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# Thiazole- and imidazole-containing peptidomimetic inhibitors of protein farnesyltransferase

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ABSTRACT

Mimetics of the C-terminal *CAAX* tetrapeptide of Ras protein were designed replacing internal dipeptide *AA* with 4-amino-2-phenylbenzoic acid and cysteine (*C*) with 2-amino-4-thiazolyl-, 2-mercapto-4-thiazolyl-, 2-mercapto-4-imidazolyl- and 2-methylmercapto-4-thiazolyl-acetic or propionic acid. The compound in which *C* is replaced by 2-amino-4-thiazolylacetic acid inhibited FTase activity in the low nanomolar range and showed antiproliferative effect on rat aortic smooth muscle cells interfering with Ras farnesylation. On the basis of these results, 2-aminothiazole can be considered as an alternative to heterocycles, such as pyridine and imidazole, normally used in FTase inhibitors designed as non-thiol *CAAX* mimetics.

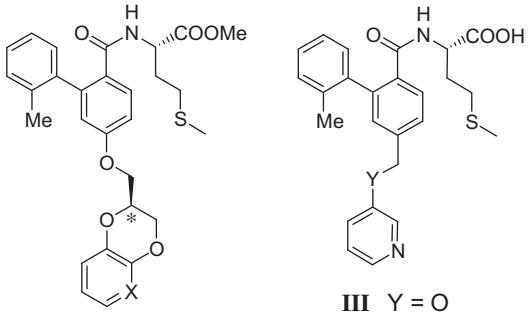


The farnesylation of the cysteine residue of the C-terminal tetrad *CAAX* of Ras protein by the zinc metalloenzyme farnesyltransferase (FTase) allows Ras to be localized, after cleavage of the *AAX* triad, to the inner surface of cell membrane and to transmit cellular proliferation signals.[1] Therefore, FTase inhibitors (FTis) are regarded as antiproliferative agents and actively pursued as antineoplastics, though the exact biological mechanism by which they exert antitumor activity is still controversial.[2] Their combination with some cytotoxic antineoplastic drugs offers promising perspectives for cancer treatment.[3–5] Moreover, the inhibition of the proliferation of smooth muscle cells (SMCs) has suggested the potential of FTis in the therapy of vascular disorders such as atherosclerosis and restenosis after angioplasty.[6–8] The use of *CAAX* as a template is one of the classical approaches to the design of FTis.[9,10] Based on this strategy, we have recently developed the *SS* stereoisomers of 2-*o*-tolyl substituted 4-hydroxybenzamide of methionine methyl ester, etherified at the phenolic function with pyridodioxan-2-ylmethyl (**I**) or benzodioxan-2-ylmethyl (**II**), which exert a significant antiproliferative effect on SMCs (30 and 6.6 μM $IC_{50}$, respectively) interfering with Ras farnesylation.[11,12]

SAR analysis of two series of **I** and **II** analogues indicates that the nature of the linker to the biphenyl core and the *o*-substitution on the latter, but not the dioxane stereochemistry, are critical features and that replacement of pyridodioxane with benzodioxane increases the antiproliferative activity and the RAS prenylation inhibition.

Compound **I** had been designed rigidifying the 3-pyridyloxymethyl substructure used to replace the metabolically labile cysteine in *CAAX* mimicking inhibitors of FTase such as **III**,[9] while compound **II** had been conceived as an isoster of **I** to eliminate the variable of nitrogen position in the aromatic ring of the bicyclic system (Chart 1).

In a continuation of our strategy to identify new FTis, we considered the substitution of 3-pyridyl with other aromatic heterocy-




**I** X = N
**II** X = CH
**III** Y = O
**IV** Y = NBn

**Chart 1.**

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cles. The 1,3-thiazole ring is a classical isostere of pyridine and thiazolyl analogues of **IV** have been described in literature.[13] They have been prepared in an attempt to improve the pharmacokinetic profile of **IV** by lowering the basicity of the heterocycle. In particular, the 3-pyridyl residue of **IV** has been replaced with 2-, 4- and 5-thiazolylmethyl registering enzyme inhibitions and cellular potencies sensibly lower than those of **IV** and, in the only case of the 5-thiazolylmethyl analogue, comparable to those of **III**.

Based on these preceding findings, 2-aminothiazole, which is as basic as pyridine and has pronounced complexation properties towards metal ions, was selected as an interesting candidate to pyridine replacement in alternative to unsubstituted thiazole. Therefore, we designed compounds **1** and **2**, where 2-amino-4-thiazolylacetic acid and 3-(2-amino-4-thiazolyl)propionic acid are, respectively, linked to the biphenyl spacer through an amidic bond. The importance of the interaction cysteine thiol-zinc for Ftase activity suggested to further modify the heterocycle replacing amino with thiol substituent. In compounds **3** and **4**, 2-mercapto-4-thiazolyl residue is the substructure which intends to mimick the cysteine chain. Contrarily to its 2-amino analogue, 2-mercaptothiazole exhibits a weakly acidic behavior and is implicated in thiol-thione tautomerism. That's why we designed also compounds **7** and **8**, analogues of **3** and **4** in which thiol is methylated and tautomerism abolished. Finally, we were drawn to consider the 2-mercapto-4-imidazolyl analogues **5** and **6**, because imidazole is a thiazole bioisostere and the use of imidazole ring as a metal ligand in metalloenzyme inhibition is documented (Chart 2).[14–16]

The isopropyl esters **1a**–**8a** were prepared as prodrugs of the acids **1**–**8** in order to facilitate cell membrane penetration and to evaluate the cell activity of the acids exhibiting FTase inhibition.

To synthesize compounds **1**–**8**, we firstly condensed the isopropyl ester of L-methionine with 2-*o*-tolyl-4-nitrobenzoic acid (**10**), obtained by hydrolysis of the previously reported methyl ester **9**.[12,17] The resultant N-nitrobenzoylated methionine ester **11** was hydrogenated to the corresponding aminobenzoylamide **12** (Scheme 1).[18,19]

All the heteroaryl acetic and heteroaryl propionic acids required for amidifying **12** had to be prepared from 4-chloroacetoacetate and 5-bromolevulinate, respectively, with the exception of commercially available (2-amino-4-thiazolyl)acetic acid. This acid only needed to be esterified, tritylated at the amino function and desesterified to (2-tritylamino-4-thiazolyl)acetic acid **13** before reacting with **12** to give **21**, namely the tritylamino analogue of **1a**.[20–23] Subsequent detritylation afforded compound **1a**.[24] The homologous 3-(2-amino-4-thiazolyl)propionic acid was synthesized from methyl 5-bromolevulinate and thiourea.[25] Tritylation and hydrolysis provided the N-protected aminothiazolyl propionic acid **14**, which was used to amidify **12**.[26–28] The resultant intermediate **22**, namely the tritylamino precursor of **2a**, was detritylated to give **2a** (Scheme 2).[29]

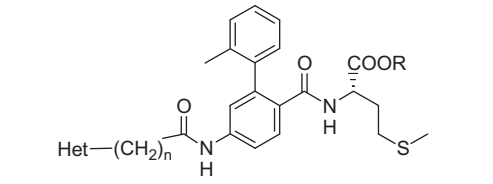
Cyclization of ethyl 4-chloroacetoacetate and methyl 5-bromolevulinate with ammonium dithiocarbamate afforded ethyl (2-mercapto-4-thiazolyl)acetate and methyl 3-(2-mercapto-4-thiazolyl)propionate, respectively, which were successively converted into acids **15** and **16** and then condensed with **12** to yield the corresponding amides **3a** and **4a** (Scheme 2).[30–35] The methylthio analogues of **3a** and **4a**, namely the compounds **7a** and **8a**, were obtained by the same strategy, but replacing (2-mercapto-4-thiazolyl)acetic acid and 3-(2-mercapto-4-thiazolyl)propionic acid with the respective S-methyl derivatives **17** and **18** (Scheme 2).[36–41]

The mercaptoimidazolyl acetic acid **19** and its propionic homologue **20** were, respectively, obtained by (a) conversion of ethyl 4-chloroacetoacetate and of methyl 5-bromolevulinate into the corresponding azides,[42,43] (b) reduction to 4-aminoacetoacetate and 5-aminolevulinate, isolated as tosylic acid salts,[44,45] (c) cyclization with potassium thiocyanate giving the mercaptoimidazole ring,[46,47] and (d) ester hydrolysis.[48,49] Condensation of **19** and **20** with **12** led to the amides **5a** and **6a**, respectively (Scheme 2).[50,51]

The isopropyl esters **1a**–**8a** were hydrolyzed obtaining the corresponding acids **1**–**8** (Scheme 2).[52–59]

The effect on protein farnesylation was first tested using a FTase fluorescent assay and FTI-276 as a reference compound.[60] FTI-276 has been reported to inhibit FTase with an $IC_{50}$ of 0.5 nM;[61] in our study, its $IC_{50}$ was 9 nM. We found that the compounds **1** and **5** significantly inhibit FTase catalytic activity in vitro with an $IC_{50}$ value equal to 49 and 122 nM, respectively, while the compounds **2**–**4** and **8** exhibited lower inhibitory activities and **6** and **7** were not active (Table 1). The concentration dependent inhibition of FTase activity of **1** is shown in Figure 1.

None of these compounds, having a carboxylic acid group, exerted significant effects on cell growth, as indicated by a cellular assay measuring inhibition of rat aortic SMC proliferation.[62] The lack of cellular activity could be explained by poor cell penetration. Therefore, the corresponding isopropyl esters **1a**–**8a**, prepared to ameliorate membrane permeability, were tested in the same assay and, as shown in Table 1, most of them proved to inhibit rat SMC proliferation with $IC_{50}$ values in the micromolar range. In particular, compound **1**, the most potent FTase inhibitor of the series, reduced rat SMC growth in a concentration dependent manner with an $IC_{50}$ value of 107 μM (Fig. 2).



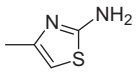
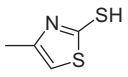
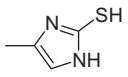
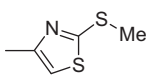
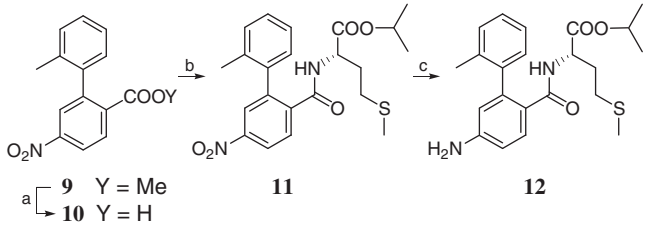
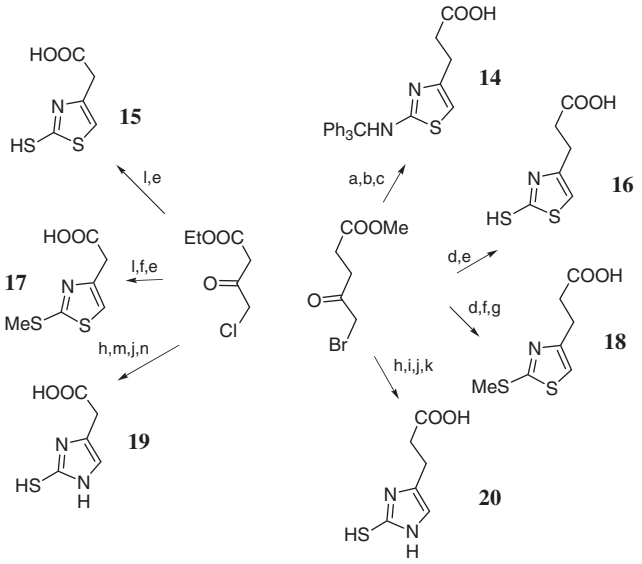

| | | | | |
|---|---|---|---|---|
| **1** | R = H | n = 1 | Het = |  |
| **1a** | R = $CHMe_2$ | | | |
| **2** | R = H | n = 2 | | |
| **2a** | R = $CHMe_2$ | | | |
| **3** | R = H | n = 1 | Het = |  |
| **3a** | R = $CHMe_2$ | | | |
| **4** | R = H | n = 2 | | |
| **4a** | R = $CHMe_2$ | | | |
| **5** | R = H | n = 1 | Het = |  |
| **5a** | R = $CHMe_2$ | | | |
| **6** | R = H | n = 2 | | |
| **6a** | R = $CHMe_2$ | | | |
| **7** | R = H | n = 1 | Het = |  |
| **7a** | R = $CHMe_2$ | | | |
| **8** | R = H | n = 2 | | |
| **8a** | R = $CHMe_2$ | | | |

**Chart 2.**




**Scheme 1.** Synthesis of the isopropyl ester of *N*-(2-*o*-tolyl-4-aminobenzoyl)-L-methionine. Reagents and conditions: (a) 2.5 N NaOH, methanol, room temperature, 12 h, 97%; (b) L-methionine isopropyl ester, HOBt, DCC, DMF, room temperature, 15 h, 94%; (c) $H_2$-Pd/C, 10% methanol, 4 h, 68%.




$12 + 13 \xrightarrow{o} 21 \xrightarrow{p} 1a \xrightarrow{q} 1$ $\quad 12 + 19 \xrightarrow{o} 5a \xrightarrow{q} 5$

$12 + 14 \xrightarrow{o} 22 \xrightarrow{p} 2a \xrightarrow{q} 2$ $\quad 12 + 20 \xrightarrow{o} 6a \xrightarrow{q} 6$

$12 + 15 \xrightarrow{o} 3a \xrightarrow{q} 3$ $\quad 12 + 17 \xrightarrow{o} 7a \xrightarrow{q} 7$

$12 + 16 \xrightarrow{o} 4a \xrightarrow{q} 4$ $\quad 12 + 18 \xrightarrow{o} 8a \xrightarrow{q} 8$

**Scheme 2.** Synthesis of the intermediate heteroarylacetic and heteroarylpropionic acids and their condensation with **12** to give the compounds **1**–**8**. Reagents and conditions: (a) thiourea, methanol, room temperature, 15 h, 78% [methyl 3-(2-amino-4-thiazolyl)propionate]; (b) trityl chloride, TEA, DCM, room temperature, 15 h, 72% ([methyl 3-(2-tritylamino-4-thiazolyl)propionate]); (c) 3 N NaOH, methanol, room temperature, 1 h, 85% (**14**); (d) ammonium dithiocarbamate, $H_2O$, room temperature 15 h and then reflux 2 h, crystallization from diisopropyl ether, 50% [methyl 3-(2-mercapto-4-thiazolyl)propionate]; (e) 2.5 N NaOH, 55 °C, 1 h, 91% (**16**), 81% (**15**) and 97% (**17**); (f) $CH_3I$, NaH, DME, THF, room temperature, 15 h, 95% [methyl 3-(2-methylthio-4-thiazolyl)propionate] and 93% [ethyl (2-methylthio-4-thiazolyl)acetate]; (g) 2.5 N NaOH, methanol, room temperature, 15 h, 95% (**18**); (h) $NaN_3$, $H_2O$, THF, 2 °C and then room temperature, 3 h (17 h for the chloroacetoacetate), 92% (methyl 5-azidolevulinate) and 95% (ethyl 4-azidoacetoacetate); (i) $H_2$ (4 bar), 10% Pd/C, TsOH, MeOH, room temperature, 4 h, crystallization from isopropanol, 83% (methyl 5-aminolevulinate tosylic acid salt); (j) KNCS, $H_2O$, reflux, 2 h, 54% [methyl 3-(2mercapto-4-imidazolyl)propionate] and 32% [ethyl (2-mercapto-4-imidazolyl)acetate]; (k) 4 N NaOH, 55 °C, 2 h, 72% (**20**); (l) ammonium dithiocarbamate, $H_2O$, room temperature 15 h and then reflux 2 h, crystallization from toluene, 46% [ethyl (2-mercapto-4-thiazolyl)acetate]; (m) $H_2$ (4 bar), 10% Pd(C), TsOH, EtOH, room temperature, 4 h, crystallization from isopropanol 28% (ethyl 4-aminoacetoacetate tosylic acid salt); (n) 3 N NaOH, MeOH, reflux, 1 h, crystallization from isopropanol, 47% (**19**); (o) DCC, HOBt, TEA, DMF, room temperature, 15 h, 35–50%;(p) HCOOH, DCM, room temperature, 2 h, 90%; (q) 1 N KOH, MeOH, room temperature, 15 h, quantitative yield.

**Table 1**
Inhibition of FTase activity and rat SMC proliferation

| Compound | FTase activity $IC_{50}$, (nM) | Compound | Cell proliferation $IC_{50}$, (μM) |
|---|---|---|---|
| **1** | 49 | **1a** | 107 |
| **2** | 390 | **2a** | n.a. |
| **3** | 538 | **3a** | 21 |
| **4** | 526 | **4a** | 25 |
| **5** | 122 | **5a** | 226 |
| **6** | n.a. | **6a** | 34 |
| **7** | n.a. | **7a** | n.a. |
| **8** | 415 | **8a** | n.a. |
| **FTI-276** | 9 | | |

n.a.: not active. The $IC_{50}$ values were determined by linear regression analysis of the logarithm of the concentration versus the percentage of the inhibitory effect.

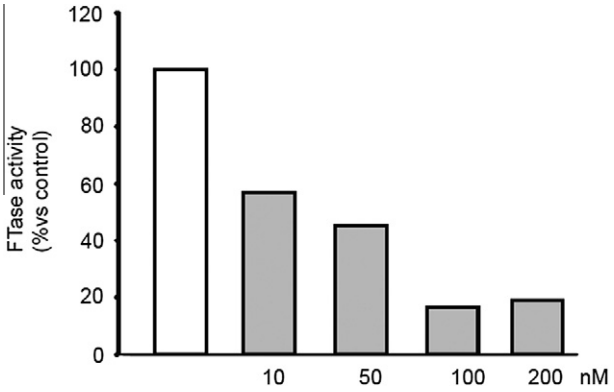



**Figure 1.** Concentration dependent inhibition of FTase activity by **1**.

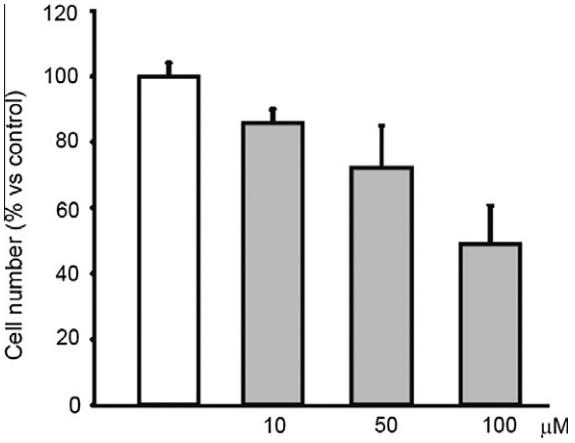



**Figure 2.** Concentration dependent effect of **1** on rat SMC proliferation.

To study whether the ability of compound **1** to interfere with FTase activity in vitro was maintained also in cultured cells, we investigated the Ras prenylation by SDS–PAGE from a total cell lysates of rat SMCs.[63] Cells were incubated for 72 h in the presence and in the absence of compound **1** at a concentration of 50 and 100 μM and in the presence of the 3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor simvastatin (2 μM) as positive control. The compound **1** interfered with Ras farnesylation in a concentration dependent manner as demonstrated by the appearance of a slower migrating band corresponding to the unprenylated form of the protein, also detected after incubation with simvastatin (Fig. 3).

Of the four designed replacements of 3-pyridyl with new heterocycles, that with 2-amino-4-thiazolyl gave the best result. In particular, compound **1**, which has a methylenecarbonylamino linker between aminothiazole and biphenyl core, exhibited a significant FTase inhibition both in vitro and in cells exerting antiproliferative effect. Comparison of FTase activity in vitro on the basis of the same fluorescent assay indicates that **1** is only little

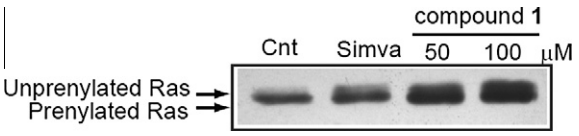



**Figure 3.** After 72 h incubation of the cells with indicated concentrations of compound **1** and 2 μM simvastatin (Simva), total cell lysates were prepared and Ras prenylation evaluated by Western blotting analysis with a specific antibody anti Ras (clone RAS10, Millipore). The slower migrating band represents the unprenylated form of Ras, while the faster migrating band is prenylated Ras.

less potent than FTI-276 (49 vs 9 nM $IC_{50}$) and, consequently, than **III**, which is reported equipotent to FTI-276 in FTase inhibition.[13] Similar basicity of 2-amino-4-thiazole to pyridine[64] and improved complexation properties[65] could account for such results and, at the same time, explain why, on the contrary, replacement with 2-mercapto-4-thiazolyl is detrimental. Compounds **3** and **4** show a modest FTase inhibition suggesting that their moderate antiproliferative activity is not due to interference with Ras prenylation. It is evident that the introduction of SH substituent instead of $NH_2$ into the 2 position of 4-thiazolyl is pejorative and that the macroscopic difference between 2-aminothiazole and 2-mercaptothiazole resides in the weak basicity of the former opposed to the weak acidity of the latter. Such a difference cannot be considered uninfluential, especially in molecules with a carboxylic head, and it is not accidental that the fragment mimicking cysteine in the known *CAAX* mimetics preferably has weakly basic or neutral character rather than acidic. Exemplary is the modest FTase inhibition of the *CAAX* mimetics with phenolic or thiophenolic groups in place of cysteine.[66,67] Moreover, the tautomeric thione-thiol equilibrium might further justify the remarkable decrease of activity.[68] Obviously, this does not mean that SH methylation is sufficient to restore the FTase activity, as demonstrated by compounds **7** and **8**, which are also modestly or totally inactive. Though 2-methylmercapto-4-thiazole doesn't substantially differ from unsubstituted 4-thiazole in basicity and complexation properties, compounds **7** and **8** are much less potent than thiazolic *CAAX* mimetics reported in literature. Therefore, the negative effect of the methylthio substituent on thiazole interaction should be of different nature from that of sulfhydryl.

The presence of SH substituent seems deleterious also in the imidazole derivatives **5** and **6**, though less than in the thiazole derivatives **3** and **4**, if we consider compound **5**. The use of imidazole to mimick cysteine in *CAAX* mimetics is widely exemplified and is generally associated with high FTase activity.[5,69,70] Here, **5** shows only a moderate FTase inhibition and a modest antiproliferative activity. The reasons, we think, could be analogous to those invoked comparing **3** with **1** and with literature thiazolyl derivatives.[13]

In conclusion, we have demonstrated that 2-aminothiazole can successfully replace cysteine in Ras *CAAX* mimetics and deserves to be considered, when designing non-thiol-FTis, an alternative to unsubstituted heterocycles, such as pyridine, imidazole and thiazole. On the contrary, the introduction of sulfhydryl into the 2 position of these two latter heterocycles seems to prejudice their ability of mimicking terminal cysteine.

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17. Compound **10**: DCM/water (pH 2) extraction; mp 166 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.26 (dd, $J$ = 8.5, 2.2 Hz, 1H), 8.14 (m, 2H), 7.27 (m, 3H), 7.07 (d, $J$ = 7.4, 1H), 2.09 (s, 3H).
18. Compound **11**: LC on silica gel (eluent: cyclohexane/EtOAc 70:30); $[\alpha]_D^{25} = +29.6$ ($c$ 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 8.27 (dd, $J$ = 8.5, 2.5 Hz, 1H), 8.05 (m, 2H), 7.30 (m, 3H), 7.17 (d, $J$ = 6.6 Hz, 1H), 6.03 (d, $J$ = 7.4 Hz, 1H), 4.94 (septet, $J$ = 6.05 Hz, 1H), 4.54 (m, 1H), 2.20 (s, 1H), 2.09 (s, 1H), 2.01 (s, 3H), 1.85 (m, 1H), 1.60 (m, 1H), 1.41 (s, 3H), 1.18 (m, 6H).
19. Compound **12**: LC on silica gel (eluent: cyclohexane/EtOAc 60:40); $[\alpha]_D^{25} = +18.7$ ($c$ 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.90 (m, 1H), 7.28 (m, 3H), 7.15 (d, $J$ = 7.9 Hz, 1H), 6.95 (d, $J$ = 8.5 Hz, 1H), 6.78 (s, 1H), 5.85 (m, 1H), 4.95 (septet, $J$ = 6.6 Hz, 1H), 4.55 (m, 1H), 2.20 (s, 2H), 2.04 (m, 6H), 1.80 (m, 1H), 1.57 (m, 1H), 1.20 (m, 6H).
20. Methyl 2-amino-4-thiazolylacetate: obtained in 91% yield as a white crystalline solid by treatment of 2-amino-4-thiazolylacetic acid with $SOCl_2$ in methanol for 12 h; mp 126 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.31 (s, 1H), 5.56 (br s, 2H), 3.77 (s, 3H), 3.58 (s, 2H).
21. Methyl 2-tritylamino-4-thiazolylacetate: obtained in 96% yield as a white crystalline solid by treatment of methyl 2-amino-4-thiazolylacetate with trityl chloride and TEA in DCM for 15 h and successive crystallization of the crude product from diisopropyl ether; mp 177 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.25–7.34 (m, 15H), 6.22 (s, 1H), 3.76 (s, 3H), 3.66 (s, 2H).
22. Compound **13**: obtained in 95% yield as a white solid by treatment of methyl 2-tritylamino-4-thiazolylacetate with 3 N NaOH in boiling methanol for 1 h; mp 152 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.25–7.34 (m, 15H), 6.05 (s, 1H), 3.58 (s, 2H).
23. Compound **21**: $^1$H-NMR (COCl3) $\delta$ 8.63 (br s, 1H), 7.90–7.82 (m, 1H), 7.41–7.06 (m, 21H), 6.41 (s, 1H), 6.02 (s, 1H), 5.88 (t, $J$ = 7.15 Hz, 1H), 4.99–4.91 (m, 1H), 4.57–4.50 (m, 1H), 2.88–2.84 (m, 2H), 2.65–2.61 (m, 2H), 2.05–1.97 (m, 6H), 1.84–1.70 (m, 2H), 1.56–1.49 (m, 2H), 1.21–1.17 (m, 6H).
24. Compound **1a**: $^1$H NMR (DMSO-$d_6$) $\delta$ 10.16 (s, 1H), 7.95 (d, $J$ = 7.43 Hz, 1H), 7.65 (dd, $J$ = 1.93 Hz, $J$ = 2.21 Hz, 1H), 7.51–7.44 (m, 2H), 7.19–7.10 (m, 4H), 6.29 (s, 1H), 4.90–4.97 (m, 1H), 4.28–4.24 (m, 1H), 3.47 (s, 2H), 2.39–2.15 (m, 2H), 2.12 (s, 3H), 2.05 (s, 3H), 1.89–1.69 (m, 2H), 1.21–1.16 (m, 6H).
25. Methyl 3-(2-amino-4-thaizolyl)propionate: mp 191.33 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.09 (br, 2H), 6.54 (s, 1H), 3.59 (s, 3H), 2.77–2.63 (m, 4H).
26. Methyl 3-(2-tritylamino-4-thaizolyl)propionate: mp 149.50 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.64 (br s, 1H), 7.39–7.29 (m, 15H), 5.93 (s, 1H), 3.68 (s, 3H), 2.96 (t, $J$ = 7.15 Hz, 2H), 2.76 (t, $J$ = 7.15 Hz, 2H).
27. Compound **14**: $^1$H NMR ($CDCl_3$) $\delta$ 10.38 (br s, 1H), 7.37–7.29 (m, 15H), 5.95 (s, 1H), 2.95–2.90 (m, 2H), 2.76–2.71 (m, 2H).
28. Compound **22**: $^1$H NMR ($CDCl_3$) $\delta$ 8.60 (br s, 1H), 7.95–7.87 (m, 1H), 7.44–7.11 (m, 21H), 6.47 (s, 1H), 6.02 (s, 1H), 5.84 (t, $J$ = 7.15 Hz, 1H), 4.97–4.92 (m, 1H), 4.57–4.50 (m, 1H), 2.88–2.84 (m, 2H), 2.65–2.61 (m, 2H), 2.05–1.97 (m, 6H), 1.86–1.78 (m, 2H), 1.58–1.51 (m, 2H), 1.21–1.17 (m, 6H).
29. Compound **2a**: $[\alpha]_D^{25} = +18.3$ ($c$ 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 8.79 (br s, 1H), 7.96–7.87 (m, 1H), 7.51–7.13 (m, 6H), 6.18 (s, 1H), 5.87 (t, $J$ = 7.15 Hz, 1H), 5.20–5.05 (br s, 2H), 4.99–4.90 (m, 1H), 4.59–4.48 (m, 1H), 2.93–2.89 (m, 2H), 2.73–2.69 (m, 2H), 2.06–1.94 (m, 6 H), 1.86–1.74 (m, 2H), 1.60–1.52 (m, 2H), 1.21–1.16 (m, 6H).
30. Ethyl 2-mercapto-4-thiazolylacetate: mp 143 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.46 (s, 1H), 4.23 (q, $J$ = 3.3 Hz, 2H), 3.58 (s, 2H), 1.29 (t, $J$ = 3.3 Hz, 3H).
31. Compound **15**: mp 166 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 6.70 (s, 1H), 3.52 (s, 2H), 3.29 (s, 1H).
32. Methyl 3-(2-mercapto-4-thiazolyl)propionate: mp 127 °C; $^1$H NMR ($CDCl_3$) $\delta$ 11.80 (s, 1H), 3.71 (s, 3H), 2.84 (t, $J$ = 6.6 Hz, 2H), 2.66 (t, $J$ = 6.6 Hz, 2H).
33. Compound **16**: mp 192 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 12.26 (s, 1H), 6.58 (s, 1H), 3.35 (s, 1H), 2.70 (m, 2H), 2.51 (m, 2H); $^1$H NMR ($D_2O$) $\delta$ 6.57 (s, 1H), 2.78 (t, $J$ = 7.2 Hz, 2H), 2.62 (t, $J$ = 7.2 Hz, 2H).
34. Compound **3a**: LC on silica gel (eluent: cyclohexane/EtOAc 50:50); $[\alpha]_D^{25} = +9.9$ ($c$ 1, $CHCl_3$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.32 (s, 1H), 8.08 (d, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 1.9 Hz, 1H), 7.52–7.42 (m, 2H), 7.16–7.05 (m, 4H), 6.73 (s, 1H), 4.84 (septet, $J$ = 6.1 Hz, 1H), 4.19–4.15 (m, 1H), 3.65 (s, 2H), 2.22–1.98 (m, 5H), 1.94 (s, 3H), 1.82–1.68 (m, 2H), 1.18–1.10 (m, 6H).
35. Compound **4a**: LC on silica gel (eluent: cyclohexane/EtOAc 50:50); $[\alpha]_D^{25} = +12.1$ ($c$ 1, $CHCl_3$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.16 (s, 1H), 8.04 (d, $J$ = 6.9 Hz, 1H), 7.60 (dd, $J$ = 8.5, 1.9 Hz, 1H), 7.54–7.40 (m, 2H), 7.18–7.02 (m, 4H), 6.54 (s, 1H), 4.84 (septet, $J$ = 6.3 Hz, 1H), 4.21–4.17 (m, 1H), 2.78–2.68 (m, 2H), 2.67–2.60 (m, 2H), 2.16–1.85 (m, 8H), 1.80–1.62 (m, 2H), 1.18–1.05 (m, 6H).
36. Ethyl 2-methylmercapto-4-thiazolyl acetate: $^1$H NMR ($CDCl_3$) $\delta$ 7.08 (s, 1H), 4.18 (q, $J$ = 3.9 Hz, 2H), 3.78 (s, 2H), 2.68 (s, 3H), 1.24 (t, $J$ = 3.9 Hz, 3H).
37. Compound **17**: mp 122 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.34 (s, 1H), 3.65 (s, 2H), 2.64 (s, 3H).

38. Methyl 3-(2-methylmercapto-4-thiazolyl)propionate: $^1$H NMR ($CDCl_3$) $\delta$ 6.83 (s, 1H), 3.67 (s, 3H), 3.03 (t, $J$ = 7.7 Hz, 2H), 2.73 (t, $J$ = 7.7 Hz, 2H), 2.66 (s, 3H).
39. Compound **18**: mp 97 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 12.14 (br s, 1H), 7.18 (s, 1H), 2.85 (t, $J$ = 7.4 Hz, 2H), 2.63 (s, 3H), 2.56 (t, $J$ = 7.4 Hz, 2H).
40. Compound **7a**: LC on silica gel (eluent: cyclohexane/EtOAc 50:50); $[\alpha]_D^{25} = +12.4$ ($c$ 1.2, $CHCl_3$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.35 (s, 1H), 8.08 (d, $J$ = 6.7 Hz, 1H), 7.62 (m, 1H), 7.49 (m, 2H), 7.36 (m, 1H), 7.15 (m, 4H), 4.84 (septet, $J$ = 6.3 Hz, 1H), 4.18 (m, 1H), 3.76 (s, 2H), 2.63 (s, 3H), 2.04 (m, 8H), 1.75 (m, 2H), 1.14 (m, 6H).
41. Compound **8a**: LC on silica gel (eluent: cyclohexane/EtOAc 60:40); $[\alpha]_D^{25} = +14.6$ ($c$ 1.2, $CHCl_3$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.13 (s, 1H), 8.03 (d, $J$ = 6.9 Hz, 1H), 7.61 (d, $J$ = 6.9 Hz, 1H), 7.46 (m, 2H), 7.15 (m, 5H), 4.83 (septet, $J$ = 6.3 Hz, 1H), 4.18 (m, 1H), 2.95 (t, $J$ = 7.2 Hz, 2H), 2.66 (t, $J$ = 7.2 Hz, 2H), 2.62 (s, 3H), 2.07 (m, 8H), 1.74 (m, 2H), 1.15 (m, 6H).
42. Ethyl 4-azidoacetoacetate: $^1$H NMR (DMSO-$d_6$) $\delta$ 4.26 (s, 2H), 4.07 (q, $J$ = 3.6 Hz, 2H), 3.60 (s, 2H), 1.17 (t, $J$ = 3.6 Hz, 3H).
43. Methyl 5-azidolevulinate: $^1$H NMR ($CDCl_3$) $\delta$ 4.00 (s, 2H), 3.64 (s, 3H), 2.69(m, 2H), 2.64 (m, 2H).
44. Ethyl 4-aminoacetoacetate tosylate: mp 111 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.07 (br s, 3H), 7.46 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.0 Hz, 2H), 4.10 (q, $J$ = 7.15 Hz, 2H), 3.98 (s, 2H), 3.70 (s, 2H), 2.15 (s, 3H), 1.10 (t, $J$ = 7.15 Hz, 3H).
45. Methyl 5-aminolevulinate tosylate: mp 130 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.99 (s, 3H), 7.46 (d, $J$ = 8.0 Hz, 2H), 7.09 (d, $J$ = 8.0 Hz, 2H), 3.96 (d, $J$ = 4.4 Hz, 2H), 3.58 (s, 3H), 2.78 (t, $J$ = 6.6 Hz, 2H), 2.50 (t, $J$ = 6.6 Hz, 2H).
46. Ethyl (2-mercapto-4-imidazolyl)acetate: mp 152 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.86 (s, 1H), 11.75 (s, 1H), 6.63 (s, 1H), 4.07 (q, $J$ = 7.2 Hz, 2H), 3.47 (s, 2H), 1.17 (t, $J$ = 7.2 Hz, 3H).
47. Methyl 3-(2-mercapto-4-imidazolyl)propionate: mp 161 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.85 (s, 1H), 11.64 (s, 1H), 6.51 (s, 1H), 3.57 (s, 3H), 2.58 (s, 4 H); $^1$H NMR ($D_2O$) $\delta$ 6.57 (s, 1H), 3.56 (s, 3H), 2.70 (m, 2H), 2.57 (m, 2H).
48. Compound **19**: mp 177 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.82 (s, 1H), 11.70 (s, 1H), 6.60 (s, 1H), 3.38 (s, 2H).
49. Compound **20**: mp 203 °C; $^1$H NMR ($D_2O$) $\delta$ 6.60 (s, 1H), 2.70 (t, $J$ = 7.4 Hz, 2H), 2.58 (t, $J$ = 7.4 Hz, 2H).
50. Compound **5a**: LC on silica gel (eluent: DCM/MeOH 95:5); $[\alpha]_D^{25} = +4.7$ ($c$ 1.3, $CHCl_3$); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.87 (s, 1H), 11.73 (s, 1H), 10.23 (s, 1H), 8.07 (d, $J$ = 7.15 Hz, 1H), 7.61 (dd, $J$ = 5.5, 3.3 Hz, 1H), 7.45 (m, 2H), 7.14 (m, 4H), 6.64 (s, 1H), 4.85 (septet, $J$ = 3.6 Hz, 1H), 4.19 (m, 1H), 3.51 (s, 2H), 2.12 (m, 4H), 1.94 (s, 3H), 1.75 (m, 2H), 1.21 (s, 1H), 1.14 (m, 6H).
51. Compounud **6a**: LC on silica gel (eluent: DCM/MeOH 95:5); $[\alpha]_D^{25} = +0.55$ ($c$ 1, acetone); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.13 (s, 1H), 8.03 (d, $J$ = 6.88 Hz, 1H), 7.61 (d, $J$ = 6.90 Hz, 1H), 7.46 (m, 2H), 7.15 (m, 5H), 4.83 (septet, $J$ = 6.33 Hz, 1H), 4.18 (m, 1H), 2.95 (t, $J$ = 7.15 Hz, 2H), 2.66 (t, $J$ = 7.15 Hz, 2H), 2.62 (s, 3H), 2.07 (m, 8H), 1.74 (m, 2H), 1.15 (m, 6H).
52. Compound **1**: $[\alpha]_D^{25} = -8.9$ ($c$ 0.5, MeOH-$d_6$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.18 (s, 1H), 7.95–7.82 (m, 1H), 7.65–7.59 (m, 1H), 7.51–7.48 (m, 2H), 7.21–7.10 (m, 4H), 6.90 (s, 2H), 6.29 (s, 1H), 4.18–4.14 (m, 1H), 3.45 (s, 2H), 2.22–1.59 (m, 10H).
53. Compound **2**: $[\alpha]_D^{25} = -4.4$ ($c$ 0.5, MeOH-$d_6$); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.13 (br s, 1H), 7.96–7.85 (m, 1H), 7.63–7.60 (m, 1H), 7.49–7.44 (m, 2H), 7.18–7.05 (m, 4H), 6.81 (s, 2H), 6.13 (s, 1H), 4.21–4.15 (m, 1H), 2.69–2.60 (m, 4H), 2.26–1.94 (m, 6H), 1.86–1.60 (m, 4H).
54. Compound **3**: $[\alpha]_D^{25} = -17.9$ ($c$ 0.5, 1 M NaOH); $^1$H NMR (DMSO-$d_6$ 100 °C) $\delta$ 10.35 (s, 1H), 7.62–7.51 (m, 2H), 7.42 (s, 1H), 7.19–7.03 (m, 4H), 6.63–6.58 (m, 2H), 4.14 (m, 1H), 3.60 (s, 2H), 2.21–1.98 (m, 6H), 1.82–1.58 (m, 4H).
55. Compound **4**: $[\alpha]_D^{25} = -10.7$ ($c$ 0.5, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.21 (s, 1H), 7.97–7.85 (m, 1H), 7.60–7.52 (m, 1H), 7.50–7.39 (m, 1H), 7.22–7.01 (m, 4H), 6.54 (s, 1H), 6.22 (br s, 1H), 4.21–4.12 (m, 1H), 2.81–2.62 (m, 4H), 2.16–1.63 (m, 10H).
56. Compound **5**: $[\alpha]_D^{25} = -7.0$ ($c$ 0.5, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.89 (br s, 1H), 11.74 (br s 1H), 10.28 (s, 1H), 7.81–7.77 (m, 1H), 7.60–7.58 (m, 1H), 7.51–7.49 (m, 2H), 7.22–7.01 (m, 4 H), 6.60 (s, 1H), 4.18–4.10 (m, 1H), 3.76 (s, 2H), 2.20–1.88 (m, 6H), 1.76–1.60 (m, 4H).
57. Compound **6**: $[\alpha]_D^{25} = +0.5$ ($c$ 0.5, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.88 (br s, 0.5H), 11.64 (0.5H), 10.15 (s, 1H), 7.59–7.63 (m, 4H), 7.22–7.05 (m, 4H), 6.49 (s, 1H), 4.10–3.98 (m, 1H), 2.66–2.58 (m, 4H), 2.20–1.88(m, 6H), 1.76–1.58 (m, 4H)
58. Compound **7**: $[\alpha]_D^{25} = -9.3$ ($c$ 0.5, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.38 (s, 1H), 7.78–7.68 (br s, 1H), 7.59–7.51 (m, 1H), 7.48–7.41 (m, 1H), 7.36 (s, 1H), 7.18–7.03 (m, 4H), 4.09 (m, 1H), 3.76 (s, 2H), 2.63 (s, 3H), 2.20–1.98 (m, 6H), 1.85–1.58 (m, 4H).
59. Compound **8**: $[\alpha]_D^{25} = -2.6$ ($c$ 0.25, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.17 (s, 1H), 8.27 (s, 1H), 7.60–7.57 (m, 1H), 7.50–7.44 (m, 2H), 7.33 (br s, 1H), 7.18–7.12 (m, 4H), 3.94–3.85 (m, 1H), 2.96–2.91 (m, 2H), 2.71–2.63 (m, 2H), 2.62 (s, 3H), 2.10–1.91 (m, 6H), 1.70–1.58 (m, 4H).
60. *In vitro FTase assay*: In vitro $IC_{50}$ data were determined against FTase using an in vitro Fluorescence Assay as previously described with minor modifications (Krzysiak, A. J.; Scott, S. A.; Hicks, K. A.; Fierke, C. A.; Gibbs, R. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5548). In brief, the substrates used were Dansyl-Gly-Cys-Val-Leu-Ser-OH peptide (Calbiochem) and farnesyl-pyrophosphate (FPP) (SIGMA). Each reaction mixture contained 0.9 μl of Dansyl peptide (final concentration 3 μM), 1.3 μl of FPP (final concentration 10 μM) in 300 μl of Assay buffer (MTT 5.8 mM, $MgCl_2$ 12 mM, $ZnCl_2$ 12 mM, Tris pH 7.5 52 mM) aliquoted in a 96 wells plate (200 μl each well). The reaction was started by adding of rat recombinant FTase (7.5 μg per reaction, Calbiochem) and conducted in the presence or absence of tested compounds and the FTase inhibitor FTI-286 as a reference. The fluorescent signal was recorder by using the Fluoroskan Ascent Microplate Fluorometer (Labsystem) every 15 s for 5 min. The $IC_{50}$ value was calculated from the fluorescent signal at the steady state.
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62. *Cell proliferation assay*: Rat aortic SMCs were seeded at a density of $2 \times 10^5$ cells/Petri dish (35 mm), and incubated with DMEM supplemented with 10% FCS. Twenty-four hours later, the medium was changed to one containing 0.4% FCS to stop cell growth, and the cultures were incubated for 72 h. At this time (time 0), the medium was replaced with one containing 10% FCS in the presence or absence of known concentrations of the tested compounds, and the incubation was continued for a further 72 h at 37 °C. Cell proliferation was evaluated by cell counting after trypsinization of the monolayers with use of a Coulter Counter model ZM (Corsini, A.; Mazzotti, M.; Raiteri, M; Soma, M. R.; Gabbiani, G.; Fumagalli, R.; Paoletti, R. *Atherosclerosis* **1993**, *101*, 117). All the compounds were dissolved in DMSO prior to dilution, being the final concentration of DMSO at a maximum of 0.5%. The concentration of compounds required to inhibit 50% of cell proliferation ($IC_{50}$) was calculated by linear regression analysis of the logarithm of the concentration versus logit.
63. *Ras prenylation assay*: Rat SMCs were seeded at a density of $4 \times 10^5$ cells/Petri dish (60 mm) and incubated under the same experimental conditions described for the cell proliferation assay. At the end of the 72 h of incubation with compound **1** and simvastatin, cells were washed twice with cold phosphate buffer saline (PBS) and lysed in 200 μl buffer (50 mM Tris HCl, pH 7.5, 150 mM NaCl, 0.5% NP-40, 1 mM PMSF, 1 mM $NaVO_4$, 1 μg/ml Aprotinin, 1 μg/ml Leupeptin and 1 μg/ml Pepstatin) for 30 min on ice. Cell lysates were cleared by centrifugation at 15,000*g* for 10 min, and protein concentrations were determined using the BCA protein assay (Pierce). Lysates were separated by SDS–PAGE under reducing conditions, transferred to Immobilon PVDF (Millipore) and subsequently immunoblotted with anti Ras antibody (Clone RAS10, Millipore), prior to visualization by enhanced chemiluminescence (ECL, Amersham Corp.) (Ferri, N.; Colombo, G.; Ferrandi, C.; Raines, E. W.; Levkau, B.; Corsini, A. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 1043).
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