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Potent Inhibitors of Farnesyltransferase and Geranylgeranyltransferase-I

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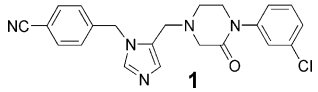
Abstract—Compound **1** has been shown to be a dual prenylation inhibitor with FPTase ($IC_{50}=2$ nM) and GGPTase-I ($IC_{50}=95$ nM). Analogues of **1**, which replaced the cyanophenyl group with various biaryls, led to the discovery of highly potent dual FPTase/GGPTase-I inhibitors. 4-Trifluoromethylphenyl, trifluoropentynyl, and trifluoropentyl were identified as good *p*-cyano replacements. © 2002 Published by Elsevier Science Ltd.

Oncogenically mutated forms of Ras are found in approximately 30% of all human cancers, including 30–50% of colon cancers and 90% of pancreatic cancers.[1] Ras must associate with the cellular membrane in order to have biological activity.[2] While several post-translational modifications to Ras help promote membrane association, only prenylation is absolutely obligatory. Because constitutively activated mutant Ras protein is found in a variety of tumors, it has been hypothesized that preventing Ras prenylation would lead to inhibition of tumor growth.[3] Of the three Ras genes transcribed in human cells (H-, N-, and K-Ras), K-Ras is the most commonly mutated gene.[4] Since K-Ras can be prenylated by either farnesyl protein transferase (FPTase) or geranylgeranyl protein transferase type I (GGPTase-I), inhibition of both enzymes is required to inhibit membrane association.[5] Because FPTase and GGPTase-I differ somewhat in their affinities for protein substrates, finding potent inhibitors of both enzymes represents a significant challenge.

Numerous FPTase inhibitors (FTIs) have been reported that mimic the tetrapeptide C-terminus of Ras (the Ca_1a_2X motif).[6,7] It had been demonstrated in prior work that imidazole is a good cysteine surrogate and that dramatic increases in FPTase potency could be achieved with specifically substituted imidazoles relative to the unsubstituted imidazole.[8,9] A highly potent FPTase inhibitor **1** was found to have inhibitory activity 50-fold more selective for FPTase ($IC_{50}=2$ nM) than GGPTase-I ($IC_{50}=95$ nM) and was selected for human clinical trials. Significant effort was put into optimizing **1** to find potent dual FTI/ GGTIs. Earlier studies have shown that the *p*-cyanobenzylimidazole group is uniquely active in conferring FPTase inhibitory activity to compounds like **1**.[10] In an earlier study, replacing the *p*-cyano with a hydrogen resulted in a loss of 5- to 10-fold in FPTase potency.[9] Herein, we describe the syntheses and inhibitory profiles of a series of compounds evaluating substituent effects on the phenyl group, which led to the discovery of highly potent dual FPTase/GGPTase-I inhibitors.



1

A preliminary study involved the synthesis of substituted 1-(biarylmethyl)imidazoles whose inhibitory activities were compared to those of 1-(4-cyanobenzyl)-imidazole (data not shown). The more potent biaryls were then incorporated into analogues of **1**. Compounds **5a–i** (Table 1) were synthesized as shown in Scheme 1. 4-Bromobenzylamine **2** was converted to the imidazole methyl alcohol **3** according to a previously

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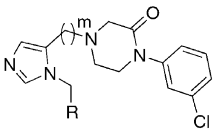
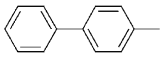
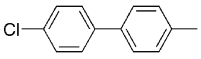
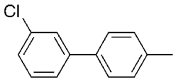
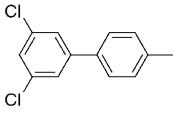
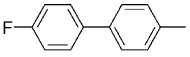
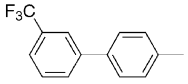
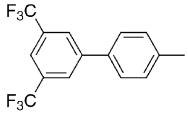
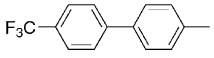
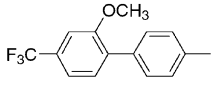
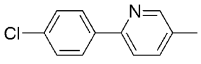
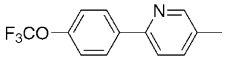
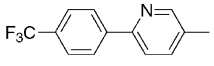
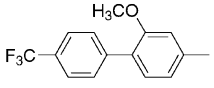
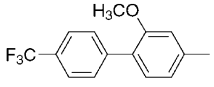
Table 1.

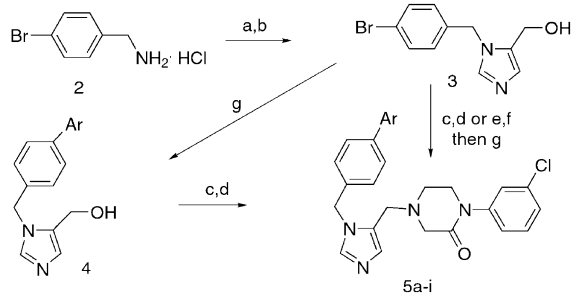


Compd	R	m	IC_{50} (nM)		
			FPTase[a]	CRAFTI[b]	GGPTase-I[c]
5a		1	12	1600	1390
5b		1	8.7	193[d]	210[e]
5c		1	17	576	8450[e]
5d		1	35	437	3030
5e		1	15	600	1340
5f		1	410	662[d]	2680
5g		1	3500	ND	1870
5h		1	5.7	29	140
5i		1	392	ND	1860
9a		1	19	250	2300
9b		1	52	ND	560
9c		1	14	159	509
13a		1	1.6	12	70[e]
13b		2	0.17	1.2	151

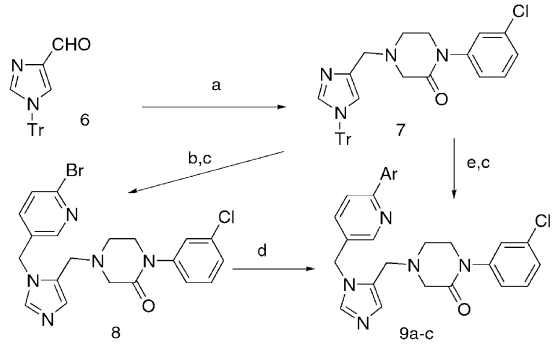
[a]Concentration of compound required to inhibit FPTase-catalyzed incorporation of [^{3}H]FPP into recombinant Ras-CVIM by 50%. The enzyme concentration was 1 nM. For IC_{50} <2 nM, enzyme concentration was 10 pM, $n=2$ otherwise noted.
[b]Cell-based Radiotracer Assay for FarnesylTransferase Inhibition, in which the concentration of compound required to displace 50% of radiolabeled FTIs from FPTase in v-Ha-ras-transformed Rat1 cells, $n=1$ otherwise noted.
[c]Concentration of compound required to inhibit 50% of the human GGPTase-I catalyzed incorporation of [^{3}H]GGPP into a biotinylated peptide corresponding to the C-terminus of human K-Ras, $n=2$ otherwise noted.
[d]$n=2$.
[e]$n=3$.

described method.[11] Bromide **3** then underwent Suzuki coupling with various substituted arylboronic acids, followed by oxidation, and reductive alkylation to provide substituted biphenyl inhibitors **5**. Alternatively, **3** was converted to the methyl chloride and alkylated with 1-(3-chlorophenyl)-2-piperazinone.[12] Subsequent Suzuki coupling introduced the substituted aryl group. Halogenated biaryls **5b–e** were synthesized and activities compared to **1** and **5a**. The compounds were evaluated for inhibition of FPTase[13] and GGPTase-I[14] in vitro. The more potent compounds were also tested in a cell-based assay (CRAFTI).[15] These compounds (**5b–e**) had modest in vitro inhibitory activity with respect to FPTase ($IC_{50}=8.7$–35 nM) and except for **5b**, were not particularly active versus GGPTase-I (Table 1). *meta*- and *para*-Trifluoromethyl substituents were also synthesized (**5f–h**). Compounds **5f** and **5g** were less potent than **1** and **5a** against either FPTase or GGPTase-I. However, the *p*-trifluoromethyl **5h** was active with respect to FPTase in vitro ($IC_{50}=5.7$ nM) and had good activity in cell culture (CRAFTI $IC_{50}=29$ nM), and was our first cyano group replacement that had good potency in vitro and in vivo. In addition, its activity versus GGPTase-I was similar to **1** ($IC_{50}=140$ nM).

To enhance polarity and hopefully improve cell activity, substituted heterobiaryls containing pyridine were



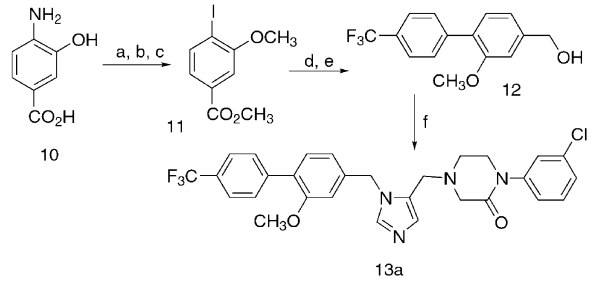
Scheme 1. Reagents and conditions: (a) 1,3-dihydroxyacetone dimer, KSCN, HOAc, *n*-BuOH, 50 °C, 100%; (b) H_2O_2, TFA, MsOH, 0–75 °C, 40%; (c) SO_3 pyr, Et_3N, DMSO, 98%; (d) 1-(3-chlorophenyl)-2-piperazinone, $Na(OAc)_3BH$, $ClCH_2CH_2Cl$, rt, 26–28%; (e) $SOCl_2$, DMF, 0 °C–rt, 86%; (f) 1-(3-chlorophenyl)-2-piperazinone, DIEA, CH_3CN, 0 °C, 61%; (g) $ArB(OH)_2$,$Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 0.05 M, 80 °C, 16–22%.



Scheme 2. Reagents and conditions: (a) 1-(3-chlorophenyl)-2-piperazinone, $Na(OAc)_3BH$, $ClCH_2CH_2Cl$, 44%; (b) 2-bromo-5-bromomethylpyridine, $CHCl_3$, 40 °C; (c) MeOH, reflux, 20%, two steps; (d) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 80 °C, 10–41%; (e) CH_3CN, 2-(4-chlorophenyl)-5-bromomethylpyridine, rt, 14%.

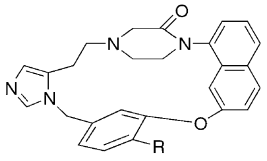
synthesized (**9a**–**c**, Scheme 2). 1-Trityl-4-imidazolecarboxaldehyde **6**[16] was reductively aminated with 1-(3-chlorophenyl)-2-piperazinone to provide **7**. Subsequent alkylation with 2-(4-chlorophenyl)-5-(bromomethyl)-pyridine[17] gave **9a**. Another way to make **9** was to alkylate **7** with 2-bromo-5-(bromomethyl)pyridine to form **8**, followed by Suzuki coupling with aryl boronic acids (**9b**–**c**). Compared to **1** and biphenyl **5h**, **9a**–**c** showed decreased potency against both FPTase and GGPTase-I (Table 1).

Another strategy to improve inhibitory activity was to influence the conformation of the aromatic rings by introducing an *ortho*-methoxy group (**5i**, Table 1). However, isomer **5i** was at least 10-fold less active than **5h** with respect to both FPTase and GGPTase-I. The methoxy group was relocated to the other phenyl ring producing **13a**. The synthetic approach to **13a** began by converting 3-hydroxy-4-aminobenzoic acid **10** to its methyl ester, followed by iodination and methylation to afford **11** (Scheme 3). Iodide **11** was coupled with 4-trifluoromethylphenyl boronic acid and reduced to alcohol **12** with LAH. Compound **12** was converted to the triflate in situ and alkylated with **7** to provide **13a**. The activity of **13a** was excellent with a 3-fold increase in potency in FPTase ($IC_{50}=1.6$ nM) and CRAFTI ($IC_{50}=12$ nM) compared to **5h**.



Scheme 3. Reagents and condtions: (a) HCl, CH_3OH, reflux, 82%; (b) $NaNO_2$, KI, HCl, 0 °C, 86%; (c) NaH, CH_3I, rt, 100%; (d) 4-CF_3-$PhB(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, 100 °C, 92%; (e) LAH, THF, rt, 49%; (f) Tf_2O, DIEA, CH_2Cl_2, then **7**, −78 °C, 72%.

Table 2.

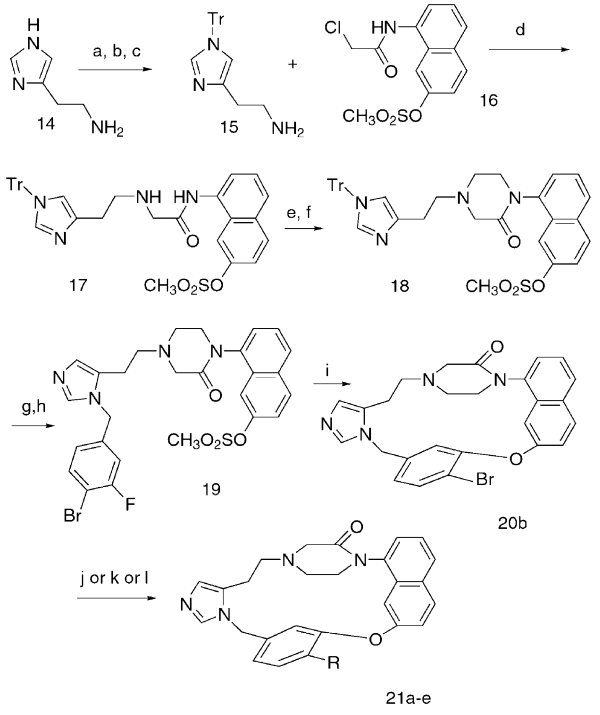


Compd	R	IC_{50} (nM)		
		FPTase[a]	CRAFTI[b]	GGPTase-I[c]
20a	CN	0.25	0.19	16[f]
20b	Br	1.2	2.0	161
21a	4-$CF_3C_6H_4$	2.1	1.1[d]	15.6
21b	H	8.0	ND	509
21c	$CH_3CH_2CH_2CH_2$	10.3	ND	2480
21d	$F_3CCH_2CH_2CC$	6.1	0.81[d]	4.8
21e	$F_3CCH_2CH_2CH_2CH_2$	3.1	0.48	60

[a,b,c,d]See corresponding footnotes in Table 1.
[f]$n=5$.

Additionally, **13a** was a good inhibitor of GGPTase-I with an $IC_{50}=70$ nM. The activity of **13a** indicates that a methoxy group is tolerated at this position, either helping to orient the two phenyl rings towards an orthogonal conformation compared to **5h**, or engaging a favorable interaction with the receptor (no further study was done). To further improve the potency of **13a**, the synthesis of **13b**, which incorporated an ethyl linkage between the imidazole and the piperazinone, was undertaken. Compound **13b** was prepared using chemistry strictly analogous to that described for the synthesis of **19** in Scheme 4 (vide infra). Although **13b** was 2-fold less active versus GGPTase-I compared to **13a**, it had excellent activity (10-fold increase) against FPTase both in vitro ($IC_{50}=0.17$ nM) and in vivo ($IC_{50}=1.2$ nM) (Table 1). Compound **13b** was also tested in PSN-1 cells for its ability to inhibit farnesylation of the FPTase substrate HDJ2 protein and geranylgeranylation of the GGPTase-I substrate Rap1a protein.[18] Processing of HDJ2 was inhibited with $EC_{50}=28$ nM and Rap1a processing was inhibited with $EC_{50}=3400$ nM.

Constrained macrocyclic analogues of **1** are highly potent FTIs.[19] In particular, imidazolylethylpiperazinone **20a** was shown to be a very active FPTase inhibitor in vitro ($IC_{50}=0.25$ nM) as well as in vivo (CRAFTI $IC_{50}=0.19$ nM). Interestingly, the 17-membered ring macrocycle **20a** had surprisingly good inhibitory activity



Scheme 4. Reagents and conditions: (a) TFAA, Et_3N, CH_2Cl_2, 0 °C–rt; (b) TrCl, Et_3N, DMF, 0 °C–rt; (c) NaOH, CH_3OH, H_2O, rt, 100% for three steps; (d) DIEA, CH_3CN, rt, 75–95%; (e) glycol aldehyde, $NaBH_3CN$, CH_3OH, rt, 100%; (f) DTAD, *n*-Bu_3P, THF, 0 °C–rt, 40–46%; (g) 4-bromo-3-fluorobenzyl alcohol, Tf_2O, *i*Pr_2NEt, −78 °C–rt; (h) CH_3OH, reflux; (i) Cs_2CO_3, DMSO, 0.05 M, 140 °C, 18–22%, three steps; (j) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 0.05 M, 80 °C, 37%; (k) Bu_3Sn-alkyne, $Pd(PPh_3)_4$, DMF, 120 °C, 58%; (l) *n*-Bu_4Sn, $PdClBn(PPh_3)_2$, HMPA, 120 °C, 5%.

versus GGPTase-I ($IC_{50}=16$ nM) compared to analogous 16-membered ring-contracted macrocycles.[19] To further increase GGPTase-I activity, modifications to **20a** were investigated. As in the linear series, various groups were introduced to replace the *p*-cyano group. The synthetic route to obtain **20a–b** and **21a–e** is described in Scheme 4. The trityl histamine **15** was available from histamine by a protection–alkylation–deprotection sequence. **15** was alkylated with **16**[19] to provide **17**. Reductive alkylation with glycol aldehyde dimer, followed by Mitsunobu-type ring closure of the piperazinone[12] yielded **18**. Alkylation of **18** with 4-bromo-3-fluorobenzyl alcohol followed by deprotection of the imidazole gave **19**. S_NAr macrocyclization of **19** proceeded to provide **20**, even with the marginally activated 3-fluoro-4-bromobenzyl group.[20] The 4-bromophenyl macrocycle **20b** underwent either Suzuki coupling with *p*-trifluoromethylphenyl boronic acid (**21a**) or Stille coupling with tetra-*n*-butyl tin (**21c**) or tributylalkynyl tin (**21d**). During purification of **21c**, a small amount of reduced by-product **21b** was isolated. Alkyl-substituted **21e** was obtained from palladium catalyzed hydrogenation of **21d**.

Interestingly, synthetic intermediate **20b** still maintained good potency in the FPTase ($IC_{50}=1.2$ nM) and CRAFTI ($IC_{50}=2.0$ nM) assays, though it was 10-fold less active versus GGPTase-I compared to the *p*-cyano analogue **20a** (Table 2). As anticipated, **21a**, which contained the *p*-trifluoromethylphenyl substituent, was a potent inhibitor. Compared to **20a**, **21a** was approximately 10-fold less active versus FPTase ($IC_{50}=2.1$ nM) and CRAFTI ($IC_{50}=1.1$ nM), although its activity versus GGPTase-I ($IC_{50}=15.6$ nM) was undiminished. Molecular modeling of the *p*-cyanophenyl group of **20a** into the FPTase active site indicated that the lipophilic binding pocket might be long enough to accommodate a longer substituent.[15] To test this hypothesis, 4-*n*-butyl analogue **21c** was synthesized. Unfortunately, **21c** was not as active as **20a** with respect to FPTase or GGPTase-I inhibition. The reduced activity of **21c** could have been due to several factors: the carbon chain might not be long enough or too flexible, resulting in weaker affinity to the enzymes. To further explore the modeling prediction, **21d** and **21e** were made. Although both **21d** and **21e** were moderately active versus FPTase with $IC_{50}=6.1$ nM and $IC_{50}=3.1$ nM, respectively, they were almost 10-fold more potent in cell culture. Because the CRAFTI assay incubates inhibitors with the enzyme for a longer time than in the FPTase assay, the difference in the CRAFTI/FPTase ratio of **21d** and **21e** may be the result of slow-binding, although this hypothesis was not directly tested.[21] HDJ2 and Rap1a processing in PSN-1 cells was inhibited by **21e** with $EC_{50}=6.9$ nM and $EC_{50}=800$ nM, respectively. The best GGPTase-I inhibitor in this series was **21d**, which was also the most balanced FTI/GGPTI. Overall, these substituted-phenyl macrocycles had good potency with respect to FPTase, GGPTase-I and especially CRAFTI.

Exploring biaryl replacements for the *p*-cyanophenyl group has led to the discovery of highly potent dual FTI/GGTI analogues of **1**. In the linear series, we identified 4-trifluoromethylphenyl (**5h**, **13a**, and **13b**) as a good *p*-cyano replacement. In the constrained macrocylic analogues of **20a**, excellent inhibitory activities against both FPTase and GGPTase-I were obtained with 4-trifluoromethylphenyl, trifluoropentynyl and trifluoropentyl substituents. Both series showed effective functional inhibition of FPTase and GGPTase-I activity in cell culture.

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