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Communications to the Editor

A New Class of Highly Potent Farnesyl Diphosphate-Competitive Inhibitors of Farnesyltransferase

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Mutation of *ras* genes is believed to be involved in 20% of human cancers. In particular, mutant *ras* genes were found in 50% of colon and 90% of pancreas cancers.[1] The *ras* protein (Ras) is synthesized as a cytosolic precursor and localized to the plasma membrane after posttranslational modifications. The key modification required for cell-transforming activity is farnesylation of Ras. This prenylation is catalyzed by the enzyme, farnesyl-protein transferase (FTase).[2] Therefore, inhibitors of FTase should serve to block cell-transforming activity by inhibiting the action of the mutated *ras* protein, thus acting as potential anticancer agents.[3]

FTase catalyzes the farnesylation of a cysteine residue of the C-terminal CaaX sequence in Ras proteins utilizing farnesyl diphosphate (FPP).[2,4] Two types of synthetic FTase inhibitors have been designed on the basis of the structure of the two substrates of the reaction, farnesyl diphosphate mimics and Ras CaaX tetrapeptide mimics. CaaX analogues were demonstrated to be potent inhibitors of FTase.[5] Although some of these analogues were found to be effective in suppressing tumor growth both in cells and in animals (nude mice transplanted with *ras*-transformed cells and oncomice),[6] no compounds of clinical therapeutic value in humans have yet been disclosed. Several groups have described

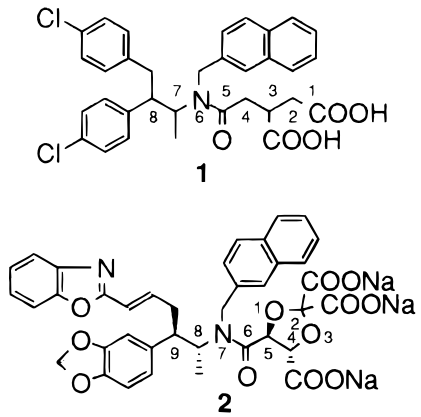

Figure 1. Structures of lead compound **1** and the potent FTase inhibitor **2**.

substrate analogues of FPP to be potent inhibitors of FTase,[7] and other groups have reported the discovery from natural sources of potent inhibitors of FTase[7,8] that were competitive with respect to FPP. However, these compounds, the potency of which was rather low compared with that of the CaaX mimic inhibitors, are not suitable for evaluation in vivo.[5,9]

We recently reported on a new structural class of squalene synthase (SS) inhibitors.[10] SS catalyzes the reductive dimerization of FPP to form squalene, and our SS inhibitors are considered to mimic the structure of the substrate, FPP. Since FTase and SS use the same substrate, we supposed that some of our SS inhibitors might be effective inhibitors of FTase. For this reason, we sought a lead compound for designing FTase inhibitors from among the compounds synthesized in our SS inhibitor program. We found that J-104,133 (**1**, Figure 1) potently inhibited rat FTase:[11] the IC_{50} value of **1** (the concentration needed to inhibit enzyme activity by 50%) determined in the presence of 0.6 μM FPP against rat FTase was 3.4 μM. Interestingly, among our SS inhibitors **1** was a very weak inhibitor of human and rat SS[12] (IC_{50} = 0.75 μM), and potent SS inhibitors were not necessarily active against FTase. However, as predicted from this relatively weak potency, **1** was inactive both in cells and in vivo. We optimized this compound

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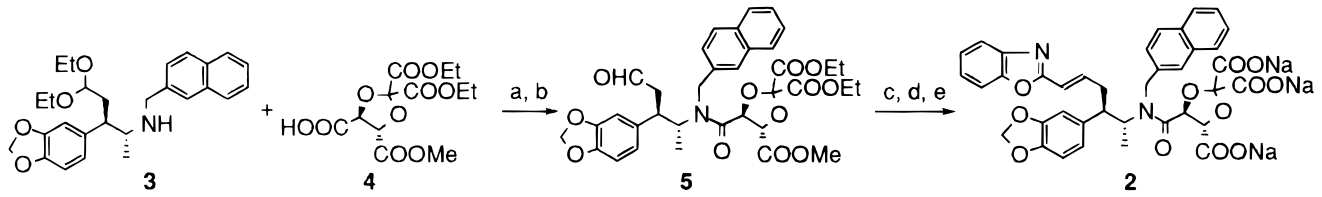
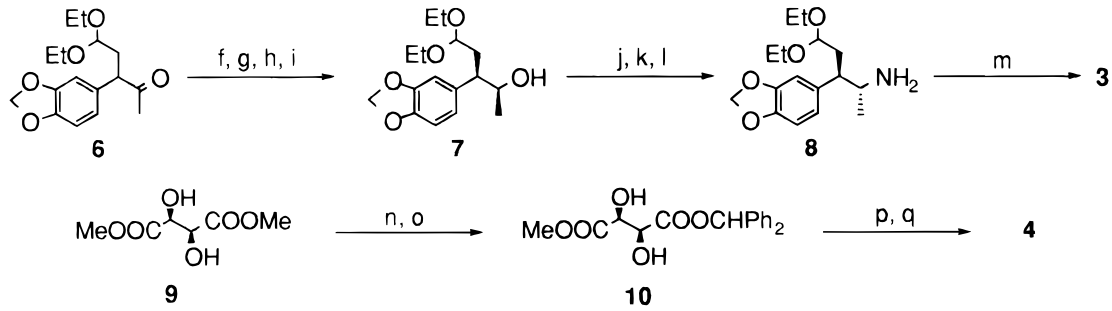
Scheme 1[a]



[a] (a) DMC, TEA; (b) HCl, aqueous THF; (c) 2-benzoxazolylmethyl (triphenyl)phosphonium chloride, NaH; (d) L:iOH, then HCl; (e) MeONa.

Scheme 2[a]



[a] (f) L-Selectride; (g) (R)-PhCH(OMe)COOH, EDCl, DMAP; (h) separation by MPLC; (i) NaOH; (j) MsCl, TEA; (k) NaN_3; (l) PPh_3, H_2O; (m) 2-naphthalenecarbaldehyde, $NaBH_4$; (n) NaOH; (o) Ph_2CN_2; (p) NaH, $Br_2C(COOEt)_2$; (q) 10% Pd/C, H_2.

through chemical modifications and discovered J-104,-134 (**2**), which was about 700 times more potent than **1** and worked both in cells and in vivo. This article describes the discovery and biological profile of **2** and discusses its basic structural requirements for inhibitory activity against FTase.

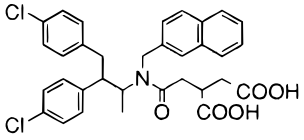
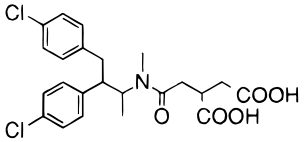
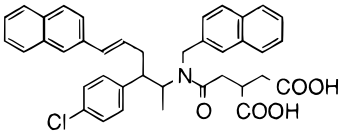
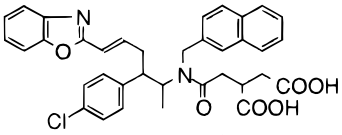
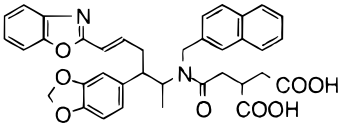
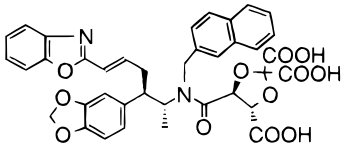
Chemistry. Compound **2**, trisodium (4*S*,5*S*)-5-[*N*-[(1*R*,2*R*,4*E*)-5-(2-bezoxazolyl)-1-methyl-2-[3,4-(methylenedioxy)phenyl]-4-pentenyl]-*N*-(2-naphthylmethyl)carbamoyl]-1,3-dioxolane-2,2,4-tricarboxylate, contains four asymmetric centers in the molecule. The stereochemistry of this compound is essentially bound to its biological activity. Therefore, synthesis of the enantiomerically pure compound was required. Compound **2** and its related derivatives were generally prepared according to the same methodology as that used for the synthesis of SS inhibitors.[10,13] Schemes 1 and 2 outline the syntheses of **2** and its key intermediates. Compound **2** was prepared by coupling reaction of a chiral amine **3** and a chiral carboxylic acid **4**. The introduction of a benzoxazolyl group into the deprotected amide **5** was performed by Wittig reaction.[14,15]

The synthesis of **3** began with the racemic ketone **6**, which was prepared by alkylation of 3,4-(methylenedioxy)phenylacetone with iodoacetaldehyde diethyl acetal.[14] The ketone **6** was diastereoselectively reduced with L-Selectride (Aldrich) to an alcohol having a (2*R**,3*S**) configuration,[17] and the racemic alcohol was esterified with (*R*)-α-methoxyphenylacetic acid in the presence of EDCI and (dimethylamino)pyridine. The obtained diastereomeric ester was separated by medium-pressure liquid chromatography, and the separated ester was hydrolyzed under alkaline conditions to generate the (2*S*,3*R*)-alcohol **7**. The assignment of the stereochemistry of **7** was performed at the ester stage by Mosher method[18] using NMR. The optically active alcohol **7** was converted to the corresponding amine **8** with complete inversion of configuration according to the reported procedure.[10,16] The obtained (2*R*,3*R*)-amine **8** was reacted with 2-naphthalenecarbaldehyde in MeOH and then reduced with $NaBH_4$ to afford the aforementioned amine **3**. The enantiomer of amine **8** having a (2*S*,3*S*) configuration was prepared in the same manner. The carboxylic acid **4** was synthesized starting from D-tartaric acid using a procedure devised from a known method.[19] For example, benzhydryl methyl D-tartrate **10**, which was obtained by partial hydrolysis of dimethyl tartrate **9**, followed by esterification with diphenyldiazomethane, was reacted with diethyl dibromomalonate in the presence of NaH. The benzhydryl ester group of the product was then removed by catalytic hydrogenation over Pd−C to give **4**. Other stereoisomers of **4** were also prepared according to a similar procedure using L- and *meso*-tartaric acid.

The coupling reaction of the amine **3** and the carboxylic acid **4** was conducted in the presence of 2-chloro-1,3-dimethylimidazolium chloride (DMC), followed by acid hydrolysis to give aldehyde **5**. The introduction of a benzoxazolyl group into **5** was accomplished by Wittig reaction[14] with (2-benzoxazolylmethyl)(triphenyl)phosphonium chloride[15] in the presence of NaH. Subsequent hydrolysis of the coupling product with LiOH afforded **2**. The trisodium salt of **2**, which was used in animal studies, was obtained as a white powder by treating **2** with MeONa in MeOH. Other stereoisomers of **2** and its related analogues were prepared using a method similar to that described above.

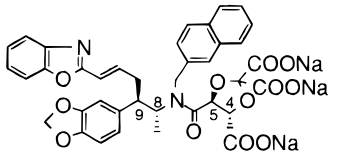
Results and Discussion. Compound **1**, depicted in Figure 1, has three chiral centers and is an equimolar mixture of the four stereoisomers: (3*R*,7*R*,8*R*), (3*R*,7*S*,-8*S*), (3*S*,7*R*,8*R*), and (3*S*,7*S*,8*S*). To determine the effect of stereochemistry on FTase inhibition, we compared the activity of **1** with that of its diasteromeric mixture compound, which has a reversed configuration (7*R**,8*S**) at the 7- and 8-positions. The compound as a stereoisomeric mixture had very little potency (6% inhibition at 1 μM), indicating that the (7*R**,8*R**) configuration was essential for biological activity. The optimization

Table 1. Inhibitory Activity of **2** and Related Compounds against Rat FTase

No.		IC_{50} for FTase (nM)
1		3400
11		>10,000
12		51
13		28
14		23
2		5.0

of **1** was carried out by chemical derivations in which we divided the molecule into four different sections (R^1–R^4) and modified each part by introducing new substituent(s) or by replacing the part with a counterpart. All of the synthesized compounds were evaluated for their ability to inhibit FTase obtained from rat brain.[20] We found that the inhibitory activity of the compounds was strictly linked to the structural features that are different from those of the SS inhibitors.[10] Of the compounds tested to date, **2** appears to be the best inhibitor of FTase. Table 1 lists the IC_{50} values of **2** and its related compounds. The most noticeable difference in structure between the SS inhibitors and the FTase inhibitors is the presence of a naphthylmethyl substituent on the nitrogen atom in the amide bond of the FTase inhibitors (R^3). When this naphthalene ring was replaced with a hydrogen atom, the resulting compound (*N*-methyl analogue) **11** failed to inhibit FTase even at 10 μM, but exhibited activity against SS (63% inhibition at 3 μM). Other findings on the structure–activity relationships (SARs) of this series of compounds are as follows: the replacement of *p*-chlorobenzyl moiety (R^1) by a 3-(2-naphthyl)-2-propenyl group enhanced potency to a great extent (in particular, 3-(2-bezoxazolyl)-2-propenyl was the best substitute for the *p*-chlorobenzyl group); the *p*-chlorophenyl part (R^2) was favorably replaced by a 3,4-(methylenedioxy)phenyl group; and a

Table 2. Inhibitory Activity of Stereoisomers of **2** against Rat FTase



		IC_{50}	
no.	configuration	FTase (nM)	RASPRO (μM)[a]
2	4*S*, 5*S*, 8*R*, 9*R*	5.0	4.3
15	4*S*, 5*S*, 8*S*, 9*S*	6.0	8.8
16	4*R*, 5*R*, 8*R*, 9*R*	3.9	10
17	4*R*, 5*R*, 8*S*, 9*S*	8.0	17
18	4*R**, 5*S**, 8*R*, 9*R*	3.9	1.2
19	4*S**, 5*R**, 8*R*, 9*R*	7.2	42%[b]

[a] RAS processing in H*ras*-transformed NIH-3T3 cells. [b] Percent inhibition at 15 μM.

Table 3. Compound 2 Competes with FPP for Binding to FTase

concentration (μM)		
FPP	Ras Peptide	IC_{50} for FTase (nM)
0.6	0.36	5.6
6.0	0.36	45
0.6	3.6	7.2

2,2,4-tricarboxy-1,3-dioxolan-5-yl group was the best carboxylic part (R^4) among a variety of carboxyl groups tested to date. The SARs of FTase inhibitors will be reported in detail in due course.

With respect to stereoisomers of **2**, we prepared all of the isomers with a (8*R*,9*R*) configuration and two isomers with a (8*S*,9*S*) configuration and tested them for inhibition of FTase and Ras processing (farnesylation) in activated H*ras*-transformed NIH/3T3 cells.[20] In the enzyme assay, all of the tested stereoisomers exhibited unexpectedly very good inhibitory activity with almost equal potency, as shown in Table 2. The IC_{50} values of **2** were dependent on the concentration of FPP and were not dependent on the concentration of the Ras terminus peptide (Table 3). Therefore, compound **2** inhibits FTase in a competitive manner with respect to FPP. These stereoisomers were assayed for the inhibition of Ras processing in whole cells. Of the compounds, **2** and J-104,135 (**18**) potently inhibited Ras processing. The mechanism by which these compounds were absorbed into the cells is unknown. It was surprising that such highly charged tricarboxylic compounds worked well in cells. We selected these two compounds for further evaluation because of their rather strong activity in cells.

The in vivo antitumor activities of **2** and **18** were determined in nude mice transplanted with activated H*ras*-transformed NIH/3T3 cells according to the previously reported procedure.[6, 20]

Female nude mice, 8–12 weeks old, were injected with the NIH/3T3 cells sc on day 0. **2** and **18** were each administered ip at 40 and 80 mg/kg once daily for 6 days beginning on day 1. The tumors were excised and weighed 7 days after the cells were injected. The inhibition of tumor growth by **2** and **18** was dose-dependent; the percent inhibition at 40 and 80 mg/kg was 37% and 79% for **2** and 28% and 52% for **18**. In

this experiment, no evidence of weight loss, diarrhea, or anorexia was noted.

The rather weak potency of **18** versus **2** seems to be due to low plasma levels of the intact drug in animals receiving **18** (data not shown). The suppression of tumor growth observed in the above-mentioned study appeared to result from the inhibition of FTase because we noted inhibition of Ras processing in the remaining tumor in animals receiving **2**.[20] The behavior of **2** and **18** in the nude mouse xenograft model is very intriguing because it is the first demonstration that FPP-competitive FTase inhibitors suppress tumor growth in vivo.

We have developed a novel class of FPP-competitive FTase inhibitors, **2** and its related analogues, by chemical optimization of **1**, which was discovered in the course of study of other FPP-mimic enzyme inhibitors (squalene synthase inhibitors). Compound **2** showed strong activity against rat FTase, which was comparable to that of the known CaaX-mimic FTase inhibitors. Compound **2** potently inhibited the processing (farnesylation) of Ras protein in *ras*-activated tumor cells, resulting in suppression of the growth of the cells. This compound significantly inhibited tumor growth in vivo in a nude mouse xenograft model. In addition, **2** weakly or poorly inhibited other enzymes that require prenyldiphosphate as a substrate, suggesting a large selectivity for FTase inhibition (IC_{50} = 1.3 μM against rat GGPTaseI,[21] no inhibition at 10 μM against SS). It showed no toxicity at 100 μM when assessed in NIH/3T3 cells. Therefore, **2** and its related analogues are considered to be a promising class of potential cancer chemotherapy agents.

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Supporting Information Available: Experimental data for 2 and 18 (1 page). Ordering information is given on any current masthead page.

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