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Non-thiol farnesyltransferase inhibitors: *N*-(4-tolylacetylamino-3-benzoylphenyl)-3-arylfurylacrylic acid amides

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Abstract—We have designed arylfurylacryl-substituted benzophenones as non-thiol farnesyltransferase inhibitors utilizing a novel aryl binding site of farnesyltransferase. These compounds display activity in the low nanomolar range.

1. Introduction

Farnesyltransferase catalyzes the post-translational modification of several proteins by the transfer of a farnesyl residue from farnesylpyrophosphate to the thiol of a cysteine side chain. Common feature of such modified proteins is the C-terminal CAAX-sequence. C represents a cysteine, which side chain is farnesylated, A amino acids, which normally, but not necessarily, carry aliphatic side chains, and X mostly methionine or serine.[1,2]

In the past years farnesyltransferase has become a major target in the development of potential anti-cancer drugs. Farnesyltransferase inhibitors have demonstrated their efficiency in various cancer cell culture assays and animal models. Few compounds are in advanced stages of clinical trials.[3–12]

Most inhibitors described in literature are peptidomimetics resembling the CAAX-tetrapeptide recognition sequence of farnesylated proteins. The majority of these CAAX-peptidomimetics exhibit a free thiol group, which is shown to coordinate the enzyme-bound zinc ion. However, free thiols are associated with several adverse drug effects[13] and, therefore, the development of farnesyltransferase inhibitors is clearly directed toward the so-called non-thiol farnesyltransferase inhibitors. The most frequently used replacements for cysteine are nitrogen-containing heterocycles. The ring nitrogen is supposed to coordinate to the enzyme-bound zinc, similarly to the cysteine thiol group.[14] However, it has been shown that nitrogen heterocycles can be replaced by aryl residues lacking the ability to coordinate metal atoms, without loosing too much of their farnesyltransferase inhibitory activity.[15,16] Therefore, the existence of at least one hitherto unknown aryl binding region in the farnesyltransferase's active site has been postulated.[17,18]

Using docking studies of model compounds of non-thiol farnesyltransferase inhibitors as well as a GRID analysis of farnesyltransferase's active site, we have identified two different aryl binding clefts in the farnesyltransferase's active site, which we suggest to be the postulated aryl binding regions, and assigned them as near and far aryl binding site.[19]

We have designed some arylfurylacryl-substituted benzophenones as non-thiol farnesyltransferase inhibitors utilizing the far aryl binding site.[19] In this study, we

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Keywords: Non-thiol farnesyltransferase inhibitors; Structure–activity relationships.

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describe extensive variation of the terminal aryl residue of the arylfuryl moiety to establish some structure–activity relationships.

2. Chemistry

The key intermediates for the synthesis of the target compounds **7** were the 5-aryl-2-furfurals **3**, which are either commercially available or were prepared via *Suzuki* coupling (modified from[20]) from 5-bromofurfural **1** and the appropriate aryl boronic acids **2**. Only 5-(4-trifluoromethylsulfanylphenyl)furfural and 5-(4-methoxycarbonylphenyl)furfural were prepared in a different manner using 5-formylfurane-2-boronic acid, 4-trifluoromethylsulfanylbromobenzene, and 4-bromobenzoic acid methyl ester, respectively, as coupling partners. The furfurals **3** were then transformed into the corresponding 3-biarylacrylic acids **4** via *Knoevenagel* condensation. The 3-biarylacrylic acids **4** were activated as acid chlorides **5** and reacted with 5-amino-2-(4-tolylacetylamino)benzophenone **6**[21] as described previously[19] (Scheme 1). The amino derivative **7aa** was prepared from the nitro derivative **7t** by tin-II-chloride reduction. **7aa** was formylated or acetylated to the corresponding derivatives **7ac** and **7ad**, respectively. The aminocarbonyl group of **7ab** was obtained by H_2O_2/NaOH hydrolysis from the cyano group. Because of the incompatibility of the tolylacetylaminobenzophenone substructure with strong alkaline conditions, 2-amino protected 2,5-diaminobenzophenone **8**[22] was acylated with 4-cyanophenylfurylacrylic acid chloride yielding the intermediate **9**. Cleavage of the trifluoroacetyl protective group occurred together with the hydrolysis of the cyano group yielding the intermediate **10**, which was acylated with tolylacetic acid chloride to get the target compound **7ab** (Scheme 2). For the preparation of **7ae** 3-[5-(4-aminosulfonylphenyl)-2-furyl]acrylic acid was not activated as an acid chloride, but with *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimid*HCl as an *O*-acyl isourea. The 4-arylfuryl isomers **11** were prepared in the same way as the 5-arylfuryl derivatives **7** starting from 4-bromofurfural.

3. Farnesyltransferase inhibition assay

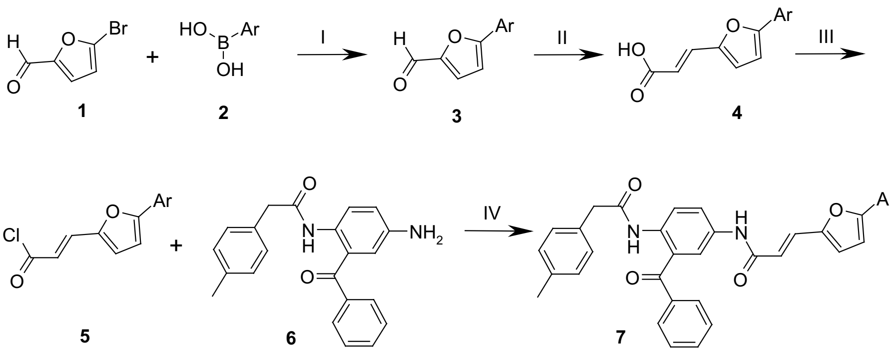
The inhibitory activity of the inhibitors was determined using the fluorescence enhancement assay as described by Pompliano.[23] The assay employs yeast farnesyltransferase (FTase) fused to Glutathione *S*-transferase at the N-terminus of the β-subunit.[24]

Farnesylpyrophosphate and the dansylated pentapeptide Ds-GlyCysValLeuSer were used as substrates. Upon farnesylation of the cysteine thiol the dansyl residue is placed in a lipophilic environment resulting in an enhancement of fluorescence at 505 nm, which is used to monitor the enzyme reaction.

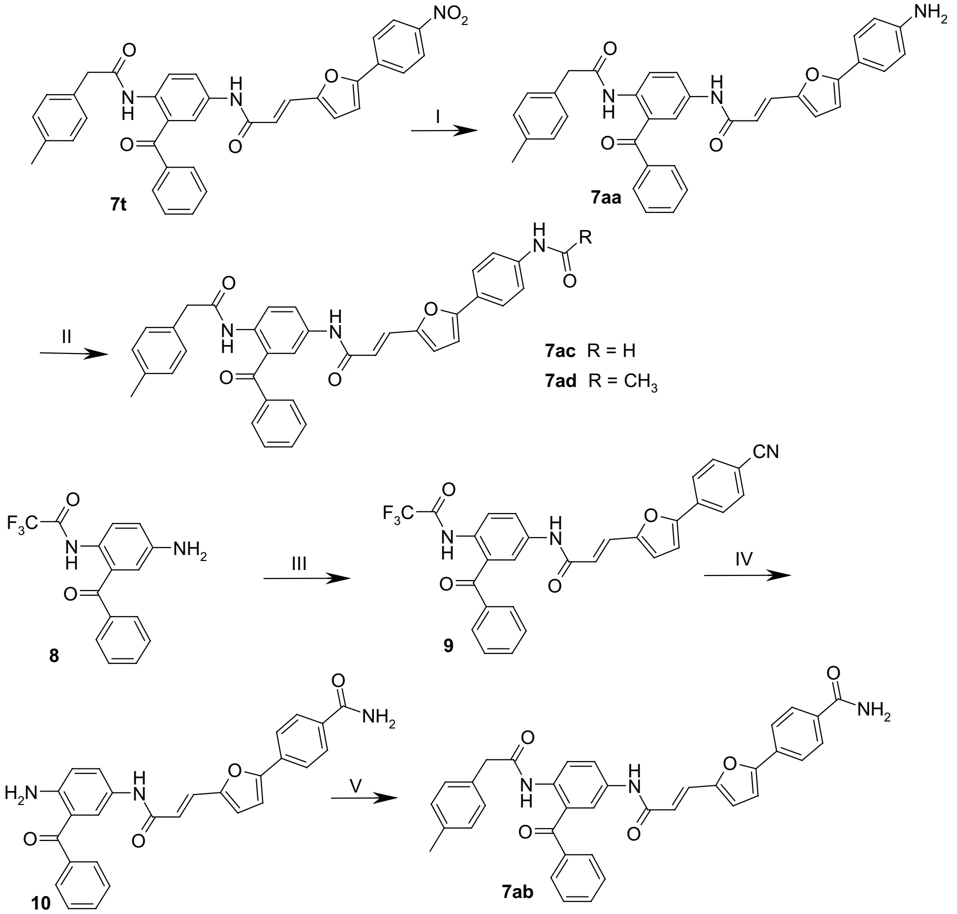
A homology model of yeast farnesyltransferase was prepared to analyze the differences between mammalian and yeast enzymes. Sequences for alpha and beta subunits of rat (Q04631 and Q02293) and yeast (P29703 and P22007) farnesyltransferase were retrieved from SWISS-Prot[25] and aligned with T-COFFEE.[26] Yeast homology models were computed based on the alignments and the rat template structure (PDB entry: 1qbq)[27] using MODELLER.[28] From 53 amino acid side chains, which constitute the active and the aryl binding sites, 10 differ between rat and yeast (81% identity). These amino acid substitutions are unlikely to affect inhibitor binding, because they are located in the periphery of the proposed ligand binding site (Fig. 1), too distant for direct protein–ligand contacts. Furthermore, most exchanges do not alter the properties of the binding side.

4. Flexible docking

Flexible docking for compounds **7d** and **7t** was performed using the program FlexX.[29] Based on the coordinates of the published crystal structure[27] 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 as implemented in the molecular



Scheme 1. Reagents and conditions: (I) $(Ph_3P)_4Pd$, K_2CO_3, toluene/ethanol/water, 5 h, reflux; (II) malonic acid, pyridine/piperidine, 2 h, reflux; (III) thionyl chloride, toluene, 2 h, reflux; (IV) toluene/dioxane, 2 h, reflux.



Scheme 2. Reagents and conditions: (I) $SnCl_2 \times H_2O$, ethyl acetate, 2h, reflux; (II) formic acid/acetic acid anhydride, THF, 10h, −10 °C to reflux or acetic acid anhydride, DMF, 10h, −15 °C to rt; (III) 5-(4-cyanophenyl)-2-furylacrylic acid chloride, toluene/dioxane, 2h, reflux; (IV) $NaOH/H_2O_2$, ethanol/dioxane, 2h, 60 °C; (V) tolylacetic acid chloride, toluene/dioxane, 2h, reflux.

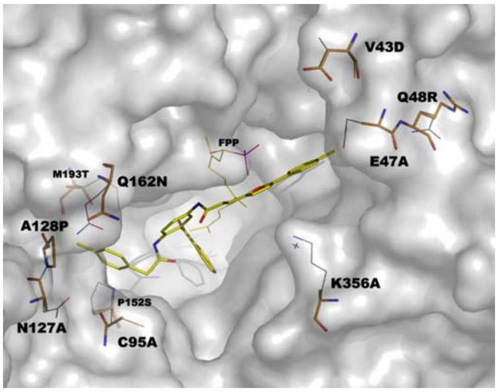


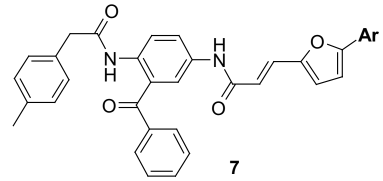
Figure 1. Homology model for yeast and rat farnesyltransferases with the docked inhibitor **7d**. Amino acid side chains of rat FTase are shown as thin lines; side chains of yeast FTase as thick lines.

modeling software package SYBYL.[30] For ligand construction the central phenyl residue of the benzophenone core structure was used as base fragment and placed into the position previously determined.[21] Subsequently, the remaining fragments of the inhibitors were placed in the active site using the incremental construction algorithm of FlexX. The docking runs provided sets of solutions, which were inspected according to their calculated energy score. The resulting geometries were evaluated using the knowledge-based scoring function DrugScore.[31] The positions of the structural water molecules for the far aryl binding site were taken from the crystal structure. Connolly surfaces were calculated for the obtained ligand conformations and water molecules occupying these regions are assumed to be replaced by the ligand.

5. Results and discussion

As stated above, arylfurylacryl-substituted benzophenones **7** (Table 1) were designed to utilize one of the aryl binding sites[19] of farnesyltransferase. Inhibitor **7a** with an unsubstituted terminal phenyl residue displayed an IC_{50} value of 100nM. Replacement of the phenyl residue by the larger 1- and 2-naphthyl moieties (**7b**, **c**) resulted in decreased activity (IC_{50} values: 165 and 190nM, respectively). A 25-fold increase in activity in comparison with the unsubstituted phenyl derivative was observed with inhibitors **7d** and **7e** having a methyl or a trifluoromethyl group in the *para* position of the terminal phenyl of the phenylfuryl moiety (IC_{50} values: 4nM both). This effect proved to be sensitive toward the position of the substituent, since the *meta* trifluoromethyl

Table 1. Farnesyltransferase inhibitory activity of 5-arylfuryl derivatives **7a–af**



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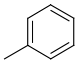
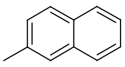
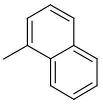
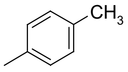
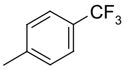
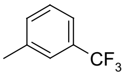
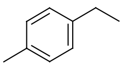
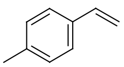
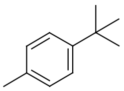
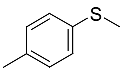
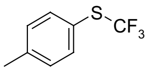
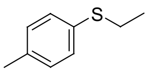
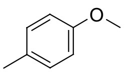
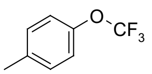
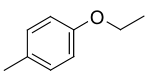
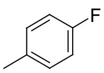
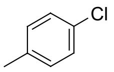
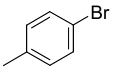
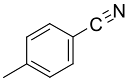
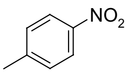
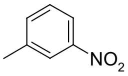
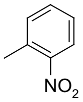
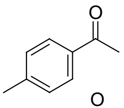
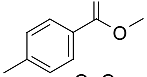
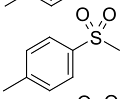
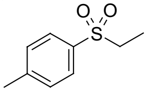
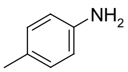
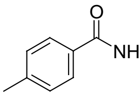
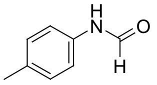
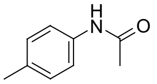
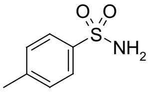
Compd	R	IC$_{50}$ (nM)
7a		100 ± 32
7b		165 ± 22
7c		190 ± 16
7d		4 ± 1
7e		4 ± 2
7f		220 ± 10
7g		90 ± 27
7h		130 ± 34
7i		115 ± 45
7j		170 ± 65
7k		140 ± 22
7l		180 ± 34
7m		510 ± 76
7n		225 ± 48
7o		450 ± 16
7p		30 ± 5
7q		150 ± 28
7r		925 ± 45
7s		105 ± 65
7t		35 ± 5
7u		710 ± 40
7v		925 ± 60
7w		225 ± 65
7x		95 ± 10
7y		30 ± 18
7z		125 ± 6
7aa		30 ± 8
7ab		330 ± 62
7ac		285 ± 38
7ad		545 ± 107
7ae		40 ± 7

derivative **7f** was considerably less active (IC$_{50}$ = 220 nM). Alkyl residues larger than methyl in the *para* position resulted in inhibitors (**7g–i**) roughly equipotent to the unsubstituted phenyl derivative **7a**, but markedly less active than the methyl or trifluoromethyl derivatives **7d**, **e** with IC$_{50}$ values between 90 and 130 nM. Replacement of the methylene group in the ethyl residue of inhibitor **7g** by a sulfur resulted in a further decrease of activity (**7j**: IC$_{50}$ = 170 nM). Replacement of the terminal methyl by trifluoromethyl somewhat attenuated this effect (**7k**: IC$_{50}$ = 140 nM) while elongation of the chain had no significant effect (**7l**: IC$_{50}$ = 180 nM). Introduction of an oxygen into the innermost position of the *para* chains yielding arylalkyl ether derivatives **7m–o** resulted in decreased activity in comparison to the ethyl derivative **7g** as well as to the thioethers **7j–l** (IC$_{50}$ values: 225–510 nM). Again,

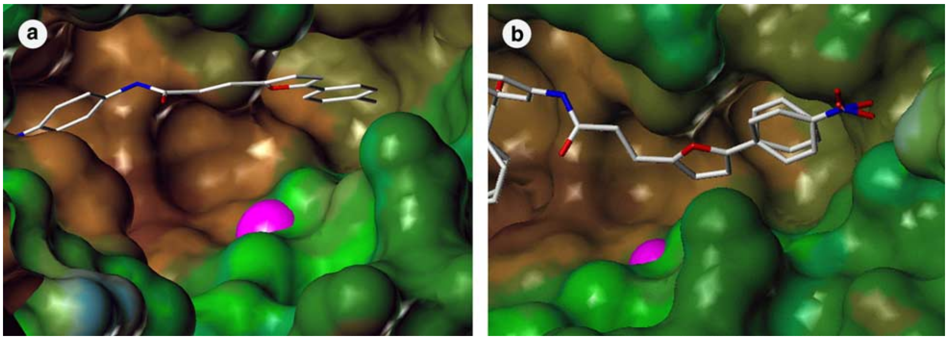


Figure 2. Details of farnesyltransferase's active site and the far aryl binding site from slightly different perspectives. Lipophilic (brown) and hydrophilic (green to blue) properties are displayed on the Connolly surface. The structural zinc is shown as a magenta sphere. (a) Methyl substituted inhibitor **7d** deeply buries its methyl group into a lipophilic area in the far aryl binding site. (b) Nitro substituted inhibitor **7t** directs its nitro group to a more hydrophilic area toward the rim of the far aryl binding site.

replacement of the terminal methyl by trifluoromethyl attenuated the effect of the hetero atom. In the series of the halogen substituted inhibitors **7p**–**r** activity was reduced with decreasing electronegativity and increasing size of the halogen substituents with IC_{50} values from 30 to 925 nM. The cyano group as a pseudo-halogen substituent fits well into this series (**7s**: $IC_{50} = 105$ nM). Introduction of the nitro group into the *para* position produced an inhibitor of considerable activity (**7t**: $IC_{50} = 35$ nM). Again, the *para* position turned out as the optimal position since shifting the nitro group into the *meta* or *ortho* position increasingly resulted in a reduction of activity (**7u**, **v**, IC_{50} values: 710 and 925 nM, respectively). Inhibitors **7w** and **7x** comprising an acetyl or a methylester moiety in the *para* position showed no better activity than the unsubstituted phenyl derivative. In contrast, the methylsulfonyl derivative **7y** proved as active as the nitro derivative **7t** ($IC_{50} = 30$ nM). Prolongation of the chain length considerably reduced activity (**7z**: $IC_{50} = 125$ nM). An amino group in the *para* position also yielded an inhibitor (**7aa**: $IC_{50} = 30$ nM) equipotent to the nitro or methylsulfonyl derivative. Combining an amino group with a carbonyl or sulfonyl structure as amides and sulfonamides (**7ab**–**ae**), respectively, did not improve activity, but in case of the amide derivatives **7ab**–**ad** reduced considerably inhibitory potency of the compounds (IC_{50} values: 285–330 nM).

Some of the structure–activity relationships described above may be explained on a structural basis. Figure 2a shows a binding mode of the *para* methyl substituted inhibitor **7d** obtained by flexible docking. The methyl group is deeply buried in a hydrophobic area in the far aryl binding site. Any substituent larger than methyl or trifluoromethyl would prevent this favorable binding mode, explaining the low activity of any alkyl (other than methyl or trifluoromethyl), alkylsulfanyl, or alkyloxy substituted derivative. However, considerable activity has also been obtained with substituents larger than methyl, as for instance with nitro or methylsulfonyl. For those inhibitors docking indicates a different binding mode with the *para* substituent not that deeply buried in the aryl binding site (what is prevented by its size), but rather directed to a more hydrophilic area at the rim of the aryl binding site. This is exemplified for the nitro derivative **7t** in Figure 2b. As shown in Figure 3, inhibitors in this binding mode displace two water

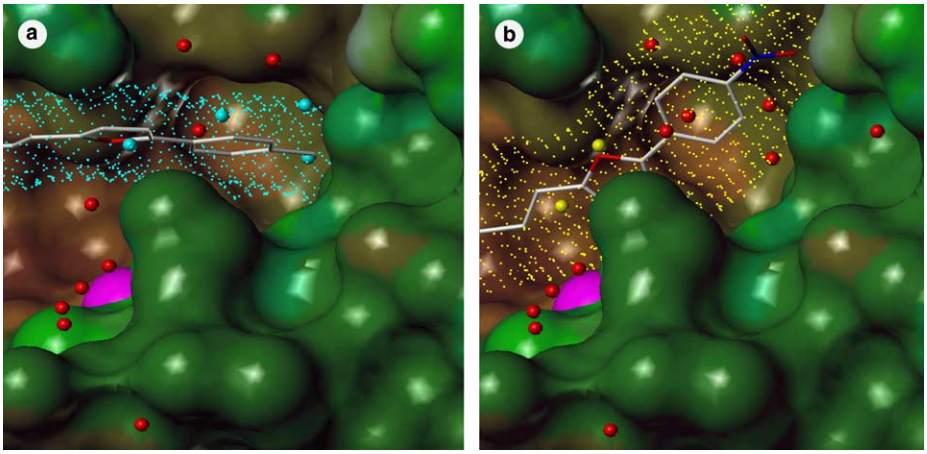


Figure 3. Details of the far aryl binding site with inhibitors **7d** (a) and **7t** (b). The Connolly surface of both inhibitors is indicated by blue and yellow dots, respectively. Structural water molecules (as observed in the crystal structure; PDB-code 1QBQ) not replaced by the inhibitors are indicated as red spheres. Water molecules replaced by the inhibitors are indicated as blue and yellow spheres, respectively. The methyl substituted inhibitor **7d** replaces two more water molecules than the nitro substituted inhibitor **7t**.

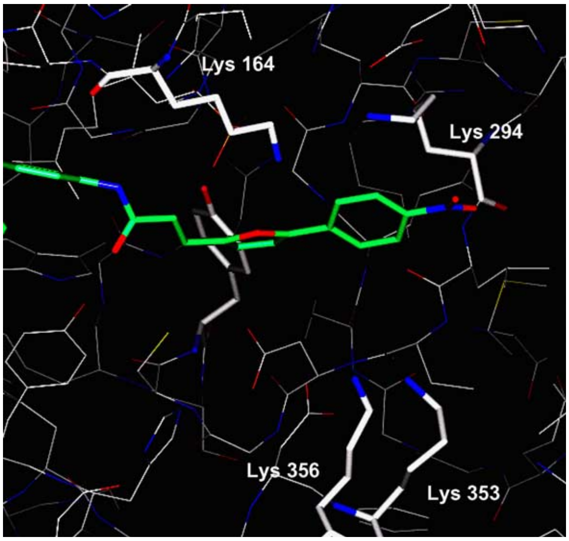
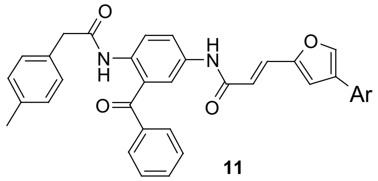


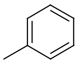
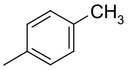
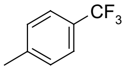
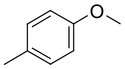
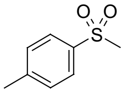
Figure 4. Details of the far aryl binding site with inhibitor **7t**. From lysine residues highlighted, Lys 294 and Lys 353 are potentially acting as hydrogen bond donors for the binding of the hydrogen bond donor atoms in different inhibitors.

molecules less from the binding site than the inhibitors capable of burying a methyl group deeply into the aryl binding site, so that the second binding mode is strongly disfavored. However, the reduction in activity for inhibitors **7u** and **7y** is not as pronounced as one could expect on the basis of the number of displaced water molecules. Common feature of the nitro or sulfonyl substituents is a hydrogen bond acceptor property. As shown in Figure 4, two lysine side chains (Lys 294β and Lys 353β) are located at the rim of the aryl binding site, which might act as the appropriate hydrogen bond donors. The so formed hydrogen bonds allow for a partial compensation of the lower gain in entropy compared to those inhibitors displacing more water. Accordingly, inhibitors bearing residues too large to fit deeply into the binding site and at the same time having no compensatory hydrogen bonding properties are penalized in terms of affinity. The presence of two amino acid side chains acting as hydrogen bond donors might also explain the relatively low activity of inhibitors **7w** and **7x**, since in contrast to the nitro or sulfonyl moieties their substituents are capable of forming only one but not two hydrogen bonds. As demonstrated by the amino substituted derivative **7aa**, hydrogen bond donor properties seem to be favorable as well.

Table 2. Farnesyltransferase inhibitory activity of 4-arylfuryl derivatives **11a–e**



11

Compd	R	IC_{50} (nM)
11a		60 ± 12
11b		180 ± 50
11c		285 ± 27
11d		5 ± 1
11e		1110 ± 270

The regioisomeric compounds **11a–e** having the aryl moiety in *para* position of the central furyl ring demonstrated completely different structure–activity relationships (Table 2), with the methyl and trifluoromethyl derivatives **11b** and **11c** showing decreased activity (IC_{50} values: 180 and 285 nM, respectively) compared to the unsubstituted derivative **11a** ($IC_{50} = 60$ nM). Notable is also the high activity of the methoxy derivative **11d** ($IC_{50} = 5$ nM) and the low activity of the methylsulfonyl derivative **11e** ($IC_{50} = 1900$ nM). As depicted in Figure 5, both the 5- and 4-isomers can be drawn in a conformation identical in terms of the orientation of the aryl substituent, but different in the position of the furyl oxygen. Obviously, the relative position of the furyl oxygen is important. When both regioisomers are drawn in a conformation pointing the furyl oxygens in identical positions, the aryl residues are in completely different orientations, accounting for different structure–activity relationships.

In summary, the 5-arylfurylacryloyl substructure designed to fit into the far aryl binding site guided us to some highly active non-thiol farnesyltransferase inhibitors. Activity of the methyl and trifluoromethyl derivatives can be explained by the placement of the terminal residue deep into the aryl binding site and the displacement of a considerable number of water molecules. Substituents too large to fit so deeply into the binding site but having hydrogen bond donor or acceptor properties also yield active farnesyltransferase inhibitors by forming hydrogen bonds with amino acid side chains at the rim of the far aryl binding site.

6. Experimental

^{1}H NMR spectra were recorded on a Jeol JMN-GX-400 and a Jeol JMN-LA-500 spectrometer. Mass spectra were obtained with a Vacuum Generator VG 7070 H using a Vector 1 data acquisition system from Teknivent or a 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 CHN analyzer type 185. 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 preparation of compounds **7q**, **r**, and **t** has been published in Ref. 19; the preparation of intermediate **8** in Ref. 22.

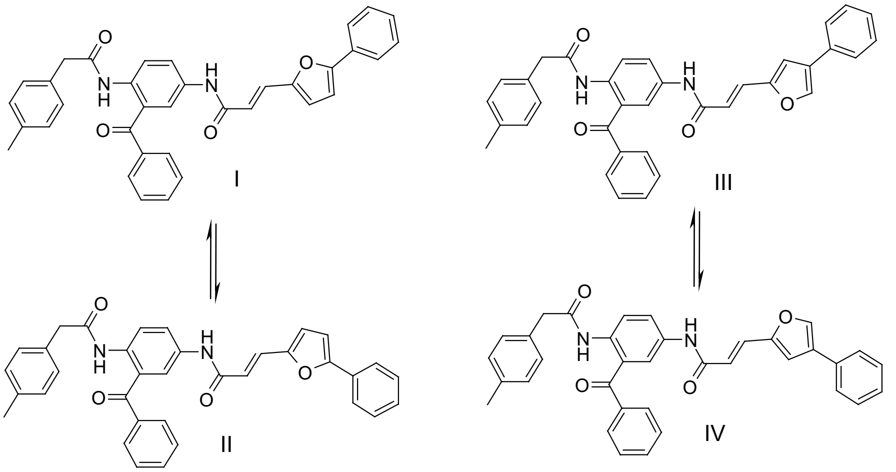


Figure 5. Conformations of the 4- and 5-arylfuryl derivatives obtained through rotation of acryloyl–furyl bond. Conformations of different regioisomers can have identical aryl orientations but different furyl oxygen positions (I and III; II and IV), or identical furyl oxygen positions but different aryl orientations (I and IV, II and III), accounting for different structure–activity relationships.

6.1. General procedure 1: Formation of 4- and 5-arylfurfurals via biaryl coupling

(a) Bromofurfural and 1.2equiv of the appropriate benzeneboronic acid derivative were dissolved or suspended in a mixture of 30mL toluene, 15mL ethanol, and 30mL of an aqueous solution of potassium carbonate (1M) under an argon atmosphere. After addition of 50mg tetrakis(triphenylphosphine)palladium(0) and 25mg [1,1′-bis(diphenylphosphine)ferrocene]palladium(II) chloride per mmol bromofurfural the mixture was heated under reflux for 5h. After cooling the mixture was extracted with dichloromethane for three times. The organic layers were combined, dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo.

(b) The appropriate bromobenzene derivative and 1.2equiv of 5-formyl-2-furan-boronic acid were dissolved in a mixture of 30mL dimethoxyethane and 30mL of an aqueous solution of sodium carbonate (2M) under an argon atmosphere. After addition of 50mg tetrakis(triphenylphosphine)palladium(0) and 25mg [1,1′-bis(diphenylphosphine)ferrocene]palladium(II) chloride per mmol bromobenzene the mixture was heated under reflux for 5h. After cooling the mixture was extracted with dichloromethane for three times. The organic layers were combined, dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo.

6.1.1. 5-Phenylfuran-2-carbaldehyde. From benzeneboronic acid (438mg, 3.6mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 327mg (63%). ^{1}H NMR ($CDCl_3$): δ 6.78 (m, 1H), 7.26 (m, 1H), 7.37 (m, 3H), 7.76 (m, 2H), 9.58 (s, 1H).

6.1.2. 5-(2-Naphthyl)furan-2-carbaldehyde. From 2-naphthylboronic acid (516mg, 3mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 573mg (86%). ^{1}H NMR ($CDCl_3$): 6.89 (m, 1H), 7.30 (m, 1H), 7.45 (m, 2H), 7.75–7.86 (m, 4H), 8.29 (m, 1H), 9.61 (s, 1H).

6.1.3. 5-(1-Naphthyl)furan-2-carbaldehyde. From 1-naphthylboronic acid (516mg, 3mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 554mg (82%). ^{1}H NMR ($CDCl_3$): δ 6.85 (m, 1H), 7.34 (m, 1H), 7.47 (m, 3H), 7.78 (m, 1H), 7.84 (m, 2H), 8.31 (m, 1H), 9.66 (s, 1H).

6.1.4. 5-(4-Methylphenyl)furan-2-carbaldehyde. From 4-methylbenzeneboronic acid (490mg, 3.6mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 407mg (73%). ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 6.72 (m, 1H), 7.18 (m, 2H), 7.24 (m, 1H), 7.65 (m, 2H), 9.55 (s, 1H).

6.1.5. 5-(4-Trifluoromethylphenyl)furan-2-carbaldehyde. From 4-trifluoromethylbenzeneboronic acid (684mg, 3.6mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 526mg (73%). ^{1}H NMR ($CDCl_3$): δ 6.88 (m, 1H), 7.28 (m, 1H), 7.65 (m, 2H), 7.86 (m, 2H), 9.61 (s, 1H).

6.1.6. 5-(4-Ethylphenyl)furan-2-carbaldehyde. From 4-ethylbenzeneboronic acid (450mg, 3mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 248mg (41%). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, $J = 7$Hz, 3H), 2.61 (q, $J = 7$Hz, 2H), 6.72 (m, 1H), 7.20 (m, 2H), 7.24 (m, 1H), 7.67 (m, 2H), 9.55 (s, 1H).

6.1.7. 5-(4-Vinylphenyl)furan-2-carbaldehyde. From 4-vinylbenzeneboronic acid (447mg, 3mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 552mg (88%). ^{1}H NMR ($CDCl_3$): δ 5.28 (d, $J = 11$Hz, 1H), 5.78 (d, $J = 18$Hz, 1H), 6.65 (dd, $J = 18/11$Hz, 1H), 6.77 (m, 1H), 7.22 (m, 1H), 7.40 (m, 2H), 7.71 (m, 2H), 9.57 (s, 1H).

6.1.8. 5-(4-*tert*-Butylphenyl)furan-2-carbaldehyde. From 4-*tert*-butylbenzeneboronic acid (535 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 650 mg (88%). ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H), 6.79 (m, 1H), 7.31 (m, 1H), 7.45 (m, 2H), 7.75 (m, 2H), 9.63 (s, 1H).

6.1.9. 5-(4-Methylsulfanylphenyl)furan-2-carbaldehyde. From 4-methylsulfanylbenzeneboronic acid (505 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 576 mg (88%). ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 6.72 (m, 1H), 7.21 (m, 3H), 7.65 (m, 2H), 9.55 (s, 1H).

6.1.10. 5-(4-Trifluoromethylsulfanylphenyl)furan-2-carbaldehyde. From 4-(trifluoromethylsulfanyl)bromobenzene (475 µL, 3 mmol) according to general procedure 1b. Purification: column chromatography (dichloromethane). Yield 532 mg (65%). ^{1}H NMR ($CDCl_3$): δ 6.93 (m, 1H), 7.33 (m, 1H), 7.72 (m, 2H), 7.86 (m, 2H), 9.68 (s, 1H).

6.1.11. 5-(4-Ethylsulfanylphenyl)furan-2-carbaldehyde. From 4-ethylsulfanylbenzeneboronic acid (728 mg, 4 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 706 mg (76%). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J = 7$ Hz, 3H), 2.99 (q, $J = 7$ Hz, 2H), 6.78 (m, 1H), 7.31 (m, 3H), 7.71 (m, 2H), 9.61 (s, 1H).

6.1.12. 5-(4-Methoxyphenyl)furan-2-carbaldehyde. From 4-methoxybenzeneboronic acid (547 mg, 3.6 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 553 mg (91%). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 6.64 (m, 1H), 6.89 (m, 2H), 7.23 (m, 1H), 7.69 (m, 2H), 9.52 (s, 1H).

6.1.13. 5-(4-Trifluoromethoxyphenyl)furan-2-carbaldehyde. From 4-trifluoromethoxybenzeneboronic acid (617 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 702 mg (91%). ^{1}H NMR ($CDCl_3$): δ 6.78 (m, 1H), 7.23–7.26 (m, 3H), 7.77 (m, 2H), 9.57 (s, 1H).

6.1.14. 5-(4-Ethoxyphenyl)furan-2-carbaldehyde. From 4-ethoxybenzeneboronic acid (600 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 591 mg (76%). ^{1}H NMR ($CDCl_3$): δ 1.43 (t, $J = 7$ Hz, 3H), 4.06 (q, $J = 7$ Hz, 2H), 6.69 (m, 1H), 6.93 (m, 2H), 7.27 (m, 1H), 7.73 (m, 2H), 9.58 (s, 1H).

6.1.15. 5-(4-Fluorophenyl)furan-2-carbaldehyde. From 4-fluorobenzeneboronic acid (420 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 539 mg (94%). ^{1}H NMR ($CDCl_3$): δ 6.71 (m, 1H), 7.08 (m, 2H), 7.25 (m, 1H), 7.75 (m, 2H), 9.57 (s, 1H).

6.1.16. 5-(4-Cyanophenyl)furan-2-carbaldehyde. From 4-cyanobenzeneboronic acid (588 mg, 4 mmol) according to general procedure 1a. Purification: column chromatography (EtOAc/hexane 3:2) and recrystallization from toluene. Yield 358 mg (46%). ^{1}H NMR (DMSO-d_6): δ 6.98 (m, 1H), 7.35 (m, 1H), 7.73 (m, 2H), 7.91 (m, 2H), 9.71 (s, 1H).

6.1.17. 5-(4-Acetylphenyl)furan-2-carbaldehyde. From 4-acetylbenzeneboronic acid (588 mg, 4 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 431 mg (67%). ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 6.90 (m, 1H), 7.27 (m, 1H), 7.84 (m, 2H), 7.95 (m, 2H), 9.62 (s, 1H).

6.1.18. 4-(5-Formyl-2-furyl)benzoic acid methylester. From 4-bromobenzoic acid methylester (860 mg, 4 mmol) according to general procedure 1b. Purification: column chromatography (dichloromethane). Yield 658 mg (71%). ^{1}H NMR (DMSO-d_6): δ 3.89 (s, 3H), 7.45 (m, 1H), 7.68 (m, 1H), 8.01 (m, 2H), 8.07 (m, 2H), 9.67 (s, 1H).

6.1.19. 5-(4-Ethylsulfonylphenyl)furan-2-carbaldehyde. From 4-ethylsulfonylbenzeneboronic acid (642 mg, 3 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 624 mg (79%). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, $J = 7$ Hz, 3H), 3.13 (q, $J = 7$ Hz, 2H), 7.00 (m, 1H), 7.34 (m, 1H), 7.98 (m, 4H), 9.70 (s, 1H).

6.1.20. 4-Phenylfuran-2-carbaldehyde. From benzeneboronic acid (218 mg, 1.8 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 209 mg (81%). ^{1}H NMR ($CDCl_3$): δ 7.34 (m, 1H), 7.45 (m, 2H), 7.71 (m, 2H), 8.01 (m, 1H), 8.61 (m, 1H), 9.67 (s, 1H).

6.1.21. 4-(4-Methylphenyl)furan-2-carbaldehyde. From 4-methylbenzeneboronic acid (245 mg, 1.8 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 248 mg (%). ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 7.22 (m, 2H), 7.39 (m, 2H), 7.49 (m, 1H), 7.91 (m, 1H), 9.68 (s, 1H).

6.1.22. 4-(4-Trifluoromethylphenyl)furan-2-carbaldehyde. From 4-trifluoromethylbenzeneboronic acid (455 mg, 2.4 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 312 mg (65%). ^{1}H NMR ($CDCl_3$): δ 7.81 (m, 2H), 7.95 (m, 2H), 8.11 (m, 1H), 8.76 (m, 1H), 9.69 (s, 1H).

6.1.23. 4-(4-Methoxyphenyl)furan-2-carbaldehyde. From 4-methoxybenzeneboronic acid (365 mg, 2.4 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 329 mg (81%). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 6.99 (m, 2H), 7.63 (m, 2H), 7.93 (m, 1H), 8.49 (m, 1H), 9.64 (s, 1H).

6.1.24. 4-(4-Methylsulfonylphenyl)furan-2-carbaldehyde. From 4-methylsulfonylbenzeneboronic acid (480 mg, 2.4 mmol) according to general procedure 1a. Purification: column chromatography (dichloromethane). Yield 274 mg (55%). ^{1}H NMR ($CDCl_3$): δ 3.08 (s, 3H), 7.55

(m, 1H), 7.70 (m, 2H), 7.79 (m, 2H), 8.06 (m, 1H), 9.74 (s, 1H).

6.2. General procedure 2: Formation of biarylylacrylic acids via *Knoevenagel* condensation

The aromatic aldehyde was dissolved in a mixture of 5 mL pyridine and 0.2 mL piperidine. After addition of 125 mg malonic acid per mmol aldehyde the mixture was heated under reflux for 2 h. After cooling this mixture was poured into a mixture of 60 mL water, 60 mL ice, and 60 mL concentrated hydrochloric acid to yield a solid. This solid was isolated and recrystallized from ethanol.

6.2.1. 3-[5-(4-*tert*-Butylphenyl)-2-furyl]acrylic acid. From 5-(4-*tert*-butylphenyl)furan-2-carbaldehyde (640 mg, 2.8 mmol) according to general procedure 2. Yield 673 mg (89%). ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9H), 6.27 (d, $J = 16$ Hz, 1H), 7.01 (m, 2H), 7.38 (d, $J = 16$ Hz, 1H), 7.45 (m, 2H), 7.71 (m, 2H).

6.2.2. 3-[5-(4-Methylsulfanylphenyl)-2-furyl]acrylic acid. From 5-(4-methylsulfanylphenyl)furan-2-carbaldehyde (568 mg, 2.6 mmol) according to general procedure 2. Yield 607 mg (90%). ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H), 6.28 (d, $J = 16$ Hz, 1H), 6.99 (m, 1H), 7.05 (m, 1H), 7.30 (m, 2H), 7.37 (d, $J = 16$ Hz, 1H), 7.73 (m, 2H).

6.2.3. 3-[5-(4-Trifluoromethylsulfanylphenyl)-2-furyl]-acrylic acid. From 5-(4-trifluoromethylsulfanylphenyl)furan-2-carbaldehyde (490 mg, 1.8 mmol) according to general procedure 2. Yield 499 mg (88%). ^{1}H NMR (DMSO-d_6): δ 6.39 (d, $J = 16$ Hz, 1H), 7.07 (m, 1H), 7.29 (m, 1H), 7.43 (d, $J = 16$ Hz, 1H), 7.78 (m, 2H), 7.97 (m, 2H), 12.39 (s, 1H).

6.2.4. 3-[5-(4-Ethylsulfanylphenyl)-2-furyl]acrylic acid. From 5-(4-ethylsulfanylphenyl)furan-2-carbaldehyde (697 mg, 3 mmol) according to general procedure 2. Yield 683 mg (65%). ^{1}H NMR (DMSO-d_6): δ 1.26 (t, $J = 7$ Hz, 3H), 3.02 (q, $J = 7$ Hz, 2H), 6.31 (d, $J = 16$ Hz, 1H), 7.02 (m, 1H), 7.08 (m, 1H), 7.36 (m, 2H), 7.40 (d, $J = 16$ Hz, 1H), 7.75 (m, 2H), 12.29 (s, 1H).

6.2.5. 3-[5-(4-Methoxyphenyl)-2-furyl]acrylic acid. From 5-(4-methoxyphenyl)furan-2-carbaldehyde (540 mg, 2.7 mmol) according to general procedure 2. Yield 446 mg (68%). ^{1}H NMR (CDCl$_3$): δ 3.77 (s, 3H), 6.29 (d, $J = 16$ Hz, 1H), 6.55 (m, 1H), 6.66 (m, 1H), 6.88 (m, 2H), 7.45 (d, $J = 16$ Hz, 1H), 7.60 (m, 2H).

6.2.6. 3-[5-(4-Trifluoromethoxyphenyl)-2-furyl]acrylic acid. From 5-(4-trifluoromethoxyphenyl)furan-2-carbaldehyde (640 mg, 2.5 mmol) according to general procedure 2. Yield 645 mg (87%). ^{1}H NMR (CDCl$_3$): δ 6.41 (d, $J = 16$ Hz, 1H), 6.76 (m, 2H), 7.26 (m, 2H), 7.53 (m, 1H), 7.75 (m, 2H).

6.2.7. 3-[5-(4-Ethoxyphenyl)-2-furyl]acrylic acid. From 5-(4-ethoxyphenyl)furan-2-carbaldehyde (582 mg, 2.7 mmol) according to general procedure 2. Yield 620 mg (89%). ^{1}H NMR (CDCl$_3$): δ 1.42 (t, $J = 7$ Hz, 3H), 4.06 (q, $J = 7$ Hz, 2H), 6.34 (d, $J = 16$ Hz, 1H), 6.60 (m, 1H), 6.71 (m, 1H), 6.91 (m, 2H), 7.49 (d, $J = 16$ Hz, 1H), 7.64 (m, 2H).

6.2.8. 3-[5-(4-Fluorophenyl)-2-furyl]acrylic acid. From 5-(4-fluorophenyl)furan-2-carbaldehyde (530 mg, 2.8 mmol) according to general procedure 2. Yield 602 mg (93%). ^{1}H NMR (DMSO-d_6): δ 6.31 (d, $J = 16$ Hz, 1H), 7.00 (m, 1H), 7.08 (m, 1H), 7.26 (m, 2H), 7.38 (d, $J = 16$ Hz, 1H), 7.86 (m, 2H).

6.2.9. 3-[5-(4-Cyanophenyl)-2-furyl]acrylic acid. From 5-(4-cyanophenyl)furan-2-carbaldehyde (345 mg, 1.75 mmol) according to general procedure 2. Yield 269 mg (64%). ^{1}H NMR (DMSO-d_6): δ 6.43 (d, $J = 16$ Hz, 1H), 7.09 (m, 1H), 7.36 (m, 1H), 7.43 (d, $J = 16$ Hz, 1H), 7.90 (m, 2H), 8.01 (m, 2H), 12.40 (s, 1H).

6.2.10. 3-[5-(4-Acetylphenyl)-2-furyl]acrylic acid. From 5-(4-acetylphenyl)furan-2-carbaldehyde (424 mg, 2 mmol) according to general procedure 2. Yield 450 mg (88%). ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H), 6.38 (d, $J = 16$ Hz, 1H), 7.05 (m, 1H), 7.30 (m, 1H), 7.41 (d, $J = 16$ Hz, 1H), 7.93 (m, 2H), 8.00 (m, 2H).

6.2.11. 3-[5-(4-Methoxycarbonylphenyl)-2-furyl]acrylic acid. From 5-(4-methoxycarbonylphenyl)furan-2-carbaldehyde (650 mg, 2.8 mmol) according to general procedure 2. Yield 431 mg (57%). ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H), 6.40 (d, $J = 16$ Hz, 1H), 7.07 (m, 1H), 7.31 (m, 1H), 7.44 (d, $J = 16$ Hz, 1H), 7.96 (m, 2H), 8.02 (m, 2H).

6.2.12. 3-[5-(4-Methylsulfonylphenyl)-2-furyl]acrylic acid. 3-[5-(4-Methylsulfanylphenyl)-2-furyl]acrylic acid (260 mg, 1 mmol) and 1.5 g oxone (potassium peroxomono sulfate triple salt) were suspended in a mixture of 15 mL THF, 15 mL ethanol, and 10 mL water. After stirring at room temperature for 12 h the mixture was filtrated. Ethanol and THF were removed in vacuo and the resulting aqueous layer was extracted with EtOAc for three times. The combined organic layers were dried over anhydrous magnesium sulfate, solvent was evaporated in vacuo, and the crude product was recrystallized from ethanol. Yield 235 mg (80%). ^{1}H NMR (DMSO-d_6): δ 3.23 (s, 3H), 6.40 (d, $J = 16$ Hz, 1H), 7.07 (m, 1H), 7.35 (m, 1H), 7.42 (m, 1H), 7.97 (m, 2H), 8.05 (m, 2H), 12.41 (s, 1H).

6.2.13. 3-[5-(4-Ethylsulfonylphenyl)-2-furyl]acrylic acid. From 5-(4-ethylsulfonylphenyl)furan-2-carbaldehyde (595 mg, 2.25 mmol) according to general procedure 2. Yield 544 mg (79%). ^{1}H NMR (DMSO-d_6): δ 1.12 (t, $J = 7$ Hz, 3H), 3.31 (q, $J = 7$ Hz, 2H), 6.42 (d, $J = 16$ Hz, 1H), 7.09 (m, 1H), 7.36 (m, 1H), 7.43 (d, $J = 16$ Hz, 1H), 7.93 (m, 2H), 8.08 (m, 2H).

6.2.14. 3-[5-(4-Aminosulfonylphenyl)-2-furyl]acrylic acid. From 5-(4-aminosulfonylphenyl)furan-2-carbaldehyde (250 mg, 1 mmol) according to general procedure 2. Yield 217 mg (74%). ^{1}H NMR (DMSO-d_6): δ 6.41 (d,

$J = 16$ Hz, 1H), 7.07 (m, 1H), 7.29 (m, 1H), 7.39 (m, 2H), 7.45 (d, $J = 16$ Hz, 1H), 7.88 (m, 2H), 8.01 (m, 2H).

6.2.15. 3-[4-Phenyl-2-furyl]acrylic acid. From 4-phenylfuran-2-carbaldehyde (204 mg, 1.2 mmol) according to general procedure 2. Yield 211 mg (82%). ^{1}H NMR (DMSO-d_6): δ 6.23 (d, $J = 16$ Hz, 1H), 7.30 (m, 2H), 7.41 (m, 3H), 7.62 (m, 2H), 8.34 (m, 1H).

6.2.16. 3-[4-(4-Methylphenyl)-2-furyl]acrylic acid. From 4-(4-methylphenyl)furan-2-carbaldehyde (223 mg, 1.2 mmol) according to general procedure 2. Yield 240 mg (88%). ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H), 6.22 (d, $J = 16$ Hz, 1H), 7.22 (m, 2H), 7.36 (m, 1H), 7.39 (d, $J = 16$ Hz, 1H), 7.52 (m, 2H), 8.28 (m, 1H).

6.2.17. 3-[4-(4-Trifluoromethylphenyl)-2-furyl]acrylic acid. From 4-(4-trifluoromethylphenyl)furan-2-carbaldehyde (288 mg, 1.2 mmol) according to general procedure 2. Yield 291 mg (86%). ^{1}H NMR (DMSO-d_6): δ 6.26 (d, $J = 16$ Hz, 1H), 7.42 (d, $J = 16$ Hz, 1H), 7.48 (m, 1H), 7.77 (m, 2H), 7.85 (m, 2H), 8.50 (m, 1H).

6.2.18. 3-[5-(3-Trifluoromethylphenyl)-2-furyl]acrylic acid. From 5-(3-trifluoromethylphenyl)furan-2-carbaldehyde (960 mg, 4 mmol) according to general procedure 2. Yield 806 mg (89%). ^{1}H NMR (DMSO-d_6): δ 6.38 (d, $J = 16$ Hz, 1H), 7.02 (m, 1H), 7.31–7.40 (m, 1H and d, $J = 16$ Hz, 1H), 7.63 (m, 2H), 8.08 (m, 2H).

6.2.19. 3-[4-(4-Methoxyphenyl)-2-furyl]acrylic acid. From 4-(4-methoxyphenyl)furan-2-carbaldehyde (303 mg, 1.5 mmol) according to general procedure 2. Yield 307 mg (84%). ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H), 6.22 (d, $J = 16$ Hz, 1H), 6.98 (m, 2H), 7.34 (m, 1H), 7.40 (d, $J = 16$ Hz, 1H), 7.55 (m, 2H), 8.23 (m, 1H).

6.2.20. 3-[5-(2-Nitrophenyl)-2-furyl]acrylic acid. From 5-(2-nitrophenyl)furan-2-carbaldehyde (869 mg, 4 mmol) according to general procedure 2. Yield 936 mg (91%). ^{1}H NMR (DMSO-d_6): δ 6.07 (d, $J = 16$ Hz, 1H), 7.01–7.09 (m, 2H), 7.32 (d, $J = 16$ Hz, 1H), 7.55 (m, 1H), 7.68 (m, 1H), 7.85–7.92 (m, 2H).

6.2.21. 3-[5-(3-Nitrophenyl)-2-furyl]acrylic acid. From 5-(3-nitrophenyl)furan-2-carbaldehyde (869 mg, 4 mmol) according to general procedure 2. Yield 904 mg (88%). ^{1}H NMR (DMSO-d_6): δ 6.42 (d, $J = 16$ Hz, 1H), 7.08 (m, 1H), 7.41 (m, 1H and d, $J = 16$ Hz, 1H), 7.70–7.76 (m, 1H), 8.16 (m, 1H), 8.26 (m, 1H), 8.56 (m, 1H).

6.2.22. 3-[4-(4-Methylsulfonylphenyl)-2-furyl]acrylic acid. From 4-(4-methylsulfonylphenyl)furan-2-carbaldehyde (250 mg, 1 mmol) according to general procedure 2. Yield 239 mg (82%). ^{1}H NMR (DMSO-d_6): δ 3.23 (s, 3H), 6.28 (d, $J = 16$ Hz, 1H), 7.41 (d, $J = 16$ Hz, 1H), 7.51 (m, 1H), 7.92 (m, 4H), 8.54 (m, 1H).

6.3. General procedure 3: Activation of various acids as acid chlorides and reaction with aromatic amines

The various carboxylic acids were dissolved in toluene and 0.1 mL $SOCl_2$ per mmol acid was added. The mixture was heated under reflux for 2 h and the volatiles were evaporated in vacuo. The resulting acyl chlorides were dissolved in toluene or dioxane (approx. 10 mL) and added to a solution of 1 equiv of *N*-(4-amino-2-benzoylphenyl)-4-tolylacetic acid amide **6** 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.

6.3.1. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-(5-phenyl-2-furyl)acrylic acid amide (7a). From 3-(5-phenyl-2-furyl)acrylic acid (107 mg, 0.5 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 175 mg (64%); mp 175 °C. IR (KBr): $\nu = 3435$, 3323, 3057, 2925, 1662, 1637, 1554, 1505 cm^{-1}. ^{1}H NMR (CDCl$_3$): 2.25 (s, 3H), 3.62 (s, 2H), 6.39 (d, $J = 16$ Hz, 1H), 6.53 (m, 1H), 6.62 (m, 1H), 7.08 (m, 2H), 7.16–7.22 (m, 3H), 7.28 (m, 2H), 7.34–7.39 (m, 3H), 7.48 (m, 2H), 7.58 (m, 2H), 7.61 (m, 2H), 7.70 (m, 1H), 7.95 (s, 1H), 8.42 (m, 1H), 10.46 (s, 1H). MS (EI): *m/z* 197 (100), 344 (22), 540 (41) M$^+$. Anal. Calcd for $C_{35}H_{28}N_2O_4$: C, 77.76; H, 5.22; N, 5.18. Found: C, 77.37; H, 5.22; N, 5.15.

6.3.2. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(2-naphthyl)-2-furyl]acrylic acid amide (7b). From 3-[5-(2-naphthyl)-2-furyl]acrylic acid (264 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 354 mg (60%); mp 210 °C. IR (KBr): $\nu = 3328$, 3057, 1679, 1663, 1628, 1549, 1506 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H), 3.33 (s, 2H), 6.74 (d, $J = 16$ Hz, 1H), 6.96 (m, 2H), 6.98 (m, 1H), 7.02 (m, 2H), 7.23 (m, 1H), 7.39 (d, $J = 16$ Hz, 1H), 7.46–7.56 (m, 4H), 7.59–7.65 (m, 2H), 7.67 (m, 2H), 7.77 (m, 1H), 7.88–7.93 (m, 4H), 7.98 (m, 1H), 8.27 (m, 1H), 10.08 (s, 1H), 10.39 (s, 1H). MS (EI): *m/z* 105 (32), 212 (84), 248 (50), 344 (100), 590 (31) M$^+$. Anal. Calcd for $C_{39}H_{30}N_2O_4$: C, 79.30; H, 5.12; N, 4.74. Found: C, 79.04; H, 5.15; N, 4.92.

6.3.3. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(1-naphthyl)-2-furyl]acrylic acid amide (7c). From 3-[5-(1-naphthyl)-2-furyl]acrylic acid (264 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 298 mg (50%); mp 110 °C. IR (KBr): $\nu = 3252$, 3052, 1668, 1622, 1594, 1545, 1508 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.24 (s, 3H), 3.58 (s, 2H), 6.39 (d, $J = 16$ Hz, 1H), 6.64–6.70 (m, 2H), 7.06 (m, 2H), 7.13 (m, 2H), 7.35–7.48 (m, 8H), 7.59–7.67 (m, 4H), 7.75–7.80 (2H), 7.94 (s, 1H), 8.28 (m, 1H), 8.39 (m, 1H), 10.43 (s, 1H). MS (EI): *m/z* 44 (100), 60 (26), 247 (92), 590 (20) M$^+$. Anal. Calcd for $C_{39}H_{30}N_2O_4$: C, 79.30; H, 5.12; N, 4.74. Found: C, 79.19; H, 5.09; N, 4.82.

6.3.4. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-methylphenyl)-2-furyl]acrylic acid amide (7d). From 3-[5-(4-methylphenyl)-2-furyl]acrylic acid (229 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 459 mg (82%); mp 193 °C. IR (KBr): $\nu = 3305$, 3026, 2921, 1662, 1627, 1553, 1506 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.30 (s, 3H), 2.34 (s, 3H), 3.68 (s, 2H), 6.42 (d, $J = 16$ Hz, 1H), 6.61

(m, 2H), 7.15 (m, 4H), 7.23 (m, 3H), 7.45 (m, 2H), 7.53–7.62 (s, 5H), 7.69 (m, 2H), 8.00 (s, 1H), 8.50 (m, 1H), 10.52 (s, 1H). MS (EI): *m/z* 211 (100), 344 (9), 554 (31) M$^+$. Anal. Calcd for $C_{36}H_{30}N_2O_4$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.64; H, 5.42; N, 5.83.

6.3.5. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-trifluoromethylphenyl)-2-furyl]acrylic acid amide (7e). From 3-[5-(4-trifluoromethylphenyl)-2-furyl]acrylic acid (282 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 434 mg (71%); mp 222 °C. IR (KBr): ν = 3321, 1660, 1618, 1555, 1507, 1326 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H), 3.37 (s, 2H), 6.74 (d, *J* = 16 Hz, 1H), 6.99–7.05 (m, 5H), 7.29 (m, 1H), 7.40 (d, *J* = 16 Hz, 1H), 7.50 (m, 2H), 7.61–7.70 (m, 4H), 7.80 (m, 3H), 7.89 (m, 1H), 7.96 (m, 2H), 10.04 (s, 1H), 10.36 (s, 1H). MS (EI): *m/z* 37 (57), 212 (33), 265 (100), 344 (40), 608 (50) M$^+$. Anal. Calcd for $C_{36}H_{27}F_3N_2O_4$: C, 71.05; H, 4.47; N, 4.60. Found: C, 71.03; H, 4.65; N, 4.78.

6.3.6. *N*-[3-Benzoyl-4-(4-methylphenylacetylamino)phenyl]-3-[5-(3-trifluoromethylphenyl)-2-furyl]acrylic acid amide (7f). From 3-[5-(3-trifluoromethylphenyl)-2-furyl]acrylic acid (226 mg, 1 mmol) according to general procedure 3. Purification: column chromatography with ethylacetate/*n*-hexane (1:1) afterwards recrystallization from *n*-hexane/acetone. Yield 256 mg (42%); mp 140 °C. IR (KBr): ν = 3263, 3086, 1669, 1642, 1624, 1549, 1502 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.33 (s, 3H), 3.69 (s, 2H), 6.51 (d, *J* = 16 Hz, 1H), 6.64 (d, *J* = 4 Hz, 1 H), 6.77 (d, *J* = 4 Hz, 1H), 7.15 (m, 2H), 7.24 (m, 2H), 7.44–7.49 (m, 4H), 7.52–7.58 (m, 2H), 7.63 (m, 1H), 7.68 (m, 3H), 7.79 (m, 1H), 7.90 (s, 1H), 7.98 (s, 1H), 8.53 (m, 1H), 10.54 (s, 1H). MS (EI): *m/z* 265 (100) 266 (16), 344 (25), 609 (15), 608 (39) M$^+$. Anal. Calcd for $C_{36}H_{27}F_3N_2O_4$: C, 71.03; H, 4.47; N, 4.60. Found: C, 70.91; H, 4.58; N, 4.67.

6.3.7. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-ethylphenyl)-2-furyl]acrylic acid amide (7g). From 3-[5-(4-ethylphenyl)-2-furyl]acrylic acid (242 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 379 mg (67%); mp 200 °C. IR (KBr): ν = 3319, 2966, 2924, 1662, 1629, 1551, 1506 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.19 (t, *J* = 7 Hz, 3H), 2.24 (s, 3H), 2.63 (q, *J* = 7 Hz, 2H), 3.35 (s, 2H), 6.66 (d, *J* = 16 Hz, 1H), 6.93 (m, 1H), 6.98 (m, 2H), 7.04 (m, 3H), 7.30 (m, 2H), 7.35 (d, *J* = 16 Hz, 1H), 7.49 (m, 2H), 7.55 (m, 1H), 7.61–7.70 (m, 5H), 7.77 (m, 1H), 7.88 (m, 1H), 10.09 (s, 1H), 10.35 (s, 1H). MS (EI): *m/z* 225 (100), 344 (11), 568 (38) M$^+$. Anal. Calcd for $C_{37}H_{32}N_2O_4$: C, 78.15; H, 5.67; N, 4.93. Found: C, 77.88; H, 5.63; N, 4.99.

6.3.8. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-vinylphenyl)-2-furyl]acrylic acid amide (7h). From 3-[5-(4-vinylphenyl)-2-furyl]acrylic acid (240 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 201 mg (35%); mp 206 °C. IR (KBr): ν = 3320, 3057, 2920, 1661, 1653, 1625, 1553, 1507 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H), 3.34 (s, 2H), 5.30 (d, *J* = 11 Hz, 1H), 5.89 (d, *J* = 18 Hz, 1H), 6.68 (d, *J* = 16 Hz, 1H), 6.75 (dd, *J* = 18/11 Hz, 1H), 6.94–6.98 (m, 3H), 7.03 (m, 2H), 7.11 (m, 1H), 7.36 (d, *J* = 16 Hz, 1H), 7.49 (m, 2H), 7.55 (m, 3H), 7.62 (m, 1H), 7.67 (m, 2H), 7.75 (m, 3H), 7.87 (m, 1H), 10.84 (s, 1H), 10.36 (s, 1H). MS (EI): *m/z* 105 (33), 211 (29), 344 (100), 476 (54), 566 (12) M$^+$ Anal. Calcd for $C_{37}H_{30}N_2O_4$: C, 78.43; H, 5.34; N, 4.91. Found: C, 78.28; H, 5.27; N, 4.99.

6.3.9. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-*tert*-butylphenyl)-2-furyl]acrylic acid amide (7i). From 3-[5-(4-*tert*-butylphenyl)-2-furyl]acrylic acid (270 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 316 mg (53%); mp 244 °C. IR (KBr): ν = 3423, 2962, 1666, 1626, 1551, 1506 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9H), 2.23 (s, 3H), 3.34 (s, 2H), 6.65 (d, *J* = 16 Hz, 1H), 6.92 (m, 1H), 6.98 (m, 2H), 7.03 (m, 3H), 7.35 (d, *J* = 16 Hz, 1H), 7.48 (m, 4H), 7.54 (m, 1H), 7.60–7.69 (m, 5H), 7.77 (m, 1H), 7.87 (m, 1H), 10.09 (s, 1H), 10.37 (s, 1H). MS (EI): *m/z* 253 (100), 326 (22), 344 (11), 596 (25) M$^+$. Anal. Calcd for $C_{39}H_{36}N_2O_4$: C, 78.50; H, 6.08; N, 4.69. Found: C, 78.37; H, 6.00; N, 4.89.

6.3.10. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-methylsulfanylphenyl)-2-furyl]acrylic acid amide (7j). From 3-[5-(4-methylsulfanylphenyl)-2-furyl]acrylic acid (260 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 300 mg (51%); mp 219 °C. IR (KBr): ν = 3454, 3322, 2961, 1663, 1552, 1507, 1400 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H), 2.52 (s, 3H), 3.35 (s, 2H), 6.66 (d, *J* = 16 Hz, 1H), 6.94 (m, 1H), 6.98 (m, 2H), 7.04 (m, 1H), 7.06 (m, 2H), 7.33–7.38 (m, 3H), 7.49 (m, 2H), 7.55 (m, 1H), 7.64 (m, 1H), 7.68 (m, 4H), 7.77 (m, 1H), 7.88 (m, 1H), 10.09 (s, 1H), 10.36 (s, 1H). MS (EI): *m/z* 243 (100), 344 (12), 586 (41) M$^+$. Anal. Calcd for $C_{36}H_{30}N_2O_4S$: C, 73.70; H, 5.15; N, 4.77. Found: C, 73.52; H, 5.13; N, 4.55.

6.3.11. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-trifluoromethylsulfanylphenyl)-2-furyl]acrylic acid amide (7k). From 3-[5-(4-trifluoromethylsulfanylphenyl)-2-furyl]acrylic acid (236 mg, 0.75 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 245 mg (57%); mp 219 °C. IR (KBr): ν = 3386, 1654, 1540, 1507, 1408, 1166, 1116 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.36 (s, 2H), 6.73 (d, *J* = 16 Hz, 1H), 7.00 (m, 3H), 7.05 (m, 2H), 7.29 (m, 1H), 7.40 (d, *J* = 16 Hz, 1H), 7.50 (m, 2H), 7.59 (m, 2H), 7.64 (m, 2H), 7.69 (m, 3H), 7.90 (m, 3H), 10.08 (s, 1H), 10.40 (s, 1H). MS (EI): *m/z* 297 (199), 344 (22), 640 (59) M$^+$. Anal. Calcd for $C_{36}H_{27}F_3N_2O_4S$: C, 67.49; H, 4.25; N, 4.37. Found: C, 67.24; H, 4.41; N, 4.48.

6.3.12. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-ethylsulfanylphenyl)-2-furyl]acrylic acid amide (7l). From 3-[5-(4-ethylsulfanylphenyl)-2-furyl]acrylic acid (137 mg, 0.5 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 162 mg (54%); mp 212 °C. IR (KBr): ν = 3326, 2921, 1660, 1550, 1505, 1400 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, $J = 7$ Hz, 3H), 2.26 (s, 3H), 3.04 (q, $J = 7$ Hz, 2H), 3.36 (s, 2H), 6.68 (d, $J = 16$ Hz, 1H), 6.94–7.07 (m, 6H), 7.35–7.50 (m, 5H), 7.54 (d, $J = 16$ Hz, 1H), 7.59–7.70 (m, 5H), 7.72–7.90 (m, 2H), 10.08 (s, 1H), 10.35 (s, 1H). MS (EI): *m/z* 257 (100), 601 (40) [M+H]$^+$. Anal. Calcd for $C_{37}H_{32}N_2O_4S$: C, 73.98; H, 5.37; N, 4.66. Found: C, 73.63; H, 5.35; N, 5.02.

6.3.13. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-methoxyphenyl)-2-furyl]acrylic acid amide (7m).** From 3-[5-(4-methoxyphenyl)-2-furyl]acrylic acid (245 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 427 mg (75%); mp 200 °C. IR (KBr): ν = 3321, 3054, 2940, 1663, 1609, 1551, 1506, 1489, 1253 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H), 3.32 (s, 2H), 3.76 (s, 3H), 6.59 (d, $J = 16$ Hz, 1H), 6.86 (m, 2H), 6.94–6.99 (m, 6H), 7.30 (m, 1H), 7.44 (m, 2H), 7.54–7.60 (m, 2H), 7.65 (m, 4H), 7.73 (m, 1H), 7.83 (m, 1H), 9.98 (s, 1H), 10.23 (s, 1H). MS (EI): *m/z* 212 (11), 227 (100), 344 (11), 570 (30) M$^+$. Anal. Calcd for $C_{36}H_{30}N_2O_5$: C, 75.77; H, 5.30; N, 4.91. Found: C, 75.58; H, 5.36; N, 5.11.

6.3.14. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-trifluoromethoxyphenyl)-2-furyl]acrylic acid amide (7n).** From 3-[5-(4-trifluoromethoxyphenyl)-2-furyl]acrylic acid (298 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 496 mg (79%); mp 204 °C. IR (KBr): ν = 3324, 1683, 1658, 1631, 1555, 1507, 1400, 1261, 1223 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.31 (s, 3H), 3.68 (s, 2H), 6.45 (d, $J = 16$ Hz, 1H), 6.62 (m, 1H), 6.68 (m, 1H), 7.13–7.24 (m, 6H), 7.41–7.47 (m, 3H), 7.56 (m, 2H), 7.62 (m, 1H), 7.64–7.70 (m, 4H), 7.99 (s, 1H), 8.50 (m, 1H), 10.51 (s, 1H). MS (EI): *m/z* 44 (35), 105 (21), 281 (100), 344 (23), 624 (30) M$^+$. Anal. Calcd for $C_{36}H_{27}F_3N_2O_5$: C, 69.23; H, 4.36; N, 4.48. Found: C, 69.41; H, 4.61; N, 4.58.

6.3.15. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-ethoxyphenyl)-2-furyl]acrylic acid amide (7o).** From 3-[5-(4-ethoxyphenyl)-2-furyl]acrylic acid (258 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 404 mg (69%); mp 183 °C. IR (KBr): ν = 3447, 2982, 1653, 1609, 1559, 1508 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.33 (t, $J = 7$ Hz, 3H), 2.24 (s, 3H), 3.35 (s, 2H), 4.07 (q, $J = 7$ Hz, 2H), 6.64 (d, $J = 16$ Hz, 1H), 6.90 (m, 2H), 6.93 (m, 2H), 6.97–7.05 (m, 4H), 7.34 (d, $J = 16$ Hz, 1H), 7.49 (m, 2H), 7.56 (m, 1H), 7.63 (m, 1H), 7.69 (m, 4H), 7.77 (m, 1H), 7.87 (m, 1H), 10.09 (s, 1H), 10.34 (s, 1H). MS (EI): *m/z* 105 (15), 157 (12), 241 (100), 584 (24) M$^+$. Anal. Calcd for $C_{37}H_{32}N_2O_5$: C, 76.01; H, 5.52; N, 4.79. Found: C, 75.79; H, 5.46; N, 4.80.

6.3.16. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-fluorophenyl)-2-furyl]acrylic acid amide (7p).** From 3-[5-(4-fluorophenyl)-2-furyl]acrylic acid (232 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 447 mg (80%); mp 200 °C. IR (KBr): ν = 3422, 3324, 1684, 1661, 1637, 1555, 1507 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.34 (s, 2H), 6.67 (d, $J = 16$ Hz, 1H), 6.93 (m, 1H), 6.97 (m, 2H), 7.03 (m, 2H), 7.07 (s, 1H), 7.32 (m, 2H), 7.35 (d, $J = 16$ Hz, 1H), 7.48 (m, 2H), 7.54 (m, 1H), 7.62 (m, 1H), 7.67 (m, 2H), 7.76 (m, 1H), 7.80 (m, 2H), 7.87 (m, 1H), 10.08 (s, 1H), 10.35 (s, 1H). MS (EI): *m/z* 215 (100), 344 (33), 558 (1) M$^+$, 559 (83) [M+H]$^+$. Anal. Calcd for $C_{35}H_{27}FN_2O_4$: C, 75.26; H, 4.87; N, 5.01. Found: C, 75.47; H, 4.84; N, 5.32.

6.3.17. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-cyanophenyl)-2-furyl]acrylic acid amide (7s).** From 3-[5-(4-cyanophenyl)-2-furyl]acrylic acid (182 mg, 0.5 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 182 mg (64%); mp 200 °C. IR (KBr): ν = 3361, 2226, 1631, 1557, 1507, 1403 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.36 (s, 2H), 6.76 (d, $J = 16$ Hz, 1H), 6.98–7.04 (m, 5H), 7.36 (m, 1H), 7.40 (d, $J = 16$ Hz, 1H), 7.50–7.68 (m, 3H), 7.69 (m, 1H), 7.79 (m, 2H), 7.88–7.91 (m, 2H), 7.94 (m, 4H), 10.08 (s,1H), 10.39 (s, 1H). MS (EI): *m/z* 222 (100), 344 (54), 566 (83) [M+H]$^+$. Anal. Calcd for $C_{36}H_{27}N_3O_4$: C, 76.45; H, 4.81; N, 7.43. Found: C, 76.34; H, 4.91; N, 7.40.

6.3.18. ***N*-[3-Benzoyl-4-(4-methylphenylacetylamino)phenyl]-3-[5-(3-nitrophenyl)-2-furyl]acrylic acid amide (7u).** From 3-[5-(3-nitrophenyl)-2-furyl]acrylic acid (257 mg, 1 mmol) according to general procedure 3. Purification: column chromatography with ethylacetate/*n*-hexane (2:3). Yield 270 mg (46%); mp 208 °C. IR (KBr): ν = 3383, 3291, 3066, 1670, 1628, 1540, 1513, 1502, 1403, 1348, 1245, 1198 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.38 (s, 2H), 6.75 (d, $J = 16$ Hz, 1H), 7.00 (m, 3H), 7.04 (m, 2H), 7.36 (d, $J = 4$ Hz, 1H), 7.42 (d, $J = 16$ Hz, 1H), 7.50 (t, $J = 8$ Hz, 2H), 7.62 (m, 2H), 7.69 (m, 2H), 7.76 (t, $J = 8$ Hz, 1H), 7.79 (m, 1H), 7.88 (m, 1H), 8.16–8.21 (m, 2H), 8.51 (m, 1H), 10.03 (s, 1H), 10.37 (s, 1H). MS (EI): *m/z* 105 (28), 212 (55), 242 (100), 344 (55), 585 (65) M$^+$. Anal. Calcd for $C_{35}H_{27}N_3O_6$: C, 71.77; H, 4.65; N, 7.18. Found: C, 71.73; H, 4.76; N, 6.99.

6.3.19. ***N*-[3-Benzoyl-4-(4-methylphenylacetylamino)phenyl]-3-[5-(2-nitrophenyl)-2-furyl]acrylic acid amide (7v).** From 3-[5-(2-nitrophenyl)-2-furyl]acrylic acid (257 mg, 1 mmol) according to general procedure 3. Purification: column chromatography with ethylacetate/*n*-hexane (1:1) afterwards recrystallization from *n*-hexane/acetone. Yield 363 mg (62%); mp 150 °C. IR (KBr): ν = 3300, 3110, 1717, 1663, 1634, 1573, 1512, 1334, 1233, 1198 cm $^{-1}$. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.37 (s, 2H), 6.54 (d, $J = 16$Hz, 1H), 6.98 (d, $J = 4$Hz, 1H), 6.99 (m, 2H), 7.02 (d, $J = 4$Hz, 1H), 7.04 (m, 2H), 7.37 (d, $J = 16$Hz, 1H), 7.48 (m, 2H), 7.61 (m, 3H), 7.67 (m, 2H), 7.73–7.79 (m, 2H), 7.88–7.93 (m, 3H), 10.02 (s, 1H), 10.36 (s, 1H). MS (EI): *m/z* 105 (66), 212 (100), 242 (64), 344 (60), 585 (61) M$^+$. Anal. Calcd for $C_{35}H_{27}N_3O_6$: C, 71.77; H, 4.65; N, 7.18. Found: C, 71.66; H, 4.75; N, 7.15.

6.3.20. ***N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-acetylphenyl)-2-furyl]acid amide (7w).** From 3-[5-(4-

acetylphenyl)-2-furyl]acrylic acid (128 mg, 0.5 mmol) according to general procedure 3. Purification: column chromatography (EtOAc/*n*-hexane 3:2). Yield 93 mg (32%); mp 208 °C. IR (KBr): *v* = 3328, 1684, 1659, 1552, 1506, 1400 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 2.49 (s, 3H), 3.34 (s, 2H), 6.73 (d, *J* = 16 Hz, 1H), 6.97–7.05 (m, 5H), 7.31 (m, 1H), 7.39 (d, *J* = 16 Hz, 1H), 7.49 (m, 2H), 7.55 (m, 1H), 7.62 (m, 1H), 7.68 (m, 2H), 7.77 (m, 1H), 7.88 (m, 3H), 8.03 (m, 2H), 10.09 (s, 1H), 10.41 (s, 1H). MS (EI): *m/z* 44 (100), 75 (76), 91 (94), 239 (60), 582 (14) M$^+$. Anal. Calcd for $C_{37}H_{30}N_2O_5$: C, 76.27; H, 5.19; N, 4.81. Found: C, 76.18; H, 5.12; N, 4.97.

6.3.21. 4-(5-{2-[3-Benzoyl-4-(4-tolylacetylamino)]phenylaminocarbonyl}vinyl-2-furyl)benzoic acid methylester (7x). From 3-[5-(4-methoxycarbonylphenyl)-2-furyl]acrylic acid (136 mg, 0.5 mmol) according to general procedure 3. Purification: column chromatography (EtOAc/*n*-hexane 3:2). Yield 154 mg (51%); mp 235 °C. IR (KBr): *v* = 3341, 1720, 1661, 1553, 1508, 1276 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.37 (s, 2H), 3.88 (s, 3H), 6.75 (d, *J* = 16 Hz, 1H), 7.00 (m, 3H), 7.06 (m, 2H), 7.30 (m, 1H), 7.40 (d, *J* = 16 Hz, 1H), 7.51 (m, 2H), 7.58 (m, 2H), 7.62–7.71 (m, 2H), 7.78 (m, 1H), 7.90 (m, 3H), 8.04 (m, 2H), 10.09 (s, 1H), 10.41 (s, 1H). MS (EI): *m/z* 255 (100), 344 (35), 598 (46) M$^+$. Anal. Calcd for $C_{37}H_{30}N_2O_6$: C, 74.23; H, 5.05; N, 4.68. Found: C, 74.06; H, 5.16; N, 4.80.

6.3.22. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-methylsulfonylphenyl)-2-furyl]acrylic acid amide (7y). From 3-[5-(4-methylsulfonylphenyl)-2-furyl]acrylic acid (221 mg, 0.75 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 356 mg (77%); mp 217 °C. IR (KBr): *v* = 3268, 1689, 1659, 1632, 1594, 1579, 1540, 1410, 1298 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H), 3.25 (s, 3H), 3.35 (s, 2H), 6.75 (d, *J* = 16 Hz, 1H), 6.98 (m, 2H), 7.03 (m, 3H), 7.36 (m, 1H), 7.41 (d, *J* = 16 Hz, 1H), 7.50 (m, 2H), 7.56 (m, 1H), 7.63 (m, 1H), 7.68 (m, 2H), 7.77 (m, 1H), 7.89 (m, 1H), 7.99 (m, 4H), 10.10 (s, 1H), 10.43 (s, 1H). MS (ESI): *m/z* 519 (30), 619 (100) [M+H]$^+$, 641 (77) [M+Na]$^+$, 657 (40) [M+K]$^+$. Anal. Calcd for $C_{36}H_{30}N_2O_6S$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.52; H, 4.75; N, 4.50.

6.3.23. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-ethylsulfonylphenyl)-2-furyl]acrylic acid amide (7z). From 3-[5-(4-ethylsulfonylphenyl)-2-furyl]acrylic acid (306 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 185 mg (29%); mp 230 °C. IR (KBr): *v* = 3443, 1700, 1653, 1508, 1145 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.13 (t, *J* = 7 Hz, 3H), 2.26 (s, 3H), 3.32 (q, *J* = 7 Hz, 2H), 3.36 (s, 2H), 6.76 (d, *J* = 16 Hz, 1H), 6.99–7.07 (m, 5H), 7.36–7.40 (m, 1H), 7.43–7.49 (m, 1H), 7.51 (m, 2H), 7.58 (m, 2H), 7.63–7.70 (m, 2H), 7.79 (m, 1H), 7.91 (m, 1H), 7.96 (m, 2H), 8.02 (m, 2H), 10.09 (s, 1H), 10.43 (s, 1H). MS (ESI): *m/z* 43 (60), 57 (46), 105 (56), 212 (43), 289 (100), 632 (12) M$^+$. Anal. Calcd for $C_{37}H_{32}N_2O_6S$: C, 70.24; H, 5.10; N, 4.43. Found: C, 69.91; H, 5.12; N, 4.48.

6.3.24. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-aminophenyl)-2-furyl]acrylic acid amide (7aa). *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-nitrophenyl)-2-furyl]acrylic acid amide **7t** (5.01 g, 8.6 mmol) and tin(II) chloride dihydrate (8.38 g, 37 mmol) were dissolved in 100 mL EtOAc. The mixture was heated under reflux for 2 h. Then, a saturated sodium bicarbonate solution was added to reach a pH of 8. After extraction with EtOAc for three times the organic layers were combined and dried with anhydrous magnesium sulfate. Solvent was evaporated in vacuo. Purification: recrystallization from tetrahydrofuran/*n*-hexane. Yield 2.48 g (89%); mp 182 °C. IR (KBr): *v* = 1653, 1611, 1547, 1488 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.37 (s, 2H), 6.57 (d, *J* = 16 Hz, 1H), 6.65 (m, 2H), 6.73 (m, 1H), 6.86 (m, 1H), 6.99 (m, 2H), 7.06 (m, 2H), 7.31 (d, *J* = 16 Hz, 1H), 7.46–7.53 (m, 4H), 7.57 (m, 1H), 7.64 (m, 1H), 7.69 (m, 2H), 7.77 (m, 1H), 7.87–7.91 (m, 1H), 10.08 (s, 1H), 10.27 (s, 1H). MS (EI): *m/z* 212 (100), 239 (19), 344 (94). 555 (50) M$^+$. Anal. Calcd for $C_{35}H_{29}N_3O_4$: C, 75.66; H, 5.26; N, 7.56. Found: C, 75.34; H, 5.28; N, 7.44.

6.3.25. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-formylaminophenyl)-2-furyl]acrylic acid amide (7ac). Formic acid (0.5 mL) and 0.2 mL acetanhydride were dissolved in 30 mL THF. The solution was cooled to −10 °C. Then, a solution of *N*-[3-benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-aminophenyl)-2-furyl]acrylic acid amide **7aa** (278 mg, 0.5 mmol) in 20 mL THF was added and the mixture was stirred for 12 h. Because the reaction has not run completely, additional 2 mL formic acid were added and the mixture was heated under reflux until no educt was left (monitored by TLC). After cooling, the mixture was poured into a saturated sodium chloride solution. The resulting mixture was extracted with EtOAc for three times and the combined organic layers were washed with sodium bicarbonate solution, citric acid solution, and brine. After drying with anhydrous magnesium sulfate the solvent was evaporated in vacuo. Purification: recrystallization from toluene/ethanol. Yield 180 mg (58%); mp 235 °C. IR (KBr): *v* = 3433, 2922, 1675, 1607, 1560, 1510 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.35 (s, 2H), 6.64 (d, *J* = 16 Hz, 1H), 6.92 (m, 1H), 6.98 (m, 3H), 7.04 (m, 2H), 7.35 (d, *J* = 16 Hz, 1H), 7.49 (m, 2H), 7.56 (m, 1H), 7.61–7.76 (m, 9H), 7.88 (m, 1H), 10.05 (s, 1H), 10.06 (s, 1H), 10.33 (s, 1H). MS (EI): *m/z* 44 (100), 240 (36), 583 (4) M$^+$. Anal. Calcd for $C_{36}H_{29}N_3O_5$: C, 74.09; H, 5.01; N, 7.29. Found: C, 73.79; H, 4.97; N, 7.19.

6.3.26. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-acetylaminophenyl)-2-furyl]acrylic acid amide (7ad). *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-aminophenyl)-2-furyl]acrylic acid amide **7aa** (555 mg, 1 mmol) was dissolved in dry DMF under an argon atmosphere. The mixture was cooled to −5 °C and 2 mL acetanhydride were added. After stirring for 12 h the mixture was poured into a saturated solution of sodium chloride to yield a solid. Purification: recrystallization from toluene/ethanol. Yield 335 mg (56%); mp 232 °C. IR (KBr): *v* = 3308, 1653, 1603, 1505 cm^{-1}. ^{1}H

NMR (DMSO-d_6): 2.07 (s, 3H), 2.26 (s, 3H), 3.36 (s, 2H), 6.66 (d, *J* = 16 Hz, 1H), 6.93 (m, 1H), 6.99 (m, 3H), 7.06 (m, 2H), 7.36 (d, *J* = 16 Hz, 1H), 7.50 (m, 2H), 7.58 (m, 1H), 7.62–7.72 (m, 7H), 7.78 (m, 1H), 7.90 (m, 1H), 10.08 (s, 2H), 10.35 (s, 1H). MS (EI): *m/z* 212 (100), 254 (95), 326 (60), 344 (90), 597 (11) M$^+$. Anal. Calcd for $C_{37}H_{31}N_3O_5$: C, 74.36; H, 5.23; N, 7.03. Found: C, 74.54; H, 5.29; N, 7.38.

6.3.27. *N*-(3-Benzoyl-4-trifluoroacetylaminophenyl)-3-[5-(4-cyanophenyl)-2-furyl]acrylic acid amide (9). From 3-[5-(4-cyanophenyl)-2-furyl]acrylic acid (239 mg, 1 mmol) and *N*-(4-amino-2-benzoylphenyl)-trifluoroacetic acid amide (308 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 338 mg (72%). ^{1}H NMR (DMSO-d_6): δ 6.78 (d, *J* = 16 Hz, 1H), 7.04 (m, 1H), 7.37 (m, 1H), 7.43 (d, *J* = 16 Hz, 1H), 7.54 (m, 3H), 7.66–7.73 (m, 3H), 7.89 (m, 1H), 7.95 (m, 4H), 8.00 (m, 1H), 10.54 (s, 1H), 11.31 (s, 1H).

6.3.28. *N*-[3-Benzoyl-4-aminophenyl]-3-[5-(4-carbamoylphenyl)-2-furyl]acrylic acid amide (10). *N*-(3-Benzoyl-4-trifluoroacetylaminophenyl)-3-[5-(4-cyanophenyl)-2-furyl]acrylic acid amide (**9**) (423 mg, 0.8 mmol) was suspended in a mixture of 15 mL ethanol and 15 mL dioxane. Five milliliters of an aqueous solution of sodium hydroxide (20 %) and 4 mL of an aqueous solution of H_2O_2 (30%) were added and the mixture was heated to 60 °C for 2 h. After cooling the mixture was extracted with EtOAc for three times. The combined organic layers were dried over anhydrous magnesium sulfate and solvent was evaporated in vacuo. Purification: recrystallization from ethanol. Yield 287 mg (79%). IR (KBr): ν = 3466, 3348, 2922, 1634, 1567, 1416, 1249 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.70 (d, *J* = 16 Hz, 1H), 6.86 (m, 1H), 6.96 (m, 3H), 7.32 (d, *J* = 16 Hz, 1H), 7.35 (m, 1H), 7.54 (m, 1H), 7.61 (m, 2H), 7.68 (m, 1H), 7.74 (m, 1H), 7.93 (m, 4H), 9.99 (s, 1H).

6.3.29. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-aminocarbonylphenyl)-2-furyl]acrylic acid amide (7ab). From *N*-[3-benzoyl-4-aminophenyl]-3-[5-(4-carbamoylphenyl)-2-furyl]acrylic acid amide **10** (165 mg, 0.3 mmol) and 4-tolylacetic acid (45 mg, 0.3 mmol) according to general procedure 3. Purification: recrystallization from ethanol. Yield 54 mg (23%); mp 198 °C. IR (KBr): ν = 3431, 1654, 1616, 1558, 1508, 1401 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.34 (s, 2H), 6.74 (d, *J* = 16 Hz, 1H), 6.98 (m, 3H), 7.03 (m, 2H), 7.22 (m, 1H), 7.34 (m, 1H), 7.49 (m, 2H), 7.56 (m, 1H), 7.62 (m, 1H), 7.66 (m, 2H), 7.77 (m, 1H), 7.83–7.89 (m, 3H), 7.94–8.00 (m, 2H), 10.09 (s, 1H), 10.42 (s, 1H). MS (EI-HR): Calcd for $C_{36}H_{29}N_3O_5$: 583.2107. Found: 583.2132 M$^+$.

6.3.30. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[5-(4-aminosulfonylphenyl)-2-furyl]acrylic acid amide (7ae). 3-[5-(4-Aminosulfonylphenyl)-2-furyl]acrylic acid (125 mg, 0.42 mmol) and *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimid*HCl (84 mg, 0.44 mmol) were suspended in 5 mL THF. *N*-(4-Amino-2-benzoylphenyl)-4-tolylacetic acid amide (131 mg, 0.38 mmol) was added and the mixture was stirred at room temperature for 5 h. Purification: column chromatography (EtOAc). Yield 172 mg (73%); mp 255 °C. IR (KBr): ν = 3336, 1664, 1618, 1548, 1508, 1154 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.35 (s, 2H), 6.74 (d, *J* = 16 Hz, 1H), 6.99 (m, 2H), 7.01–7.06 (m, 3H), 7.30 (m, 1H), 7.40 (m, 3H), 7.49–7.57 (m, 3H), 7.63–7.70 (m, 3H), 7.78 (m, 1H), 7.89–7.97 (m, 3H), 10.12 (s, 1H), 10.44 (s, 1H). MS (EI): *m/z* 212 (84), 326 (90), 344 (100), 619 (11) M$^+$. Anal. Calcd for $C_{35}H_{29}N_3O_6S$: C, 67.84; H, 4.72; N, 6.78. Found: C, 67.57; H, 4.67; N, 6.57.

6.3.31. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-(4-phenyl-2-furyl)acrylic acid amide (11a). From 3-(4-phenyl-2-furyl)acrylic acid (191 mg, 0.9 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 379 mg (70%); mp 228 °C. IR (KBr): ν = 3299, 1655, 1629, 1560, 1509 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.34 (s, 2H), 6.61 (d, *J* = 16 Hz, 1H), 6.97 (m, 2H), 7.03 (m, 2H), 7.27 (m, 2H), 7.35–7.41 (m, 3H), 7.45–7.50 (m, 2H), 7.56 (m, 1H), 7.60–7.64 (m, 3H), 7.67 (m, 2H), 7.76 (m, 1H), 7.87 (m, 1H), 8.30 (m, 1H), 10.07 (s, 1H), 10.35 (s, 1H). MS (ESI-HR): Calcd for $C_{35}H_{27}N_2O_4$: 539.1971. Found: 539.2003 [M+H]$^+$. Anal. Calcd for $C_{35}H_{27}N_2O_4$: C, 77.76; H, 5.22; N, 5.18. Found: C, 77.52; H, 5.20; N, 5.37.

6.3.32. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[4-(4-methylphenyl)-2-furyl]acrylic acid amide (11b). From 3-[4-(4-methylphenyl)-2-furyl]acrylic acid (230 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 422 mg (85%); mp 256 °C. IR (KBr): ν = 3425, 1671, 1623, 1560, 1515 cm^{-1}. ^{1}H NMR (DMSO-d_6): 2.24 (s, 3H), 2.29 (s, 3H), 3.34 (s, 2H), 6.60 (d, *J* = 16 Hz, 1H), 6.97 (m, 2H), 7.03 (m, 2H), 7.19 (m, 2H), 7.23 (m, 1H), 7.35 (m, 1H), 7.46–7.50 (m, 4H), 7.55 (m, 1H), 7.62 (m, 1H), 7.67 (m, 2H), 7.75 (m, 1H), 7.86 (m, 1H), 8.24 (m, 1H), 10.06 (s, 1H), 10.33 (s, 1H). MS (EI): *m/z* 211 (60), 344 (31), 554 (100) M$^+$. Anal. Calcd for $C_{36}H_{30}N_2O_4$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.77; H, 5.47; N, 5.03.

6.3.33. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[4-(4-trifluoromethylphenyl)-2-furyl]acrylic acid amide (11c). From 3-[4-(4-trifluoromethylphenyl)-2-furyl]-acrylic acid (282 mg, 1 mmol) according to general procedure 3. Purification: recrystallization from toluene. Yield 381 mg (71%); mp 248 °C. IR (KBr): ν = 3422, 3125, 1669, 1620, 1559, 1508, 1326 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.34 (s, 2H), 6.64 (d, *J* = 16 Hz, 1H), 6.93–9.98 (m, 2H), 7.02 (m, 2H), 7.38 (m, 2H), 7.45–7.50 (m, 2H), 7.56 (m, 1H), 7.60–7.68 (m, 3H), 7.76 (m, 3H), 7.85 (m, 3H), 8.46 (m, 1H), 10.07 (s, 1H), 10.37 (s, 1H). MS (EI): *m/z* 212 (24), 265 (41), 344 (30), 476 (28), 608 (100) M$^+$. Anal. Calcd for $C_{36}H_{27}F_3N_2O_4$: C, 71.05; H, 4.47; N, 4.80. Found: C, 70.82; H, 4.62; N, 4.78.

6.3.34. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[4-(4-methoxyphenyl)-2-furyl]acrylic acid amide (11d). From 3-[4-(4-methoxyphenyl)-2-furyl]acrylic acid

(244 mg, 1 mmol) according to general procedure 3. Purification: column chromatography (EtOAc/*n*-hexane 3:2). Yield 106 mg (21%); mp 241 °C. IR (KBr): $v = 3317, 1671, 1662, 1512, 1251\,cm^{-1}$. ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.36 (s, 2H), 3.78 (s, 3H), 6.60 (d, $J = 16$ Hz, 1H), 6.98 (m, 4H), 7.05 (m, 2H), 7.25 (m, 1H), 7.36 (d, $J = 16$ Hz, 1H), 7.48–7.59 (m, 5H), 7.62–7.70 (m, 3H), 7.70 (m, 1H), 7.88 (m, 1H), 8.20 (m, 1H), 10.08 (s, 1H), 10.34 (s, 1H). MS (EI): *m/z* 227 (80), 344 (39), 570 (100) M^+. Anal. Calcd for $C_{36}H_{30}N_2O_5$: C, 75.77; H, 5.30; N, 4.91. Found: C, 75.51; H, 5.32; N, 5.18.

6.3.35. *N*-[3-Benzoyl-4-(4-tolylacetylamino)phenyl]-3-[4-(4-methylsulfonylphenyl)-2-furyl]acrylic acid amide (11e). From 3-[4-(4-methylsulfonylphenyl)-2-furyl]-acrylic acid (228 mg, 0.8 mmol) according to general procedure 3. Purification: recrystallization from toluene/ethanol. Yield 244 mg (56%); mp 248 °C. IR (KBr): $v = 3307, 1671, 1623, 1508, 1308\,cm^{-1}$. ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H), 3.29 (s, 3H), 3.37 (s, 2H), 6.66 (d, $J = 16$ Hz, 1H), 6.99 (m 2H), 7.05 (m, 2H), 7.40 (m, 2H), 7.50 (m, 2H), 7.58–7.70 (m, 4H), 7.78 (m, 1H), 7.87–7.97 (m, 5H), 8.52 (m, 1H), 10.09 (s, 1H), 10.38 (s, 1H). MS (EI): *m/z* 212 (45), 275 (58), 326 (100), 344 (60), 618 (10) M^+. Anal. Calcd for $C_{36}H_{30}N_2O_6S$: C, 69.89; H, 4.89; N, 4.53 found: C, 69.64; H, 4.55; N, 4.44.

7. Enzyme preparation

Yeast farnesyltransferase was used as a fusion protein to Glutathione *S*-transferase at the N-terminus of the β-subunit. Farnesyltransferase was expressed in *Escherichia coli* DH5α grown in LB media containing ampicillin and chloramphenicol for co-expression of pGEX-DPR1 and pBC-RAM2 for farnesyltransferase production.[24] The enzyme was purified by standard procedures with glutathione-agarose beads for selective binding of the target protein.

8. Farnesyltransferase assay

The assay was conducted as described.[23] Farnesylpyrophosphate (FPP) was obtained as a solution of the ammonium salt in methanol–10 mM aqueous NH_4Cl (7:3) from Sigma-Aldrich. Dansyl-GlyCysValLeuSer (Ds-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 ZnCl2, 5 mM dithiothreitol (DTT), 7 µM Ds-GCVLS, 20 µM FPP, 5 nmol (approx.) yeast GST-farnesyltransferase, and 1% of various concentrations of the test compounds dissolved in dimethylsulfoxide (DMSO). The progress of the enzyme reaction was followed by monitoring 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} values (concentrations resulting in 50% inhibition) were calculated from initial velocity of three independent measurements of four to five different concentrations of the respective inhibitor.

9. Molecular modeling

All molecular modeling was carried out using SYBYL[30] version 6.8/6.9 running on a Silicon Graphics O2 (R10000). Flexible docking was performed using FlexX[29] version 1.11. During ligand construction, the FlexX command MAPREF and the perturbate algorithm was used for the placement of the base fragment. Default parameters were employed except the MAX_ENERGY value, which was set to $10\,kJ\,mol^{-1}$.

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