**): M.p. 219–220.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.54 (*d*, *J* = 16.0, 1 H); 7.05 (*d*, *J* = 8.0, 2 H); 7.43 (*d*, *J* = 8.0, 2 H); 7.49 (*d*, *J* = 16.0, 1 H); 7.63–7.87 (*m*, 4 H); 9.11 (br. *s*, 1 H); 10.45 (*s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}BrN_2O_4S$ (397.25): C 45.35, H 3.30, N 7.05; found: C 45.44, H 3.28, N 7.05.

*(2*E*)-3-{4-[(4-Chlorophenyl)amino]sulfonyl}phenyl}*-N*-hydroxyprop-2-enamide* (**15.3**): M.p. 201–202°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.52 (*d*, *J* = 16.0, 1 H); 7.08 (*d*, *J* = 8.0, 2 H); 7.29 (*d*, *J* = 8.0, 2 H); 7.45 (*d*, *J* = 16.0, 1 H); 7.63–7.89 (*m*, 5 H); 10.43 (br. *s*, 1 H); 10.83 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{13}ClN_2O_4S$ (352.80): C 51.07, H 3.71, N 7.94; found: C 51.14, H 3.70, N 7.86.

*(2*E*)*-N*-Hydroxy-3-{4-[([1,1′-biphenyl]-4-ylamino)sulfonyl]phenyl}prop-2-enamide* (**15.4**): M.p. 211–211.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.53 (*d*, *J* = 16.0, 1 H); 7.19 (*d*, *J* = 8.0, 2 H); 7.32–7.69 (*m*, 8 H); 7.72–7.92 (*m*, 4 H); 9.09 (br. *s*, 1 H); 10.45 (*s*, 1 H); 10.85 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{18}N_2O_4S$ (394.45): C 63.94, H 4.60, N 7.10; found: C 63.51, H 4.37, N 7.11.

*(2*E*)*-N*-Hydroxy-3-{4-[(naphthalen-2-ylamino)sulfonyl]phenyl}prop-2-enamide* (**15.5**): M.p. 198.5–199.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.54 (*d*, *J* = 16.0, 1 H); 7.16 (*dd*, *J* = 2.0, 8.0, 1 H); 7.29–8.12 (*m*, 11 H); 9.11 (br. *s*, 1 H); 10.07 (*s*, 1 H); 10.87 (*s*, 1 H). Anal. calc. for $C_{19}H_{16}N_2O_4S \cdot 0.3\ H_2O$ (373.81): C 61.05, H 4.48, N 7.49; found: C 60.96, H 4.28, N 7.56.

*(2*E*)-3-{4-[(9-Ethyl-9*H*-carbazol-3-yl)amino]sulfonyl}phenyl}*-N*-hydroxyprop-2-enamide* (**15.6**): M.p. 198.5–199.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.26 (*t*, *J* = 6.9, 3 H); 4.39 (*q*, *J* = 6.9, 2 H); 6.50 (*d*, *J* = 15.8, 1 H); 7.07–7.20 (*m*, 2 H); 7.38–7.49 (*m*, 3 H); 7.57 (*d*, *J* = 8.2, 1 H); 7.62 (*d*, *J* = 8.8, 2 H); 7.67 (*d*, *J* = 8.8, 2 H);

7.83 (*d*, *J* = 2.0, 1 H); 8.04 (*d*, *J* = 7.6, 1 H); 9.13 (br. *s*, 1 H); 10.11 (br. *s*, 1 H); 10.83 (*s*, 1 H). Anal. calc. for $C_{23}H_{21}N_3O_4S$ (435.51): C 63.43, H 4.86, N 9.65; found: C 62.99, H 4.73, N 9,59.

*(2*E*)-3-{4-[(Benzylamino)sulfonyl]phenyl}*-N-*hydroxyprop-2-enamide* (**15.7**): M.p. 190–191.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.99 (*d*, *J* = 6.2, 2 H); 6.57 (*d*, *J* = 16.2, 1 H); 7.20–7.30 (*m*, 5 H); 7.51 (*d*, *J* = 16.2, 1 H); 7.73 (*d*, *J* = 8.6, 2 H); 7.80 (*d*, *J* = 8.8, 2 H); 8.21 (*t*, *J* = 6.2, 1 H); 9.15 (br. *s*, 1 H); 10.88 (*s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S$ (332.38): C 57.82, H 4.85, N 8.43; found: C 57.38, H 4.74, N 8.25.

*Methyl (2*E*)-3-(3-Aminophenyl)prop-2-enoate* (*m***17**). A mixture of *m***16** (10.0 g, 48 mmol) and $SnCl_2 \cdot 2\,H_2O$ (54 g, 240 mmol) in anh. EtOH (200 ml) was heated at 80° for 1 h. The mixture was allowed to cool to r.t., then the solvent was partially evaporated (up to *ca.* ½ volume). The residue was poured in ice-water, neutralized (pH *ca.* 7) with sat. Na_2CO_3 soln., and the resulting mixture extracted with AcOEt. The org. extract was washed with sat. NaCl soln. and dried (Na_2SO_4). The soln. was filtered through a small amount of SiO_2 and evaporated: *m***17** (8.5 g, 99%). ^{1}H-NMR ($CDCl_3$, 90 MHz): 3.69 (br. *s*, 2 H); 3.79 (*s*, 3 H); 6.39 (*d*, *J* = 16.0, 1 H); 6.61–7.03 (*m*, 3 H); 7.18 (*t*, *J* = 7.6, 1 H); 7.62 (*d*, *J* = 16.0, 1 H).

*Methyl (2*E*)-3-{3-{[[(1*E*)-2-phenylethenyl]sulfonyl}amino}phenyl}prop-2-enoate* (*m***18.6**). A soln. of (1*E*)-2-phenylethenesulfonyl chloride (0.59 g, 2.82 mmol) in dioxane (3 ml) was added to a mixture of *m***17** (0.50 g, 2.82 mmol) in dioxane (12 ml) and $NaHCO_3$ (0.36 g, 4.28 mmol) in H_2O (8 ml), and the resultant soln. was stirred at r.t. until completion of the reaction (TLC). The mixture was evaporated and the residue partitioned between AcOEt and 2M HCl. The org. phase was washed successively with H_2O, sat. NaCl soln., dried (Na_2SO_4), and evaporated and the residue purified by CC (SiO_2, $CHCl_3$/AcOEt 50 : 1): 0.68 g (70%) of *m***18.6**. White solid. ^{1}H-NMR ($CDCl_3$, 90 MHz): 3.78 (*s*, 3 H); 6.39 (*d*, *J* = 16.0, 1 H); 6.77 (*d*, *J* = 15.8, 1 H); 6.78 (*s*, 1 H); 7.17–7.48 (*m*, 9 H); 7.49 (*d*, *J* = 15.8, 1 H); 7.58 (*d*, *J* = 16.0, 1 H).

*(2*E*)-3-{3-{[[(1*E*)-2-Phenylethenyl]sulfonyl}amino}phenyl}prop-2-enoic Acid* (*m***19.6**). As described for *m***10.1**, with *m***18.6**: 90% of *m***19.1**. White solid. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.41 (*d*, *J* = 16.0, 1 H); 7.12–7.51 (*m*, 9 H); 7.55–7.81 (*m*, 3 H); 10.16 (br. *s*, 1 H); (br. *s*, 1 H).

*(2*E*)-*N*-Hydroxy-3-{3-{[[(1*E*)-2-phenylethenyl]sulfonyl}amino}phenyl}prop-2-enamide* (*m***20.6**). As described for *m***11.1**, with *m***19.1**; crystallization from AcOEt: 42% of *m***20.6**. White crystals. M.p. 171°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.38 (*d*, *J* = 16.0, 1 H); 7.07–7.80 (*m*, 12 H); 9.03 (br. *s*, 1 H); 10.16 (*s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{16}N_2O_4S$ (344.39): C 59.29, H 4.68, N 8.13; found: C 59.13, H 4.70, N 7.92.

*(2*E*)-*N*-Hydroxy-3-{4-[(phenylsulfonyl)amino]phenyl}prop-2-enamide* (*p***20.1**). As described for *p***40**, with *p***18.1**: 31% of *p***20.1**. M.p. 189–191°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.30 (*d*, *J* = 15.8, 1 H); 7.12 (*d*, *J* = 8.5, 2 H); 7.32 (*d*, *J* = 15.8, 1 H); 7.45 (*d*, *J* = 8.5, 2 H); 7.48–7.86 (*m*, 6 H); 9.01 (*s*, 1 H); 10.56 (*s*, 1 H); 10.72 (*s*, 1 H). Anal. calc. for $C_{15}H_{14}N_2O_4S$ (318.35): C 56.59, H 4.43, N 8.80, S 10.07; found: C 56.03, H 4.24, N 8.66, S 10.02.

3-{[(R)sulfonylamino]phenyl}-N-*hydroxypropenamides m***20.1**–*m***20.5** *and p***20.2**–*p***20.4** were obtained as described for *m***20.6**.

*(2*E*)-*N*-Hydroxy-3-{3-[(phenylsulfonyl)amino]phenyl}prop-2-enamide* (*m***20.1**): M.p. 172°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.35 (*d*, *J* = 16.0, 1 H); 6.96–7.92 (*m*, 10 H); 9.03 (br. *s*, 1 H); 10.38 (*s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{14}N_2O_4S$(318.35): C 56.59, H 4.43, N 8.80; found: C 56.48, H 4.57, N 8.45.

*(2*E*)-*N*-Hydroxy-3-{3-{[(4-methylphenyl)sulfonyl]amino}phenyl}prop-2-enamide* (*m***20.2**): M.p. 147°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.32 (*s*, 3 H); 6.36 (*d*, *J* = 16.0, 1 H); 6.94–7.76 (*m*, 9 H); 9.03 (br. *s*, 1 H); 10.32 (*s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{16}N_2O_4S$ (332.38): C 57.82, H 4.85, N 8.43; found: C 57.73, H 4.86, N 8.36.

*(2*E*)-3-{3-{[(3,4-Dimethoxyphenyl)sulfonyl]amino}phenyl}*-N-*hydroxyprop-2-enamide* (*m***20.3**): M.p. 158°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.72 (*s*, 3 H); 3.80 (*s*, 3 H); 6.36 (*d*, *J* = 16.0, 1 H); 6.89–7.52 (*m*, 8 H); 9.03 (br. *s*, 1 H); 10.16 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_6S$ (378.41): C 53.96, H 4.79, N 7.40; found: C 53.74, H 4.71, N 7.35.

*(2*E*)-3-{3-[([1,1′-Biphenyl]-4-ylsulfonyl)amino]phenyl}*-N-*hydroxyprop-2-enamide* (*m***20.4**): M.p. 115°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.38 (*d*, *J* = 16.0, 1 H); 6.98–7.65 (*m*, 10 H); 7.87 (*s*, 4 H); 9.03 (br. *s*, 1 H); 10.45 (br. *s*, 1 H); 10.78 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{18}N_2O_4S$ containing 1.3% of inorganic impurities (394.45): C 63.11, H 4.54, N 7.01; found: C 63.16, H 4.53, N 6.93.

*(2*E*)-3-{4-[([1,1′-Biphenyl]-4-ylsulfonyl)amino]phenyl}*-N-*hydroxyprop-2-enamide* (*p***20.2**): M.p. 190–191.5°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.29 (*d*, *J* = 16.0, 1 H); 7.16 (*d*, *J* = 8.0, 2 H); 7.24–7.78 (*m*, 8 H); 7.86 (*m*, 4 H); 8.94 (br. *s*, 1 H); 10.57 (*s*, 1 H); 10.66 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{18}N_2O_4S$ (394.45): C 63.94, H 4.60, N 7.10; found: C 63.64, H 4.45, N 7.00.

*(2*E*)-3-{4-{[(3,4-Dimethoxyphenyl)sulfonyl]amino}phenyl}*-N-*hydroxyprop-2-enamide* (*p***20.3**): M.p. 178.5–179°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.72 (*s*, 3 H); 3.78 (*s*, 3 H); 6.32 (*d*, *J* = 16.0, 1 H); 7.00–7.65

(*m*, 8 H); 8.98 (br. *s*, 1 H); 10.32 (br. *s*, 1 H); 10.69 (*s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_6S$ (378.41): C 53.96, H 4.79, N 7.40; found: C 53.58, H 4.56, N 7.62.

*(2*E*)-*N*-Hydroxy-3-{4-{[[(1*E*)-2-phenylethenyl]sulfonyl}amino}phenyl]prop-2-enamide* (*p***20.4**): ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.33 (*d*, *J* = 15.8, 1 H); 7.21 (*d*, *J* = 8.4, 1 H); 7.25 (*s*, 1 H); 7.33 (*s*, 1 H); 7.37 – 7.45 (*m*, 3 H); 7.49 (*d*, *J* = 8.6, 1 H); 7.53 (*d*, *J* = 15.8, 1 H); 7.66 – 7.76 (*m*, 2 H); 9.02 (*s*, 1 H); 10.36 (*s*, 1 H); 10.72 (*s*, 1 H). Anal. calc. for $C_{17}H_{16}N_2O_4S$ (344.39): C 59.23, H 4.56, N 8.26, S 9.25; found: C 59.29, H 4.68, N 8.13, S 9.31.

3-Bromo-N-*phenylbenzenesulfonamide* (*m***22**). At r.t., 3-bromobenzenesulfonyl chloride (*m***21**; 1.0 g, 3.9 mmol) was added to a mixture of benzenamine (0.47 g, 5.1 mmol) in MeCN (10 ml) and Na_2CO_3 (1.3 g, 12.3 mmol) in H_2O (10 ml). The mixture was stirred at r.t. for 1 h and extracted with AcOEt (30 ml). The extract was dried (Na_2SO_4) and evaporated: *m***22** (1.15 g, 94%). Oil which solidified upon standing. M.p. 98 – 100°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.94 – 7.48 (*m*, 5 H); 7.50 – 7.96 (*m*, 4 H); 10.36 (*s*, 1 H).

3-(3-Hydroxyprop-1-ynyl)-N-*phenylbenzenesulfonamide* (*m***23**). A mixture of *m***22** (1.0 g, 3.2 mmol), benzene (2.4 ml), [Pd(PPh_3)$_4$] (0.4 g, 0.34 mmol), CuI (0.032 g, 0.16 mmol), Et_3N (2.4 ml, 17.2 mmol), and prop-2-yn-1-ol (1.0 ml, 17.2 mmol) was refluxed under Ar for 30 min. The mixture was diluted with 5% HCl soln. (50 ml) and extracted with AcOEt (50 ml). The extract was washed successively with 5% $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue purified by CC (SiO_2, AcOEt/hexane 1:1): *m***23** (0.59 g, 64%). Oil. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 4.29 (*d*, *J* = 6.0, 2 H); 5.36 (*t*, *J* = 6.0, 1 H); 6.94 – 7.32 (*m*, 5 H); 7.35 – 7.91 (*m*, 4 H); 10.32 (*s*, 1 H).

3-(3-Oxoprop-1-ynyl)-N-*phenylbenzenesulfonamide* (*m***24**). *m***23** (0.55 g, 1.9 mmol) was dissolved in a soln. of *Dess – Martin* reagent in CH_2Cl_2 (0.157 g/ml, 8.2 ml), and the mixture was stirred at r.t. for 30 min. The mixture was partitioned between H_2O (50 ml) and Et_2O (50 ml) and the org. phase washed with 5% Na_2CO_3 soln. and H_2O, dried (Na_2SO_4), and evaporated: *m***24** (0.47 g, 72%). Oil. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.96 – 7.41 (*m*, 5 H); 7.54 – 8.07 (*m*, 4 H); 9.45 (*s*, 1 H); 10.41 (*s*, 1 H).

*Methyl (2*E*)-5-{3-[(Phenylamino)sulfonyl]phenyl}pent-2-en-4-ynoate* (*m***25**). To a soln. of methyl (dimethoxyphosphinyl)acetate (0.81 g, 4.5 mmol) in dry THF (20 ml) under Ar at r.t., NaH (0.12 g, 5.0 mmol) was added. The mixture was stirred at r.t. for 1 h, and a soln. of *m***24** (0.44 g, 1.5 mmol) in dry THF (20 ml) was added dropwise at 15 – 20°. The mixture was stirred at r.t. for 1 h and quenched with 3% HCl soln. (20 ml). The product was extracted with AcOEt (50 ml), the extract washed with 5% $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue purified by CC (SiO_2, AcOEt/hexane 1:2): *m***25** (0.39 g, 74%). White solid. M.p. 134 – 136°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 3.73 (*s*, 3 H); 6.49 (*d*, *J* = 15.5, 1 H); 7.03 (*d*, *J* = 15.5, 1 H); 7.01 – 7.38 (*m*, 5 H); 7.41 – 7.89 (*m*, 4 H, C_6H_4); 10.34 (*s*, 1 H).

*(2*E*)-5-{3-[(Phenylamino)sulfonyl]phenyl}pent-2-en-4-ynoic Acid* (*m***26**). As for *m***10.1**, with *m***25**: 95% of *m***26**. White crystals. M.p. 188 – 190°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.36 (*d*, *J* = 15.8, 1 H); 6.92 (*d*, *J* = 15.8, 1 H); 7.01 – 7.36 (*m*, 5 H); 7.38 – 7.89 (*m*, 4 H); 10.32 (*s*, 1 H).

*(2*E*)-*N*-Hydroxy-5-{3-[(phenylamino)sulfonyl]phenyl}pent-2-en-4-ynamide* (*m***27**). To a soln. of *m***26** (0.25 g 0.77 mmol) in CH_2Cl_2 (5 ml), oxalyl chloride (0.42 g 3.1 mmol) was added. The mixture was stirred at r.t. for 1 h and then evaporated. The residue was dissolved in MeCN (5 ml), and the obtained soln. was added to a mixture of $NH_2OH \cdot HCl$ (0.3 g, 4.3 mmol) and $NaHCO_3$ (0.3 g, 3.6 mmol) in H_2O (8 ml). The resulting mixture was stirred for 10 min and then extracted with AcOEt (30 ml). The org. phase was extracted with 10% Na_2CO_3 soln. and the aq. phase acidified with 3% HCl soln. The precipitate was filtered and dried: *m***27** (0.12 g, (46%). M.p 88 – 90°. R_f (MeCN/H_2O 10:1) 0.5. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.41 (*d*, *J* = 15.8, 1 H); 6.82 (*d*, *J* = 15.8, 1 H); 6.92 – 7.41 (*m*, 5 H); 7.47 – 8.01 (*m*, 4 H); 8.94 – 11.21 (br. *s*, 3 H). Anal. calc. for $C_{17}H_{14}N_2O_4S \cdot 0.4\ H_2O$ (349.57): C 58.58, H 4.27, N 8.01; found: C 58.12, H 4.03, N 7.80.

*(2*E*)-*N*-Hydroxy-5-{4-[(phenylamino)sulfonyl]phenyl}pent-2-en-4-ynamide* (*p***27**). As described for *m***27**. M.p. 161 – 163°. ^{1}H NMR ((D$_6$)(DMSO, HMDSO (hexamethyldisiloxane)) 6.38 (*d*, *J* = 16.0, 1 H); 6.78 (*d*, *J* = 16.0, 1 H); 6.89 – 7.43 (*m*, 5 H); 7.67 (*d*, *J* = 9.0, 2 H); 7.78 (*d*, *J* = 9.0, 2 H); 10.05 (br. *s*, 3 H). Anal. calc. for $C_{17}H_{14}N_2O_4S \cdot 0.4\ H_2O$ (349.57): C 58.86, H 4.21, N 8.08; found: C 58.36, H 3.93, N 7.82.

Methyl 6-[(Phenylsulfonyl)amino]hexanoate (**29.1**). To a mixture of methyl 6-aminohexanoate hydrochloride (**28**; 1.82 g, 10 mmol) in MeCN (10 ml) and Na_2CO_3 (2.6 g, 24.6 mmol) in H_2O (10 ml), benzenesulfonyl chloride (0.88 g, 5.0 mmol) was added. The mixture was stirred at r.t. for 6 h and then extracted with AcOEt (30 ml), the extract dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2, hexane/AcOEt 2:1): **29.1** (1.28 g, 90%). Oil. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 0.90 – 1.63 (*m*, 6 H); 2.21 (*t*, *J* = 7.0, 2 H); 2.71 (*q*, *J* = 6.0, 2 H); 3.58 (*s*, 3 H); 7.40 – 7.72 (*m*, 3 H); 7.72 – 7.89 (*m*, 2 H).

N-*Hydroxy-6-[(phenylsulfonyl)amino]hexanamide* (**30.1**). A soln. of MeONa (6 mmol) in MeOH (5 ml) was added to a soln. of $NH_2OH \cdot HCl$ (0.28 g, 4 mmol) in MeOH (8 ml). The mixture was stirred at r.t. for 10 min, and the precipitate was filtered off. Then **29.1** (0.36 g, 1 mmol) was added to the filtrate, and the mixture

was heated to the complete dissolving. The resultant mixture was stirred for 4 h at r.t. and evaporated. The residue was dissolved in H_2O (10 ml) and acidified with 3% HCl soln. The precipitate was filtered off and crystallized from MeOH: **30.1** (0.19 g, 52%). White crystals. M.p. 80–82°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 0.98–1.58 (*m*, 6 H); 1.87 (*t*, *J* = 7.5, 2 H); 2.69 (*q*, *J* = 6.0, 2 H); 7.38–7.69 (*m*, 4 H); 7.69–7.87 (*m*, 2 H); 8.58 (*s*, 1 H); 10.27 (*s*, 1 H). Anal. calc. for $C_{12}H_{18}N_2O_4S$ (286.35): C 50.33, H 6.34, N 9.78; found: C 50.48, H 6.25, N 9.69.

N-*Hydroxy-6-{[[4-(methylsulfonyl)phenyl]sulfonyl]amino}hexanamide* (**30.2**). As described for **30.1**. M.p. 161–163°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.01–1.61 (*m*, 6 H); 1.72–1.98 (*m*, 2 H); 2.49 (*s*, 3 H, overlapped with DMSO); 2.63–2.91 (*m*, 2 H); 7.85 (*t*, *J* = 6.0, 1 H), 7.85 (*d*, *J* = 8.6, 2 H); 8.15 (*d*, *J* = 8.6, 2 H); 8.59 (br. *s*, 1 H); 10.27 (*s*, 1 H). Anal. calc. for $C_{13}H_{20}N_2O_6S_2$ (364.44): C 42.84, H 5.53, N 7.69; found: C 42.85, H 5.43, N 7.58.

N-*Hydroxy-6-{[[(1E)-2-phenylethenyl]sulfonyl]amino}hexanamide* (**30.3**). As described for **30.1**. M.p. 107–109°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 0.98–1.66 (*m*, 6 H); 1.91 (*t*, *J* = 6.5, 2 H); 2.86 (*t*, *J* = 6.5, 2 H); 7.13 (*d*, *J* = 16.0, 1 H); 7.36 (*d*, *J* = 16.0, 1 H); 7.36–7.87 (*m*, 5 H); 8.38–9.43 (br. *s*, 3 H). Anal. calc. for $C_{14}H_{20}N_2O_4S$ (312.39): C 53.83, H 6.45, N 8.97; found: C 53.30, H 6.32, N 8.53.

3-{[(6-Methoxy-6-oxohexyl)amino]sulfonyl}benzenecarboxylic Acid (**29.4**). As described for **29.1**, with 3-(chlorosulfonyl)benzenecarboxylic acid: 82% of **29.4**. White solid. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 0.94–1.65 (*m*, 6 H); 2.21 (*t*, *J* = 7.0, 2 H); 2.74 (*q*, *J* = 6.0, 2 H); 3.67 (*s*, 3 H); 7.61–7.94 (*m*, 2 H); 7.94–8.14 (*m*, 1 H); 8.14–8.29 (*m*, 1 H); 8.29-8.45 (*m*, 1 H).

Methyl 6-{{[3-{[(Methylphenyl)amino]carbonyl}phenyl]sulfonyl}amino}hexanoate (**29.4a**). To a suspension of **29.4** (0.33 g, 1.0 mmol) in CH_2Cl_2 (10 ml), oxalyl chloride (0.36 g, 3.0 mmol) and 1 drop of DMF were added. The mixture was stirred at r.t. for 1 h and evaporated. The residue was dissolved in MeCN (8 ml) and the obtained soln. added to 4-methylbenzenamine (0.32 g, 3.0 mmol) in MeCN (8 ml). The mixture was stirred at r.t. for 1.5 h, poured into AcOEt (50 ml), washed successively with H_2O (20 ml), 5% HCl soln. (30 ml), H_2O (20 ml), and dried (Na_2SO_4). After evaporation the residue was dried *in vacuo:* **29.4a** (0.327 g, 78%). Oil. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 0.98–1.63 (*m*, 6 H); 2.22 (*t*, *J* = 7.0, 2 H); 2.27 (*s*, 3 H); 2.72 (*q*, *J* = 6.0, 2 H); 3.67 (*s*, 3 H); 7.18 (*d*, *J* = 8.5, 2 H); 7.51–7.83 (*m*, 2 H); 7.64 (*d*, *J* = 8.5, 2 H); 7.83–8.07 (*m*, 1 H); 8.07–8.34 (*m*, 2 H); 10.41 (*s*, 1 H).

3-{[[6-(Hydroxyamino)-6-oxohexyl]amino}sulfonyl}-N-*(4-methylphenyl)benzenecarboxamide* (**30.4**). As described for **30.1**; crystallization from MeCN: 54% of **30.4**. M.p. 137–138°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.02–1.61 (*m*, 6 H); 1.87 (*t*, *J* = 6.6, 2 H); 2.29 (*s*, 3 H); 2.61–2.89 (*m*, 2 H); 7.16 (*d*, *J* = 8.5, 2 H); 7.65 (*d*, *J* = 8.5, 2 H); 7.72–8.29 (*m*, 4 H); 8.32 (br. *s*, 1 H); 8.61 (br. *s*, 1 H); 10.27 (br. *s*, 1 H); 10.38 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{25}N_3O_5S$ (419.50): C 57.26, H 6.01, N 10.02; found: C 57.22, H 5.88, N 9.92.

Sodium 6-Ethoxy-6-oxohexane-1-sulfonate (**32**, *n* = 5). To a soln. of ethyl 6-bromohexanoate (**31**; 2.48 g, 11.0 mmol) in EtOH (6 ml), a soln. of Na_2SO_3 (2.16 g, 20.6 mmol) in H_2O (9 ml) was added, and the mixture was refluxed for 1 h. After evaporation, the obtained solid was extracted with boiling EtOH in a *Soxhlet* extraction apparatus for 15–20 h. The extract was evaporated and the residue crystallized from EtOH/Et_2O (1:10): **32** (*n* = 5) (2.71 g, 99%). White crystals. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.05–1.78 (*m*, 6 H); 1.17 (*t*, *J* = 7.2, 3 H); 2.26 (*t*, *J* = 7.5, 2 H); 2.26 (*t*, *J* = 7.5, 2 H); 4.05 (*q*, *J* = 7.2, 2 H).

Ethyl 6-[(Phenylamino)sulfonyl]hexanoate (**33.1**). **32** (*n* = 5; 1.68 g, 6.8 mmol) was mixed with PCl_5, and the mixture was carefully pestled in a mortar. After the reaction came to the end (cease of the foaming), the mixture was extracted with dry benzene (50 ml). The extract was evaporated and the residue dried *in vacuo* and dissolved in benzene (10 ml). To this soln., benzenamine (1.648 g, 17.7 mmol) was added. The mixture was stirred at r.t. for 24 h, and partitioned between AcOEt and 1M HCl. The org. phase was washed with H_2O and sat. NaCl soln., dried (Na_2SO_4), and evaporated, and the crude product purified by CC (SiO_2, petroleum ether/*t*-BuOMe 3:2): 0.927 g (45%) of **33.1**. Oil. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.03–1.81 (*m*, 6 H); 1.15 (*t*, *J* = 7.1, 3 H); 2.23 (*t*, *J* = 6.8, 2 H); 3.07 (*t*, *J* = 7.6, 2 H); 4.04 (*q*, *J* = 7.1, 2 H); 7.00–7.47 (*m*, 5 H); 9.76 (*s*, 1 H).

N-*Hydroxy-6-[(phenylamino)sulfonyl]hexanamide* (**34.1**). To a mixture of **33.1** (0.45 g, 1.5 mmol) and $NH_2OH \cdot HCl$ (0.43 g, 6.2 mmol) in MeOH (5 ml), 3.43M MeONa (2.62 ml, 9.0 mmol) in MeOH was added, and the mixture was stirred at r.t. for 40 min. The mixture was poured into sat. NaH_2PO_4 soln. (15 ml) and extracted with AcOEt. The extract was washed with H_2O and sat. NaCl soln., dried (Na_2SO_4), and evaporated and the residue washed with Et_2O and crystallized from AcOEt: **34.1** (0.30 g, 69%). White crystals. M.p. 97–98°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.02–1.78 (*m*, 6 H); 1.90 (br. *t*, *J* = 6.4, 2 H); 3.06 (*t*, *J* = 7.0, 2 H); 6.94–7.60 (*m*, 5 H); 8.66 (br. *s*, 1 H); 9.76 (br. *s*, 1 H); 10.36 (br. *s*, 1 H). Anal. calc. for $C_{12}H_{18}N_2O_4S$ (286.35): C 50.33, H 6.34, N 9.78, S 11.20; found: C 50.10, H 6.22, N 9.83, S 11.10.

ω-(Aminosulfonyl)-N-*hydroxyalkanamides* **34.2**–**34.6** were obtained as described for **34.1**.

N-*Hydroxy-5-[(phenylamino)sulfonyl]pentanamide* (**34.2**): M.p. 128–129°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.37–1.78 (*m*, 4 H); 1.92 (*t*, *J* = 5.9, 2 H); 3.07 (*t*, *J* = 7.0, 2 H); 6.97–7.47 (*m*, 5 H); 8.69 (*s*, 1 H);

9.78 (*s*, 1 H); 10.33 (*s*, 1 H). Anal. calc. for $C_{11}H_{16}N_2O_4S$ (272.33): C 48.52, H 5.92, N 10.29, S 11.77; found: C 48.57, H 5.92, N 10.21, S 11.65.

N-*Hydroxy-5-[(naphthalen-2-ylamino)sulfonyl]pentanamide* (**34.3**): M.p. 163–164°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.39–1.78 (*m*, 4 H); 1.93 (*t*, *J* = 6.4, 2 H); 3.16 (*m*, 2 H, overlapped with H_2O); 7.30–7.61 (*m*, 3 H); 7.67 (*d*, *J* = 2.0, 1 H); 7.76–7.99 (*m*, 3 H); 8.67 (br. *s*, 1 H); 10.00 (br. *s*, 1 H); 10.31 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{18}N_2O_4S$ (322.39): C 55.89, H 5.63, N 8.69, S 9.95; found: C 55.83, H 5.52, N 8.68, S 9.95.

N-*Hydroxy-5-[(phenylamino)sulfonyl]heptanamide* (**34.4**): M.p. 94–95°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.07–1.51 (*m*, 6 H); 1.53–1.73 (*m*, 2 H); 1.89 (*t*, *J* = 7.2, 2 H); 3.04 (*t*, *J* = 7.6, 2 H); 7.03–7.40 (*m*, 5 H); 8.67 (*s*, 1 H); 9.78 (*s*, 1 H); 10.33 (*s*, 1 H). Anal. calc. for $C_{13}H_{20}N_2O_4S$ (300.38): C 51.98, H 6.71, N 9.33, S 10.67; found: C 51.83, H 6.64, N 9.23, S 10.65.

N-*Hydroxy-8-[(phenylamino)sulfonyl]octanamide* (**34.5**): M.p. 87–88°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.08–1.51 (*m*, 8 H); 1.52–1.73 (*m*, 2 H); 1.90 (*t*, *J* = 7.2, 2 H); 3.05 (*t*, *J* = 7.6, 2 H); 7.02–7.39 (*m*, 5 H); 8.66 (*s*, 1 H); 9.74 (*s*, 1 H); 10.32 (*s*, 1 H). Anal. calc. for $C_{14}H_{22}N_2O_4S$ (314.41): C 53.48, H 7.05, N 8.91, S 10.20; found: C 53.23, H 7.05, N 8.82, S 10.25.

N-*Hydroxy-8-{[methyl(phenyl)amino]sulfonyl}octanamide* (**34.6**): M.p. 65.5–66.5°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.06–1.72 (*m*, 10 H); 1.91 (*t*, *J* = 7.2, 2 H); 3.09 (*t*, *J* = 7.6, 2 H); 3.25 (*s*, 3 H); 7.21–7.50 (*m*, 5 H); 8.64 (*s*, 1 H); 10.31 (*s*, 1 H). Anal. calc. for $C_{15}H_{24}N_2O_4S$ (328.43): C 54.86, H 7.37, N 8.53, S 9.76; found: C 54.68, H 7.30, N 8.55, S 9.70.

N-*Hydroxy-3-{3-[(phenylamino)sulfonyl]phenyl}propanamide* (**35.1**). A mixture of *m***11.1** (0.200 g, 0.63 mmol) and 10% Pd/C (170 mg) in MeOH (5 ml) was hydrogenated at r.t. for 4 h. The catalyst was filtered off, the solvent evaporated, and the residue crystallized from Et_2O: **35.1** (0.110 g, 55%). White crystals. M.p. 62°. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 2.19 (*t*, *J* = 7.5, 2 H); 2.82 (*t*, *J* = 7.5, 2 H); 6.88–7.27 (*m*, 5 H); 7.28–7.66 (*m*, 5 H); 10.18 (*s*, 1 H); 10.36 (*s*, 1 H). Anal. calc. for $C_{15}H_{16}N_2O_4S \cdot 0.5\ Et_2O$ (357.42): C 57.13, H 5.92, N 7.84; found: C 57.03, H 5.94, N 7.70.

3-[3-(Aminosulfonyl)phenyl]propanamides **35.2**–**35.6** were obtained as described for **35.1**.

N-*Hydroxy-3-{3-{[4-(methylphenyl)amino]sulfonyl}phenyl}propanamide* (**35.2**): M.p. 170°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.18 (*s*, 3 H); 2.23 (*t*, *J* = 7.7, 2 H); 2.84 (*t*, *J* = 7.7, 2 H); 6.95 (*d*, *J* = 8.6, 2 H); 7.02 (*d*, *J* = 8.6, 2 H); 7.36–7.56 (*m*, 3 H); 7.58 (*s*, 1 H); 8.75 (*s*, 1 H); 9.98 (br. *s*, 1 H); 10.40 (*s*, 1 H). Anal. calc. for $C_{16}H_{18}N_2O_4S$ (334.40): C 57.47, H 5.43, N 8.38; found: C 57.39, H 5.40, N 8.17.

N-*Hydroxy-3-{3-{[(2-methoxyphenyl)amino]sulfonyl}phenyl}propanamide* (**35.3**): M.p. 129°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.23 (*t*, *J* = 7.9, 2 H); 2.85 (*t*, *J* = 7.9, 2 H); 3.49 (*s*, 3 H); 6.86 (*dt*, *J* = 1.3, 8.2, 1 H); 6.89 (*d*, *J* = 8.2, 1 H); 7.11 (*dt*, *J* = 1.6, 8.0, 1 H); 7.19 (*dd*, *J* = 1.6, 8.0, 1 H); 7.35–7.57 (*m*, 4 H); 8.75 (*s*, 1 H); 9.41 (*s*, 1 H); 10.41 (*s*, 1 H). Anal. calc. for $C_{16}H_{18}N_2O_5S$ (350.40): C 54.85, H 5.18, N 7.99; found: C 54.93, H 5.14, N 7.95.

N-*Hydroxy-3-{3-{[(4-methoxyphenyl)amino]sulfonyl}phenyl}propanamide* (**35.4**): M.p. 129°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.23 (*t*, *J* = 7.6, 2 H); 2.84 (*t*, *J* = 7.6, 2 H); 3.66 (*s*, 3 H); 6.79 (*d*, *J* = 9.0, 2 H); 6.95 (*d*, *J* = 9.0, 2 H); 7.38–7.61 (*m*, 4 H); 8.75 (*s*, 1 H); 9.85 (*s*, 1 H); 10.39 (*s*, 1 H). Anal. calc. for $C_{16}H_{18}N_2O_5S$ (350.40): C 54.85, H 5.18, N 7.99; found: C 54.64, H 5.01, N 7.85.

3-{3-[([1,1′-Biphenyl]-4-ylamino)sulfonyl]phenyl}-N-*hydroxypropanamide* (**35.5**): M.p. 108°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 2.25 (*t*, *J* = 7.6, 2 H); 2.86 (*t*, *J* = 7.6, 2 H); 7.18 (*d*, *J* = 8.5, 2 H); 7.31 (*t*, *J* = 7.3, 1 H); 7.35–7.49 (*m*, 4 H); 7.50–7.65 (*m*, 3 H); 7.54 (*d*, *J* = 8.5, 2 H); 7.67 (*s*, 1 H); 8.75 (*s*, 1 H); 10.39 (*s*, 2 H). Anal. calc. for $C_{21}H_{20}N_2O_4S \cdot 0.3$ AcOEt (422.89): C 63.05, H 5.34, N 6.62; found: C 63.05, H 5.25, N 6.56.

N-*Hydroxy-3-{3-{[(3-phenylpropyl)amino]sulfonyl}phenyl}propanamide* (**35.6**): Foam. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.64 (*quint.*, *J* = 7.3, 2 H); 2.29 (*t*, *J* = 7.6, 2 H); 2.46–2.60 (*m*, 2 H, overlapped with DMSO); 2.75 (*q*, *J* = 6.3, 2 H); 2.90 (*t*, *J* = 7.6, 2 H); 7.06–7.32 (*m*, 5 H); 7.43–7.53 (*m*, 2 H); 7.54–7.68 (*m*, 3 H); 8.76 (*s*, 1 H); 10.41 (*s*, 1 H). R_f (CH_2Cl_2/MeOH 20:1) 0.53. Anal. calc. for $C_{18}H_{22}N_2O_4S \cdot 0.15\ H_2O$ (365.15): C 59.21, H 6.16, N 7.67; found: C 59.22, H 6.05, N 7.45.

Ethyl 2-(4-Nitrophenoxy)acetate (*p***37**). To a mixture of 4-nitrophenol (*p***36**; 4.17 g, 30.0 mmol) and K_2CO_3 (4.25 g, 30.8 mmo) in MeCN (35 ml), ethyl 2-bromoacetate (l, 31.5 mmol) was added, and the resulting suspension was stirred at 60° for 3.5 h. The mixture was evaporated and the residue successively washed with H_2O, dried, and washed with petroleum ether/AcOEt 4:1: *p***37** (6.2 g, 91%). ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.20 (*t*, *J* = 7.0, 3 H); 4.16 (*q*, *J* = 7.0, 2 H); 4.94 (*s*, 2 H); 7.12 (*d*, *J* = 9.0, 2 H); 8.16 (*d*, *J* = 9.0, 2 H).

Ethyl 2-(4-Aminophenoxy)acetate (*p***38**). A mixture of *p***37** (6.2 g, 27.5 mmol) and 10% Pd/C (2.0 g) in MeOH (120 ml) was hydrogenated at r.t. for 2.5 h. The catalyst was filtered off and the solvent evaporated: *p***38** (4.9 g, 91%). Colored crystals, darkening in air. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.16 (*t*, *J* = 7.0, 3 H); 4.10 (*q*, *J* = 7.0, 2 H); 4.95 (*s*, 2 H); 5.08 (br. *s*, 2 H); 6.61 (*d*, *J* = 9.0, 2 H); 6.71 (*d*, *J* = 9.0, 2 H).

Ethyl 2-{4-[(Phenylsulfonyl)amino]phenoxy}acetate (*p***39**). To combined solns. of *p***38** (4.9 g, 25 mmol) in acetone (40 ml) and $NaHCO_3$ (2.1 g, 25 mmol) in H_2O (30 ml), benzenesulfonyl chloride (3.2 ml, 25 mmol) was added, and the mixture was stirred at r.t. for 2 h. The acetone was evaporated, and the precipitated crystals were filtered and washed with H_2O and Et_2O: *p***39** (7.55 g, 90%). ^{1}H-NMR ((D_6)DMSO, 200 MHz): 1.20 (*t*, *J* = 7.2, 2 H); 4.14 (*q*, *J* = 7.2, 2 H); 4.68 (*s*, 2 H); 6.82 (*d*, *J* = 9.0, 2 H); 6.98 (*d*, *J* = 9.0, 2 H); 7.49–7.64 (*m*, 3 H); 7.64–7.75 (*m*, 2 H); 9.98 (*s*, 1 H).

N-*Hydroxy-2-{4-[(phenylsulfonyl)amino]phenoxy}acetamide* (*p***40**). To a mixture of *p***39** (7.55 g, 22.5 mmol) and $NH_2OH \cdot HCl$ (4.7 g, 67.5 mmol) in THF (32 ml) and MeOH (3 ml) at 10°, a soln. of KOH (6.3 g, 112.5 mmol) in MeOH (32 ml) and H_2O (6.5 ml) was added over 5 min. The mixture was stirred at r.t. for 2 h and supplemented with H_2O (35 ml). The pH of the medium was brought to 7 by 3M HCl (*ca.* 20 ml), the mixture extracted with AcOEt (2 × 75 ml), the extract dried (Na_2SO_4) and evaporated, and the oily residue converted to crystals by treating with petroleum ether/AcOEt 4:1 (80 ml) followed by washing with Et_2O: *p***40** (6.0 g, 83%). M.p. 147° (dec.). ^{1}H-NMR ((D_6)DMSO, 200 MHz): 4.36 (*s*, 2 H); 6.81 (*d*, *J* = 9.1, 2 H); 6.97 (*d*, *J* = 9.1, 2 H); 7.46–7.64 (*m*, 3 H); 7.65–7.73 (*m*, 2 H); 8.96 (br. *s*, 1 H); 9.97 (br. *s*, 1 H); 10.76 (br. *s*, 1 H). Anal. calc. for $C_{14}H_{14}N_2O_5S$ (322.34): C 52.17, H 4.38, N 8.69; found: C 52.24, H 4.27, N 8.42.

N-*Hydroxy-2-{3-[(phenylsulfonyl)amino]phenoxy}acetamide* (*m***40.1**). As described for *p***40**. M.p. 148–150°. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 4.35 (*s*, 2 H); 6.58 (*dd*, *J* = 2.1, 8.1, 1 H); 6.68 (*dd*, *J* = 1.6, 8.1, 1 H); 6.74 (*t*, *J* = 2.0, 1 H); 7.11 (*t*, *J* = 8.1, 1 H); 7.48–7.65 (*m*, 3 H); 7.74–7.82 (*m*, 2 H); 8.96 (*s*, 1 H); 10.35 (br. *s*, 1 H); 10.83 (*s*, 1 H). Anal. calc. for $C_{14}H_{14}N_2O_5S$ (322.34): C 52.17, H 4.38, N 8.69; found: C 51.93, H 4.31, N 8.14.

N-*Hydroxy-2-{3-[(naphthalen-1-ylsulfonyl)amino]phenoxy}acetamide* (*m***40.2**). As described for *p***40**. Foam. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 4.29 (*s*, 2 H); 6.48 (*dd*, *J* = 1.8, 8.2, 1 H); 6.61 (*dd*, *J* = 1.2, 8.0, 1 H); 6.67 (*t*, *J* = 1.6, 1 H); 7.03 (*t*, *J* = 8.1, 1 H); 7.63 (*t*, *J* = 7.7, 1 H); 7.65 (*t*, *J* = 7.4, 1 H); 7.74 (*dt*, *J* = 1.2, 7.6, 1 H); 8.06 (*d*, *J* = 8.0, 1 H); 8.20 (*d*, *J* = 7.6, 1 H); 8.24 (*d*, *J* = 7.6, 1 H); 8.72 (*d*, *J* = 8.4, 1 H); 8.93 (br. *s*, 1 H); 10.78 (br. *s*, 2 H). Anal. calc. for $C_{18}H_{16}N_2O_5S \cdot 0.5\ H_2O \cdot 0.3$ AcOEt (407.83): C 56.55, H 4.79, N 6.87; found: C 56.87, H 4.61, N 6.57.

3-Formyl-N-*phenylbenzenesulfonamide* (**41**). To *m***6** (6.3 g, 30.3 mmol), benzene (25 ml), $SOCl_2$ (6.5 ml, 89.6 mmol), and DMF (0.1 ml, 1.3 mmol) were added, and the resultant suspension was stirred under reflux for 4 h. The mixture was evaporated, the residue dried *in vacuo* and dissolved in dioxane (5 ml), and the soln. added to a mixture of benzenamine (4.5 ml, 47.3 mmol) and $NaHCO_3$ (4.8 g, 57.2 mmol) in H_2O (20 ml). The mixture was stirred at r.t. for 24 h and supplemented with AcOEt. The aq. phase was separated, the pH of the medium brought to 4 by 2M HCl and extracted with AcOEt. The combined org. solns. were washed with 2M HCl and sat. NaCl soln., dried (Na_2SO_4), and evaporated, and the oily residue was treated with CH_2Cl_2/AcOEt 50:1 to give white crystals. The crystals were filtered off. The filtrate was evaporated and the residue purified by CC (SiO_2, CH_2Cl_2/AcOEt 50:1). The obtained product from CC was combined with the crystals: **41** (4.58 g, 58%). ^{1}H-NMR ((D_6)DMSO, 90 MHz): 6.91–7.39 (*m*, 5 H); 7.78 (*t*, *J* = 7.6, 1 H); 8.03 (*dt*, *J* = 1.7, 7.8, 1 H); 8.14 (*dt*, *J* = 1.7, 7.5, 1 H); 8.25 (*t*, *J* = 1.7, 1 H); 10.06 (*s*, 1 H); 10.44 (br. *s*, 1 H).

Methyl (4Z)- and (4E)-5-{3-[(Phenylamino)sulfonyl]phenyl}pent-4-enoate (*Z*)- and (*E*)-**42**, resp. To a mixture of **41** (0.192 g, 0.73 mmol) and $[Ph_3P(CH_2)_3COOMe]I$ (1.09 g, 2.2 mmol) in THF (5 ml), a 60% suspension of NaH in mineral oil (0.088 g, 2.2 mmol) was added, and the resulting mixture was stirred at r.t. for 3 h. The mixture was poured into sat. NaH_2PO_4 soln. and extracted with AcOEt. The extract was washed with sat. NaCl soln., dried (Na_2SO_4), and evaporated and the crude product purified by CC (SiO_2, petroleum ether/*t*-BuOMe 2:3: **42** (0.079 g, 31%). The mixture **42** was separated by prep. HPLC (hexane/AcOEt 3:1): (*Z*)-**42** (0.0293 g, 12%) and (*E*)-**42** (0.0181 g, 7%).

Data of (Z)-**42**: ^{1}H-NMR ((D_6)DMSO, 90 MHz): 2.33–2.57 (*m*, 4 H); 3.68 (*s*, 3 H); 5.51–5.89 (*m*, 1 H); 6.40 (*d*, *J* = 11.6, 1 H); 6.83 (br. *s*, 1 H); 6.96–7.29 (*m*, 5 H); 7.30–7.50 (*m*, 2 H); 7.52–7.82 (*m*, 2 H).

Data of (E)-**42**: ^{1}H-NMR ((D_6)DMSO, 90 MHz): 2.30–2.61 ((*m*, 4 H); 3.69 (*s*, 3 H); 5.97–6.39 (*m*, 1 H); 6.39 (*d*, *J* = 16.0, 1 H); 6.51 (br. *s*, 1 H); 6.92–7.48 (*m*, 7 H); 7.56 (*dt*, *J* = 1.6, 7.4, 1 H); 7.71 ((*t*, *J* = 1.5, 1 H).

(4Z)-N-*Hydroxy-5-{3-[(phenylamino)sulfonyl]phenyl}pent-4-enamide* (**45.1**). As described for **30.1**, with (*Z*)-**42**. CC (SiO_2, $CHCl_3$/MeOH 9:1) gave 41% of **45.1**. Foam. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 2.07 (*t*, *J* = 7.2, 2 H); 2.40 (*q*, *J* = 7.1, 2 H); 5.67 (*dt*, *J* = 7.0, 11.8, 1 H); 6.42 (*d*, *J* = 11.8, 1 H); 6.96–7.14 (*m*, 3 H); 7.17–7.29 (*m*, 2 H); 7.47–7.67 (*m*, 4 H); 8.76 (*s*, 1 H); 10.30 (br. *s*, 1 H); 10.43 (*s*, 1 H). Anal. calc. for $C_{17}H_{18}N_2O_4S \cdot 0.2$ AcOEt (364.02): C 58.73, H 5.43, N 7.70, S 8.81; found: C 58.64, H 5.43, N 7.54, S 8.86.

(4E)-N-*Hydroxy-5-{3-[(phenylamino)sulfonyl]phenyl}pent-4-enamide* (**45.2**). As described for **30.1**, with (*E*)-**42**. CC (SiO_2, $CHCl_3$/MeOH 9:1) gave 46% of **45.2**. Foam. ^{1}H-NMR ((D_6)DMSO, 200 MHz): 2.12 (*t*, *J* = 7.3, 2 H); 2.41 (*q*, *J* = 6.9, 2 H); 6.30 (*dt*, *J* = 6.3, 15.9, 1 H); 6.45 (*d*, *J* = 15.9, 1 H); 6.96–7.13 (*m*, 3 H); 7.16–7.28 (*m*, 2 H); 7.45 (*t*, *J* = 7.6, 1 H); 7.52–7.63 (*m*, 2 H); 7.72 (*s*, 1 H); 8.73 (*d*, *J* = 1.6, 1 H); 10.25 (br. *s*, 1 H); 10.43 1(*s*,

1 H). Anal. calc. for $C_{17}H_{18}N_2O_4S \cdot 0.1$ AcOEt (355.21): C 58.84, H 5.33, N 7.89, S 9.03; found: C 58.47, H 5.31, N 7.57, S 9.00.

5-[3-[(Phenylamino)sulfonyl]phenyl]pentanoic Acid (**44**). A crude mixture **42** was hydrolyzed to **43** as described for *m***10.1** and hydrogenated as described for **35.1**:**44**. ^{1}H-NMR ($CDCl_3$, 90 MHz): 1.41–1.86 (*m*, 4 H); 2.34 (*t*, *J* = 6.5, 2 H); 2.61 (*t*, *J* = 6.5, 2 H); 6.82 (br. *s*, 1 H); 6.94–7.74 (*m*, 9 H).

N-*Hydroxy-5-[3-[(phenylamino)sulfonyl]phenyl]pentanamide* (**45.3**). As described for *m***11.1**, with **44**. CC (SiO_2, CH_2Cl_2/MeOH 9:1) gave 66% of **45.3**. Foam. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 1.33–1.60 (*m*, 4 H); 1.94 (*t*, *J* = 6.5, 2 H); 2.59 (*t*, *J* = 6.8, 2 H); 7.01 (*t*, *J* = 7.4, 1 H); 7.07 (*d*, *J* = 7.8, 2 H); 7.22 (*d*, *J* = 7.8, 2 H); 7.37–7.49 (*m*, 2 H); 7.50–7.61 (*m*, 2 H); 8.67 (*s*, 1 H); 10.19 (br. *s*, 1 H); 10.34 (*s*, 1 H). Anal. calc. for $C_{17}H_{20}N_2O_4S \cdot 0.15$ AcOEt (361.63): C 58,46, H 5.91, N 7.75, S 8.87; found: C 58.56, H 5.91, N 7.77, S 8.81.

3-[(Phenylamino)sulfonyl]benzenecarboxylic Acid (**46**). To a soln. of **41** (0.100 g, 0.38 mmol) in acetone (2 ml) at 2°, 2.64M *Jones* reagent (0.16 ml, 0.42 mmol) was added, and the mixture was stirred at 2–4° for 1.5 h. Then, i-PrOH (2 ml) was added and the mixture stirred for 0.5 h and poured into sat. NaCl soln. The mixture was extracted with AcOEt, the extract washed with sat. NaCl soln., dried (Na_2SO_4), and evaporated, and the residue dried *in vacuo*: **46** (0.104 g, 98%). White solid. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 6.86–7.39 (*m*, 5 H); 7.65 (*t*, *J* = 7.8, 1 H); 7.92 (*d*, *J* = 7.8, 1 H); 8.11 (*d*, *J* = 7.8, 1 H); 8.27 (*s*, 1 H); 10.34 (br. *s*, 1 H).

Methyl 3-[(Phenylamino)sulfonyl]benzenecarboxylate (**47**). To a soln. of **46** (0.133 g, 0.48 mmol) in MeOH (2 ml) was added a soln. of AcCl (0.102 ml, 1.44 mmol) and MeOH (1 ml), prepared beforehand. The resulting mixture was stirred at r.t. for 24 h and at 65° for 1 h. After evaporation, the crude product was purified by CC (SiO_2, petroleum ether/AcOEt 2:1): **47** (0.118 g, 84%). White solid. ^{1}H-NMR ($CDCl_3$, 90 MHz): 3.97 (*s*, 3 H); 6.54 (br. *s*, 1 H); 6.97–7.36 (*m*, 5 H); 7.53 (*t*, *J* = 7.8, 1 H); 7.94 (*dt*, *J* = 1.5, 8.0, 1 H); 8.23 (*dt*, *J* = 1.5, 7.6, 1 H); 8.50 (*t*, *J* = 1.5, 1 H).

N-*Hydroxy-3-[(phenylamino)sulfonyl]benzamide* (**48**). As described for **34.1**, with **47**. CC (SiO_2, $CHCl_3$/MeOH 5:1) gave 30% of **48**. White crystals. M.p. 158–159°. ^{1}H-NMR ((D$_6$)DMSO, 200 MHz): 6.97–7.13 (*m*, 3 H); 7.22 (*t*, *J* = 7.7, 2 H); 7.61 (*t*, *J* = 7.8, 1 H); 7.85 (*d*, *J* = 7.8, 1 H); 7.92 (*d*, *J* = 7.8, 1 H); 8.18 (*s*, 1 H); 9.20 (*s*, 1 H); 10.39 (br. *s*, 1 H); 11.40 (br. *s*, 1 H). Anal. calc. for $C_{13}H_{12}N_2O_4S$ (292.32): C 53.42, H 4.14, N 9.58, S 10.97; found: C 53.45, H 4.01, N 9.56, S 10.92.

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