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Design, Synthesis and Early Structure–Activity Relationship of Farnesyltransferase Inhibitors Which Mimic Both the Peptidic and the Prenylic Substrate

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Abstract—Inhibition of the farnesylation of ras proteins has been identified as a promising target in tumor therapy. Only a few farnesyltransferase inhibitors are bisubstrate analogues displaying features of both substrates, the farnesylpyrophosphate and the C-terminal CAAX-tetrapeptide sequence of the ras protein. These known bisubstrate analogues consist of an AAX-tripeptide and a farnesyl residue connected through various linkers. We have developed a class of novel compounds that mimic a bisubstrate inhibitor structure and that differ from the known ones by lacking peptidic or farnesylic substructures. Long chain fatty acids and aryl-substituted carboxylic acids were used as farnesyl surrogates. These structures were linked to isoleucine amide, benzoic acid amide, *N*-substituted aminobenzenesulfonamides and N^{α}-aryl-substituted methionine derivatives, respectively, which function as AA- or AAX-mimetics.

Introduction

Ras proteins are members of the family of small guanyl nucleotide binding proteins. They serve as molecular switches in the signal transduction cascade which controls cell differentiation and proliferation. Point mutations in the Ras oncogene yield ras proteins whose GTPase activity can no longer be activated upon binding of GTPase activating proteins (GAP's). These mutated ras proteins are locked in their GTP-bound active state and thereby are constantly relaying growth signals to the nucleus. In approximately 30% of all human cancers, including 90% of pancreatic, 50% of colon, and 50% of thyroid tumors, these mutated ras proteins are found. To perform both, their normal and their oncogene activity, ras proteins must undergo a series of post-translational modifications. First the C-terminal CAAX amino acid sequence (C: cysteine, A: aliphatic amino acid, X: methionine or serine) of the ras protein is recognized by the enzyme farnesyltransferase (FFase) and farnesylated at the cysteine side chain thiol. In this reaction, farnesyl-pyrophosphate (FPP) is serving as the prenyl group donor (Fig. 1). After proteolytic removal of the AAX tripeptide, the resulting C-terminal *S*-farnesyl cysteine is reversibly converted into its methyl ester. In some cases additional palmitoylation occurs at a nearby downstream cysteine. From these post-translational modification events only the farnesylation is obligatory for ras activity.[1,2]

Inhibition of the farnesylation reaction reverses the transformation caused by oncogenic ras. Therefore, inhibition of farnesyltransferase was identified as a promising target in cancer therapy. Intense efforts of several groups have resulted in a large number of different FTase inhibitors.[2] Most researchers utilized the CAAX recognition motif as a template for their inhibitor development. In comparison to CAAX-mimetics, stable non-substrate analogues of the second substrate farnesylpyrophosphate are much less common.[2]

A third approach for inhibitor design are bisubstrate analogues: molecules that contain structural elements of both substrates, the CAAX-tetrapeptide and the farnesyl-pyrophosphate. Such bisubstrate inhibitors are of particular interest because of two reasons: first, bisubstrate analogues are lacking the free thiol found in most of the CAAX peptidomimetics. A free thiol is an undesireable molecular feature in potential drugs both due to its inherent sensitivity towards oxidation and more importantly, as a source of serious adverse effects as seen with the ACE inhibitor captoprile.[3] Second, recent studies on the mechanism of the farnesyltransferase reaction revealed

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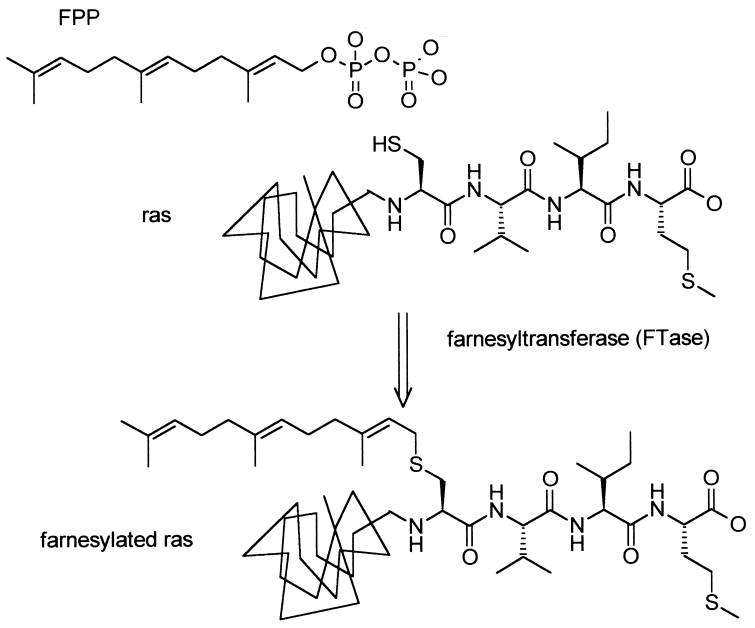


Figure 1. Farnesylation of ras proteins.

that the FTase has an unusually high affinity for its reaction product, the farnesylated ras protein which only is released from the enzyme upon binding of a further FPP molecule.[4] Because of the high affinity of the farnesyltransferase to its reaction product, structural analogues of the farnesylated ras protein should be particularly usefull enzyme inhibitors.[4] Molecules which are composed of the C-terminal tetrapeptide of the ras protein and the farnesyl residue can be considered as bisubstrate analogues as well as analogues of the farnesylated ras protein, as product analogues.

Only a few bisubstrate analogues (or product analogues) have been published. Recently, the natural product pepticinnamine E **1** has been shown to act as a bisubstrate inhibitor.[5] In addition to this sole molecule, few synthetic bisubstrate inhibitors had been published. Representative examples of which (**2**–**5**)[6–8] are shown in Figure 2.

Inhibitor design

All synthetic bisubstrate analogues (e.g. **2**–**5**) contain an unmodified AAX tripeptide motif and the farnesyl residue. These inhibitors only significantly differ in the nature of the linker connecting the tripeptide and the farnesyl residue. We intended to develop a novel class of farnesyltransferase inhibitors designed to be bisubstrate analogues which differ from the known ones in lacking prenylic or peptidic substructures. In a first approach we replaced the AAX-peptide by several peptidomimetics yielding homofarnesosyl-substituted CAAX-peptidomimetics.[9a] In a second step, we also replaced the homofarnesoyl residue by non-prenylic lipophilic structures thereby yielding novel type inhibitors of the farnesyltransferase.[9b] These novel, fully synthetic compounds are conveniently composed of three modular building blocks: (1) a farnesyl-mimetic (2) a linker and (3) an AAX- or AA-peptidomimetic. While the compounds are intended to be non-peptidic, non-prenylic bisubstrate analogue farnesyltransferase inhibitors by design, determination of their biochemical mechanism has not been established. Known bisubstrate analogues contain amidic structures in their peptidic substructure which are sensitive toward hydrolytic or enzymatic degradation and several allylic positions in the farnesyl residue which are susceptible towards oxidation. In contrast, our compound lack those sensitive structures (Fig. 3).

In a previous study on a series of non-prenylic farnesylpyrophosphate analogue FTase inhibitors, we had identified the 4-benzyloxycinnamoyl moiety (**8**) as a useful farnesyl surrogate.[10] The structure of the natural product FPP-analogue FTase inhibitor chaetomellic acid (**6**) (Fig. 4) suggests that long chain alkyl residues may be suitable substituents for the farnesyl residue.[11] Therefore, the palmitoyl (**7**) and the 4-benzyloxycinnamoyl (**8**) moieties were fused with AA- and AAX-mimetic partial structures of several CAAX-peptidomimetic FTase inhibitors through a β-alanyl (**9**) linker. We used the 2,3-dimethylphenylamides of isoleucine (**10**),[12] 3-aminobenzoic acid (**11**)[13] and 3-aminobenzenesulfonic acid (**12**),[14] respectively, as AA-mimetic substructures and *N*-(4-aminobenzoyl)methionine methyl ester (**13**)[15] and *N*-(4-aminophenylsulfonyl)methionine methyl ester (**14**)[14] as AAX-mimetic substructures. The β-alanyl moiety (**9**) was chosen as a linker because the distance between its carbonyl carbon and its nitrogen resembles the distance between the carbonyl carbon and the thiol sulfur in cysteine.

Chemistry

For the preparation of the target structures **18**–**22** a convergent strategy was chosen. The corresponding amines of the peptidomimetic partial structures **10**–**14** and the *N*-Acyl-β-alanine derivatives **17** (Table 1) were prepared independently and joined in the last step of the

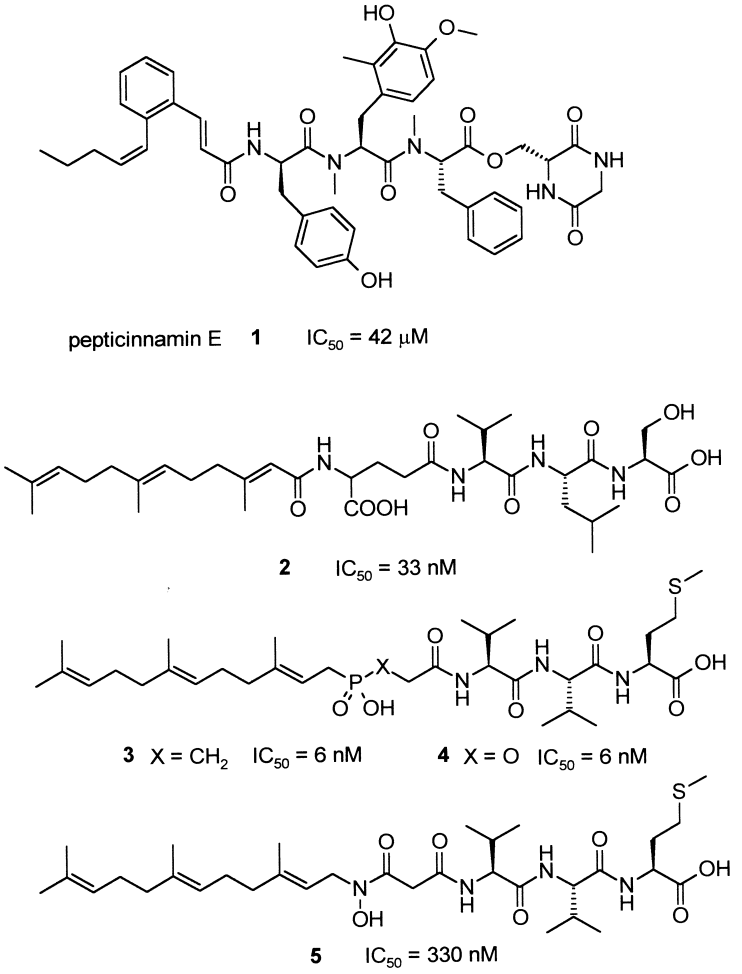


Figure 2. Literature known bisubstrate analogues.

synthesis. The *N*-acyl-β-alanine derivatives **17a–o** were prepared by addition of the appropriate acid chlorides **15** to β-alanine **16** (Scheme 1) following a known procedure.[16] The cinnamic acid chlorides used in this reaction were prepared in two steps from commercially available aldehydes and malonic acid.[17] 2-(3-Phenoxybenzyloxy) acetic acid was obtained from 2-chloroacetic acid and 3-phenoxybenzyl alcohol.[18] The *N*-acyl-β-alanine derivatives **17** were activated as mixed anhydrides using *iso*-butyl chloroformate and coupled to the appropriate amines (**26**, **29**, **32a–i**, **37** and **38**) to yield the target structures **18–22** (Scheme 1). The amines employed in this reaction were prepared as follows. *N*-Boc-isoleucine (**24**) was activated as mixed anhydride and reacted with 2,3-dimethylaniline to the corresponding amide (**25**), which was then deprotected with hydrochloric acid to the corresponding hydrochloride **26** prior to coupling with the *N*-acyl-β-alanines **17c** and **17i**. 3-Nitro-*N*-(2,3-dimethylphenyl)benzamide (**28**) was prepared from 3-nitrobenzoyl chloride **27** and 2,3-dimethylaniline and then reduced to the corresponding 3-amino derivative **29** using tin(II)chlonde in refluxing ethyl acetate.[19] *N*-Substituted 3-aminobenzenesulfonamides **32a–g** were prepared in the same way from 3-nitrobenzenesulfonyl chloride (**30**) and the appropriate amines. The *N*-substituted methionine derivatives **37** and **38** were prepared in the same manner from 4-nitrobenzoyl chloride (**33**) and 4-nitrobenzenesulfonyl chloride (**34**), respectively, and methionine methyl ester hydrochloride. (Scheme 2).

Farnesyltransferase inhibition assay

The inhibitory activity of the potential synthetic inhibitors was determined using the fluorescence enhancement assay as described by Pompliano.[20] The assay employed yeast farnesyltransferase (FTase) fused to Glutathione *S*-transferase at the N-terminus of the β-subunit.[21] Yeast farnesyltransferase is a close homologue and functionally similar to the human enzyme; it is widely used for the evaluation of farnesyltransferase inhibitors. Farnesylpyrophosphate and the dansylated pentapeptide Ds-Gly-CysValLeuSer were used as substrates. Upon farnesylation of the cysteine thiol the dansyl residue is placed in a lipophilic environment which results in an enhancement of fluorescence at 505 nm which is used to monitor the enzyme reaction.

Antiproliferation assay

The target compounds were tested against cell lines K-562 (chronic myeloid leukaemic cell line),[22] THP-l (acute

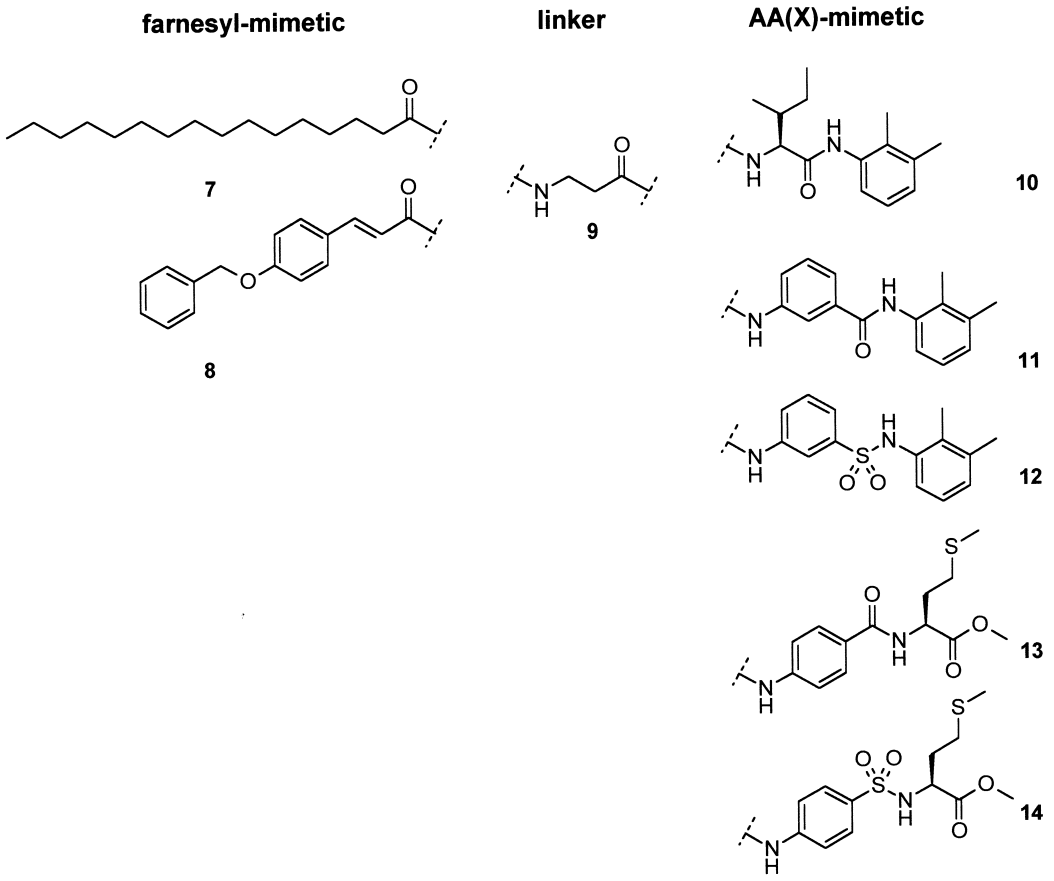


Figure 3. The novel non-peptidic, non-prenylic inhibitors are composed of three building blocks.

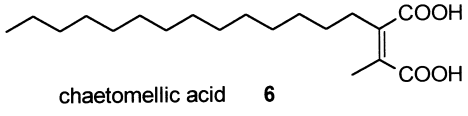
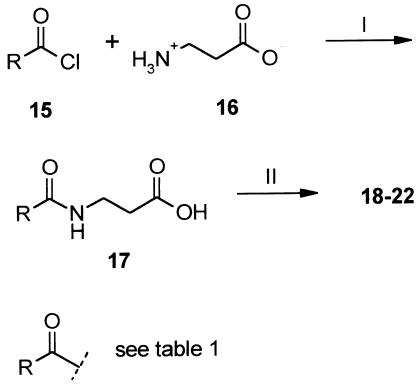


Figure 4. Chaetomellic acid.

monocytic leukaemic cell line)[23] and HL-60 (acute myeloid leukaemic cell line)[24] for their antiproliferative effects. The cells were incubated with different concentrations of the test compounds and an automatic volumetric cell analysis was carried out during the logarithmic phase of cell proliferation.

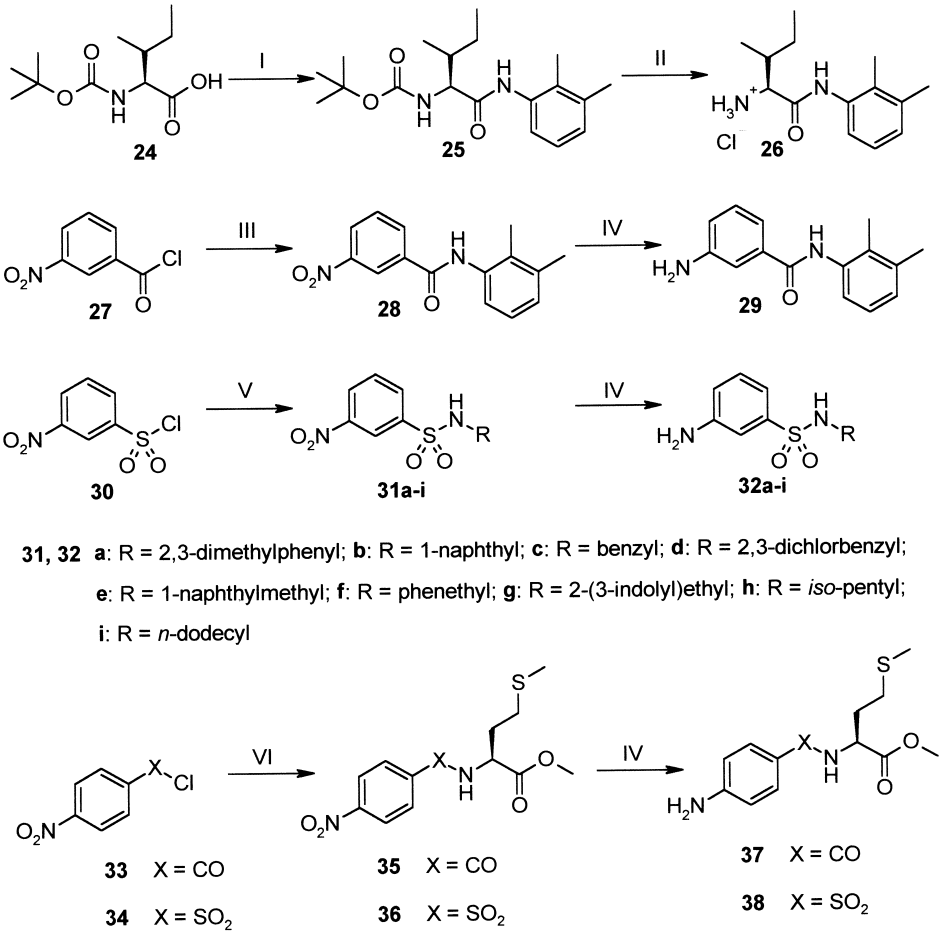
Results and Discussion

In the first two series of compounds, the palmitoyl (**7**) and the 4-benzyloxycinnamoyl (**8**) moieties were used as non-prenylic farnesyl surrogates and connected via the β-alanyl (**9**) spacer to the AA- or AAX-mimetic substructures **10**–**14** of several CAAX-peptidomimetic FTase inhibitors yielding compounds **18a**–**e** and **19a**–**e** (Chart 1, Table 2). All but two of the compounds showed farnesyltransferase inhibitory activity in the low micromolar range. Comparison of the palmitoyl derivatives **18** to the respective 4-benzyloxycinnamoyl derivatives **19** revealed in all cases a higher inhibitory activity of the palmitoyl derivatives. Furthermore, the amide derivatives were more active than the corresponding sulfonamides,



Scheme 1. (I) (a) potassium carbonate, acetone/water, 0 °C, 1 h, then rt, 1 h, (b) concentrated HCl; (II) (a) *i*-BuOCOCl, NMM, DMF, −15 °C, 5 min; (b) **26**, NMM or **29** or **32a**–**i** or **37** or **38**, DMF, −15 °C→rt, overnight.

for example, **18a** was three times more active than **18b** or **18c** being twice as active as **18d**. While the 4-benzyloxycinnamoyl derivatives of isoleucineamide (**19e**) and *N*-benzenesulfonylmethionine methyl ester (**19b**) showed a considerable lower inhibitory activity, all derivatives of the remaining three peptidomimetic substructures displayed inhibitory activities in the same range of magnitude. Therefore, lead structures for early investigation on



Scheme 2. (I) (a) *i*-BuOCOCl, NMM, DMF, −15 °C, 5 min, (b) 2,3-dimethylaniline, DMF, −15 °C→rt, overnight; (II) HCl/dioxane, rt, 2 h; (III) 2,3-dimethylaniline, NMM, dichloromethane, 0 °C→rt, overnight; (IV) $SnCl_2 \times 2H_2O$, ethyl acetate, reflux, 2 h; (V) R-NH_2, NMM, dichloromethane, 0 °C→rt, overnight; (VI) methionine methyl ester hydrochloride, NMM, dichloromethane, 0 °C→rt, overnight.

Table 1. *N*-Acyl-β-alanines **17**

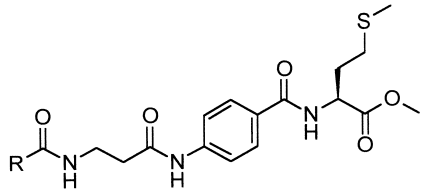
Compound	R-CO-
17a	Lauroyl ($C_{12:0}$)
17b	Myristoyl ($C_{14:0}$)
17c	Palmitoyl ($C_{16:0}$)
17d	Margarinoyl ($C_{17:0}$)
17e	Stearoyl ($C_{18:0}$)
17f	Arachidoyl ($C_{20:0}$)
17g	Elaidoyl ($C_{18:1\ (9t)}$)
17h	Oleoyl ($C_{18:1\ (9c)}$)
17i	Linoleoyl ($C_{18:2\ (9c,12c)}$)
17j	4-Benzyloxycinnamoyl
17k	4-(2-Phenylethenyl)cinnamoyl
171	4-Phenylcinnamoyl
17m	(4-Benzyloxyphenyl)oxyacetyl
17n	(3-Phenyloxybenzyl)oxyacetyl
17o	1-Naphthylacetyl

Table 2. Farnesyltransferase inhibitory activity of compounds **18a–e** and **19a–e**

Compound	IC_{50}±SD (μM)	Compound	IC_{50}±SD (μM)
18a	3.7±0.7	**19a**	7.0±1.3
18b	13.0±3.5	**19b**	52.8±4.8
18c	5.6±0.3	**19c**	8.1±0.3
18d	9.8±2.6	**19d**	14.0±0.6
18e	7.8±0.3	**19e**	29.2±1.6

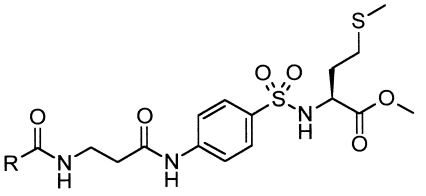
structure–activity relationship were choosen from these compounds.

With our first series of compounds we intended to investigate the influence of the nature of the long chain fatty acid on the inhibitory potency of these compounds using **18d** as a lead (Table 3). Usage of the four methylene units shorter C-12 lauroyl moiety (compound **20a**) instead of the palmitoyl residue resulted in an approximately 3-fold loss in inhibitory activity. The C-14 myristoyl derivative **20b** and the C-17 margarinoyl derivative **20c** displayed nearly the same activity as the C-16 palmitoyl substituted lead structure **18d**. In contrast, compound **20d**, carrying the stearyl moiety which is by two methylene units longer than the palmitoyl residue, was 4-fold more active then the palmitoyl derivative ($IC_{50} = 2.5\ \mu M$). With this compound, we reached the peak in activity in this series since the compound **20e**, carrying the C-20 arachidoyl residue displayed the same activity as the lead structure **18d**. The C-18 chain was used to explore the influence of the presence and the configuration of double bonds in the alkyl chain (compounds **20f–h**). In any case, the presence of double bond in the alkyl chain caused a moderate decrease in inhibitory activity. This



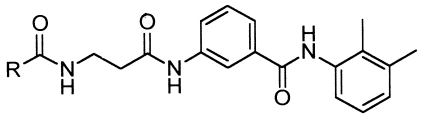
18a R-CO = palmitoyl

19a R-CO = 4-benzyloxycinnamoyl



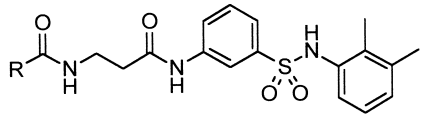
18b R-CO = palmitoyl

19b R-CO = 4-benzyloxycinnamoyl



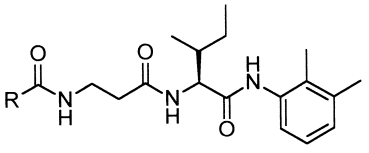
18c R-CO = palmitoyl

19c R-CO = 4-benzyloxycinnamoyl



18d R-CO = palmitoyl

19d R-CO = 4-benzyloxycinnamoyl



18e R-CO = palmitoyl

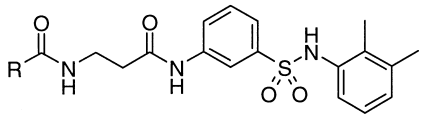
19e R-CO = 4-benzyloxycinnamoyl

Chart 1. Compounds **18a–c** and **19a–e**.

effect was most pronounced with the *E*-configurated double bond, present in the elaidoyl derivative **20e**, whereas inversion of the *E*- into the *Z*-configuration (oleoyl derivative **20f**) attenuated the double bond effect. Introduction of a second *Z*-configurated double bond resulted in a 2-fold more active compound (linoleoyl derivative **20h**) whose IC_{50} of 3.8 μM was still slightly higher than that of **20d** leaving the stearoyl derivative as the most active in this series.

Compound **18d** was also chosen as a lead for the investigation of the influence of the *N*-substituent of the sulfonamide group of the terminal portion of the peptidomimetic substructure (Table 4). A 2-fold improvement of inhibitory activity was observed upon the repacement of the 2,3-dimethylphenyl residue by a 1-naphthyl group as in

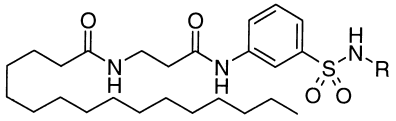
Table 3. Influence of the nature of the long chain fatty acid on the inhibitory potency



18d, 20a-h

Compound	R-CO—	IC_{50}±SD (μM)
18d	Palmitoyl ($C_{16:0}$)	9.8±2.6
20a	Lauroyl ($C_{12:0}$)	31.1±1.1
20b	Myristoyl ($C_{14:0}$)	12.4±0.7
20c	Margarinoyl ($C_{17:0}$)	12.7±0.9
20d	Stearoyl ($C_{18:0}$)	2.5±0.8
20e	Arachidoyl ($C_{20:0}$)	9.9±2.7
20f	Elaidoyl ($C_{18:1\ (9t)}$)	13.4±0.4
20g	Oleoyl ($C_{18:1\ (9c)}$)	8.7±0.8
20h	Linoleoyl ($C_{18:2\ (9c,12c)}$)	3.8±0.3

Table 4. Influence of the nature of the *N*-substituent on the inhibitory potency



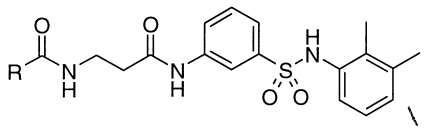
18d, 21a-h

Compound	-R	IC_{50}±SD (μM)
18d	2,3-Dimethylphenyl	9.8±2.6
21a	1-Naphthyl	4.3±0.1
21b	Benzyl	15.0±0.2
21c	2,3-Dichlorobenzyl	24.0±4.0
21d	1-Naphthylmethyl	10.7±1.4
21e	2-Phenylethyl	9.7±0.4
21f	2-(3-Lindolyl)ethyl	8.1±0.5
21g	*iso*-Pentyl	11.2±1.7
21h	*n*-Docecyl	7.9±1.0

compound **21a**. The benzylamides **21b** and **21c** were considerably less active than the lead **18d**, while the 1-naphthylmethyl derivative **21d** displayed almost the same activity as **18d**. No significant changes were observed upon the replacement of the 2,3-dimethylphenyl residue in **18d** by phenethyl (**21e**), 3-indolylethyl (**21f**), *iso*-pentyl (**21g**) or dodecanyl (**21h**).

A more pronounced sensitivity towards changes in molecular geometry was observed upon variation of the aromatic farnesyl surrogate in compound **19d** (Table 5). Replacement of the oxymethylene bridge connecting the two phenyl residues in **19d** by an *E*-configurated vinyl bridge in **22a** yielded a strongly fluorescent compound. Only at a concentration as low as 1 μM could a reliable value (9%) of its farnesyltransferase inhibition be obtained, indicating an IC_{50} well above 15 μM thereby representing no improvement over the lead structure. However, total omission of the bridge between the two aromatic residues in the farnesyl surrogate as in the biphenyl derivative **22b** resulted in a 4-fold improvement of the inhibitory activity. Replacement of the *E*-configurated vinyl bridge connecting the phenyl residue and

Table 5. Influence of the nature of the arylic acyl substituent on the inhibitory potency



19d, 22

Compound	R-CO-	IC_{50}±SD (μM)
19	4-Benzyloxycinnamoyl	14.0±0.6
22a	4-(2-Phenylethenyl)cinnamoyl	9% inh. at 1 μM[a]
22b	4-Phenylcinnamoyl	3.4±0.4
22c	(4-Benzyloxyphenyl)oxyacetyl	215±25
22d	(3-Phenyloxybenzyl)oxyacetyl	126±4
22e	1-Naphthylacetyl	65.8±5.8

[a]Due to high fluorescence emission of **22a** higher inhibitor concentrations could not be determined.

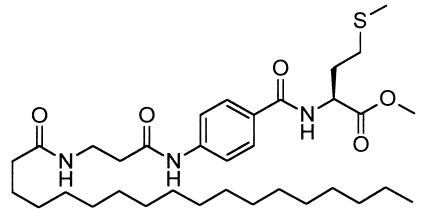


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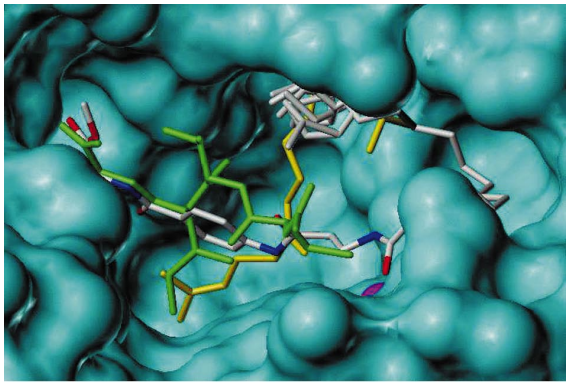
Figure 5. Combination of the *N*-benzoylmethionine peptidomimetic substructure of **18a** and the stearoyl residue of **20d**.

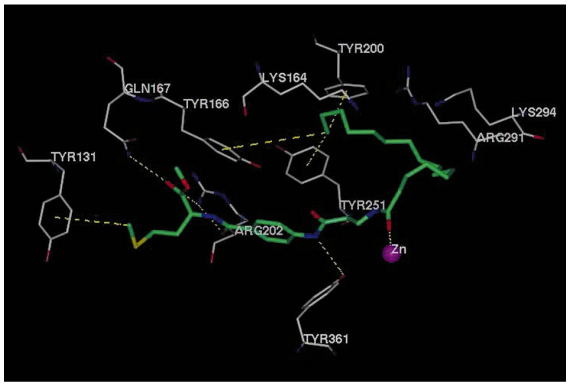
the carbonyl group in **19d** by a conformationally more flexible oxymethylene bridge (compound **22c**) was detrimental to activity, thereby stating the importance of an *E*-configurated double bond in this position of the molecule. Almost inactive compounds were also obtained with the use of a (3-phenyloxybenzyl)oxyacetyl (compound **22d**) and a l-naphthylacetyl (compound **22e**) residue as farnesyl surrogates.

As described above, replacement of the palmitoyl residue by a stearoyl moiety in the benzenesulfonamide derivative **18d** resulted in a 4-fold improvement in activity. However, the corresponding *N*-benzoylmethionine derivative **23** (Fig. 5) carrying a stearoyl instead of a palmitoyl showed the same activity ($IC_{50} = 3.8$ μM) as the lead **18a**.

Using the coordinates of the published[25] crystal structure of a ternary complex of farnesyltransferase, a farnesylpyrophosphate analogue and *N*-Ac-Cys-Val-lle-seleno-MetOH, a molecular surface of the farnesyltransferase's active site was calculated using the program MOLCAD which is implemented in the molecular modeling software package SYBYL.[26] Compound **18a** was docked into the active site using the flexible docking program FlexX.[27] The C-terminal methionine of **18a** was used as starting fragment and placed at the same position as the seleno-methionine of *N*-Ac-Cys-Val-Ile-selenoMetOH in the crystal structure. Then, the program placed the remainder of the molecule fragment by fragment into the active site searching for favorable interactions between the ligand and the amino acid side chains while avoiding steric overlaps. As shown in Figure 6a, FlexX



(a)



(b)

Figure 6. (a) Compound **18a** docked into the farnesyltransferase's active site by FlexX. Colors: protein surface: cyan; zinc: magenta; *N*-Ac-Cys-Val-Ile-selenoMetOH: green; FPP: yellow; **18a**: carbon: white, nitrogen: blue, oxygen: red. (b) Interactions between **18a** and amino acid side chains of the active site as calculated by FlexX. Colors: nitrogen: blue, oxygen: red, carbon of amino acid side chains: white, carbon of **18a**: green blue.

placed **18a** into the farnesyltransferase's active site in a way that it occupies considerable portions of the peptide as well as the farnesylpyrophosphate binding regions thus let it look like a bisubstrate analogue as postulated. Figure 6b shows interactions found by FlexX between **18a** and amino acid side chains in the active site. Interactions are calculated between the methionine side chain and Tyr 131α. Like the carbonyl group of seleno-methionine in the crystal structure the carbonyl moiety of methionine of **18a** shows a hydrogen bond to Gln 167α and to the guanidino group of Arg 202β. This side chain also forms a hydrogen bond to the carbonyl of the central aminobenzoyl moiety. Another hydrogen bond is formed between the hydroxy group of Tyr 361β and the amide nitrogen in the 4-position of the aminobenzoyl moiety. The docking program calculated an interaction between the carbonyl oxygen of the amide moiety connecting the β-alanyl linker to the palmitoyl residue and the zinc. The middle portion of the palmitoyl alkyl chain is placed in 2.8 to 3.8 Å distance to the side chains of Lys 164α, Lys 294β and Arg 291β which form the positively charged cleft binding the pyrophosphate portion of FPP.[25] For the terminal portion of the fatty acid hydrophobic interactions are found towards Tyr 166α, Tyr 200α and Tyr 251β which form a part of the prenyl

Table 6. Antiproliferative activity (GI_{50} (μM)) of selected compounds

Compound	HL-60	THP-1	K-562
18d	9.0	17.6	10.8
20h	9.0	13.6	14.9
22b	9.0	9.0	9.8

binding cleft.[25] Thus, several interactions calculated between **18a** and amino acid side chains of the peptide as well as the prenylphosphate binding regions provide arguments for our substances being bisubstrate analogues.

Selected compounds were assayed against three different tumor cell lines (Table 6). Antiproliferative effects were observed in the low micromolar range, thus showing that that type of compounds is able to penetrate the cell membrane.

Conclusion

We have described inhibitors of farnesyltransferase which mimic structural features of both the peptidic and the prenylic substrate of the farnesyltransferase and provided some computational evidence that they could act as bisubstrate analogues. The compounds are composed of a peptidomimetic substructure and simple aromatic or aliphatic lipophilic structures to mimic the farnesyl moiety. Early structure–activity relationships have been established which form the basis for future development of this class of farnesyltransferase inhibitors. Our compounds are much more readily accessible than known bisubstrate inhibitors from inexpensive starting material. A particular advantage is the lack of sensitive peptidic of prenyl substructures.

Our compounds are not only interesting as intermediate steps towards the development of potential anti-cancer agents but also as tools for studying the structure of enzyme-inhibitor interactions.[1c,5]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Jeol JMN-GX-400 and a Jeol JMN-LA-500 spectrometer. Mass spectra were obtained with a Vacuum Generators VG 7070 H using a Vector 1 data acquisition system from Tecnivent or an AutoSpec mass spectrometer from Micromass. IR spectra were recorded on a Nicolet 510P FTIR-spectrometer. Microanalyses were obtained from a CH analyzer according to Dr. Salzer from Labormatic and from a Hewlett Packard CHN-analyzer type 185 and are within ±0.4% of the theoretical values. Melting points were obtained with a Leitz-microscope and are uncorrected. Column chromatography was carried out using silica gel 60 (0.062–0.200 mm) from Merck. The following compounds used as starting materials have been described in the literature: **15m**,[28] **17a**,[29] **17c**,[30] **17e**,[31] **17f**,[32] **17h**,[31] **17o**,[33] **26**,[12] **29**,[13] **37**,[34] **38**,[35] **32a**,[13] **32g**,[36]**32b**,[37] **32i**.[38] 4-Substituted cinnammic acids chlorides **15j–l** have been prepared as described.[10]

2-(3-Phenoxybenzyloxy)acetic acid chloride 15n. 3-Phenoxybenzyl alcohol (1.74 mL, 10 mmol) and 2-chloroacetic acid (480 mg, 10 mmol) were dissolved in dry THF (60 mL) under Ar. After addition of NaH (880 mg of a 60% suspension in oil, 22 mmol) the mixture was heated to reflux for 12 h. Then, the mixture was diluted with water, acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate. An oil was obtained after removal of the solvent. Yield 2.2 g, 86%. ^{1}H NMR (500 MHz, $CDC1_3$) δ 4.14 (s, 2H), 4.61 (s, 2H), 6.93–7.01 (m, 4H), 7.07–7.12 (m, 2H), 7.31–7.35 (m, 3H). This oil was dissolved in toluene (30 mL) and after addition of thionyl chloride (1.72 mL) heated to 80 °C for 2 h. The residue obtained after removal of the volatiles in vacuo was used for the preparation of **17n** without further characterization.

General procedure for the preparation of the *N*-acyl-β-alanines 17a–o. β-Alanine and K_2CO_3 (430 mg per mmol β-alanine) were dissolved in water (40 mL) and cooled to 0 °C. The appropriate acyl chloride (1 equiv) dissolved in acetone (40 mL) was added dropwise. Stirring was continued for 1 h at 0 °C and 1 h at room temperature. Then, most of the acetone was removed on a rotary evaporator and the resulting aqueous solution was acidified with concentrated hydrochloric acid to pH 1. The precipitate was collected, washed with water and dried. The products were used without further purification.

3-(Tetradecanoylamino)propionic acid (17b). Prepared as described above from myristoyl chloride (2.46 g, 10 mmol) and β-alanine (890 mg, 10 mmol). Yield: 2.72 g (91)%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7 Hz, 3H), 1.23 (m, 20H), 1.45 (m, 2H), 2.00 (m, 2H), 2.48 (m, 2H), 3.21 (m, 2H).

3-(Heptadecanoylamino)propionic acid (17d). Prepared as described above from heptadecanoic acid chloride (1.44 g, 5 mmol) and β-alanine (445 mg, 5 mmol). Yield: 1.42 g (83%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7 Hz, 3H), 1.25 (m, 26H), 1.47 (m, 2H), 2.01 (m, 2H), 2.47 (m, 2H), 3.23 (m, 2H).

3-(9-(*E*)-Octadecenoylamino)propionic acid (17g). Prepared as described above from elaidic acid chloride (600 mg, 2 mmol) and β-alanine (178 mg, 2 mmol). Yield: 551 mg (78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7 Hz, 3H), 1.26 (m, 20H), 1.45 (m, 2H), 1.92 (m, 4H), 2.00 (t, J = 7 Hz, 2H), 2.31 (t, J = 7 Hz, 2H), 3.20 (m, 2H), 5.35 (m, 2H).

3-(9-(*Z*),13-(*Z*)-Octadecadienoylamino)propionic acid (17i). Prepared as described above from linoleic acid chloride (896 mg, 3 mmol) and β-alanine (267 mg, 3 mmol). Yield: 737 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H), 1.29 (m, 14H), 1.58 (m, 2H), 2.02 (m, 4H), 2.14 (m, 2H), 2.57 (m, 2H), 2.72 (m, 2H), 3.47 (m, 2H), 5.31 (m, 4H).

3-{[3-(4-Benzyloxyphenyl)acryloyl]amino}propanoic acid (17j). Prepared as described above from 4-benzyloxycinnamoyl chloride (1.64 g, 6 mmol) and β-alanine (534 mg, 6 mmol). Yield: 1.7 g (87%). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 2.43 (t, 2H, $J=7$ Hz), 3.36 (m, 2H), 5.14 (s, 2H), 6.48 (d, 1H), $J=16$ Hz), 7.02–7.04 (m, 2H), 7.31–7.55 (m, 8H), 8.03 (t, 1H, $J=5.5$ Hz).

3-[3-[4-(2-Phenylethenyl)phenyl]acryloyl]aminopropionic acid (17k). Prepared as described above from 4-(2-phenylethenyl)cinnamic acid chloride (641 mg, 2.38 mmol) and β-alanine (211 mg, 2.38 mmol). Yield: 658 mg (86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (t, $J=7$ Hz, 2H), 3.37 (m, 2H), 6.64 (d, $J=16$ Hz, 1H), 7.29 (m, 3H), 7.38 (m, 3H), 7.54 (m, 2H), 7.62 (m, 4H), 8.12 (m, 1H).

3-[(3-Biphenylylacryloyl)amino]propanoic acid (17l). Prepared as described above from 4-phenylcinnamoyl chloride (704 mg, 3.16 mmol) and β-alanine (280 mg, 3.16 mmol). Yield: 660 mg (71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.48 (m, 2H), 3.40 (m, 2H), 6.68 (d, $J=16$ Hz, 1H), 7.37 (m, 1H), 7.48 (m, 3H), 7.64 (m, 2H), 7.69–7.74 (m, 4H), 8.16 (m, 1H), 12.25 (s, 1H).

3-{[(4-Benzyloxyphenyl)oxyacetyl]amino}propanoic acid (17m). Prepared as described above from (4-benzyloxyphenyl)oxyacetic acid chloride (1.37 g, 4.94 mmol) and β-alanine (440 mg, 4.94 mmol). Yield: 1.3 g (80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (m, 2H), 3.33 (m, 2H), 4.36 (s, 2H), 5.03 (s, 2H), 6.84–6.95 (m, 4H), 7.26–7.43 (m, 5H), 8.02 (s, 1H).

3-{[(3-Phenyloxybenzyl)oxyacetyl]amino}propanoic acid (17n). This compound was prepared as described above from 2-(3-phenoxybenzyloxy)acetic acid chloride (2.37 g, 8.6 mmol) and β-alanine (765 mg, 8.6 mmol). Yield: 1.52 g (54%); oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (t, 2H, $J=6$ Hz), 3.48 (q, 2H, $J=6$ Hz), 3.91 (s, 2H), 4.45 (s, 2H), 6.85–6.96 (m, 4H), 7.01–7.05 (m, 2H), 7.21–7.28 (m, 3H).

General procedure for the preparation of 3-nitrobenzenesulfonamides 31. To a solution of the amine in dry dichloromethane and *N*-methylmorpholine [NMM] (0.24mL per mmol amine) 3-nitrobenzenesulfonyl chloride (**30**) (220 mg, per mmol amine) was added at 0 °C. Stirring was continued overnight. The reaction mixture was diluted with dichloromethane and washed successively with 2 N citric acid, satd $NaHCO_3$-soln and brine and dried with $MgSO_4$. The products obtained after removal of the solvent were used without further purification.

Preparation of *N*-benzyl-3-nitrobenzenesulfonamide (31c). Prepared as described above from **30** (1.1 g, 5 mmol) and benzyl amine (0.55 mL, 5 mmol). Yield: 905 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (d, $J=6$ Hz, 2H), 5.01 (t, $J=6$ Hz, 1H), 7.16 (m, 2H),7.22 (m, 3H), 7.66 (m, 1H), 8.12 (m, 1H), 8.36 (m, 1H), 8.59 (m, 1H).

***N*-(2,3-Dichlorobenzyl)-3-nitrobenzenesulfonamide (31d).** Prepared as described above from **30** (607 mg, 2.75 mmol) and 2,3-dichlorobenzyl amine (485 mg, 2.75 mmol). Yield: 690 mg (70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (d, $J=6$ Hz, 2H), 5.28 (t, $J=6$ Hz, 1H), 7.04 (m, 1H), 7.18 (m, 1H), 7.22 (m, 1H), 7.56 (m, 1H), 7.96 (m, 1H), 8.25 (m, 1H), 8.40 (m, 1H).

***N*-(1-Naphthylmethyl)-3-nitrobenzenesulfonamide (31e).** Prepared as described above from **30** (2.21 g, 10 mmol) and 1-naphthylmethyl amine (1.57 g, 10 mmol). Yield: 2.2 g (64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (m, 2H), 4.94 (s, 1H), 7.20–7.26 (m, 2H), 7.36–7.41 (m, 3H), 7.61 (m, 1H), 7.68 (m, 1H), 7.78 (m, 1H), 7.88 (m, 1H), 8.14 (m, 1H), 8.38 (s, 1H).

3-Nitro-*N*-(2-phenylethyl)benzenesulfonamide (31f). Prepared as described above from **20** (1.1 g, 5 mmol) and 2-phenylethyl amine (0.97 mL, 5 mmol). Yield: 930 mg (61%). ^{1}H NMR (400 MHz, $CDCl_{33}$) δ 2.73 (q, $J=7$ Hz, 2H), 3.24 (m, 2H), 4.58 (t, $J=6$ Hz, 1H), 7.00 (m, 2H), 7.18 (m, 3H), 7.64 (m, 1H), 8.01 (m, 1H), 8.32 (m, 1H), 8.51 (m, 1ff).

***N*-(3-Methylbutyl)-3-nitrobenzenesulfonamide (31h).** Prepared as described above from **30** (1.1 g, 5 mmol) and *iso*-pentyl amine (0.58 mL, 5 mmol). Yield: 800 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, $J=7$ Hz, 6H), 1.31 (q, $J=7$ Hz, 2H), 1.53, (m, 1H), 2.97 (q, $J=7$ Hz, 2H), 4.63 (t, $J=6$ Hz, 1H), 7.69 (m, 1H), 8.14 (m, 1H), 8.37 (m, 1H), 8.64 (m, 1H).

General procedure for the preparation of the 3-aminobenzenesulfonamides 32. To a solution of the nitro compound (**31**) in ethyl acetate $SnCl_2\times H_2O$ (1.125 g per mmol nitro compound) was added. Then, the solution was refluxed for 2 h. The cooled solution was diluted with water and the pH was adjusted to 7–8 by addition of satd $NaHCO_3$-solution. The aqueous phase was extracted with ethyl acetate (3×100–200 mL) and the combined organic extracts were thoroughly washed with brine and dried over $MgSO_4$. The products obtained after removal of the solvent were used without further purification.

3-Amino-*N*-benzylbenzenesulfonamide (32c). Prepared as described above from **31c** (0.900 g, 3.1 mmol). Yield: 420 mg (52%). ^{1}H NMR (400 MHz, $CDC1_3$) δ 3.84 (s, 2H), 4.06 (d, $J=6$ Hz, 2H), 4.56 (t, $J=6$ Hz, 1H), 6.79 (m, 1H), 7.08 (m, 1H), 7.12–7.17 (m, 3H), 7.19–7.25 (m, 4H).

3-Amino-*N*-(2,3-dichlorobenzyl)benzenesulfonamide (32d). Prepared as described above from **31d** (670 mg, 1.86 mmol). Yield: 615 mg (quant). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 2H), 4.25 (d, $J=6$ Hz, 2H), 5.04 (t, $J=6$ Hz, 1H), 6.77 (m, 1H), 7.06 (m, 1H), 7.10–7.14 (m, 2H), 7.18–7.24 (m, 2H), 7.34 (m, 1H).

3-Amino-*N*-(1-naphthylmethyl)benzenesulfonamide (32e). Prepared as described above from **31e** (2.2 g, 6.43 mmol). Yield: 1.73 g (86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 2H), 4.48 (m, 2H), 6.80 (m, 1H), 7.10 (m, 1H), 7.18–7.31 (m, 4H), 7.42 (m, 2H), 7.72 (m, 1H), 7.77 (m, 1H), 7.84 (m, 1H).

3-Amino-*N*-(2-phenylethyl)benzenesulfonamide (32f). Prepared as described above from **31f** (0.826 g, 2.7 mmol). Yield: 524 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (q, $J=7$ Hz, 2H), 3.20 (m, 2H), 3.87 (s, 2H), 4.31 (t, $J=7$ Hz, 1H), 6.82 (m, 1H), 7.08 (m, 3H), 7.12 (m, 1H), 7.25 (m, 4H).

3-Amino-*N*-(3-methylbutyl)benzenesulfonamide (32h). Prepared as described above from **31h** (0.79 g, 2.9 mmol). Yield: 600 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, $J=7$ Hz, 6H), 1.33 (m, 2H), 1.51, (m, 1H), 2.94 (m, 2H), 3.88 (s, 2H), 4.47 (m, 1H), 6.83 (m, 1H), 7.14–7.25 (m, 3H).

General procedure for the preparation of the *N*-acyl-β-alanine amides 18–22. The appropriate *N*-acyl-β-alanine **17** was dissolved in a sufficient amount of dry DMF in a flame dried flask under an atmosphere of Ar. After addition of N-methylmorpholine [NMM] (0.25 mL per mmol acid) the solution was cooled to −15 °C and isobutyl chloroformate (0.13 mL per mmol acid) was added. A solution of the amine component (1 equiv) in dry DMF was added after 5 min. When **26** was used as the amine component, additional NMM (0.25 mL per mmole) was added. The mixture was allowed to warm up to room temperature overnight and then poured into brine (400–800 mL). In case a solid precipitate was formed, this was collected by suction and thoroughly washed with water. Otherwise, the aqueous mixture was extracted with EtOAc (3×100 mL) and the combined organic extracts were washed successively with 2N citric acid, satd $NaHCO_3$-soln and brine and dried with $MgSO_4$. The residue obtained after removal of the solvent was purified by recrystallisation or flash chromatography.

***N*-{4-[(3-Hexadecanoylamino)propanoylamino]benzoyl}-methionine methyl ester (18a).** Prepared as described above from **17c** (654 mg, 2 mmol) and **37** (564 mg, 2 mmol) and purified by flash chromatography (ethyl acetate). Yield: 917 mg (78%); mp 141 °C. IR (KBr) ν 3295, 2920, 2850, 1750, 1660, 1640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.15–1.19 (m, 24H), 1.46 (m, 2H), 1.97–2.08 (m, 7H), 2.52–2.58 (m, 4H), 3.32 (m, 2H), 4.64 (s, 3H), 4.65 (m, 1H), 7.65–7.68 (m, 2H), 7.82–7.84 (m, 2H), 8.27 (s, 1H), 8.55 (m, 1H), 10.10 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 14.4, 21.9, 25.2, 28.7, 28.9, 29.2, 29.8, 30.1, 31.1, 34.7, 34.8, 35.2, 36.4, 51.5, 51.7, 117.9, 127.8, 128.2, 141.8, 165.9, 169.7, 172.0, 172.3. MS (EI) *m*/*z* 591 (M$^+$), 518, 517, 310. Anal. calcd for $C_{32}H_{53}N_3O_5S$: C, 64.94; H, 9.03; N, 7.10; found: C, 65.00; H, 9.01; N, 7.37.

***N*-{4-[(3-Hexadecanoylamino)propanoylamino]phenylsulfonyl}methionine methyl ester (18b).** Prepared as described above from **17c** (392 mg, 1.2 mmol) and **38** (382 mg, 1.2 mmol) and purified by flash chromatography (ethyl acetate). Yield: 32 mg (4%); mp 142 °C. IR (KBr) ν 3320, 2920, 1735, 1685, 1645 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.14–1.26 (m, 24H), 1.44 (m, 2H), 1.69–1.84 (m, 2H), 1.92 (s, 3H), 2.00 (m, 2H), 2.25–2.41 (m, 2H), 2.51 (m, 2H), 3.29 (m, 2H), 3.91 (m, 1H), 7.64–7.67 (m, 2H), 7.72–7.75 (m, 2H), 7.83 (m, 1H), 8.16 (m, 1H), 10.23 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 14.3, 21.9, 25.2, 28.5, 28.7, 28.9, 29.0, 31.1, 31.3, 34.8, 35.2, 36.5, 51.7, 54.2, 118.5, 127.4, 134.6, 142.6, 170.0, 171.4, 172.2. MS (EI) *m*/*z* 627 (M$^+$), 402, 310, 162, 93. Anal. calcd for $C_{31}H_{53}N_3O_6S_2$: C, 59.30; H, 8.51; N, 6.69; found: C, 59.31; H, 8.48; N, 6.48.

***N*-{2-[3-(2,3-Dimethylphenylaminocarbonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (18c).** Prepared as described above from **17c** (327 mg, 1 mmol) and **29** (240 mg, 1 mmol) and purified by flash chromatography (ethyl acetate:n-hexane, 3:2). Yield: 451 mg (82%); mp 107 °C. IR (KBr) ν 3300, 2920, 2850, 1640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 3H), 1.13–1.29 (m, 24H), 1.45 (m, 2H), 2.00 (m, 2H), 2.09 (s, 3H), 2.27 (s, 3H), 2.48 (m, 2H), 3.31 (m, 2H), 7.05–7.11 (m, 3H), 7.41 (m, 1H), 7.63 (m, 1H), 7.82 (m, 2H), 8.11 (m, 1H), 9.82 (s, 1H), 10.05 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.9, 14.2, 20.1, 22.1, 25.2, 25.3, 28.7, 28.8, 28.9, 29.0, 31.3, 34.1, 34.8, 35.0, 35.4, 36.5, 118.8, 121.8, 121.9, 124.6, 125.2, 127.5, 128.6, 132.6, 134.3, 134.9, 135.3, 139.4, 165.4, 169.7, 172.2. MS (EI) *m*/*z* 549(M$^+$), 126, 113. Anal. calcd for $C_{34}H_{51}N_3O_3$: C, 74.28; H, 9.35; N, 7.64; found C, 74.34; H, 9.53; N, 7.81.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (18d).** Prepared as described above from **17c** (490 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 600 mg (68%); mp 145 °C. IR (KBr) ν 3350, 1695, 1640, 1320, 1160 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, 3H, $J=7$ Hz), 1.18–1.22 (m, 24H), 1.44 (m, 2H), 1.96 (s, 3H), 2.01 (t, 2H, $J=7$ Hz), 2.16 (s, 3H), 2.48 (m, 2H), 3.29 (m, 2H), 6.70 (m, 1H), 6.92 (m, 1H), 6.98 (m, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.77 (m, 1H), 7.82 (m, 1H), 8.05 (s, 1H), 9.49 (s, 1H), 10.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 21.9, 25.2, 28.5, 28.7, 28.9, 31.1, 34.8, 35.2, 36.3, 116.8, 120.9, 122.3, 124.5, 125.2, 127.9, 129.2, 133.6, 134.5, 137.3, 139.5, 141.1, 169.8, 171.1. MS (EI) *m*/*z* 585 (M$^+$), 310, 120. Anal. calcd for $C_{33}H_{51}N_3O_4S$: C, 67.66; H, 8.77; N, 7.17; found C, 67.29; H, 8.43; N, 7.38.

***N*$^\alpha$-3-(Hexadecanoylamino)propanoyl-*N*-(2,3-dimethylphenyl)isoleucine amide (18e).** Prepared as described above from **17c** (491 mg, 1.5 mmol) and **26** (351 mg, 1.5 mmol) and recrystallized from dioxane. Yield: 395 mg (48%); mp 201 °C. IR (KBr) ν 3275, 2920, 1640 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84–0.91 (m, 9H), 1.22 (m, 25H), 1.46 (m, 3H), 2.00 (m, 3H), 2.04 (s, 3H), 2.23 (s, 3H), 2.50 (m, 2H), 3.56 (m, 2H), 4.35 (m, 1H), 7.00 (m, 3H), 7.08 (m, 2H). MS (EI) *m*/*z* 543, 525, 311, 310 (M$^+$). Anal. calcd for $C_{33}H_{57}N_3O_3$ C, 72.88; H, 10.56; N, 7.73; found: C, 72.83; H, 10.33; N, 8.10.

***N*-{4-{3-[3-(4-Benzyloxyphenyl)acryloylamino]propanoylamino}benzoyl}methionine methyl ester (19a).** Prepared as described above from **17j** (325 mg, 1 mmol) and **37** (282 mg, 1 mmol). Yield: 310 mg (53%); mp 218 °C. IR (KBr) ν 1745, 1660, 1635 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03–2.05 (m, 5H), 2.49–2.61 (m, 4H), 3.35 (m, 2H), 3.64 (s, 3H), 4.57 (m, 1H), 5.13 (s, 2H), 6.48 (d, 1H, $J=16$ Hz), 7.02–7.04 (m, 2H), 7.36–7.49 (m, 7H), 7.67–7.71 (m, 2H), 7.81–7.85 (m, 2H), 8.04 (m, 1H), 8.58 (d, 1H, $J=8$ Hz), 10.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.5, 29.9, 30.1, 36.4, 38.9, 51.6, 51.8, 114.9, 115.1, 118.1, 119.9, 127.5, 127.9, 128.2, 128.3, 128.5, 128.9, 136.7, 138.0, 143.0, 159.2, 165.1, 166.0, 169.9, 172.4. MS (EI) *m*/*z* 92, 91. Anal. calcd for $C_{32}H_{35}N_3O_6S$: C, 65.18; H, 5.98; N, 7.13; found: C, 65.48; H, 5.72; N, 6.78.

***N*-{4-{3-[3-(4-Benzyloxyphenyl)acryloylamino]propanoylamjno}phenylsulfonyl}methionine methyl ester (19b).** Prepared as described above from **17j** (489 mg, 1.5 mmol) and **38** (477 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate). Yield: 497 mg (53%); mp 194 °C. IR (KBr) ν 3285, 1740, 1655, 1600 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.68–1.82 (m, 2H), 1.92 (s, 3H), 2.25–2.27 (m, 2H), 2.52—2.54 (m, 2H), 3.35 (m, 2H), 3.42 (s, 3H), 3.90 (m, 1H), 5.12 (s, 2H), 6.46 (d, $J=16$ Hz, 1H), 7.01–7.04 (m, 2H), 7.30–7.38 (m, 3H), 7.40–7.48 (m, 3H), 7.64–7.67 (m, 2H), 7.73–7.76 (m, 2H), 8.00 (m, 1H), 8.19 (m, 1H), 10.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.3, 29.0, 31.3, 34.8, 35.3, 36.4, 51.8, 54.2, 69.2, 115.1, 118.5, 119.8, 127.4, 127.6, 127.8, 128.3, 128.9, 134.6, 136.7, 138.0, 142.4, 159.3, 165.1, 170.1, 170.3, 171.4. MS (EI) *m/z* 625 (M^+), 325, 162, 147, 91. Anal. calcd for $C_{31}H_{35}N_3O_7S_2$: C, 59.50; H, 5.64; N, 6.72; found: C, 59.45; H, 5.34; N, 6.44.

3-(4-Benzyloxyphenyl)-*N*-{2-[3-(2,3-dimethylphenylaminocarbonyl)phenylaminocarbonyl]ethyl}acrylamide (19c). Prepared as described above from **17j** (490 mg, 1.5 mmol) and **29** (360 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 630 mg (77%); mp 183 °C. IR (KBr) ν 3295, 1660, 1605, 1510 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 2.09 (s, 3H), 2.28 (s, 3H), 2.56 (t, $J=7$ Hz, 2H), 3.47 (m, 2H), 5.13 (s, 2H), 6.50 (d, $J=16$ Hz, 1H), 7.02–7.04 (m, 2H), 7.06–7.12 (m, 2H), 7.30–7.34 (m, 3H), 7.37–7.39 (m, 1H), 7.41–7.44 (m, 2H), 7.47–7.49 (m, 2H), 7.64 (m, 1H), 7.83 (m, 1H), 8.10 (t, $J=6$ Hz, 1H), 8.14 (s, 1H), 9.85 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.1, 20.0, 35.1, 36.4, 69.2, 115.1, 118.7, 119.8, 121.8, 124.4, 125.1, 127.4, 127.6, 127.8, 128.3, 128.5, 128.9, 132.5, 135.3, 136.7, 136.8, 138.1, 139.2, 159.0, 165.2, 165.3, 169.9. MS (EI) *m/z* 547 (M^+), 249, 174. Anal. calcd for $C_{34}H_{33}N_3O_4$: C, 74.59; H, 6.03; N, 7.68; found: C, 74.65; H, 6.14; N, 7.70.

3-(4-Benzyloxyphenyl)-*N*-{2-[3-(2,3-dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}acrylamide (19d). Prepared as described above from **17j** (488 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate). Yield: 110 mg (13%); mp 190 °C. IR (KBr) ν 3425, 1655, 1600, 1310, 1155 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.15 (s, 3H), 2.55 (t, 2H, $J=7$ Hz), 3.43 (m, 2H), 5.13 (s, 2H), 6.48 (d, 1H, $J=16$ Hz), 6.69–6.71 (m, 1H), 6.90–7.04 (m, 4H), 7.27–7.49 (m, 10H), 7.78–7.80 (m, 1H), 8.05–8.07 (m, 2H), 9.49 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 20.0, 35.0, 36.3, 69.2, 116.9, 119.8, 121.0, 122.4, 124.6, 125.2, 127.5, 127.6, 127.7, 127.9, 128.3, 128.9, 129.3, 133.6, 124.5, 126.7, 137.4, 138.1, 139.5, 141.1, 159.2, 165.2, 169.8. MS (EI) *m/z* 565 (MI), 276, 120, 91. Anal. calcd for $C_{33}H_{33}N_3O_5S$: C, 67.91; H, 5.70; N, 7.20; found: C, 67.53; H, 5.66; N, 7.56.

***N*$^{\alpha}$-{3-[3-(4-Benzyloxyphenyl)acryloylamino]propanoyl}-*N*-(2,3-dimethylphenyl)isoleucine amide (19e).** Prepared as described above from **17j** (488 mg, 1.5 mmol) and **26** (405 mg, 1.5 mmol) and purified by flash chromatography (1. ethyl acetate:*n*-hexane, 3:2, 2. ethyl acetate:methanol, 3:1). Yield: 720 mg (92%); mp >250 °C. IR (KBr) ν 3415, 1650 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 3H), 0.93 (m, 3H), 1.19 (m, 1H), 1.55 (m, 1H), 1.85 (m, 1H), 2.05 (s, 3H), 2.23 (s, 3H), 2.37 (t, 1H, $J=7$ Hz), 2.43 (t, 1H, $J=7$ Hz), 3.36 (m, 2H), 4.37 (m, 1H), 5.14 (s, 2H), 6.48 (d, 1H, $J=16$ Hz), 6.97–7.09 (m, 5H), 7.31–7.88 (m, 8H), 8.00 (m, 1H), 8.06 (m, 1H), 9.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.9, 13.8, 15.4, 19.9, 24.4, 35.1, 35.4, 36.4, 57.3, 69.2, 115.0, 115.1, 119.9, 123.5, 124.9, 126.8, 127.5, 127.7, 128.3, 128.9, 131.2, 135.8, 136.7, 137.9, 159.2, 165.1, 170.2, 170.5; MS (ESI) *m/z* 542 ($[M+H]^+$), 564 ($[M+Na]^+$). HRMS calcd for $C_{33}H_{40}N_3O_4$: 542.3019; found: 542.3075. Anal. calcd for $C_{33}H_{39}N_3O_4$: C, 73.17; H, 7.26; N, 7.76; found: C, 72.82; H, 7.57; N, 7.44.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl}ethyl}dodecanoic acid amide (20a).** Prepared as described above from **17a** (407 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 300 mg (38%); mp 172 °C. IR (KBr) ν 3350, 3240, 1695, 1640, 1320, 1160 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, 3H, $J=7$ Hz), 1.19–1.26 (m, 16H), 1.45 (m, 2H), 1.96 (s, 3H), 2.02 (t, 2H, $J=7$ Hz), 2.16 (s, 3H), 2.49 (m, 2H), 3.30 (m, 2H), 6.71 (m, 1H), 6.95 (m, 1H), 7.00 (m, 1H), 7.28 (m, 1H), 7.44 (m, 1H), 7.78 (m, 1H), 7.83 (m, 1H), 8.06 (s, 1H), 9.50 (s, 1H), 10.17 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 22.0, 25.2, 28.5, 28.6, 28.7, 28.8, 28.85, 28.9, 31.2, 34.8, 35.3, 36.4, 116.8, 120.9, 122.4, 124.6, 125.2, 127.9, 129.3, 133.6, 134.5, 137.4, 139.6, 141.1, 169.8, 172.2. MS (EI) *m/z* 529 (M^+), 254, 120. Anal. calcd for $C_{29}H_{43}N_3O_4S$: C, 65.75; H, 8.18; N, 7.93; found: C, 65.61; H, 7.80; N, 7.66.

***N*-(2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}tetradecanoic acid amide (20b).** Prepared as described above from **17b** (449 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield 240 mg (29%); mp 170 °C. IR (KBr) ν 3350, 1640, 1320, 1160 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.85 (t, 3H, $J=7$ Hz), 1.19–1.26 (m, 20H), 1.45 (m, 2H), 1.97 (s, 3H), 2.02 (t, 2H, $J=7$ Hz), 2.17 (s, 3H), 2.49 (m, 2H), 3.31 (m, 2H), 6.72 (m, 1H), 6.93 (m, 1H), 7.00 (m, 1H), 7.28 (m, 1H), 7.44 (m, 1H), 7.78 (m, 1H), 7.83 (m, 1H), 8.06 (s, 1H), 9.50 (s, 1H), 10.17 (s, 1H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 22.0, 25.2, 28.5, 28.6, 28.7, 28.8, 28.9, 31.2, 34.8, 35.3, 36.4, 116.8, 120.9, 122.3, 124.6, 125.2, 127.9, 129.3, 133.6, 134.6, 137.3, 139.6, 141.1, 169.8, 172.2. MS (EI) *m/z* 557 (M^+), 282, 120. Anal. calcd for $C_{31}H_{47}N_3O_4S$. C, 66.75, H, 8.49, N, 7.53, found: C, 66.41, 14, 8.15, N, 7.83.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}heptadecanoic acid amide (20c).** Prepared as described above from **17d** (682 mg, 2 mmol) and **32a** (552 mg, 2 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 910 mg (76%); mp 143 °C. IR (KBr) ν 3315, 2920, 2850, 1650 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.19–1.26 (m, 26H), 1.45 (m, 2H), 1.97 (s, 3H), 2.02 (m, 2H), 2.16 (s, 3H), 2.48 (m, 2H), 3.30 (m, 2H), 6.73 (m, 1H), 6.92 (m, 1H), 6.97 (m, 1H), 7.29 (m, 1H), 7.42 (m, 1H), 7.76 (m, 2H), 8.04 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 13.6, 13.8, 19.8, 21.8, 25.0, 28.4, 28.6, 28.7, 31.0, 34.7, 35.2, 36.3, 116.8, 120.8, 122.3, 124.4, 125.1, 127.7, 129.1, 134.5, 137.2, 139.4, 169.7, 172.0. MS (EI) m/z 599 (10, M^+), 121 (50), 120 (100). HRMS calcd for $C_{34}H_{53}N_3O_4S$: 599.3757; found: 599.3747. Anal. calcd for $C_{34}H_{53}N_3O_4S$: C, 68.08; H, 8.91; N, 7.00; found: C, 68.13; H, 8.95; N, 6.97.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}octadecanoic acid amide (20d).** Prepared as described above from **17e** (530 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 236 mg (45%); mp 123 °C. IR (KBr) ν 3345, 3250, 2920, 2850, 1695, 1655, 1640 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.18–1.27 (m, 28H), 1.44 (m, 2H), 1.96 (s, 3H), 2.01 (m, 2H), 2.16 (s, 3H), 2.48 (m, 2H), 3.30, m, 2H), 6.71 (m, 1H), 6.92 (m, 1H), 6.97 (m, 1H), 7.43 (m, 1H), 7.77 (m, 1H), 7.82 (m, 1H), 8.05 (m, 1H), 10.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 22.0, 25.2, 28.6, 28.7, 28.9, 31.2, 34.8, 35.2, 36.4, 116.8, 120.9, 122.3, 124.4, 125.2, 127.7, 129.2, 133.2, 134.6, 137.3, 139.5, 141.2, 169.8, 172.1. MS (EI) m/z 613 (M^+), 121, 120. Anal. calcd for $C_{35}H_{55}N_3O_4S$: C, 68.48; H, 9.03; N, 6.84; found: C, 68.42; H, 9.45; N, 6.50.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}eicosanoic acid amide (20e).** Prepared as described above from **17f** (600 mg, 1.56 mmol) and **32a** (440 mg, 1.56 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 700 mg (70%); mp 120 °C. IR (KBr) ν 3350, 3250, 2920, 2850, 1695, 1640 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz), 1.18–1.22 (m, 32H), 1.46 (m, 2H), 1.96 (s, 3H), 2.01 (t, $J=7$ Hz, 2H), 2.16 (s, 3H), 2.48 (m, 2H), 3.29 (m, 2H), 6.70 (m, 1H), 6.92 (m, 1H), 6.99 (m, 1H), 7.28 (m, 1H), 7.43 (m, 1H), 7.77 (m, 1H), 7.81 (m, 1H), 8.05 (m, 1H), 10.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 22.0, 25.2, 28.6, 28.7, 28.9, 31.2, 34.8, 25.2, 36.3, 116.8, 120.9, 122.4, 124.6, 125.2, 127.9, 129.3, 133.3, 134.5, 137.3, 139.6, 169.5, 172.1. MS (EI) m/z 641 (M^+), 578, 366, 121, 120. Anal. calcd for $C_{37}H_{59}N_3O_4S$: C, 69.23; H, 9.26; N, 6.55; found: C, 68.92; H, 9.54; N, 6.15.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}-(*E*)-9-octadecenoic acid amide (20f).** Prepared as described above from **17g** (530 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:n-hexane, 3:2). Yield: 588 mg (64%); mp 111 °C. IR (KBr) ν 3340, 3300, 3240, 2920, 2850, 1695, 1645 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.18–1.26 (m, 20H), 1.44 (m, 2H), 1.91 (s, 4H), 1.96 (s, 3H), 2.01 (m, 2H), 2.16 (s, 3H), 2.47 (m, 2H), 3.30 (m, 2H), 5.33 (m, 2H), 6.70 (m, 1H), 6.92 (m, 1H), 6.98 (m, 1H), 7.27 (m, 1H), 7.34 (m, 1H), 7.77 (m, 1H), 7.82 (m, 1H), 8.05 (m, 1H), 9.49 (s, 1H), 10.17 (s, 1H). MS (EI) m/z 611 (M^+), 121, 120. Anal. calcd for $C_{35}H_{53}N_3O_4S$: C, 68.70; H, 8.73; N, 6.87; found: C, 68.88; H, 8.40; N, 6.45.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl} - (*Z*) - 9 - octadecenoic acid amide (20g).** Prepared as described above from **17h** (530 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 390 mg (43%); mp 125 °C. IR (KBr) ν 3350, 1655, 1320, 1160 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, 3H, $J=7$ Hz), 1.21–1.29 (m, 21H), 1.45 (m, 2H), 1.95–2.01 (m, 6H), 2.02 (m, 2H), 2.17 (s, 3H), 2.48 (m, 2H), 3.31 (m, 2H), 5.30 (m, 2H), 6.73 (m, 1H), 6.92 (m, 1H), 6.98 (m, 1H), 7.28 (m, 1H), 7.42 (m, 1H), 7.68 (m, 1H), 7.77 (m, 1H), 8.04 (s, 1H), 9.36 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 13.9, 20.0, 21.9, 25.2, 26.5, 28.5, 28.7, 29.0, 31.1, 34.8, 35.2, 36.4, 116.8, 120.9, 122.4, 124.6, 125.2, 127.9, 129.3, 129.5, 133.6, 134.5, 137.3, 139.5, 141.9, 169.8, 172.1. MS (EI) m/z 611 (M^+), 335, 120. Anal. calcd for $C_{35}H_{53}N_3O_4S$: C, 68.70; H, 8.73; N, 6.87; found: C, 68.47; H, 8.40; N, 6.80.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}-(*Z,Z*)-9,13-octadecadienoic acid amide (20h).** Prepared as described above from **17i** (527 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 816 mg (89%); mp 107 °C. IR (KBr) ν 3345, 3240, 3065, 1695, 1655, 1640 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J=7$ Hz, 3H), 1.21–1.35 (m, 14H), 1.54 (m, 2H), 1.98 (s, 3H), 2.01 (m, 4H), 2.14 (m, 2H), 2.18 (s, 3H), 2.65 (t, $J=6$ Hz, 2H), 2.73 (t, $J=7$ Hz, 2H), 3.58 (m, 2H), 5.26–5.37 (m, 4H), 6.47 (m, 1H), 6.92–6.94 (m, 2H), 6.95–6.98 (m, 1H), 7.07 (m, 1H), 7.25–7.31 (m, 2H), 7.84 (m, 1H), 8.11 (m, 1H), 9.12 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 20.6, 22.6, 25.6, 25.7, 27.2, 29.1, 29.2, 29.3, 29.6, 31.5, 35.4, 36.7, 37.2, 117.9, 122.7, 123.7, 123.8, 125.8, 128.0, 128.5, 129.4, 130.0, 130.2, 132.0, 133.8, 138.0, 139.1, 140.4, 170.5, 174.3. MS (EI) m/z 609 (M^+), 121, 120, 106. Anal. calcd for $C_{35}H_{51}N_3O_4S$: C, 68.93; H, 8.43; N, 6.89; found: C, 68.75; H, 8.39; N, 7.02.

***N*-{2-[3-(1-Naphthylaminosulfonyl)phenylaminocarbonyljethyl}hexadecanoic acid amide (21a).** Prepared as described above from **17c** (290 mg, 0.89 mmol) and **32b** (265 mg, 0.89 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 362 mg (67%); mp 51 °C. IR (KBr) ν 2920, 2850, 1660, 1650, 1640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 3H), 1.17–1.25 (m, 24H), 1.45 (m, 2H), 2.00 (m, 1H), 2.16 (m, 1H), 2.44 (m, 2H), 3.27 (m, 2H), 7.13 (m, 1H), 7.31–7.48 (m, 5H), 7.68–7.77 (m, 2H), 7.79 (m, 1H), 7.86 (m, 1H), 8.05 (m, 1H), 8.11 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.5, 22.6, 25.0, 25.8, 29.1, 29.22, 29.26, 29.3, 29.5, 29.6, 31.8, 34.2, 35.9, 37.0, 117.6, 121.6, 123.1, 123.8, 126.0, 126.5, 126.7, 128.4, 129.9, 130.0, 134.3, 140.2, 170.2, 172.8, 175.0. MS (EI) m/z 607 (M^+), 352, 298, 142. Anal. calcd for $C_{35}H_{49}N_3O_4S$: C, 69.16; H, 8.13; N, 6.91; found: C, 69.21; H, 8.28; N, 6.91.

***N*-{2-[3-(Benzylaminosulfonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (21b).** Prepared as described above from **17c** (523 mg, 1.6 mmol) and **32c** (420 mg, 1.6 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 650 mg (71%); mp 103 °C. IR (KBr) ν 3315, 2955, 2850, 1660, 1640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, $J=7$ Hz, 3H), 1.19–1.23

(m, 24H), 1.47 (m, 2H), 2.02 (t, $J=7$ Hz, 2H), 2.49 (m, 2H), 3.31 (m, 2H), 3.96 (d, $J=6$ Hz, 2H), 7.21–7.29 (m, 4H), 7.45–7.47 (m, 2H), 7.75 (m, 1H), 7.84 (m, 1H), 8.10 (m, 1H), 8.18 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 21.9, 25.2, 28.5, 28.6, 28.7, 28.8, 31.2, 34.8, 35.2, 36.4, 46.0, 116.8, 120.7, 122.2, 127.0, 127.4, 128.1, 129.4, 137.6, 139.6, 141.1, 169.8, 172.2. MS (EI) m/z 571 (M^+), 402, 311, 310. Anal. calcd for $C_{32}H_{49}N_3O_4S$: C, 67.22; H, 8.64; N, 7.35; found: C, 66.86; H, 8.39; N, 7.41.

***N*-{2-[3-(2,3-Dichlorobenzylaminosulfonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (21c).** Prepared as described above from **17c** (608 mg, 1.86 mmol) and **32d** (615 mg, 1.86 mmol) and purified by flash chromatography (ethyl acetate:n-hexane, 3:2). Yield: 1.18 g (99%); mp 124 °C. IR (KBr) ν 3315, 2920, 2850, 1655, 1645 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.81 (t, J = 7 Hz, 3H), 1.15–1.20 (m, 24H), 1.43 (m, 2H), 2.00 (m, 2H), 2.48 (m, 2H), 3.30 (m, 2H), 4.09 (s, 2H), 7.27 (m, 1H), 7.36 (m, 1H), 7.41–7.48 (m, 3H), 7.72 (m, 2H), 8.14 (s, 1H), 8.18 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 21.9, 25.2, 28.6, 28.7, 28.8, 28.89, 28.9, 31.2, 34.9, 25.3, 44.2, 116.9, 120.7, 122.5, 127.8, 128.2, 129.3, 129.4, 130.1, 131.6, 137.6, 139.7, 140.9, 169.9, 172.2. MS (EI) m/z 639 (10, M^+), 330 (23), 310 (100), 174 (40). Anal. calcd for $C_{32}H_{47}Cl_2N_3O_4S$: C, 59.99; H, 7.39; N, 6.56; found C, 60.06; H, 7.40; N, 6.55.

***N*-{2-[3-(1-Naphthylmethylaminosulfonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (21d).** Prepared as described above from **17c** (654 mg, 2 mmnol) and **32e** (624 mg, 2 mmol) and purified by flash chromatography (ethyl acetate:n-hexane, 3:2). Yield: 845 mg (68%); mp 126 °C. IR (KBr) ν 3315, 3050, 2920, 2850, 1660, 1640 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.85 (t, $J=7$ Hz, 3H), 1.19–1.27 (m, 24H), 1.47 (m, 2H), 2.04 (m, 2H), 2.51 (m, 2H), 3.34 (m, 2H), 4.42 (d, $J=6$ Hz, 2H), 7.42 (m, 2H), 7.50–7.53 (m, 4H), 7.77–7.79 (m, 2H), 7.82 (m, 1H), 7.90 (m, 1H), 8.04–8.08 (m, 2H), 8.22 (s, 1H), 10.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 21.9, 25.2, 28.5, 28.6, 28.7, 28.8, 28.87, 28.9, 31.2, 34.9, 35.3, 44.3, 117.1, 120.8, 122.4, 123.4, 125.6, 126.4, 128.0, 128.3, 129.4, 130.8, 132.6, 133.2, 139.6, 140.9, 169.8, 172.2. MS (EI) m/z 619 (15, M^+), 555 (20), 120 (100). Anal. calcd for $C_{36}H_{51}N_3O_4S$: C, 69.53; H, 8.27; N, 6.76; found: C, 69.54; H, 8.15; N, 6.67.

***N*-{2-{3-[(2-Phenylethyl)aminosulfonyl]phenylaminocarbonyl}ethyl}hexadecanoic acid amide (21e).** Prepared as described above from **17c** (490 mg, 1.5 mmol) and **32f** (414 mg, 1.5 mmol) and recrystallized from toluene. Yield: 700 mg (80%); mp 93 °C. IR (KBr) ν 3310, 2920, 2850, 1640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 3H), 1.28–1.23 (m, 24H), 1.44 (m, 2H), 2.06 (m, 2H), 2.46 (m, 2H), 2.67 (m, 2H), 2.95 (m, 2H), 3.26 (m, 2H), 7.14–7.19 (m, 4H), 7.22–7.26 (m, 2H), 7.68 (m, 1H), 7.75 (m, 1H), 7.83 (m, 1H), 8.16 (m, 1H), 10.20 (m, 1H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 20.0, 25.2, 28.6, 28.7, 28.9, 30.6, 31.2, 33.9, 35.3, 44.6, 116.8, 120.7, 122.3, 126.1, 128.2, 128.5, 129.5, 138.6, 139.7, 140.9, 169.9, 172.2, 172.8. MS (EI) m/z 585 (M^+), 494, 423, 239. Anal. calcd for $C_{33}H_{51}N_3O_4S$: C, 67.66; H, 8.77; N, 7.17; found: C, 67.90; H, 8.91; N, 7.26.

***N*-{2-{3-[2-[(3-Indoly)ethyl]aminosulfonyl]phenylaminocarbonyl}ethyl}hexadecanoic acid amide (21f).** Prepared as described above from **17c** (1079 mg, 3.3 mmol) and **32g** (1040 mg, 3.3 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 1.8 g (87%); mp 105 °C. IR (KBr) ν 3395, 3315, 2920, 2850, 1655, 164.0 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, $J=7$ Hz, 3H), 1.14–1.20 (m, 24H), 1.50 (m, 2H), 2.08 (m, 2H), 2.55 (m, 2H), 2.84 (m, 2H), 3.24 (m, 2H), 3.53 (m, 1H), 4.62 (m, 1H), 6.18 (m, 1H), 6.68 (m, 1H), 6.98 (m, 1H), 7.10 (m, 1H), 7.24–7.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 22.7, 25.4, 25.7, 29.3, 29.5, 29.7, 31.9, 35.4, 36.8, 37.3, 43.2, 111.3, 111.4, 117.9, 118.5, 119.5, 122.3, 122.4, 122.7, 123.0, 129.6, 138.2, 139.4, 140.4, 170.1, 172.0. MS (EI) m/z 625 (M^+), 624, 130. Anal. calcd for $C_{35}H_{52}N_3O_4S$: C, 67.27; H, 8.39; N, 8.97; found: C, 67.05; H, 8.68; N, 8.63.

***N*-{2-{3-[(3-Methylbutyl)aminosulfonyl]phenylaminocarbonyl}ethyl}hexadecanoic acid amide (21g).** Prepared as described above from **17c** (810 mg, 2.5 mmol) and **32h** (600 mg, 2.5 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 900 mg (65%); mp 103 °C. IR (KBr) ν 3315, 2920, 2850, 1655, 1640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (d, $J=7$ Hz, 6H), .84 (m, 3H), 1.18–1.27 (m, 24H), 1.43 (m, 2H), 1.55 (m, 1H), 2.00 (m, 2H), 2.49 (m, 4H), 2.74 (m, 2H), 3.32 (m, 2H), 7.38–7.48 (m, 3H), 7.73 (m, 1H), 7.82 (m, 1H), 8.15 (m, 1H), 10.18 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 21.9, 22.0, 24.7, 25.2, 28.5, 28.6, 28.8, 28.9, 31.2, 34.8, 35.3, 36.4, 37.8, 40.7, 116.8, 120.6, 122.1, 129.4, 139.6, 141.0, 169.8, 172.2. MS (EI) m/z 551 (M^+), 310. Anal. calcd for $C_{30}H_{53}N_3O_4S$: C, 65.30; H, 9.68; N, 7.61; found: C, 65.62; H, 9.62; N, 8.01.

***N*-{2-[3-(Dodecylaminosulfonyl)phenylaminocarbonyl]ethyl}hexadecanoic acid amide (21h).** Prepared as described above from **17c** (654 mg, 2 mmol) and **32i** (680 mg, 2 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 559 mg (43%); mp 84 °C. IR (KBr) ν 3350, 2920, 2850, 1659, 1655, 1635 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 6H), 1.13–1.45 (m, 44H), 1.58 (m, 2H), 2.30 (m, 2H), 2.48 (m, 2H), 2.72 (m, 2H), 3.24 (m, 2H), 7.40 (m, 1H), 7.47 (m, 2H), 7.73 (m, 1H), 8.13 (m, 1H), 10.10 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.8, 22.0, 24.9, 25.9, 28.4, 28.5, 28.9, 31.2, 36.3, 42.4, 116.7, 120.5, 122.0, 129.4, 139.7, 141.1, 171.5. MS (EI) m/z 650 (M^+), 423, 184. Anal. calcd for $C_{37}H_{67}N_3O_4S$: C, 68.37; H, 10.39; N, 6.46; found: C, 68.27; H, 10.75; N, 6.41.

3-[4-(2-Phenylethenyl)phenyl]-*N*-{2-[3-(2,3-dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}acrylamide (22a). Prepared as described above from **17k** (320 mg, 1 mmol) and **32a** (276 mg, 1 mmol) and purified by flash chromatography (ethyl acetate). Yield 132 mg (22%); mp > 200 °C. IR (KBr) ν 3275, 2925, 1655, 1600 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.15 (s, 3H), 2.56 (t, $J=7$ Hz, 2H), 3.46 (m, 2H), 6.65 (m, 1H), 6.69 (m, 1H), 6.92 (m, 1H), 6.98 (m, 1H), 7.27–7.31 (m, 3H), 7.36–7.40 (m, 3H), 7.54 (m, 2H), 7.59–7.66 (m, 4H), 7.80 (m, 1H), 8.06 (s, 1H), 8.19 (m, 1H), 9.52 (s, 1H), 10.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.7, 20.7,

35.6, 37.0, 117.2, 121.3, 122.3, 122.9, 125.1, 125.6, 128.0, 128.3, 129.1, 129.2, 129.5, 130.4, 130.8, 131.0, 134.5, 134.9, 135.4, 136.1, 137.5, 138.0, 138.8, 139.4, 140.2, 141.8, 165.7, 170.8. MS (EI) *m/z* 579 (M^+), 276, 233, 120. Anal. calcd for $C_{34}H_{33}N_3O_4S$: C, 70.44; H, 5.74; N, 7.25; found: C, 70.26; H, 5.34; N, 7.46.

3-Biphenylyl-*N*-{2-[3-(2,3-dimethylphenylaminosulfonyl)-phenylaminocarbonyl]ethyl}acrylamide (22b). Prepared as described above from **17l** (443 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and purified by flash chromatography (ethyl acetate). Yield: 249 mg (30%); mp 230 °C. IR (KBr) ν 3350, 1695, 1660, 1600 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.15 (s, 3H), 2.57 (t, $J=6$ Hz, 2H), 3.47 (q, $J=6$ Hz, 2H), 6.66–6.71 (m, 2H), 6.90–6.98 (m, 2H), 7.26–7.32 (m, 1H), 7.34–7.38 (m, 1H), 7.42–7.44 (m; 4H), 7.61–7.63 (m, 2H), 7.69–7.71 (m, 4H), 7.79–7.81 (m, 1H), 8.06 m, 1H), 8.19 (d, $J=6$ Hz, 1H), 9.48 (s, 1H), 10.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.0. 20.0, 34.7, 36.3, 116.5, 120.8, 121.8, 122.0, 124.1, 125.0, 126.2, 127.3, 127.9, 128.5, 129.2, 133.4, 133.7, 134.3, 137.1, 137.8, 138.9, 139.1, 140.6, 140.8, 165.0, 169.5. MS (EI) *m/z* 553 (M^+), 223, 222, 207. Anal. calcd for $C_{32}H_{30}N_3O_4S$: C, 69.42; H, 5.64; N, 7.59; found: C, 69.55; H, 5.65; N, 7.97.

2-(4-Benzyloxyphenyloxy)-*N*-{2-[3-(2,3-dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}acetamide (22c). Prepared as described above from **17m** (628 mg, 2 mmol) and **32a** (552 mg, 2 mmol) and washed with ethyl acetate: *n*-hexane, 3:2 and *n*-hexane. Yield: 450 mg (38%); mp 153 °C. IR (KBr) ν 3185, 1660, 1600, 1310, 1155 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.98 (s, 3H), 2.17 (s, 3H), 2.55 (t, 2H, $J=7$ Hz), 3.44 (m, 2H), 4.38 (s, 2H), 5.00 (s, 2H), 6.73–6.75 (m, 1H), 6.87–6.95 (m, 5H), 6.98–6.99 (m, 1H), 7.28–7.31 (m, 2H), 7.35–7.45 (m, 5H), 7.76–7.78 (m, 1H), 7.97 (m, 1H), 8.06 (s, 1H), 9.39 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 20.0, 34.7, 36.1, 67.7, 69.6, 115.6, 115.7, 116.9, 121.0, 122.5, 124.6, 125.2, 127.4, 127.6, 128.0, 128.2, 129.3, 137.2, 137.5, 139.5, 141.1, 151.9, 152.8, 167.8, 169.8. MS (EI) *m/z* 587 (M^+), 210, 120, 91. Anal. calcd for $C_{32}H_{33}N_3O_6S$: C, 65.40; H, 5.66; N, 7.15; found: C, 65.10; H, 5.60; N, 6.79.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}-2-(3-phenyloxyphenyloxy)acetamide (22d).** Prepared as described above from **17n** (600 mg, 2.32 mmol) and **32a** (640 mg, 2.32 mmol) and purified by flash chromatography (1. ethyl acetate:*n*-hexane, 3:2; 2. ethyl acetate). Yield: 410 mg (30%); mp 45 °C. IR (KBr) ν 3300, 1660, 1250, 1155 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.15 (s, 3H), 2.52 (t, 2H, $J=7$ Hz), 3.39 (m, 2H), 3.87 (s, 2H), 4.50 (s, 2H), 6.70 (m, 1H), 6.88–6.92 (m, 2H), 6.97–7.00 (m, 4H), 7.09–7.13 (m, 2H), 7.27–7.44 (m, 5H), 7.78 (m, 1H), 7.83 (m, 1H), 8.03 (s, 1H), 9.47 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 20.0, 34.5, 36.1, 69.2, 71.7, 116.9, 117.6, 118.5, 121.0, 122.4, 123.3, 124.6, 125.2, 128.0, 129.8, 129.9, 133.6, 134.4, 139.3, 139.9, 141.0, 156.6, 168.7, 170.0. MS (EI) *m/z* 587 (M^+), 330, 183, 120. MS (ESI) *m/z* 588 $[M+H]^+$, 610 $[M+Na]^+$. HRMS calcd for $C_{32}H_{34}N_3O_6S$: 588.2168; found: 588.2152. Anal. calcd for $C_{32}H_{33}N_3O_6S$: C, 65.40; H, 5.66; N, 7.15; found: C, 65.48; H, 5.78; N, 6.77.

***N*-{2-[3-(2,3-Dimethylphenylaminosulfonyl)phenylaminocarbonyl]ethyl}-1-naphthylacetamide (22e).** Prepared as described above from **17o** (386 mg, 1.5 mmol) and **32a** (414 mg, 1.5 mmol) and recrystallized from toluene/dioxane/petroleum ether. Yield: 653 mg (85%); mp 110 °C. IR (KBr) ν 3415, 1655 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H), 2.15 (s, 3H), 2.49 (m, 2H), 3.35 (m, 2H), 3.87 (s, 2H), 6.71–6.73 (m, 1H), 6.92–7.03 (m, 2H), 7.28–7.30 (m, 1H), 7.38–7.45 (m, 5H), 7.76–7.78 (m, 2H), 7.86–7.89 (m, 1H), 8.02–8.06 (m, 2H), 8.23 (m, 1H), 9.50 (s, 1H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 20.0, 35.0, 36.1, 115.1, 116.9, 119.8, 121.0, 122.4, 124.6, 125.2, 127.5, 127.6, 127.7, 127.9, 128.3, 128.9, 129.3, 133.6, 134.5, 136.7, 137.4, 138.1, 139.5, 141.1, 169.8, 170.0. MS (EI) *m/z* 515 (M^+), 168, 120. Anal. calcd for $C_{29}H_{29}N_3O_4S$: C, 67.55; H, 5.67; N, 8.15; found C, 67.59; H, 5.72; N, 8.12.

***N*-{4-[(3-Octadecanoylamlno)propanoylaminolbenzoyl}-methionine methyl ester (23).** Prepared as described above from **17e** (530 mg, 1.5 mmol) and **37** (423 mg, 2 mmol) and purified by flash chromatography (ethyl acetate:*n*-hexane, 3:2). Yield: 150 mg (16%); mp 122 °C. IR (KBr) ν 3290, 2920, 2850, 1745, 1630 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, $J=7$ Hz, 3H), 1.15–1.20 (m, 28H), 1.43 (m, 2H), 1.95–2.04 (m, 7H), 2.50–2.56 (m, 4H), 3.28 (m, 2H), 3.59 (s, 3H), 4.53 (m, 1H), 7.60–7.63 (m, 2H), 7.76–7.78 (m, 2H), 8.25 (s, 1H), 8.50 (m, 1H), 10.06 (s, 1H). MS (EI): *m/z* 619 (M^+), 545, 457, 338, 212, 120. HRMS calcd for $C_{34}H_{57}N_3O_5S$: 619.4019; found: 619.4059.

Farnesyltransferase assay

The assay employed yeast farnesyltransferase (FTase) fused to Glutathione *S*-transferase at the N-terminus of the β-subunit. FTase was expressed in *Escherichia coli* DH5α grown in LB media containing ampicillin and additional chloramphenicol for co-expression of pGEX-DPR1 and pBC-RAM2 for FTase production.[21] The enzyme was purified by standard protocol using glutathione-agarose beads for selective binding of the target proteins. The assay was carried out as described.[5,20] FPP was obtained as ammonium salt solution in methanol: 10 mM aqueous NH_4Cl (7:3) from Sigma-Aldrich. Dansyl-GCVLS was custom synthesized by ZMBH, Heidelberg, Germany. The assay mixture (100 μL volume) contained 50 mM Tris/HCl pH 7.4, 5 mM $MgCl_2$, 10 μM, $ZnCl_2$, 5 mM DTT, 7 μM Ds-GCVLS, 20 μM FPP and approx. 5 nmol yeast GST-FTase[21] and 1% of various concentrations of the test compounds dissolved in DMSO. The progress of the enzyme reaction was followed by the enhancement of the fluorescence emission at 505 nM (excitation: 340 nM). The reaction was started by addition of the enzyme and run in a Quartz cuvette thermostatted at 30 °C. Fluorescence emission was recorded with a Perkin Elmer LS50B spectrometer. IC_{50}s were calculated from initial velocity of three independent measurements of each inhibitor concentration and expressed as mean±SD.

Cells and culture conditions

Established suspended human leukaemic cell lines K-562 cells (chronic myeloid leukaemic cell line), HL-60

cells (acute myeloid leukaemic cell line) and THP-1 cells (acute monocytic leukaemic cell line) were cultured in RPMI 1640 medium (Gibco, cat.-no. 15140-114), supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin and 10% FBS.

Test conditions

For each experiment, approximately 10,000 cells were seeded with 0.1 mL culture medium, containing sodium bicarbonate, but without HEPES, into 96-well microplates (NUNC). The plates were previously prepared with dilutions of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512 and 1:1024 of test substances in 0.1 mL medium. The cells were incubated for 72 h at 37 °C in a humidified atmosphere and 5% CO_2.

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