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Synthesis of 1H-pyridin-2-one derivatives as potent and selective farnesyltransferase inhibitors

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Abstract—Two novel series of potent and selective FTase inhibitors have been synthesized using structure-based design. Medicinal chemistry efforts led to the discovery of compound **4e** with potent cellular activity and good oral bioavailability in dog. A synthetic route toward novel heterocycles 1,5-dimethyl-6-oxo-4-aryl-1,6-dihydro-pyridine-2-carbonitrile was established. The structure of compound **5c** was confirmed by X-ray crystallography.

Mutated Ras proteins are found in over 30% of human cancers. To participate in the transduction of extracellular mitogenic signals to the nucleus, Ras proteins need to be S-farnesylated by farnesyltransferase (FTase). It has been shown that inhibitors of FTase can stop protein farnesylation and suppress the growth of Ras-dependent tumor cells both in cell culture and in rodents. Emerging evidence suggests that Ras may not be the only substrate of FTase associated with oncogenesis. While the exact mechanism of FTase inhibitors remains elusive, FTase inhibitors are promising agents in cancer therapy due to their excellent efficacy and low systemic toxicity in pre-clinical animal models. Extensive drug discovery efforts have resulted in the discovery of several potent FTase inhibitors that have shown efficacy as antitumor agents in human clinical trials.[1]

One of the three protein-isoprenyltransferases identified in mammalian cells is geranylgeranyltransferase type I (GGTase-I). Both FTase and GGTase-I are heterodimeric proteins that share a common alpha subunit. Furthermore, FTase and GGTase-I have similar protein substrate requirements. It has been found that a far greater number of proteins are the substrates of GGTase-I while only about 50 mammalian proteins are post-translationally modified with farnesyl group.[2] Thus, a FTase inhibitor must be selective for FTase over the closely related enzyme GGTase-I to avoid severe, nonspecific side effects.[3]

In our continuing search for novel FTase inhibitors, compound **1** was identified as a potent and selective FTase inhibitor (Fig. 1).[4] Further modification reveals that the A-ring of compound **1** can be replaced with a 1-methyl-3-cyano-5-aryl-pyridin-2-one moiety exemplified by compound **2**.[5] The pyridone-containing compound **2** shows excellent enzymatic activity against FTase, potent cellular activity, and good selectivity for FTase over GGTase-I.

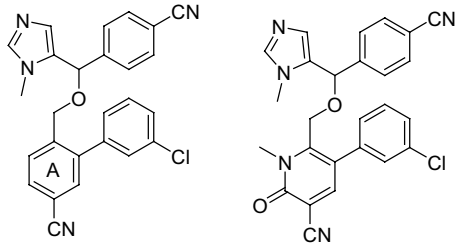

Figure 1.

Keywords: Farnesyltransferase; FTase inhibitor; 1H-pyridin-2-one derivative.
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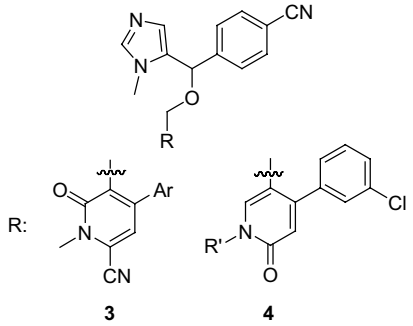


Figure 2.

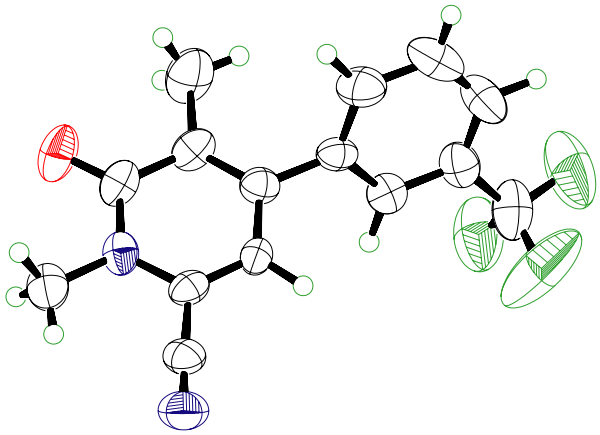
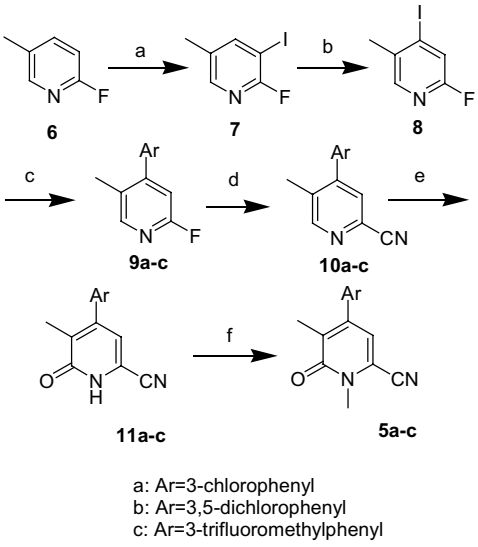
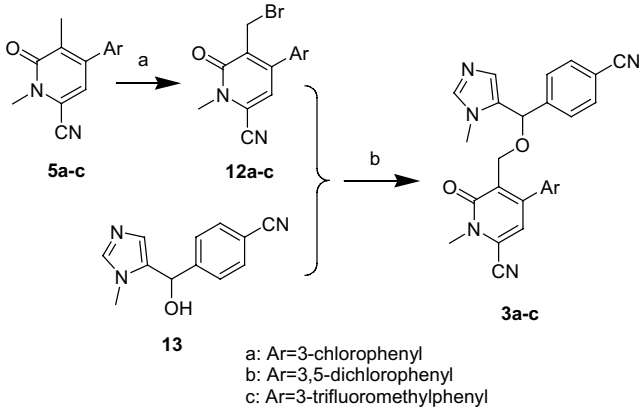


Figure 3. ORTEP structure of compound **5c**.



Scheme 1. Reagents and conditions: (a) (1) LDA, THF, −78 °C; (2) I_2, −78 °C to rt, 74%; (b) (1) LDA, THF, −78 °C; (2) H_2O, −78 °C to rt, 90%; (c) substituted phenylboronic acids, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene/EtOH, reflux, 84%; (d) NaCN, DMSO, 110 °C, 45%; (e) (1) H_2O_2, CH_3COOH, 100 °C, 6 h; (2) Ac_2O, reflux overnight; (3) H_2O, dioxane, CH_3COONa, reflux 3 h, 38% in three steps, (f) MeI, NaH, DMF, 76%.



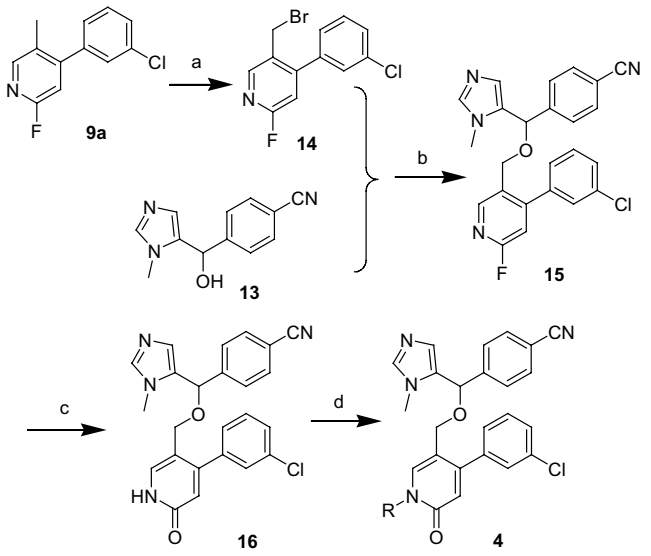
Scheme 2. Reagents and conditions: (a) NBS, CCl_4, and benzoyl peroxide; (b) Ag_2O, CH_2Cl_2.

To further expand our study on the A-ring of compound **1**, two new pyridone moieties were investigated (Fig. 2). In this paper, the synthesis and biological evaluation of these two series of novel FTase inhibitors are reported. The preparation of novel heterocycles of the formula 1,5-dimethyl-6-oxo-4-aryl-1,6-dihydro-pyridine-2-carbonitrile **5a**–**c** is reported as well.

The synthesis of compounds **5a**–**c** is shown in Scheme 1. 2-Fluoropyridine **6** was treated with LDA followed by I_2 to give compound **7**. Compound **8** was prepared through a method called 'iodine-dancing' by treating compound **7** with LDA followed by quenching with H_2O.[6] The Suzuki coupling of 4-iodopyridine **8** with various aryl boronic acids gave biaryl compounds **9a**–**c**. Displacement of the fluorine atom of compounds **9a**–**c** with a cyano group was achieved by using NaCN in DMSO to give 2-cyanopyridines **10a**–**c**. The pyridine-*N*-oxide of compounds **10a**–**c**, generated by the treatment with H_2O_2 in acetic acid, was reacted with acetic anhydride to give the corresponding 2-pyridylacetate. The 2-pyridylacetates were subsequently hydrolyzed to give pyridones **11a**–**c**. This three-step sequence usually gives compound **11** in approximately 30–40% overall yield from compound **10**. N-methylation of compounds **11a**–**c** with MeI and NaH in DMF gave compounds **5a**–**c** in good yield. Since the general structure of compound **5** had not been reported previously, a singe crystal X-ray structure of compound **5c** was solved to confirm its identity (Fig. 3).

Scheme 2 illustrates the synthesis of compounds **3a**–**c**. Bromination of the methyl group of compounds **5a**–**c** in CCl_4 with NBS and benzoyl peroxide gave compounds **12a**–**c**. Compounds **3a**–**c** were prepared by the coupling of **12** and 4-[hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-benzonitrile **13** in CH_2Cl_2 with Ag_2O.

Compounds **4a**–**h** were prepared as shown in Scheme 3. The methyl group of compound **9a** was converted to bromomethyl with NBS and benzoyl peroxide in CCl_4. Coupling of compounds **13** and **14** in CH_2Cl_2 in the presence of Ag_2O yielded ether **15**. Attempts to hydrolyze the 2-fluoropyridine moiety to give the corresponding pyridone through methods reported in



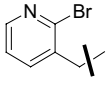
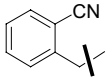
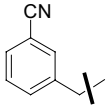
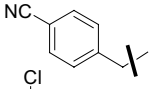
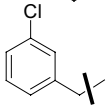
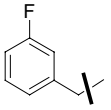
Scheme 3. Reagents and conditions: (a) NBS, CCl_4, and benzoyl peroxide; (b) Ag_2O, CH_2Cl_2; (c) acetic acid–H_2O (9:1), 100 °C, 16 h; (d) alkylbromides, NaH, DMF, 76%.

literature, such as treatment with 3 N HCl at reflux temperature,[7] proved to be too harsh for compound **15**, resulting in cleavage of the ether bond. It was found that when compound **15** was heated in a mixture of acetic acid and water (9:1) at 100 °C over night, the 2-fluoropyridine moiety of compound **15** could be converted to pyridone **16** in 90% yield without any breakage of the ether bond. Finally, N-alkylation of compound **16** was accomplished with various alkyl bromides in DMF in the presence of NaH to give compounds **4a**–**c**.

Table 1 illustrates the SAR study on these two pyridone-containing FTase inhibitors. All of the compounds show potent activity against FTase and excellent selectivity for FTase over GGTase-I. It should be noted that, although compound **3a** shows only slightly reduced activity in the enzymatic assay against FTase compared to its isomeric counterpart, compound **2**, its cell-based activity is 22-fold less potent than that of compound **2**. The reason for this disparity is not clear. Replacement of the 3-chlorophenyl moiety of compound **3a** with a 3,5-dichlorophenyl group (compound **3b**) has little impact on the biological activity. However, replacement of the chlorine with a larger trifluoromethyl group (compound **3c**) results in a 6-fold loss in activity against FTase.

It appears that a large R group is needed for compound **4** to maintain good activity against FTase since compounds **16** and **4a**–**b**, which bear small substitutents on

Table 1. SAR study for compounds **3a**–**c**, **4a**–**h**, and **16**[a]

Compound	Ar	R	IC_{50} (FTase)[b] (nM)	IC_{50} (GGTase)[c] (nM)	EC_{50}[d] (nM)
3a	3-Cl–Ph	—	1.2 (2)	>10,000 (2)	11.4 (2)
3b	3,5-Di-Cl–Ph	—	1.1	9400	15
3c	3-CF_3–Ph	—	7.5	3600	Nd[e]
16	—	H	11	6200	Nd
4a	—	CH_3	12	>10,000	Nd
4b	—	CH_2CN	19	>10,000	Nd
4c	—		3.0	6600	Nd
4d	—		2.3	7700	Nd
4e	—		1.3 (2)	1900 (2)	9 (2)
4f	—		5.0	>10,000	Nd
4g	—		2.1	1200	10
4h	—		2.1	2000	15

[a] All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses.
[b] Compound concentration needed to reduce the bovine FTase-catalyzed incorporation of [^{3}H]FPP into a biotin-linked K-ras (B) decapeptide (KKSKTKCVIM) by 50%.
[c] Compound concentration needed to reduce the bovine GGTase-catalyzed incorporation of [^{3}H]FPP into a biotin-linked K-ras (B) decapeptide (CVLL) by 50%.
[d] Compound concentration needed to reduce farnesylation of NIH3T3 H-ras transformed cell by 50%.
[e] Not determined.

the nitrogen of the pyridone ring, are less active than compounds **4c**–**h**. Although compound **4e**, which contains a 3-cyanobenzyl group exhibits better activity against FTase than compound **4f**, which contains a 4-cyanobenzyl group, the substitution pattern does not seem to have a large impact on enzymatic activity against FTase. It is interesting to note that the replacement of the cyano group of compound **4f** with its bioisosteres, chlorine and fluorine, results in little change in activity against FTase. However, compound **4e** shows slightly better activity in the whole-cell based assay (EC_{50}) than compound **4h**. The pharmacokinetic properties of compound **4e** were studied in dog. At 1 mg/kg dose, compound **4e** was shown to have 47% oral bioavailability with 1.4 h oral $t_{1/2}$ and 0.53 L/(h kg) plasma clearance.

In conclusion, we have demonstrated that the A-ring of compound **1** can be replaced with two new pyridone moieties, leading to two novel series of potent and selective pyridone-containing FTase inhibitors. In addition to its potent whole-cell activity, compound **4e** was shown to possess good oral bioavailability in dog. Synthesis of a novel heterocycle, 1,5-dimethyl-6-oxo-4-aryl-1,6-dihydro-pyridine-2-carbonitrile, was achieved in reasonable yield. The structure of compound **5c** was confirmed by single crystal X-ray structure.

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