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# Synthesis and Biological Evaluation of 4-[3-biphenyl-2-yl-1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-prop-2-ynyl]-1-yl-benzonitrile as Novel Farnesyltransferase Inhibitor

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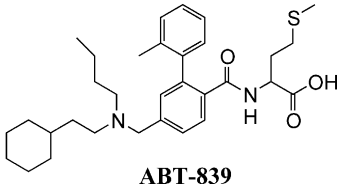
**Abstract**—Farnesyltransferase inhibitors (FTIs) have emerged as a novel class of anti-cancer agents. Analogues of the potent FTI, 4-[3-biphenyl-1-hydroxy-1-(3-methyl-3H-imidazol-4-yl)-prop-2-ynyl]-1-yl-benzonitrile, were synthesized and tested in vitro for their inhibitory activities. The synthesis and detailed biological data of this series of analogues are presented.


Ras proteins play an important role in normal cellular physiology and pathophysiology and are also commonly found in human tumors.[1,2] An essential prerequisite for the function of the Ras protein is its association with the plasma membrane. Ras proteins are initially synthesized in the cytoplasm where they undergo posttranslational farnesylation of the cysteine unit of the so-called CAAX box (C, cysteine; A, any aliphatic amino acid; X, serine or methionine) in the pre-Ras protein by the enzyme protein: farnesyltransferase (FT).[3] Once the protein substrate is farnesylated, the AAX tripeptide is cleaved and the new C-terminal cysteine carboxylate is methylated. The processed proteins become localized to the cell membrane, a step that is essential for their function. This association transmits extracellular signals to the nucleus and leads to cell proliferation.[4,5]

The antitransforming properties of farnesyltransferase inhibitors (FTIs), a novel class of cancer therapeutics, has been widely investigated in the past decade.[6–9] FTIs were originally developed with the aim of inhibiting the posttranslational prenylation and oncogenic activity of Ras. It has become apparent that inhibition of Ras prenylation is not necessary for these compounds to exhibit antitumor activity. Instead, inhibiting Rho-B and possibly other cellular proteins might also account for the efficacy against malignant tumors.[10–13] Although the mechanism of action of these agents is still debated, FTIs have shown impressive efficacy in preclinical models of human cancers.

Abbott's first generation FTI, ABT-839, was potent and selective, but low selectivity was observed between FTase and GGTase-1. The goal of our research is to identify a structurally distinct FTI that maintains or exceeds the potency of ABT-839 and has high selectivity favoring FT inhibition as well.




**ABT-839**

Tolyl and naphthyl analogues were prepared based on the reaction sequences shown in Scheme 1. The starting aldehyde **1** was prepared from the corresponding bromide by Suzuki reaction with various phenylboronic acids. (Scheme 1) Formation of secondary alcohols **2** may be accomplished by formation of imidazole anion with *n*-butyl lithium followed by addition of the anion to the aldehyde. The TES group was then removed with

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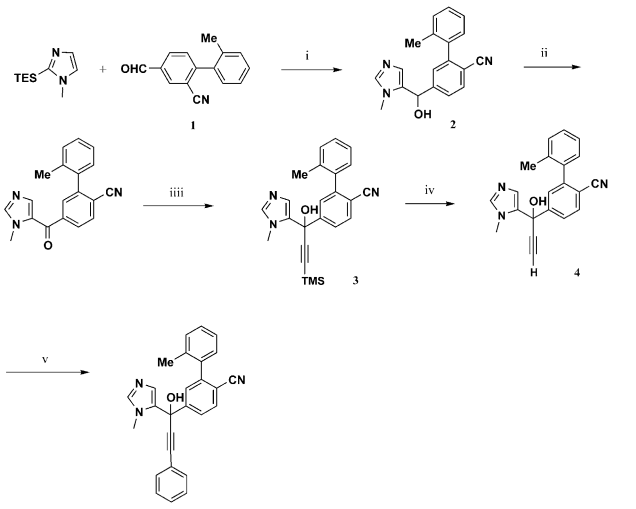
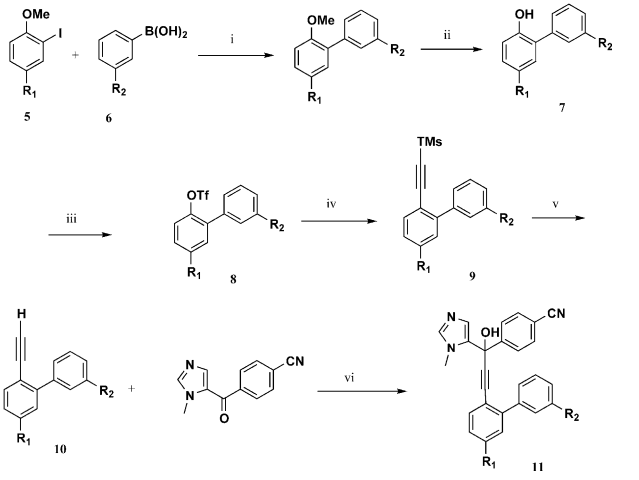


**Scheme 1.** (i) *n*-BuLi, TBAF, −78 °C; (ii) $MnO_2$, $CH_2Cl_2$; (iii) *t*-BuLi, (Trimethylsilyl)acetylene; (iv) $K_2CO_3$, MeOH; (v) $Pd(PPh_3)_2Cl_2$, bromobenzene.

TBAF. Oxidation followed by addition of an acetylenic anion that was generated by reaction of acetylene with *t*-butyl lithium provided the desired tertiary alcohol **3**. Removal of the trimethylsilyl group with potassium carbonate gave the common intermediate **4** that was coupled with various phenyl bromides utilizing Heck reaction conditions.

Scheme 2 illustrates that biphenyl analogues may be synthesized using a route similar to that shown in Scheme 1. Thus, coupling of a substituted phenyl iodide **5** with a substituted phenylboronic acid **6** provided the phenol **7** after the removal of the methyl group with boron tribromide. Conversion of the phenol into the corresponding triflate **8** followed by the Heck reaction with acetylene gave the protected acetylene **9**. Removal of the trimethylsilyl group with base provided the acetylene **10** which is easily converted to the corresponding lithium acetylide by treatment with *n*-butyl lithium. Addition of lithium acetylide to the imidazole ketone generated the desired alcohol **11**.



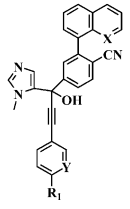
**Scheme 2.** (i) $Pd(PPh_3)_4$; (ii) $BBr_3$, $CH_2Cl_2$; (iii) $PhN(Tf)_2$, i-$PrNEt_2$; (iv) $Pd(PPh_3)_2Cl_2$, (trimethylsilyl)acetylene; (v) $K_2CO_3$, MeOH; (vi) *n*-BuLi.

In this study, tolyl, naphthyl and biphenyl analogues of imidazole acetylenic alcohol were tested for their inhibitory activity against both FTase and GGTase-1 enzymes. The effects of varying the substituents at the C3- and C4-positions of the phenyl ring of the naphthyl series as shown in Table 1 have been studied in detail. Table 1 reveals that the 4-CN analogue (**19**) is the most potent compound to inhibit FTase in the naphthyl series. For the inhibition against FTase, both electron-donating and withdrawing groups are tolerated at the C4- position. In contrast, introduction of the electron-donating $NH_2$ group to the C3- position provided the compound with weak inhibitory potency against GGTase-1 (**14** vs **12**).

The inhibitory activity at the C4-position appears to be governed by steric effects. Analogue (**16**) which possesses a large pentyl group at the C4-position is less potent than either the Et (**18**) or acetylene (**15**) substitutions. The same trend is observed for the inhibition of the GGTase-1 enzyme (Table 1).

Table 1 also demonstrates that introduction of a nitrogen atom to the naphthyl ring results in decreased potency in both the FTase and GGTase-1 assays (**17** vs **19**). In general, the naphthyl series shows poor selectivity with the exception of compound **14** that has 131-fold selectivity in favor of Ftase inhibition. It has also been revealed that introduction of a Cl, CN or acetylene group at the C4-position of the phenyl ring in the naphthyl series results in a 17–170-fold increase in Ras processing potency compared with analogue **12**.

**Table 1.** FTase inhibition, GGTase-1 inhibition, and Ras processing data for biphenyl analogues **12**–**20**



| Cmpds | $R_1$ | X | Y | FTase $IC_{50}$ (nM)[a] | GGTase $IC_{50}$ (nM)[b] | Selectivity (GGT /FT) | Ras $EC_{50}$ (nM)[c] |
|---|---|---|---|---|---|---|---|
| **12** | H | CH | CH | 0.8 | 3.1 | 4 | 170 |
| **13** | 4-Cl | CH | CH | 0.8 | 9.5 | 12 | 9.5 |
| **14** | 3-$NH_2$ | CH | CH | 0.7 | 92 | 131 | NT |
| **15** | 4-CCH | CH | CH | 0.7 | 16 | 23 | <1.0 |
| **16** | 4-$C_5H_{11}$ | CH | CH | 12 | 360 | 30 | 3.8 |
| **17** | 4-CN | N | CH | 1 | 83 | 83 | <1.0 |
| **18** | 4-Et | CH | CH | 0.7 | 18 | 26 | 130 |
| **19** | 4-CN | CH | CH | 0.28 | 10 | 36 | 7.9 |
| **20** | 4-Me | CH | N | 1.0 | 40 | 40 | 49 |

[a]Concentration of compound required to reduce the human FTase-catalyzed incorporation of [$^3$H]FPP into recombinant Ras CVIM by 50%.
[b]Concentration of compound required to reduce the human GGTase-catalyzed incorporation of [$^3$H]GGPP into biotinylated peptide corresponding to the C-terminal of human K-Ras by 50%.
[c]Compound concentration needed to reduce 50% of farnesylation in NIH-3T3H-ras cell line.

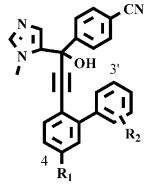
To improve the selectivity against FTase, we have also synthesized several biphenyl analogues as shown in Table 2. It reveals that both electron-donating and withdrawing groups are tolerated at the $R_1$- and $R_2$-positions with the 3,5-Cl analogue (**26**) being the most potent compound against FTase in the biphenyl series. In general, compounds having the biphenyl structure are the most selective, whereas the naphthyl analogues (Table 1) are the least selective.

Table 2 also reveals that replacement of the chloro atom (**21**) at the C3′-position of the phenyl ring with a methoxy group (**27**) causes a 150-fold increase in selectivity. Further increase in selectivity was observed when the chloro atom was replaced with a CN at C4- position of the phenyl ring (**27** vs **22**).

Introduction of various groups such as Cl, CN and CO-*n*-Bu to the C4-position in the biphenyl series has little effect on FTase (cf. **27, 22** and**28**) activity. However, a decrease in inhibitory potency against GGTase-1 is observed. (Table 2) Replacing the 3-OMe with Cl in the biphenyl series causes a 25-fold reduction in Ras processing activity. In contrast, little effect is observed when the 4-CN group is replaced with a Cl atom. (**27** vs **21**; **27** vs **22**)

We then turned our attention to the effect of the acetylenic linker on the inhibitory potency. Table 3 indicates that reduction of the acetylene moiety of the tolyl analogue to a saturated bond results in a 10-fold decrease in potency in the inhibition of both the FTase and GGTase-1 enzymes (**23** vs **24**). A similar SAR trend is observed when the acetylene moiety is removed (**25** vs **26**). In contrast to the tolyl analogue, reduction of the acetylene moiety in the biphenyl series has little effect on the inhibition of FTase (**22** vs **27**). However, a 5-fold decrease in potency is observed in

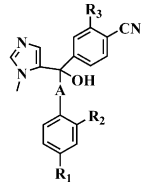
**Table 2.** FTase inhibition, GGTase-1 inhibition, and Ras processing data for biphenyl analogues **21**–**28**




| Compd | $R_1$ | $R_2$ | FTase $IC_{50}$ (nM)[a] | GGTase $IC_{50}$ (nM)[b] | Selectivity (GGT /FT) | Ras $EC_{50}$ (nM)[c] |
|---|---|---|---|---|---|---|
| **21** | Cl | 3-Cl | 1.4 | 100 | 7 | 100 |
| **22** | CN | 3-OMe | 0.37 | 4100 | 11,100 | 2.74 |
| **23** | CN | 3,4-$OCH_2O$– | 0.68 | 5600 | 8200 | 1.4 |
| **24** | CN | 3-OEt | 0.73 | 2400 | 3290 | 0.1 |
| **25** | CN | 3-$OCF_3$ | 0.41 | 430 | 1050 | NT |
| **26** | CN | 3,5-Cl | 0.079 | 1100 | 14,000 | 3.86 |
| **27** | Cl | 3-OMe | 0.69 | 740 | 1070 | 4.0 |
| **28** | CO-*n*-Bu | 3-OMe | 1.1 | >10,000 | >9100 | <0.1 |

[a]Concentration of compound required to reduce the human FTase-catalyzed incorporation of [$^3$H]FPP into recombinant Ras CVIM by 50%.
[b]Concentration of compound required to reduce the human GGTase-catalyzed incorporation of [$^3$H]GGPP into biotinylated peptide corresponding to the C-terminal of human K-Ras by 50%.
[c]Compound concentration needed to reduce 50% of farnesylation in NIH-3T3H-ras cell line.

**Table 3.** FTase inhibition, GGTase-1 inhibition, and Ras processing data for biphenyl analogues **23**–**27** and **22**




| Compd | $R_1$ | $R_2$ | $R_3$ | A | FTase $IC_{50}$ (nM)z[a] | GGTase $IC_{50}$ (nM)[b] | Selectivity (GGT /FT) | Ras $EC_{50}$ (nM)[c] |
|---|---|---|---|---|---|---|---|---|
| **23** | H | H | 2-Me-Ph | $CH_2CH_2$ | 33 | 1800 | 54 | NT |
| **24** | H | H | 2-Me-Ph | C≡C | 3.3 | 240 | 73 | NT |
| **25** | 4-CN | H | 2-Me-Ph | C≡C | 0.84 | 210 | 250 | 9.8 |
| **26** | 4-CN | H | 2-Me-Ph | bond | 6 | 1200 | 200 | <1.0 |
| **27** | 4-CN | 3-OMe-Ph | H | $CH_2CH_2$ | 0.66 | 870 | 1318 | 1.24 |
| **22** | 4-CN | 3-OMe-Ph | H | C≡C | 0.37 | 4100 | 11100 | 2.74 |

[a]Concentration of compound required to reduce the human FTase-catalyzed incorporation of [$^3$H]FPP into recombinant Ras CVIM by 50%.
[b]Concentration of compound required to reduce the human GGTase-catalyzed incorporation of [$^3$H]GGPP into biotinylated peptide corresponding to the C-terminal of human K-Ras by 50%.
[c]Compound concentration needed to reduce 50% of farnesylation in NIH-3T3H-ras cell line.

the inhibition of GGTase-1 (Table 3). It has also been demonstrated that reduction of the acetylene moiety has little effect on the Ras processing activity in the biphenyl series.

In summary, we have shown that varying the substituent pattern at the phenyl or naphthyl rings of an imidazole acetylenic alcohol such as compound **12** alters the inhibitory properties of these compounds. The inhibitory activity (Tables 1–3) indicates that large substituents are not well tolerated at the C4-position of the phenyl ring. In general, compounds having the biphenyl structure as shown in Table 1 possess the weakest inhibitory activities against the GGTase-1 enzyme. In contrast, the naphthyl analogues possess the most potent activity against GGTase-1. The selectivity for FTase inhibition over GGTase-1 is highest in the biphenyl series as shown in Table 2. This study has also shown that reduction of the acetylene moiety decreases the potency in the tolyl series. However, only a small effect is observed in the biphenyl series. The most potent analogue identified from this study is compound **26** which is 50-fold more potent than ABT-839, a potent FTase inhibitor identified previously ($IC_{50} = 3.9$ nM).

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