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Synthesis and biological evaluation of 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1*H*-imidazole as novel farnesyltransferase inhibitor

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Abstract—Farnesyltransferase inhibitors (FTIs) have emerged as a novel class of anti-cancer agents. Analogs of the potent FTI, 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1*H*-imidazole, were synthesized and tested in vitro for their inhibitory activities. The most promising compound identified from this series is analog **29** that possesses potent enzymatic and cellular activities.
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GTP-bound Ras proteins are responsible for initiating an intracellular phosphorylation cascade, and consequently play an important role in normal cellular physiology and pathophysiology.[1] Oncogenic Ras proteins commonly found in human tumors[1,2] are locked in the activated GTP-bound state, which leads to a continuously activated phosphorylation cascade. 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 the pre-Ras protein undergoes posttranslational farnesylation of the cysteine unit of the so-called CAAX box (C, cysteine; A, any aliphatic amino acid; X, serine or methionine) 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 relocated to the cell membrane. Here then transmit extracellular signals to the nucleus that lead to cell proliferation.[4,5]

The antitransforming properties of farnesyltransferase inhibitors (FTIs), a novel class of cancer therapeutics, have been widely investigated in the past decade.[6–10] 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, inhibition of Rho-B and possibly other cellular proteins might also account for the efficacy against malignant tumors.[11–14] Although the mechanism of action of these agents is still debated, FTIs have shown impressive efficacy in preclinical models of human cancers.

The goal of our research is to identify additional molecules within this class of FTIs that not only have good in vitro potency but may also have different physical properties (i.e., solubility and crystallinity). Our initial discovery of compound **1** as a potent, nonpeptidic, nonsulhydryl, selective inhibitor of FT prompted an investigation of SAR centered around this compound. We have previously discovered that modification of the phenyl ring of the biaryl skeleton in **1** affected the inhibitory potency of analogs.[15] We have also thoroughly examined the effect of the linker of biaryl moeity on the potency.[16] It has been demonstrated that introduction of an acetylenic or vinyicl linkage between the two biphenyl rings has little impact on the potency. To continue our search for more potent FTIs, we then turned our attention to identify the new chemotype of FTIs. After examination of the X-ray cocrystal structural[17] of compound **1**, we thought we might be able to move the 4-cyanophenyl ring to imidazole moiety, as shown in Figure 1, to give compound **A**. It was

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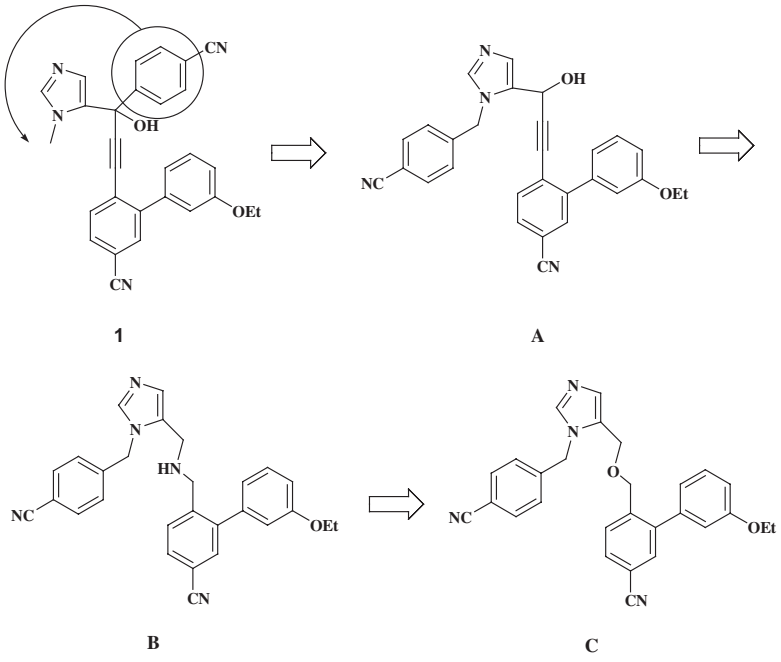


Figure 1.

anticipitated that these modifications would increase or at least maintain the potency. We also planned to replace the acetylenic moeity with an amino linker to give compound **B** or compound **C** if the compound **A** turns out to be a weak inhibitor or possesses an undesired biological profile in vitro.

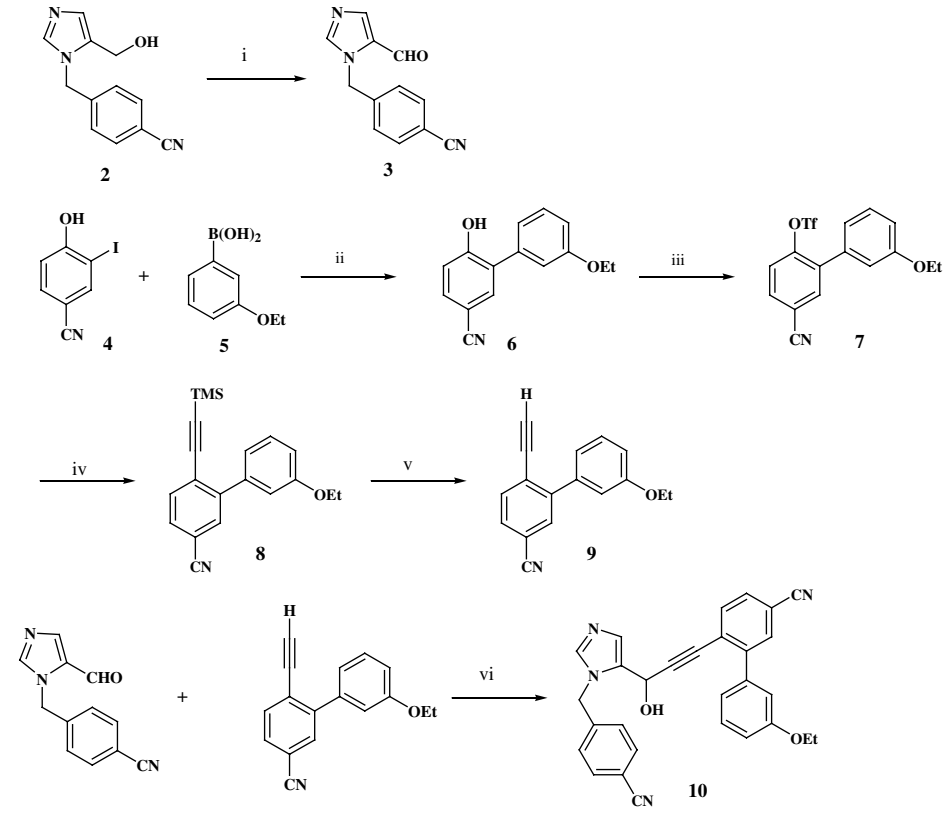
An example of the preparation of the acetylenic alcohol analogs is depicted in Scheme 1. Formation of the aldehyde **3** was accomplished by oxidation of 5-hydroxymethylimidazole[18] **2** with pyridinium sulfur trioxide. Biphenyl acetylene **10** was prepared from the corresponding iodophenyl **4** via a five-step reaction sequence. Thus, coupling of **4** with phenylboronic acid **5** under Suzuki reaction conditions provided the biphenyl compound **6**. Treatment of phenol **6** with *N*-phenylbis(trifluoromethanesulfonimide) in the presence of triethylamine gave the triflate **7**, which was coupled with trimethylsilyl acetylene utilizing Sonogashira reaction conditions to give the acetylene analog **8**. Removal of the trimethylsilyl group with base provided the acetylene **9**, which was easily converted into lithium acetylide by treatment with *tert*-butyl lithium. Addition of lithium acetylide to the imidazole aldehyde **3** generated the desired alcohol **10**.

The amino analog **15** was synthesized using the reaction sequence shown in Scheme 2. Thus, coupling of a bromo-toluene **11** with boronic acid **5** under Suzuki reaction condition provided the biphenyl toluene **12**. Bromination of the toluene **12** with NBS gave the corresponding bromide **13** in good yield. Treatment of bromide **13** with ammonia furnished the aminomethyl compound **14**, which then underwent reductive amination reaction with imidazole aldehyde **3** to provide the desired amino analog **15**.

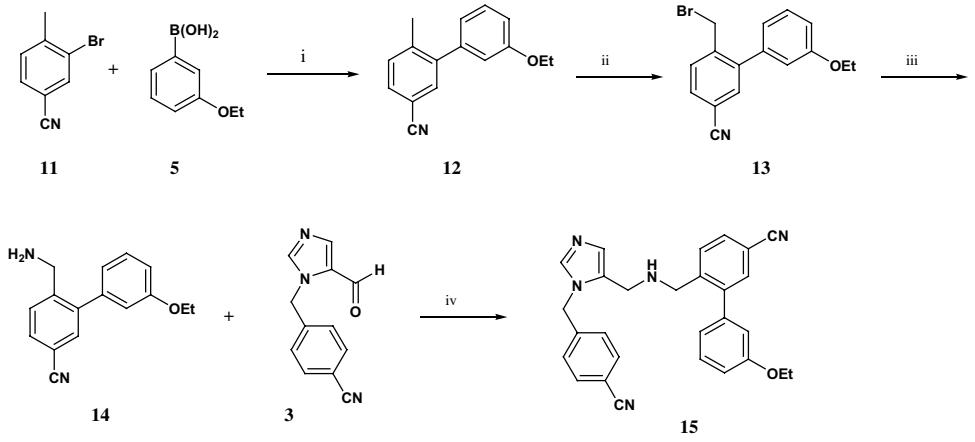
The ether analogs were prepared using a reaction sequence similar to that shown in Scheme 2. For example, treatment of **2** with bromide **13** in the presence of potassium hydroxide gave the ether analog **23**.

Acetylenic, amino, and ether analogs of 4-cyanobenzyl imidazole FTIs were tested for their inhibitory activity against both FTase and GGTase-1 enzymes. The effects of moving the 4-cyanopheny moiety to the imidazole ring of the phenyl acetylene **1** is shown in Table 1 with two representative examples. The potency of compound **10** (Table 1) was similar to that of lead compound **1** (Table 2) in both the FTase and GGTase-1 assays, and they also possess similar selectivity against FTase. Unfortunately, compound **10** shows 167-fold decrease in Ras processing potency compared with the lead compound **1**. A similar SAR trend was also observed when the ethoxy moeity was replaced with a methoxy group (**16** vs **17**). Compared with **17**, a 21-fold decrease in cellular potency was observed with compound **16**. Since analogs **10** and **16** provide weaker inhibitors, we then turned our attention to the replacement of the acetylenic linker with an aminomethyl moiety as described previously. It was hoped that this modification would increase the cellular potency.

As indicated in Table 3, replacement of the acetylene moiety with an amino methyl linker resulted in a 52-fold increase in potency against FTase enzyme. In contrast, only a small change was observed in the potency against GGTase-1 (**1** vs **18**), and consequently the selectivity improved 56-fold. Unfortunately, the cellular activity of compound **18** is 13-fold less potent than compound **1**. Furthermore, compound **18** has a poor pharmacokinetic (PK) profile, which we speculate might be derived from oxidation of the amino group. To avoid this problem,



Scheme 1. Reagents and conditions: (i) $PySO_3$, DMSO; (ii) $Pd(PPh_3)_4$, toluene, dioxane; (iii) $PhN(Tf)_2$, NEt_3; (iv) $PdCl_2(PPh_3)_2$, CuI, HCCTMS, DMF; (v) K_2CO_3, MeOH; (vi) *t*-BuLi, **3**, −78 °C.



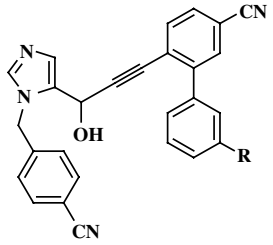
Scheme 2. Reagents and conditions: (i) $Pd(PPh_3)_4$, CsF, DME; (ii) NBS, CH_2Cl_2; (iii) NH_4OH; MeOH; (iv) $NaCNBH_4$, HOAc.

we then introduced acetyl (**20**) or sulfonyl (**21**) groups to the nitrogen atom. However, these changes resulted in 22- and 150-fold decreases in inhibitory potency against FTase, respectively. In contrast, an approximately 4-fold decrease in potency against GGTase-1 was observed. In general, the introduction of electron-withdrawing groups to the nitrogen atom resulted in only poor selectivity compared with that of compound **18**. We also found that the cellular activity of compounds **20** and **21** was much weaker than that of compound **18**. Furthermore, the bioavailability of compound **21** is zero in rat (unpublished result).

We also introduced a methyl group to the nitrogen atom of aminomethyl series. This resulted in only a slight decrease in Ras processing potency compared with analog **18**. Small changes in potency were also observed in the enzymatic assays against both FTase and GGTase-1 (**18** vs **19**). Unfortunately, no improvement in the PK profile of this compound was observed.

Replacement of acetylene with an aminomethyl group resulted in increased potency against FTase and better selectivity for FTase, but resulted in no improvement in PK, we then turned our attention to

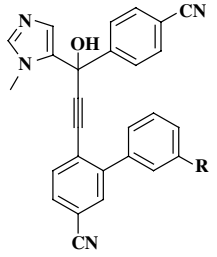
Table 1. FTase inhibition, GGTase-1 inhibition, and Ras processing data for acetylenic analogs **10** and **16**



Compds	R	FTase IC_{50} (nM)[a]	GGTase IC_{50} (nM)[b]	Selectivity (GGT/FT)	Ras EC_{50} (nM)[c]
10	OEt	0.6	6600	11,000	16.7
16	OMe	1.2	12,000	10,000	57.5

[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-3T3 H-Ras cell line.

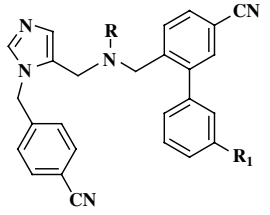
Table 2. FTase inhibition, GGTase-1 inhibition, and Ras processing data for acetylenic analogs **1** and **17**



Compds	R	Ftase IC_{50} (nM)[a]	GGTase IC_{50} (nM)[b]	Selectivity (GGT/FT)	Ras EC_{50} (nM)[c]
1	OEt	0.73	2400	3288	0.1
17	OMe	0.37	4100	11,081	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-3T3 H-Ras cell line.

Table 3. FTase inhibition, GGTase-1 inhibition, and Ras processing data for acetylenic analogs **18**–**21**

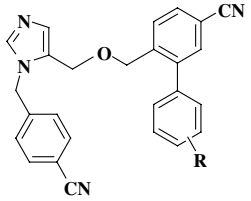


Compds	R	R_1	Ftase IC_{50} (nM)[a]	GGTase IC_{50} (nM)[b]	Selectivity (GGT/FT)	Ras EC_{50} (nM)[c]
18	H	OEt	0.014	2600	185,700	1.34
19	Me	OEt	0.034	1100	32,350	1.57
20	COMe	OEt	0.31	10,000	32,250	16
21	SO_2Me	OEt	2.1	10,000	4760	100

[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-3T3 H-Ras cell line.

the replacement of the nitrogen atom with oxygen. Ether analogs of 4-cyanobenzyl imidazole FTIs were tested for their inhibitory activity against both FTase and GGTase-1 enzymes. The effect of replacing nitrogen atom with oxygen in the amino analog **18** is shown in Table 4.

Table 4. FTase inhibition, GGTase-1 inhibition, and Ras processing data for acetylenic analogs **22**–**29**



Compds	R	FTase IC_{50} (nM)[a]	GGTase IC_{50} (nM)[b]	Selectivity (GGT/FT)	Ras EC_{50} (nM)[c]
22	3-OMe	0.46	10,000	21,700	32
23	3-OEt	0.27	3200	11,850	21.9
24	3-Cl	0.37	6800	18,380	7.7
25	3-OCF_3	0.37	990	2700	<100
26	4-OEt	1.2	2300	1920	<100
27	4-OCF_3	0.62	1300	2100	52
28	4-*t*-Bu	0.36	870	2420	>100
29	3,4-OCH_2O–	0.1	3200	32,000	1.65

[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-3T3 H-Ras cell line.

As indicated in Table 4, replacement of the nitrogen atom of the amino methyl analog resulted in a 19-fold decrease in potency in the inhibition of FTase enzymes (**18** vs **23**). In contrast to this result, little change in potency was observed in the inhibition of GGTase-1. Consequently, the selectivity is worse in the ether series than the corresponding amino series (**18** vs **23**). In general, ether analogs were less potent inhibitors of Ras processing activity than their corresponding amino analogs.

Since compound **23** provided only moderate enzymatic and cellular activities, we then focused our attention on SAR studies of the phenyl ring in the ether series. The 3,4-methylenedioxy analog (**29**) was found to be the most potent FTase inhibitor in this series so far. Both electron-donating and withdrawing groups are tolerated at the C3- and C4-positions. To probe the steric volume at the C4-position of the phenyl pocket we replaced the trifluoromethoxy group with a bulky *tert*-butyl group, and found this had little impact on the potency (**27** vs **28**). The same phenomenon was also observed at the C3-position.

With regard to activity against GGTase, the introduction of electron withdrawing groups such as trifluoromethyl or chloro resulted in an increase in potency. In addition, a large group at the C4-position also caused an increase in potency. In general, the ether series showed only moderate selectivity with the exception of compounds **22**, **24**, and **29**, which have more than 15,000-fold selectivity in favor of FTase inhibition.

The introduction of a trifluoromethoxy or methoxy group to the C3-position of the phenyl ring in the ether series was found to result in a decrease in Ras processing potency compared with analog **23**. Introduction of an ethoxy or trifluoromethoxy group at the C4-position caused a similar reduction in potency, and potency was further reduced by replacement of the trifluoromethoxy moiety with a *tert*-butyl group (cf. **27** and **28**). The only acceptable substituent with regard to Ras processing was found to be the methylenedioxy moiety (**29**). In addition, compound **29** has oral bioavailability of 11.3% in rat compared with the complete lack of bioavailabilty observed in the compound **21**.

In summary, we have varied the substituent pattern at the imidazole ring of the imidazole acetylenic alcohol **1** and examined the resultant effects on inhibitory activity. The results (Table 1) indicated that moving the 4-cyanophenyl moeity is not well tolerated. Replacement of acetylene moiety of compound **18** with an amino methyl linker increased the potency in inhibition of FTase enzyme and selectivity (Table 3), but the compound suffered from poor oral bioavailability in rat. To further improve the PK property of the inhibitors, we replaced the nitrogen atom with oxygen. In general, compounds having the ether linkage (Table 4) possessed potent inhibitory activities against the FTase enzyme. The highest selectivity for FTase inhibition over GGTase-1 was observed in compound **29**. This compound is more potent in inhibition of FTase enzyme and possesses better selectivity. It also has reasonable bioavailability in rat. Further SAR studies are in progress.

References and notes

1. (a) Clarke, S. *Annu. Rev. Biochem.* **1992**, *61*, 355; (b) Sawyer, C. L.; Denny, C. T. *Cell* **1994**, *77*, 171.
2. Barbacid, M. *Annu. Rev. Biochem.* **1987**, *56*, 779.
3. Lowy, D. R.; Willumsen, B. M. *Annu. Rev. Biochem.* **1993**, *62*, 851.
4. Zhang, F. L.; Casey, P. J. *Annu. Rev. Biochem.* **1996**, *65*, 241.
5. Clarke, S.; Vogel, J. P.; Deschenes, R. J.; Stock, J. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4643.

6. Gutierrez, L.; Magee, A. I.; Marshall, C. J.; Hancock, J. F. *EMBO J.* **1989**, *8*, 1093.
7. Kohl, N. E.; Mosser, S. D.; deSolms, S. J.; Giuliani, E. A.; Pompliano, D. L.; Graham, S. L.; Smith, R. L.; Scolnick, E. M.; Oliff, A. J.; Gibbs, J. B. *Science* **1993**, *260*, 1934.
8. James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C.; Lucas, B. K.; Levinson, A. D.; Marster, J. C., Jr. *Science* **1993**, *260*, 1937.
9. Nigam, M.; Seong, C.-M.; Qian, Y.; Hamilton, A. D.; Sebti, S. M. *J. Biol. Chem.* **1993**, *268*, 20695.
10. Bell, I. M. *J. Med. Chem.* **2004**, *47*, 1869.
11. Wallace, A.; Koblan, K. S.; Hamilton, K.; Marqui-Omar, D. J.; Miller, P. J.; Mosser, S. D.; Omer, C. A.; Schaber, M. D.; Cortese, R.; Oliff, A. I.; Gibbs, J. B.; Pessi, A. *J. Biol. Chem.* **1996**, *271*, 31306.
12. Prendergast, G. *Curr. Opin. Cell Biol.* **2000**, 166.
13. Du, W.; Lebowitz, P. F.; Prendergast, G. C. *Mol. Cell. Biol.* **1999**, *19*, 183.
14. Prendergast, G. C.; Du, W. *Drug Resist. Update* **1999**, *2*, 81.
15. Lin, N.-H.; Wang, L.; Cohen, J.; Gu, W.-Z.; Frost, D.; Zhang, H.; Rosenberg, S.; Sham, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1293.
16. Lin, N.-H.; Wang, L.; Cohen, J.; Gu, W.-Z.; Frost, D.; Zhang, H.; Rosenberg, S.; Sham, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3821.
17. Dinsmore, C.; Bell, I. M. *Curr. Top. Med. Chem.* **2003**, *3*, 1075–1093.
18. Williams, T. M.; Bergman, J. M.; Brashear, K.; Breslin, M. J.; Dinsmore, C. J.; Hutchinson, J. H.; MacTough, S. C.; Stump, C. A.; Wei, D. D.; Zartman, C. B.; Bogusky, M. J.; Culberson, J. C.; Buser-Doepner, C.; Davide, J.; Greenberg, I. B.; Hamilton, K. A.; Koblan, K. S.; Kohl, N. E.; Liu, D.; Lobell, R. B.; Mosser, S. D.; O'Neill, T. J.; Rands, E.; Schaber, M. D.; Wilson, F.; Senderak, E.; Motzel, S. L.; Gibbs, J. B.; Graham, S. L.; Heimbrook, D. C.; Hartman, G. D.; Oliff, A. I.; Huff, J. R., *J. Med. Chem.* **1999**, *42*, 3779–3784.