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Non-Thiol Farnesyltransferase Inhibitors: Evaluation of Different AA(X)-Peptidomimetic Substructures in Combination with Arylic Cysteine Replacements

In the course of our studies on non-thiol farnesyltransferase inhibitors based on the 2,5-diaminobenzophenone AAX-peptidomimetic substructure, we have developed the (4-nitrophenyl)butyryl (R^1), the (2-naphthyl)acryloyl (R^2), the 4-nitrocinnamoyl (R^3), and the 5-(4-nitrophenyl)furylacryloyl (R^4) groups as useful cysteine replacements. In this study, we combined these four groups with other AA(X)-peptidomimetic substructures (**5**–**10**: R = H) reported in the literature. The 5-(4-nitrophenyl)furylacryloyl moiety (R^4) turned out to be the most useful non-thiol cysteine replacement yielding in all cases the most active inhibitors. By combination of this 5-(4-nitrophenyl)furylacryloyl moiety (R^4) with the structurally simple AAX-peptidomimetics 4-aminobenzophenone (**5**) and 4-aminodiphenylsulfone (**6**) potent, readily accessible non-thiol farnesyltransferase inhibitors were obtained (IC_{50} = 12 nM and 10 nM).

Keywords: Farnesyltransferase inhibitors; Peptidomimetics

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Introduction

One of the most important posttranslational modifications of proteins is protein prenylation [1], which is the transfer of either a farnesyl or a geranylgeranyl residue from the corresponding pyrophosphates to the thiol of a cysteine side chain of proteins carrying the C-terminal CAAX-sequence (C: cysteine, A: amino acid with aliphatic side chain, X: variable amino acid). Due to the involvement of farnesylated proteins in carcinogenesis, inhibition of farnesyltransferase has received much interest in recent years [2–5]. Farnesyltransferase inhibitors have been demonstrated to inhibit a wide range of tumor cell lines in vitro and to display synergistic effects with other tumor therapeutics [6–8]. Farnesyltransferase inhibitors are therefore regarded as a major emerging strategy in tumor therapy.

Most farnesyltransferase inhibitors described to date are structural analogs of the CAAX recognition sequence of farnesylated proteins, and thus carry a free thiol function. However, a free thiol is an undesirable feature in potential drugs because of its sensitivity towards oxidation and, more importantly, as a potential source of severe adverse drug effects such as taste disturbance and, more seriously, skin reactions [9]. Development is therefore directed towards the so called “non-thiol” farnesyltransferase inhibitors [2–4]. We [10, 11] and others [12–15] have shown that the cysteine residue in CAAX-peptidomimetic farnesyltransferase inhibitors can be replaced by aryl moieties, a finding that led to the postulation of two hitherto unknown aryl binding sites in or near the farnesyltransferase’s active site [13, 14]. Employing flexible docking of several non-thiol farnesyltransferase inhibitors known from literature and some model compounds based on our benzophenone scaffold [16–18] as well as performing GRID searches, we have identified two regions in or near farnesyltransferase’s active site which we suggest as being the postulated aryl binding sites [10, 19].

In the course of our studies on non-thiol farnesyltransferase inhibitors based on the 2,5-diaminobenzophenone AAX-peptidomimetic substructure [16–18], we have investigated a number of different aryl-containing moieties as cysteine replacements. These different aryl-containing cysteine replacements stem either from structural variations of model compounds which we used to explore the aryl binding sites [11, 19] or from docking experiments and subsequent synthesis and evaluation of residues displaying a good fit into the aryl binding site in these docking studies [10, 19]. The (4-nitrophenyl)butyryl (R^1), the (2-naphthyl)acryloyl (R^2), the 4-nitrocinnamoyl (R^3), and the 5-(4-nitrophenyl)furylacryloyl residue (R^4), turned out to be useful cysteine replacements, as for instance in compounds **1**–**4** (Figure 1) [10, 11, 19].

In this study, we combined these four residues with various AA(X)-peptidomimetic substructures (**5**–**10**: R = H) (Table 1) reported in the literature [20–23] which are

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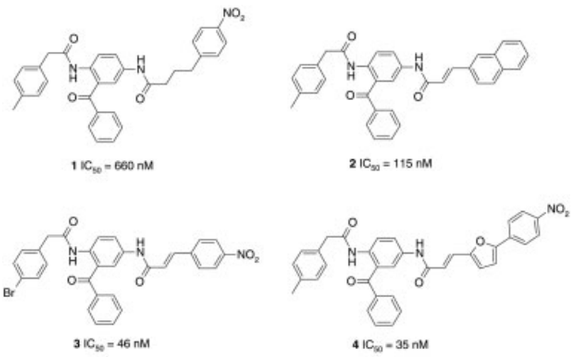


Figure 1. Structures and activity of 2,5-benzophenone-based non-thiol farnesyltransferase inhibitors **1**–**4**.

structurally different from our benzophenone scaffold. Our aim was to evaluate novel peptidomimetic substructures in combination with cysteine replacements originating from our studies in order to find possible novel lead structures for further development of non-thiol farnesyltransferase inhibitors. Potential candidates for further development should display nanomolar activity and should give easy access to structural variations. AA(X)-peptidomimetic substructures were selected from the literature on the basis of structural simplicity and potential for structural variation.

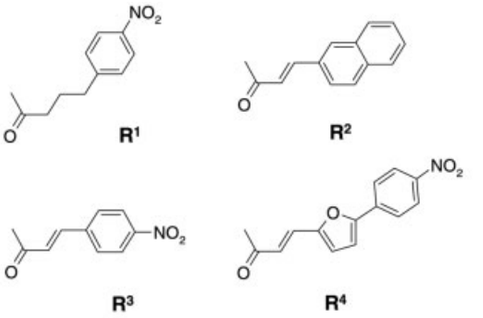
Chemistry

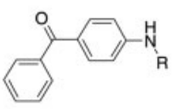
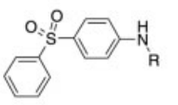
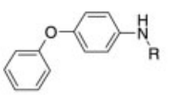
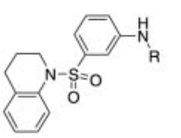
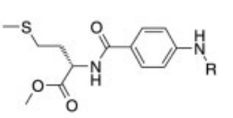
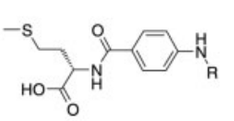
Target compounds **5a**–**d** to **10a**–**d** (Table 1) were prepared by acylation of the respective peptidomimetic moieties (**5**–**10**: R = H) [20–23] using 4-nitrocinnamoyl chloride, 3-[5-(4-nitrophenyl)-2-furyl]acryloyl chloride, 3-(2-naphthyl)acryloyl chloride, and 4-(4-nitrophenyl)butyryl chloride, respectively.

Biological evaluation

The inhibitory activity of the compounds on farnesyltransferase was determined using a fluorescence enhancement assay. This assay, established by Pompliano et al. [24] (Merck Inc.) as an easy to handle test system for the evaluation of potential farnesyltransferase inhibitors, yields equivalent results to those assays which employ ras and tritium-labeled FPP as substrates [24]. The assay employed yeast farnesyltransferase (FTase) fused to glutathione S-transferase at the N-terminus of the β-subunit [25]. Yeast farnesyltransferase is a close homolog and functionally similar to the human enzyme; it is widely used for the evaluation of farnesyltransferase inhibitors [25]. All active site amino acid side chains which are in contact with the inhibitors are identical in human, rat, and yeast farnesyltransferase [26]. Farnesylpyrophosphate and the dansylated pentapeptide Ds-GlyCysValLeuSer were used as substrates. Upon farnesylation of the cysteine thiol the dansyl residue is

Table 1. Structures and farnesyltransferase inhibitory activity[a] of compounds **5**–**10**.



Compd.	AA(X)-peptidomimetic	R	IC_{50} (nM)
5a		R^1	1500 ± 100
5b		R^2	> 10000
5c		R^3	485 ± 20
5d		R^4	12 ± 2
6a		R^1	440 ± 20
6b		R^2	5500 ± 250
6c		R^3	650 ± 30
6d		R^4	10 ± 1
7a		R^1	3700 ± 900
7b		R^2	> 10000
7c		R^3	46 ± 6
7d		R^4	36 ± 2
8a		R^1	3600 ± 1200
8b		R^2	760 ± 10
8c		R^3	960 ± 40
8d		R^4	49 ± 2
9a		R^1	> 10000
9b		R^2	> 10000
9c		R^3	> 10000
9d		R^4	870 ± 90
10a		R^1	1600 ± 400
10b		R^2	1400 ± 400
10c		R^3	3900 ± 200
10d		R^4	90 ± 3

[a] The reported [23] value of a standard inhibitor FTI-276 (thiol-containing) is 0.5 nM.

placed into a lipophilic environment; the resulting enhancement of fluorescence at 505 nm is used to monitor the enzyme reaction.

Molecular modeling

Flexible docking of inhibitors **5d**, **6d**, and **7d** was performed using the program FlexX [27]. Based on the coordinates of the published crystal structure [28] of a ternary complex of farnesyltransferase, a farnesylpyrophosphate analog and *N*-acetyl-Cys-Val-Ile-selenoMetOH (PDB-code 1QBQ), we have calculated the solvent-accessible surface of the farnesyltransferase's active site using the program MOLCAD which is implemented in the molecular modeling software package SYBYL [29]. Farnesylpyrophosphate was included as part of the enzyme's molecular surface. The position of the 5-(4-nitrophenyl)furyl moiety as has been calculated for inhibitor **4** in a previous study [19] was used as a starting fragment for the docking of inhibitors **5d**, **6d**, and **7d** into the farnesyltransferase's active site. Subsequently, the docking program places the remaining fragments of the inhibitors in a piece-wise fashion into the active site searching for favorable hydrophobic and H-bond interactions while avoiding steric overlaps. The docking runs provided sets of solutions which were inspected according to their suggested binding energy.

Results and discussion

Combination of the (4-nitrophenyl)butyryl residue (R^1) with AA(X)-peptidomimetic substructures **5**–**10** (R = H) did not result in particularly active compounds (**5**–**10a**) (Table 1). Most of the compounds displayed micromolar acitivity. Only the 4-aminodiphenylsulfone derivative **6a** showed a submicromolar IC_{50} value of 440 nM which represented a slight improvement compared to the 2,5-diaminobenzophenone derivative **1**. In contrast to the 2,5-diaminobenzophenone derivative **2**, the (2-naphthyl)acroyl residue (R^2) yielded only weakly active compounds (**5**–**10b**). Only the sulfonamide **8b** displayed submicromolar activity (IC_{50} = 760 nM), but this compound was still about 7-fold less potent than the corresponding 2,5-diaminobenzophenone **2** (IC_{50} = 115 nM).

The 4-nitrocinnamoyl (R^3) derivatives **5**–**10c** displayed variable inhibitory activity with IC_{50} values ranging from 46 nM to >10 µM. Peak inhibition of farnesyltransferase was obtained with the biaryl ether derivative **7c** (IC_{50} = 46 nM) while the *N*-(4-aminobenzoyl)methionine derivatives **9c** and **10c** were only weakly active (IC_{50} >10 µM and 3.9 µM, respectively). Submicromolar activity was recorded for the 4-aminobenzophenone derivative **5c** (IC_{50} = 485 nM) and the sulfonamide **8c** (IC_{50} = 960 nM). Replacement of the carbonyl function of the benzophenone **5c** by a sulfonyl group resulted in a slight reduction of activity (**6c**: IC_{50} = 650 nM). Inhibitory activity recorded for the 5-(4-nitrophenyl)furylacryloyl (R^4) derivatives **5**–**10d** was significantly higher than in the other series of compounds. Furthermore, the range of IC_{50} values was significantly smaller with values between 10 nM and 870 nM. In this series of compounds, peak activity was obtained with the 4-aminobenzophenone peptidomimetic substructure (**5d**: IC_{50} = 12 nM). Replacement of the carbonyl moiety by a sulfonyl group resulted in an equally potent inhibitor (**6d**: IC_{50} = 10 nM), whereas the biaryl ether derivative **7d** was 3-fold less active than benzophenone (IC_{50} = 36 nM). As in the series of the 4-nitrocinnamoyl (R^3) derivatives **5**–**10c**, in the series of the 5-(4-nitrophenyl)furylacryloyl (R^4) derivatives the *N*-(4-aminobenzoyl)methionine methyl ester **9d** displayed the weakest activity (IC_{50} = 870 nM). Saponification of the carboxylic ester moiety of **9d** resulted in an almost 10-fold improvement in activity (**10d**: IC_{50} = 90 nM) although this compound is still nearly one order of magnitude less potent than the structurally more simple inhibitors **5d** and **6d**.

Compared to the original 4-nitrocinnamoyl (R^3) substituted 2,5-diaminobenzophenone **3**, the most active novel 4-nitrocinnamoyl derivative **7c** displayed the same farnesyltransferase inhibitory activity. In the case of the 5-(4-nitrophenyl)furylacryloyl (R^4) substituted inhibitors, the most active novel derivatives, the 4-aminobenzophenone **5d** and the 4-aminodiphenylsulfone **6d**, are about 3-fold more active than the 2,5-diaminobenzophenone **4**.

Figure 2 shows the eight energetically most favorable solutions of the docking run performed with the 4-aminobenzophenone inhibitor **5d**. In this figure, hydrophobic (brown color) and hydrophilic (green color) properties are displayed on the enzyme's surface. The 5-(4-nitrophenyl)furyl moiety is placed in the aryl binding site (indicated by a yellow box) which is located next to the CAAX-peptide binding site (indicated by a light blue box). The 4-aminobenzophenone peptidomimetic substructure occupies the upper portion of the peptide binding site. Figure 3 shows inhibitor **5d** in the same orientation as in Figure 2 but with the enzyme's surface omitted and the active site amino acids visible. Amino acid side chains which contribute to inhibitor binding are highlighted. The 5-(4-nitrophenyl)furyl moiety is surrounded by the amino acid side chains which make up the aryl binding site (Tyr 300β, Leu 295β, Lys 294β, Lys 353β and Lys 356β). For the 4-aminobenzophenone peptidomimetic substructure a hydrogen bond is calculated between the benzophenone carbonyl oxygen and the guanidino group of Arg 202β. In addition to this polar interaction there are hydrophobic contacts between the two phenyl

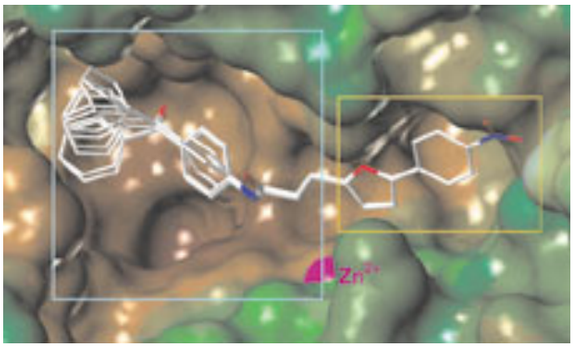


Figure 2. Eight energetically most favorable solutions of the docking run performed with the 4-aminobenzophenone inhibitor **5d** (colors: carbon: white; oxygen: red; nitrogen: blue). Hydrophobic (brown color) and hydrophilic (green color) properties are displayed on the enzyme's surface. Aryl binding site: yellow box; CAAX-peptide binding site: light blue box.

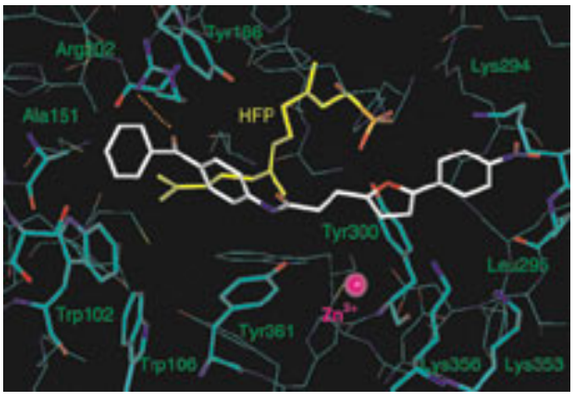


Figure 3. Inhibitor **5d** (colors as in Figure 2) in the same orientation as in Figure 2. Enzyme's surface omitted and the amino acids visible. Amino acid side chains contributing to inhibitor binding highlighted. The hydrogen bond is shown as an orange dotted line. HFP: Hydroxyfarnesylphosphonate, a FPP-analog.

residues and the lower portion of the farnesyl residue as well as the side chains of Tyr 166α, Ala 151β, Trp 102β, Trp 106β, and Tyr 361β. The docking run of the 4-aminodiphenylsulfone inhibitor **6d** provides two clusters of reasonable solutions. One (not shown) is identical to the solution obtained for the 4-aminobenzophenone **5d** as described in Figures 2 and 3. Figure 4 shows the second solution for the 4-aminodiphenylsulfone inhibitor **6d** which is different from the first set as the phenylsulfonyl moiety is rotated around the bond between the sulfonyl sulfur and the central phenyl residue shifting the terminal

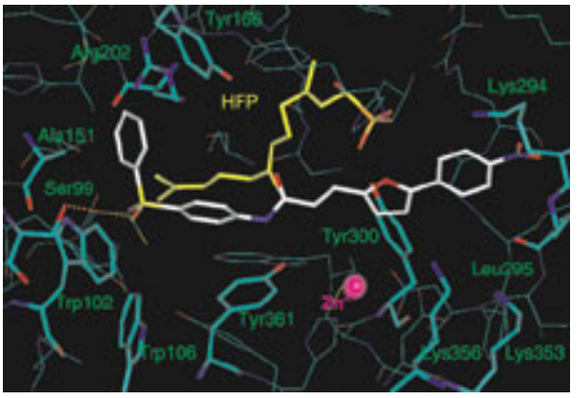


Figure 4. Second solution for the 4-aminodiphenylsulfone inhibitor **6d** (colors as in Figure 2; sulfur: yellow). The hydrogen bond is shown as an orange dotted line. HFP: Hydroxyfarnesylphosphonate, a FPP-analog.

phenyl upwards. In this conformation a hydrogen bond is calculated between one sulfonyl oxygen and the hydroxy group of Ser 99β. The solution provided for the biaryl ether derivative **7d** (not shown) is nearly identical to that calculated for the 4-aminobenzophenone inhibitor **5d** with the exception of the hydrogen bond to the side chain of Arg 202β which is not found for **7d**, presumably because of the larger distance between the guanidino group and the acceptor oxygen. The lack of the hydrogen bond may be the explanation for the lower activity of the biaryl ether derivative **7d** in comparison to the 4-aminobenzophenone **5d** and the 4-aminodiphenylsulfone **6d**.

From this study two major results warrant mention. First, the 5-(4-nitrophenyl)furylacryloyl moiety (R^4) turned out to be the most useful non-thiol cysteine replacement yielding in every case the most active inhibitors when combined with different AA(X)-peptidomimetic substructures. Secondly, by combination of this 5-(4-nitrophenyl)-furylacryloyl moiety (R^4) with the structurally simple AAX-peptidomimetics 4-aminobenzophenone (**5**) and 4-aminodiphenylsulfone (**6**), potent, readily accessible non-thiol farnesyltransferase inhibitors were obtained. These compounds may serve as lead structures for further development.

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Gesellschaft is gratefully acknowledged. I. Sattler wishes to thank Prof. Dr. S. Grabley for generous support and Ms. S. Egner for technical assistance.

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 Teknivent or an AutoSpec mass spectrometer from Micromass. IR spectra were recorded on a Nicolet 510P FT-IR-spectrometer. Microanalyses were obtained from a CH analyzer according to Dr. Salzer from Labormatic and from a Hewlett Packard type 185 CHN analyzer. All compounds gave microanalyses within ± 0.4% of the theoretical values. Column chromatography was carried out using silica gel 60 (0.062–0.200 mm) from Merck. Peptidomimetic moieties **5**–**10** (R = H) are commercially available or were prepared as described [17–20].

General procedure: Reaction of carboxylic acid chlorides with various AA(X)-peptidomimetics

Appropriate acyl chlorides were dissolved in toluene or dioxane (approx. 10 mL) and added to a solution of the appropriate aromatic amine in hot toluene (approx. 50 mL). The mixtures were heated under reflux for 2 h. Then, the solvent was removed in vacuo to give the crude products.

Acyl chlorides were prepared form the corresponding carboxylic acids. These were dissolved in toluene and 0.1 mL of $SOCl_2$ per mmol acid was added. The mixture was heated under reflux for 2 h and the volatiles were evaporated in vacuo. The residue obtained was used for the acylation step as described above.

N-(4-Benzoylphenyl)-4-(4-nitrophenyl)butyric acid amide **5a**

From 4-(4-nitrophenyl)butyric acid chloride (0.342 g, 1.5 mmol) and 4-aminobenzophenone (0.395 g, 1.5 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.54 g (91%). – Mp 172 °C. – IR (KBr): ν = 3431, 2853, 1692, 1636, 1596, 1507 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 2.05 (m, 2H), 2.36 (t, *J* = 7 Hz, 2H), 2.76 (t, *J* = 7 Hz, 2H), 7.29 (m, 2H), 7.41 (m, 3H), 7.51 (m, 1H), 7.56 (m, 2H), 7.69 (m, 2H), 7.73 (m, 2H), 8.07 (m, 2H). – EI-MS: *m/z* (%) 388 (12) [M$^+$], 120 (100), 119 (97), 239 (40). Anal. ($C_{23}H_{20}N_2O_4$) C, H, N.

N-(4-Benzoylphenyl)-3-(2-naphthyl)acrylic acid amide **5b**

From 3-(2-naphthyl)acrylic acid chloride (0.324 g, 1.5 mmol) and 4-aminobenzophenone (0.296 g, 1.5 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.46 g (81%). – Mp 194 °C. – IR (KBr): ν = 3456, 3339, 3071, 1687, 1633, 1594, 1558, 1525 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 6.99 (d, *J* = 16 Hz, 1H), 7.51 (m, 5H), 7.63 (m, 1H), 7.70 (m, 2H), 7.75 (m, 2H), 7.77 (d, *J* = 16 Hz, 1H), 7.88 (m, 2H), 7.95 (m, 3H), 8.13 (m, 1H), 10.55 (s, 1H). – EI-MS: *m/z* (%) 377 (18) [M$^+$], 181 (100), 59 (40), 152 (29). Anal. ($C_{26}H_{19}NO_2$) C, H, N.

N-(4-Benzoylphenyl)-4-nitrocinnamic acid amide **5c**

From 4-nitrocinnamic acid chloride (0.422 g, 2.0 mmol) and 4-aminobenzophenone (0.395 g, 2.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.64 g (86%). – Mp 240 °C. – IR (KBr): ν = 3362, 3080, 1685, 1636, 1619, 1596, 1516 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 7.03 (d, *J* = 16 Hz, 1H), 7.55 (m, 2H), 7.65 (m, 1H), 7.71 (m, 2H), 7.76 (m, 3H), 7.88 (m, 4H), 8.28 (m, 2H), 10.65 (s, 1H). – EI-MS: *m/z* (%) 372 (16) [M$^+$], 146 (100), 197 (37), 176 (35). Anal. ($C_{22}H_{16}N_2O_4$) C, H, N.

N-(4-Benzoylphenyl)-3-[5-(4-nitrophenyl)-2-furyl]acrylic acid amide **5d**

From 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride (0.221 g, 0.8 mmol) and 4-aminobenzophenone (0.158 g, 0.8 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.22 g (63%). – Mp 250 °C. – IR (KBr): ν = 3444, 3361, 1682, 1653, 1628, 1598, 1521 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 6.81 (d, *J* = 16 Hz, 1H), 7.02 (m, 1H), 7.37 (m, 2H), 7.43 (d, *J* = 16 Hz, 1H), 7.48 (m, 1H), 7.59 (m, 1H), 7.65 (m, 2H), 7.70 (m, 2H), 7.82 (m, 2H), 7.96 (m, 2H), 8.27 (m, 2H), 10.55 (s, 1H). – EI-MS: *m/z* (%) 438 (2) [M$^+$], 44 (100), 73 (88), 129 (46). Anal. ($C_{26}H_{18}N_2O_5$) C, H, N.

N-(4-Phenylsulfonylphenyl)-4-(4-nitrophenyl)butyric acid amide **6a**

From 4-(4-nitrophenyl)butyric acid chloride (0.273 g, 1.2 mmol) and 4-aminodiphenylsulfone (0.280 g, 1.2 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.35 g (68%). – Mp 184 °C. – IR (KBr): ν = 3446, 3333, 2923, 1695, 1593, 1538, 1513 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 1.93 (m, 2, H), 2.36 (m, 2H), 2.76 (m, 2H), 7.48 (m, 2H), 7.59 (m, 2H), 7.64 (m, 1H), 7.78 (m, 2H), 7.86 (m, 2H), 7.90 (m, 2H), 8.12 (m, 2H), 10.24 (s, 1H). – EI-MS: *m/z* (%) 424 (37) [M$^+$], 275 (100), 233 (72), 136 (18). Anal. ($C_{22}H_{20}N_2O_5S$) C, H, N.

N-(4-Phenylsulfonylphenyl)-3-(2-naphthyl)acrylic acid amide **6b**

From 3-(2-naphthyl)acrylic acid chloride (0.216 g, 1.0 mmol) and 4-aminodiphenylsulfone (0.217 g, 1.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.30 g (71%). – Mp 208 °C. – IR (KBr): ν = 3435, 3337, 3062, 1724, 1679, 1627, 1592, 1527 cm^{-1}.- ^{1}H NMR (DMSO-d$_6$): δ = 6.89 (d, *J* = 16 Hz, 1H), 7.49 (m, 2H), 7.54 (m, 2H), 7.59 (m, 1H), 7.69 (m, 1H), 7.72 (d, *J* = 16 Hz, 1H), 7.87 (m, 9H), 8.07 (m, 1H), 10.54 (s, 1H). – EI-MS: *m/z* (%) 413 (18) [M$^+$], 181 (100), 182 (14), 153 (14). Anal. ($C_{25}H_{19}NO_3S$) C, H, N.

N-(4-Phenylsulfonylphenyl)-4-nitrocinnamic acid amide **6c**

From 4-nitrocinnamic acid chloride (0.253 g, 1.2 mmol) and 4-aminodiphenylsulfone (0.280 g, 1.2 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.30 g (62%). – Mp 243 °C. – IR (KBr): ν = 3374, 1687, 1623, 1592, 1515 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 7.01 (d, *J* = 16 Hz, 1H), 7.61 (m, 2H), 7.65 (m, 1H), 7.72 (d, *J* = 16 Hz, 1H), 7.88 (m, 2H), 7.92 (m, 6H), 8.27 (m, 2H), 10.75 (s, 1H). – EI-MS: *m/z* (%) 408 (44) [M$^+$], 176 (100), 233 (30), 130 (12). Anal. ($C_{21}H_{16}N_2O_5S$) C, H, N.

N-(4-Phenylsulfonylphenyl)-3-[5-(4-nitrophenyl)-2-furyl]acrylic acid amide **6d**

From 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride (0.166 g, 0.6 mmol) and 4-aminodiphenylsulfone (0.140 g, 0.6 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.18 g (64%). – Mp 238 °C. – IR (KBr): ν = 3424, 1712, 1687, 1632, 1597, 1522 cm^{-1}. – ^{1}H NMR (DMSO-d$_6$): δ = 6.77 (d, *J* = 15 Hz, 1H), 7.04 (m, 1H), 7.40 (m, 1H), 7.44 (d, *J* = 15 Hz, 1H), 7.58 (m, 3H), 7.87 (m, 6H), 7.97 (m, 2H), 8.29 (m, 2H), 10.67 (s, 1H). – EI-MS: *m/z* (%) 474 (16) [M$^+$], 242 (100), 243 (14), 196 (12). Anal. ($C_{25}H_{18}N_2O_6S$) C, H, N.

N-(4-Phenoxyphenyl)-4-(4-nitrophenyl)butyric acid amide **7a**

From 4-(4-nitrophenyl)butyric acid chloride (0.173 g, 0.8 mmol) and 4-aminodiphenyl ether (0.142 g, 0.76 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.28 g (62%). – Mp 94 °C. – IR (KBr): ν = 3460, 3133, 2945, 2862, 1663, 1598, 1541, 1521 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.66 (m, 2H), 1.94 (m, 2H), 2.33 (t, *J* = 7 Hz, 2H), 2.74 (t, *J* = 7 Hz, 2H), 2.75 (t, *J* = 7 Hz, 2H), 3.74 (t, *J* = 7 Hz, 2H), 7.04 (m, 2H), 7.14 (m, 1H), 7.19 (m, 1H), 7.41 (m, 1H), 7.48 (m, 2H), 7.56 (m, 1H), 7.76 (m, 1H); 8.03 (m, 1H), 8.13 (m, 2H), 10.09 (s, 1H). – EI-MS: *m/z* (%) 479 (86) [M^+], 132 (100), 133 (46), 480 (26). Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

N-(4-Phenoxyphenyl)-3-(2-naphthyl)acrylic acid amide **7b**

From 3-(2-naphthyl)acrylic acid chloride (0.173 g, 0.8 mmol) and 4-aminodiphenyl ether (0.148 g, 0.8 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.23 g (79%). – Mp 182 °C. – IR (KBr): ν = 3423, 3266, 1656, 1623, 1598, 1506 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 6.89 (d, *J* = 16 Hz, 1H), 6.3 (m, 4H), 7.03 (m, 1H), 7.30 (m, 2H), 7.49 (m, 2H), 7.68 (m, 4H), 7.87 (m, 1H), 7.90 (m, 2H), 8.05 (m, 1H), 10.13 (s, 1H). – EI-MS: *m/z* (%) 365 (45) [M^+], 181 (100), 190 (76), 152 (51). Anal. ($C_{25}H_{19}NO_2$) C, H, N.

N-(4-Phenoxyphenyl)-4-nitrocinnamic acid amide **7c**

From 4-nitrocinnamic acid chloride (0.317 g, 1.5 mmol) and 4-aminodiphenyl ether (0.277 g, 1.5 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.27 g (61%). – Mp 162 °C. – IR (KBr): ν = 3424, 3227, 1659, 1625, 1522 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 6.62 (d, *J* = 16 Hz, 1H), 6.94 (m, 4H), 7.03 (m, 1H), 7.26 (m, 2H), 7.47 (m, 1H), 7.52 (m, 2H), 7.59 (m, 2H), 7.72 (d, *J* = 16 Hz, 1H), 8.17 (m, 2H). – EI-MS: *m/z* (%) 360 (46) [M^+], 185 (100), 146 (77), 176 (22). Anal. ($C_{21}H_{16}N_2O_4$) C, H, N.

N-(4-Phenoxyphenyl)-3-[5-(4-nitrophenyl)-2-furyl]acrylic acid amide **7d**

From 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride (0.270 g, 1.0 mmol) and 4-aminodiphenyl ether (0.185 g, 1.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.25 g (57%). – Mp 195 °C. – IR (KBr): ν = 3453, 1704, 1659, 1624, 1598, 1506 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 6.62 (d, *J* = 15 Hz, 1H), 6.71 (m, 1H), 6.92 (m, 1H), 6.99 (m, 4H), 7.07 (m, 1H), 7.30 (m, 2H), 7.46 (m, 1H), 7.52 (m, 1H), 7.57 (m, 2H), 7.81 (m, 2H), 8.24 (m, 2H). – EI-MS: *m/z* (%) 426 (37) [M^+], 242 (100), 185 (86), 212 (55). Anal. ($C_{25}H_{18}N_2O_5$) C, H, N.

N-[3-[1-(1,2,3,4-Tetrahydro)quinolinyl]sulfonylphenyl]-4-(4-nitrophenyl)butyric acid amide **8a**

From 4-(4-nitrophenyl)butyric acid chloride (0.173 g, 0.8 mmol) and 3-[1-(1,2,3,4-tetrahydro)quinolinyl]sulfonylaniline (0.219 g, 0.76 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.28 g (62%). – Mp 94 °C. – IR (KBr): ν = 3460, 3133, 2945, 2862, 1663, 1598, 1541, 1521 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.66 (m, 2H), 1.94 (m, 2H), 2.33 (t, *J* = 7 Hz, 2H), 2.74 (t, *J* = 7 Hz, 2H), 2.75 (t, *J* = 7 Hz, 2H), 3.74 (t, *J* = 7 Hz, 2H), 7.04 (m, 2H), 7.14 (m, 1H), 7.19 (m, 1H), 7.41 (m, 1H), 7.48 (m, 2H), 7.56 (m, 1H), 7.76 (m, 1H); 8.03 (m, 1H), 8.13 (m, 2H), 10.09 (s, 1H). – EI-MS: *m/z* (%) 479 (86) [M^+], 132 (100), 133 (46), 480 (26). Anal. ($C_{25}H_{25}N_3O_5S$) C, H, N.

N-[3-[1-(1,2,3,4-Tetrahydro)quinolinyl]sulfonylphenyl]-3-(2-naphthyl)acrylic acid amide **8b**

From 3-(2-naphthyl)acrylic acid chloride (0.173 g, 0.8 mmol) and 3-[1-(1,2,3,4-tetrahydro)quinolinyl]sulfonylaniline (0.230 g, 0.8 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.23 g (60%). – Mp 164 °C. – IR (KBr): ν = 3429, 3059, 2958, 2855, 1744, 1685, 1630, 1596, 1543 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.67 (m, 2H), 2.44 (m, 2H), 3.82 (m, 2H), 6.75 (d, *J* = 16 Hz, 1H), 7.00 (m, 1H), 7.07 (m, 1H), 7.15 (m, 1H), 7.23 (m, 1H), 7.37 (m, 1H), 7.49 (m, 2H), 7.68 (m, 1H), 7.78 (m, 2H); 7.82 (m, 3H), 7.88 (d, *J* = 16 Hz, 1H), 7.94 (m, 1H), 8.29 (m, 1H), 8.32 (m, 1H). – EI-MS: *m/z* (%) 468 (77) [M^+], 181 (100), 132 (56), 469 (25). Anal. ($C_{28}H_{24}N_2O_3S$) C, H, N.

N-[3-[1-(1,2,3,4-Tetrahydro)quinolinyl]sulfonylphenyl]-4-nitrocinnamic acid amide **8c**

From 4-nitrocinnamic acid chloride (0.253 g, 1.2 mmol) and 3-[1-(1,2,3,4-tetrahydro)quinolinyl]sulfonylaniline (0.346 g, 1.2 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.46 g (82%). – Mp 248 °C. – IR (KBr): ν = 3417, 1687, 1653, 1636, 1596, 1539, 1517 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.68 (m, 2H), 2.50 (m, 2H), 3.76 (m, 2H), 6.93 (d, *J* = 16 Hz, 1H), 7.05 (m, 2H), 7.15 (m, 1H), 7.26 (m, 1H), 7.48 (m, 1H), 7.55 (m, 1H), 7.70 (d, *J* = 16 Hz, 1H), 7.88 (m, 3H); 8.16 (m, 1H), 8.26 (m, 2H), 10.57 (s, 1H). – EI-MS: *m/z* (%) 463 (22) [M^+], 132 (100), 117 (26), 130 (24). Anal. ($C_{24}H_{21}N_3O_5S$) C, H, N.

N-[3-[1-(1,2,3,4-Tetrahydro)quinolinyl]sulfonylphenyl]-3-[5-(4-nitrophenyl)-2-furyl]acrylic acid amide **8d**

From 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride (0.277 g, 1.0 mmol) and 3-[1-(1,2,3,4-tetrahydro)quinolinyl]sulfonylaniline (0.288 g, 1.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.345 g (65%). – Mp 238 °C. – IR (KBr): ν = 3433, 1697, 1653, 1598, 1535, 1517 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.70 (m, 2H), 2.51 (m, 2H), 3.78 (m, 2H), 6.78 (d, *J* = 16 Hz, 1H), 7.06 (m, 3H), 7.16 (m, 1H), 7.25 (m, 1H), 7.43 (m, 2H), 7.48 (m, 1H), 7.58 (m, 1H), 7.89 (m, 1H), 7.88 (m, 3H); 8.01 (m, 1H), 8.19 (m, 1H), 8.32 (m, 2H), 10.56 (s, 1H). – EI-MS: *m/z* (%) 529 (21) [M^+], 132 (100), 242 (86), 73 (68). Anal. ($C_{28}H_{23}N_3O_6S$) C, H, N.

N-[4-[4-(4-Nitrophenyl)butyroylamino]benzoyl]methionine methyl ester **9a**

From 4-(4-nitrophenyl)butyric acid chloride (0.173 g, 0.8 mmol) and *N*-[(4-amino)benzoyl]methionine methyl ester (0.214 g, 0.76 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.33 g (90%). – Mp 119 °C. – IR (KBr): ν = 3309, 3295, 3284, 1746, 1687, 1634, 1595, 1517 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 2.09 (m, 7H), 2.27 (m, 1H), 2.40 (t, *J* = 7 Hz, 2H), 2.57 (m, 2H), 2.81 (t, *J* = 7 Hz, 2H), 3.77 (m, 3H), 4.90 (m, 1H), 6.93 (m, 1H), 7.34 (m, 2H), 7.49 (s, 1H), 7.58 (m, 2H), 7.75 (m, 2H), 8.13 (m, 2H). – EI-MS: *m/z* (%) 473 (1) [M^+], 120 (100), 311 (64), 295 (41). Anal. ($C_{23}H_{27}N_3O_6S$) C, H, N.

N-[4-[3-(2-Naphthyl)acryloylamino]benzoyl]methionine methyl ester **9b**

From 3-(2-naphthyl)acrylic acid chloride (0.173 g, 0.8 mmol) and *N*-(4-aminobenzoyl)methionine methyl ester (0.226 g, 0.8 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.25 g (68%). – Mp 213 °C. – IR (KBr): ν = 3428, 2924, 1738, 1634, 1504 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.97 (m, 5H), 2.47 (m, 2H), 3.57 (m, 3H), 4.50

(m, 1H), 6.89 (d, *J* = 16 Hz, 1H), 7.47 (m, 2H), 7.68 (m, 2H), 7.71 (m, 2H), 7.80 (m, 2H), 7.82 (m, 1H), 7.88 (m, 2H), 8.05 (m, 1H), 8.47 (m, 1H), 10.31 (s, 1H). – EI-MS: *m/z* (%) 462 (35) [M^+], 181 (100), 388 (93), 300 (88). Anal. ($C_{26}H_{26}N_2O_4S$) C, H, N.

N-[4-(4-Nitrocinnamoylamino)benzoyl]methionine methyl ester **9c**

From 4-nitrocinnamic acid chloride (0.211 g, 1.0 mmol) and *N*-(4-aminobenzoyl)methionine methyl ester (0.282 g, 1.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.29 g (62%). – Mp 222 °C. – IR (KBr): ν = 3407, 3376, 1713, 1687, 1634, 1598, 1539, 1522 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.98 (m, 5H), 2.47 (m, 2H), 3.57 (m, 3H), 4.49 (m, 1H), 6.94 (d, *J* = 16 Hz, 1H), 7.63 (d, *J* = 16 Hz, 1H), 7.70 (m, 2H), 7.80 (m, 4H), 8.20 (m, 2H), 8.48 (m, 1H), 10.42 (s, 1H). – EI-MS: *m/z* (%) 457 (18) [M^+], 295 (100), 383 (75), 296 (28). Anal. ($C_{22}H_{23}N_3O_6S$) C, H, N.

N-[4-[3-[5-(4-Nitrophenyl)-2-furyl]acryloylamino]benzoyl]methionine methyl ester **9d**

From 3-[5-(4-nitrophenyl)-2-furyl]acrylic acid chloride (0.277 g, 1.0 mmol) and *N*-(4-aminobenzoyl)methionine methyl ester (0.282 g, 1.0 mmol) according to the general procedure. Purification: recrystallization from toluene. Yield: 0.40 g (76%). – Mp 204 °C. – IR (KBr): ν = 3441, 3307, 1719, 1687, 1632, 1597, 1527 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.99 (m, 5H), 2.47 (m, 2H), 3.56 (m, 3H), 4.50 (m, 1H), 6.77 (d, *J* = 16 Hz, 1H), 6.98 (m, 1H), 7.34 (m, 1H), 7.39 (d, *J* = 16 Hz, 1H), 7.70 (m, 2H), 7.79 (m, 2H), 7.93 (m, 2H), 8.24 (m, 2H), 8.47 (m, 1H), 10.39 (s, 1H). – EI-MS: *m/z* (%) 523 (56) [M^+], 212 (100), 242 (78), 120 (48). Anal. ($C_{26}H_{25}N_3O_7S$) C, H, N.

N-[4-[4-(4-Nitrophenyl)butyroylamino]benzoyl]methionine **10a**

N-[4-[4-(4-nitrophenyl)butyroylamino]benzoyl]methionine methyl ester (**9a**) (0.236 g, 0.5 mmol) was dissolved in a mixture of THF/methanol and 1N LiOH (1.1 equivalents) was added and stirred at room temperature for 12 h. Then, most of the solvent was removed in vacuo and the residual solution was diluted with water. The pH was adjusted to 2–3 by addition of 1N HCl. The aqueous phase was extracted with EtOAc (3 × 50–100 mL) and the combined organic extracts were thoroughly washed with brine and dried over $MgSO_4$. The product **10a** was obtained after the removal of the solvent. Yield: 0.22 g (97%). – Mp 92 °C. – IR (KBr): ν = 3433, 2922, 1737, 1690, 1637, 1597, 1520 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.88 (m, 2H), 1.97 (m, 5H), 2.29 (t, *J* = 7 Hz, 2H), 2.48 (m, 2H), 2.70 (t, *J* = 7 Hz, 2H), 4.42 (m, 1H), 7.42 (m, 2H), 7.57 (m, 2H), 7.74 (m, 2H), 8.08 (m, 2H), 8.29 (m, 1H), 9.93 (s, 1H). – EI-MS: *m/z* (%) 459 (1) [M^+], 179 (100), 120 (74), 137 (72). Anal. ($C_{22}H_{25}N_3O_6S$) C, H, N.

N-[4-[3-(2-Naphthyl)acryloylamino]benzoyl]methionine **10b**

From *N*-[4-[3-(2-naphthyl)acryloylamino]benzoyl]methionine methyl ester (**9b**) (0.200 g, 0.45 mmol) as described above for **10a**. Yield: 0.16 g (83%). – Mp 220 °C. – IR (KBr): ν = 3453, 1712, 1631, 1558, 1519 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.96 (m, 5H), 2.49 (m, 2H), 4.45 (m, 1H), 6.95 (d, *J* = 16 Hz, 1H), 7.65 (d, *J* = 16 Hz, 1H), 7.71 (m, 2H), 7.81 (m, 4H), 8.21 (m, 2H), 8.36 (m, 1H), 10.41 (s, 1H). – EI-MS: *m/z* (%) 448 (4) [M^+], 181 (100), 369 (26), 182 (20). Anal. ($C_{25}H_{24}N_2O_4S$) C, H, N.

N-[4-(4-Nitrocinnamoylamino)benzoyl]methionine **10c**

From *N*-[4-(4-nitrocinnamoylamino)benzoyl]methionine methyl ester (**9c**) (0.200 g, 0.43 mmol) as described above for **10a**. Yield: 0.17 g (97%). – Mp 190 °C. – IR (KBr): ν = 3442, 1713, 1690, 1634, 1598, 1520, 1500 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.97 (m, 5H), 2.49 (m, 2H), 4.43 (m, 1H), 6.93 (d, *J* = 16 Hz, 1H), 7.63 (d, *J* = 16 Hz, 1H), 7.69 (m, 2H), 7.80 (m, 4H), 8.19 (m, 2H), 8.34 (m, 1H), 10.39 (s, 1H). – EI-MS: *m/z* (%) 443 (1) [M^+], 176 (100), 120 (36), 312 (33). Anal. ($C_{21}H_{21}N_3O_6S$) C, H, N.

N-[4-[3-[5-(4-Nitrophenyl)-2-furyl]acryloylamino]benzoyl]methionine **10d**

From *N*-[4-[3-[5-(4-nitrophenyl)-2-furyl]acryloylamino]benzoyl]methionine methyl ester (**9d**) (0.260 g, 0.5 mmol) as described above for **10a**. Yield: 0.19 g (72%). – Mp 216 °C. – IR (KBr): ν = 3417, 1701, 1627, 1599, 1522 cm^{-1}. – ^1H NMR (DMSO-d_6): δ = 1.99 (m, 5H), 2.50 (m, 2H), 4.46 (m, 1H), 6.78 (d, *J* = 16 Hz, 1H), 7.00 (m, 1H), 7.36 (m, 1H), 7.40 (d, *J* = 16 Hz, 1H), 7.71 (m, 2H), 7.81 (m, 2H), 7.95 (m, 2H), 8.26 (m, 2H), 8.35 (m, 1H), 10.39 (s, 1H). – EI-MS: *m/z* (%) 509 (1) [M^+], 242 (100), 120 (26), 243 (16). Anal. ($C_{25}H_{23}N_3O_7S$) C, H, N.

Farnesyltransferase assay

The assay was carried out as described [21]. 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 5 nmol GST-FTase 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). Fluorescence emission was recorded with a Perkin Elmer LS50B spectrometer. IC_{50} values (concentrations resulting in 50% inhibition) were calculated from initial velocity of three independent measurements of four to five different concentrations of inhibitor.

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