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Synthesis and activity of 1-aryl-1′-imidazolyl methyl ethers as non-thiol farnesyltransferase inhibitors

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Abstract—A series of imidazole-containing methyl ethers (**4**–**5**) have been designed and synthesized as potent and selective farnesyltransferase inhibitors (FTIs) by transposition of the D-ring to the methyl group on the imidazole of the previously reported FTIs **3**. Several compounds such as **4h** and **5b** demonstrate superior enzymatic activity to the current benchmark compound tipifarnib (**1**) with IC_{50} values in the lower subnanomolar range, while maintaining excellent cellular activity comparable to tipifarnib. The compounds are characterized as being simple, easier to make, and possess no chiral center involved.

Cancer is an extremely complicated disease encompassing hundreds of different disorders. Emerging science within the past decade has created many opportunities for fundamentally new approaches to tackle this disease.[1,2] One such approach targets *Ras*, an oncogene that is among the most frequently activating mutated genes in tumors.[3] *Ras* plays a major role in intracellular signaling pathways that control cancer cell proliferation.[4] Activation of Ras proteins requires posttranslational farnesylation, a process of covalently attaching a 15-carbon farnesyl moiety to conserved cysteine residues.[5] Therefore, the search for inhibitors of farnesyltransferase (FTase) for the treatment of cancer has generated considerable recent interest.[6,7] Many FTase inhibitors (FTIs) have demonstrated excellent antitumor efficacy in preclinical human xenograft models and several compounds are now in Phase II/III clinical trials.[8–10]

Tipifarnib (R115777, **1**) is one of the most potent and selective non-thiol containing FTI in clinical trials.[11,12] In the preceding paper, we reported the discovery of pyridones **2** and related analogs as potent FTIs obtained through deletion of the B-ring of tipifarnib.[13,14] Further structural refinement of those analogs resulted in the identification of a series of biphenyl FTIs **3** (Fig. 1).[15] Using a similar strategy as described in the preceding paper—transposition of the D-ring to the methyl group on the imidazole in **3**[13]—led to a series of methyl ethers **4**–**5** that are potent, and selective FTIs.[16] We report here the design, synthesis, and biological activity of this promising new series.

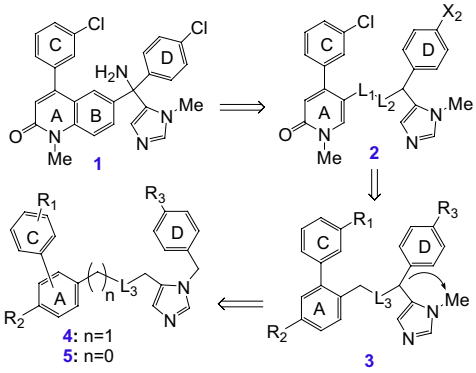

Figure 1. Modifications of **1** through **2** and **3** lead to achiral 1-aryl-1′-imidazolyl methyl ethers (**4**, **5**).

The required benzyl bromides **8** were prepared from **6** through Suzuki coupling then NBS bromination (Scheme 1).[13,15,17]

Keywords: Farnesyltransferase inhibitors; Anticancer; Tipifarnib.
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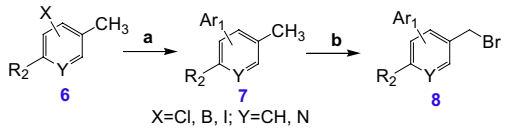


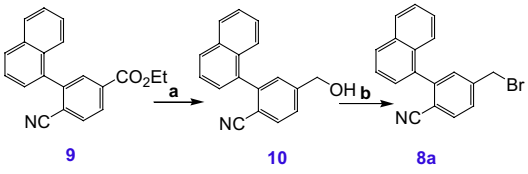
Scheme 1. Reagents and conditions: (a) $Ar_1B(OH)_2$, $Pd(OAc)_2$, Cy-MAP1, CsF, dioxane, rt, overnight; (b) NBS, AIBN, CCl_4, reflux, 12 h.

Reduction of ester **9**[18] with $Ca(BH_4)_2$ at room temperature provided alcohol **10** in 80% yield, which was quantitatively converted to naphthylbenzyl bromide **8a** when treated with tribromophosphine (Scheme 2).

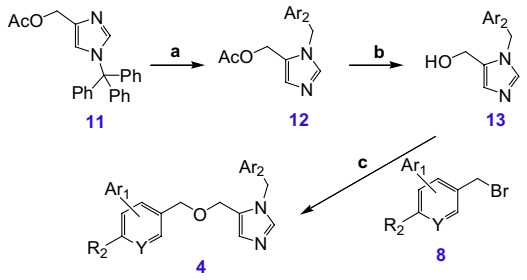
The dimethyl ethers (**4**) were prepared as described in Scheme 3. *N*-Tritylimidazole **11** underwent regio-selective alkylation with arylmethyl bromide using reaction conditions developed by Anthony et al.[19] to provide the *N*-arylmethyl imidazole (**12**), which was hydrolyzed to give alcohol **13**. Coupling of alcohol **13** with the bromides (**8**) in the presence of silver oxide furnished the substituted dimethyl ethers (**4**).

Preparation of dimethylamine **16** is illustrated in Scheme 4. Accordingly, benzylbromide **8a** is converted to benzylamines **14** in a two-step sequence by reaction with sodium azide and subsequent reduction with triphenylphosphine (28% yield). Aldehyde **15**[13] underwent reductive amination with amine **14** to afford the dimethylamine (**16**) in 50% yield.

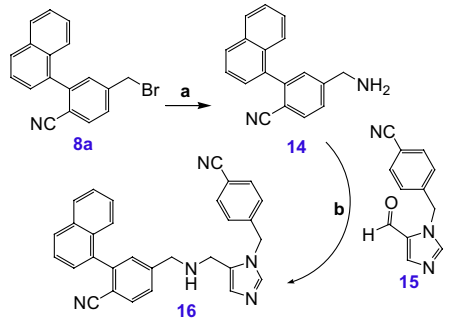
Synthesis of the compounds with a two-atom linker between the imidazole and aryl groups are illustrated in Schemes 5 and 6. Suzuki coupling of **17** with 3-chlorobenzeneboronic acid gave biphenyl **18** in 89% yield. Compound **18** underwent demethylation (98% yield) and the resulting phenol (**19**) was reacted with chloride



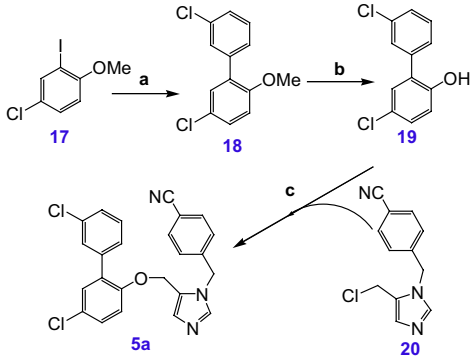
Scheme 2. Reagents and conditions: (a) $Ca(BH_4)_2$, THF/EtOH, rt, overnight, 80%; (b) PBr_3, DMF/CH_2Cl_2, 0 °C, 2 h, 100%.



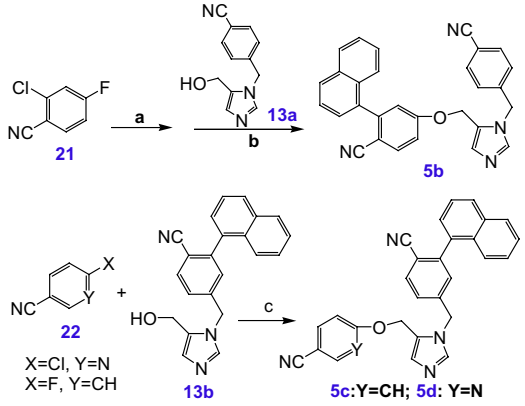
Scheme 3. Reagents and conditions: (a) Ar_2CH_2Br, AcOEt, 60 °C, 20 h; (b) $LiOH{\cdot}H_2O$, THF/H_2O, rt, 1 h; (c) AgO, CH_2Cl_2, rt, 1 day.



Scheme 4. Reagents and conditions: (a) (i) NaN_3, acetone, reflux, 4 h; (ii) PPh_3, THF/H_2O, reflux 1 h, 28%; (b) $NaBH(OAc)_3$, CH_2Cl_2, rt, overnight, 50%.



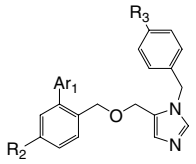
Scheme 5. Reagents and conditions: (a) 3-chorophenylboronic acid, $Pd(Ph_3)_4$, $NaHCO_3$, toluene/EtOH/H_2O, reflux, 3 h, 89%; (b) BBr_3, CH_2Cl_2, rt, 1 h, 98%; (c) K_2CO_3, DMF, 55 °C, 6 h, 31%.



Scheme 6. Reagents and conditions: (a) 1-naphthylboronic acid, $Pd(OAc)_2$, Cy-MAP-1, CsF, dioxane, rt, 2 days, 92%; (b) NaH, DMF, rt, overnight, 68%; (c) **13b**, NaH, DMF, rt, overnight, 38–48%.

20[20] to furnish the desired product **5a** in 31% yield. Similarly, **5b** was prepared in good yield from **21** through Suzuki coupling and nucleophilic condensation with **13a** (Scheme 6). Coupling of alcohol **13b** (prepared in Scheme 3 from the corresponding bromide)[21] with the *para*-cyano activated aryl halide (**23**), yielded targets **5c–d** in 38–48% yield.

Table 1. Activity of biaryl farnesyltransferase inhibitors



Compd	Ar_1	R_2	R_3	IC_{50} (nM) FT[a]	IC_{50} (nM) GGT[b]	EC_{50} (nM) Ras[c] processing
4a		Cl	CN	0.62	8200	30%[d]
4b		CN	CN	0.37	6800	7.7
4c		CN	$MeSO_2$	96	NT[e]	NT[e]
4d		CN	Cl	2.2	>10,000	0%[d]
4e		CN	Cl	1.4	>10,000	34
4f		CN	CN	1.2	2300	52%[d]
4g		CN	CN	0.49	990	54%[d]
4h		CN	CN	0.65	1300	52
4i		CN	CN	13	NT[e]	92%[d]
4j		CN	CN	1.3	>10,000	77
4k		CN	CN	0.44	870	49%[d]
4l		CN	CN	4.3	8600	1.6
4m		CN	CN	7.6	>10,000	25%[d]
4n		CN	CN	0.37	730	10%[d]
4o		CN	CN	0.60	>10,000	53%[d]
4p		CN	Cl	8.3	>10,000	11%[d]
4q		CN	CN	0.81	NT[e]	54%
4r		CN	CN	0.92	3400	53%[d]
4s		CN	CN	1.3	2300	43%[d]
1	Tipifarnib[f]			0.65	1100	1.6

[a] Bovine farnesyltransferase.
[b] Bovine geranylgeranyltransferase.
[c] In H-ras NIH-3T3 cells.
[d] Inhibition at 100 nM.
[e] Not tested.
[f] Data from racemic mixtures.

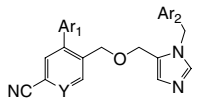
Biological activities of the compounds were determined against bovine FTase and cellular Ras processing in H-*ras* transformed cells.[22] Selectivity against geranylgeranyltransferase (GGTase), a closely related enzyme that is responsible for prenylating the majority of prenylated proteins, was also tested. These results are summarized in Tables 1–4.

The substituted dimethyl ethers (**4**) demonstrate excellent activity against FTase with IC_{50} values ranging from 0.37 to 96 nM (Table 1). In general, the dimethyl ethers (**4**) are 2- to 5-fold more potent than the corresponding compounds **3**,[15] while the activity against the GGTase decreases in comparison with **3**.[15] A cyano group, either at R_2, R_3, or both, dramatically boosts the activity, particularly in the Ras processing assay. Cyano analog **4b**, with an EC_{50} of 7.7 nM in the Ras processing assay, is much more potent than the corresponding chloride (**4a**). Although the exact roles the cyano group plays are not clear, the potency enhancement may attribute to the tight fit of the cyano groups into small pockets of the right size of a cyano group and with proper vector off the aromatic ring. From the X-ray structure,[13] the D-ring cyano group (R_3) fits into a small pocket and accepts hydrogen bonds from the main chain NH of both Tyr361 and Phe360 of the β-subunit. Whereas the A-ring cyano group (R_2) occupies a small hydrophobic pocket formed by the bound farnesylphosphate and Arg202 of the β-subunit and accepts a hydrogen bond from the OH of Tyr166.

The effect of the position of the substituents at Ar_1 on activity is not clear. In general, the 3-substituted analogs are superior. Although being moderate in enzymatic activity (4.3 nM), **4l** is the most potent FTI in the cellular assay as shown in Table 1, with an EC_{50} of 1.6 nM in inhibiting Ras processing.

Although the dimethyl ethers with disubstituted or bicyclic Ar_1 (**4n–s**) demonstrate good enzymatic activity, they show poor cellular efficacy (Table 1). It appears that a bicyclic aryl group such as naphthalene (**4r–s**) is

Table 2. Activity of biaryl farnesyltransferase inhibitors



Compd	Ar_1	Y	Ar_2	IC_{50} (nM)		EC_{50} (nM) Ras[c] processing
				FT[a]	GGT[b]	
4t		N		4.3	810	26%[d]
4u		CH		1.7	2200	155
4v		CH		3.0	>10,000	43%[d]
4w		CH		4.4	>10,000	49%[d]
4x		CH		1.5	>10,000	35%[d]
4y		CH		0.58	>10,000	17
4z		CH		4.7	5500	29
4aa		CH		3.0	>10,000	16
4bb		CH		>1000	NT[e]	NT[e]

[a] See Table 1.
[b] See Table 1.
[c] See Table 1.
[d] Inhibition at 100 nM.
[e] Not tested.

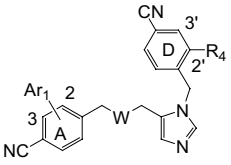
less desirable as a C-ring component compared with substituted phenyl groups.

With the hope of improving cellular potency by lowering the Log *P*, the A- and D-rings are substituted by pyridines and pyridones (e.g., CLog *P* values of **4b** and **4u** are 3.5 and 2.0, respectively). However, the compounds (**4t**–**bb**) are generally less potent than the phenyl analogs, with IC_{50} values ranging from 0.58 to 4.7 nM and an EC_{50} of 16 nM for the best compound (**4aa**) (Table 2). The pyridone (**4bb**) is completely inactive.

Other more drastic modifications including addition of an extra aryl group at C-3′ of the D-ring led to sharply lowered activity, especially in the Ras processing assay (**4cc**–**ee**, Table 3). Notably, transposition of the C-ring aryl groups from the A-ring to C-2′ of the D-ring has little effect on the activity (**4s** vs **4ff**), confirming the molecular modeling result that the C-ring is actually very close in space to the D-ring. However, further transposition of the naphthylene from C-2 to C-3 on the A-ring resulted in a nearly four-fold drop in activity (**4s** vs **4gg**). In general, the compounds with these modifications (Table 3) are inferior to the earlier series mainly because of their sharply reduced cellular activity. Replacing the oxygen in **4gg** with a nitrogen resulted in sharply increased Ras processing activity (**16**).

The activity of compound **5a** (Table 4), which has a two-atom linker, drops six-fold as compared with **4a**, suggesting that a three-atom linker is perhaps optimal when the C-ring is attached at the 2-position (*meta* to the cyano group of the A-ring or D-ring). However, more potent compounds are obtained in the two-atom linked series by attaching the C-ring *ortho* to the cyano group on either the A-ring or the D-ring. Thus compound **5b**, with a 1-naphthyl group at the 3-position of the A-ring, is significantly more potent than the corresponding three-carbon-linked C-2 analog (**4s**) with an IC_{50} of 0.38 nM. Compound **5b** is the most potent compound of the current study in the cellular Ras processing assay, with an EC_{50} of 1.2 nM, versus

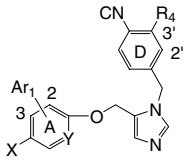
Table 3. Activity of biaryl farnesyltransferase inhibitors



Compd	Ar_1	W	R_4	IC_{50} (nM) FT[a]	IC_{50} (nM) GGT[b]	EC_{50} (nM) Ras[c] processing
4cc		O		10	87	0%[d]
4dd		O		340	NT[e]	NT[e]
4ee		O		6.8	1400	0%[d]
4ff	H	O		0.96	2100	461
4gg		O	H	4.8	1300	5%[d]
16		NH	H	6.5	220	5%[d]

[a] See Table 1.
[b] See Table 1.
[c] See Table 1.
[d] Inhibition at 100 nM.
[e] Not tested.

Table 4. Activity of biaryl farnesyltransferase inhibitors



Compd	Ar_1	X	Y	R_4	IC_{50} (nM) FT[a]	IC_{50} (nM) GGT[b]	EC_{50} (nM) Ras[c] processing
5a		Cl	CH	H	4.0	1800	0%[d]
5b		CN	CH	H	0.38	240	1.2
5c	H	CN	CH		0.32	565	49%[d]
5d	H	CN	N		0.90	420	60

[a] See Table 1.
[b] See Table 1.
[c] See Table 1.
[d] Inhibition at 100 nM.

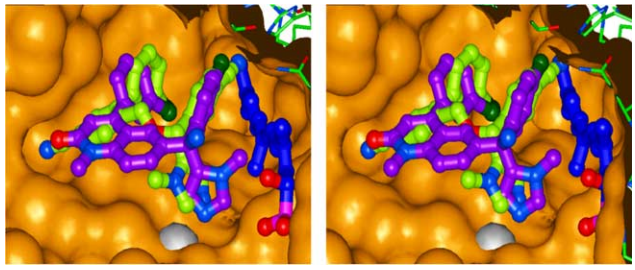


Figure 2. Stereo view of an overlay of a model of compound **4b** (in green) over the X-ray crystal structure of tipifarnib (**1**)[13] (in purple) on complex with FTase in the active site. Zn^{+2} is in shown in gray and hydroxy farnesylpyrophosphate in blue.

1.6 nM for tipifarnib (**1**). Similarly, compounds **5c–d**, with a 1-naphthyl group at the 3′-position of the D-ring (*ortho* to the cyano group) are both subnanomolar FTase inhibitors. Unfortunately, the improvement in FTase inhibitory activity of **5b–d** is accompanied by the unfavorably increased activity against GGTase. On average, selectivity for FTase of compounds **5b–d** is more than 10-fold lower than that of the corresponding three-atom linked analogs in Table 1.

Stereo view of an overlay of a model of **4b**, which was modeled based on the crystal structure of the close chemical analog,[15] and the X-ray crystal structure of tipifarnib (**1**)[13] is shown in Figure 2. The model of **4b** superimposes very well with tipifarnib with a 2.3 Å distance between the active site Zn^{+2} and the imidazole nitrogen. The A-ring extends out over the loop of residues Asp359-Phe360 forming a good van der Waals contact with the loop. The C-ring is stacked against Trp106 and Trp102 and the D-ring stacks along the hydroxy farnesyl pyrophosphate (HFP). The C- and D-rings also stack together forming a strong p/p interaction.

We have previously reported the discovery of pyridones (**2**) and close related analogs as potent FTIs based on structural modifications of tipifarnib (**1**).[13,14] Further structural refinements led to the identification of a series of promising biphenyl FTIs as represented by **3**.[15] In the current studies, a series of imidazole-containing methyl ethers (**4–5**) have been designed and synthesized as potent and selective farnesyltransferase inhibitors (FTIs) by transposition of the D-ring to the methyl group on the imidazole of **3**. Several compounds such as **4l** and **5b** demonstrate potent in vitro enzymatic activity with IC_{50} values in the subnanomolar range, while maintaining excellent cellular activity comparable to tipifarnib. These encouraging results warrant further efforts to optimize the properties of the molecules in this series.

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