Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 2918–2922

Benzimidazolones and indoles as non-thiol farnesyltransferase inhibitors based on tipifarnib scaffold: synthesis and activity

Qun Li,* Tongmei Li, Keith W. Woods, Wen-Zhen Gu, Jerry Cohen, Vincent S. Stoll, Tomas Galicia, Charles Hutchins, David Frost, Saul H. Rosenberg and Hing L. Sham

Cancer Research, GPRD, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

Received 18 February 2005; revised 8 March 2005; accepted 14 March 2005
Available online 21 April 2005

Abstract—A series of analogs of tipifarnib (**1**) has been synthesized as inhibitors of FTase by substituting the benzimidazolones and indoles for the 2-quinolone of tipifarnib. The novel benzimidazolones are potent and selective FTase inhibitors (FTIs) with IC_{50} values of the best compounds close to that of tipifarnib. The current series demonstrate good cellular activity as measured in their inhibiting the Ras processing in NIH-3T3 cells, with compounds **2c** and **2f** displaying EC_{50} values of 18 and 22 nM, respectively.

Farnesyltransferase (FTase) inhibitors have been shown to inhibit the growth of a variety of experimental human xenograft models and to be effective for the treatment of several cancers in recent clinical trials.[1,2] By blocking the prenylation of Ras proteins and other oncoprotein targets that play major roles in a number of intracellular signaling pathways that control cell proliferation, FTase inhibitors are generally believed to have reduced intrinsic toxicity as compared with conventional cytotoxic agents. Among the several FTase inhibitors in Phase III clinical trials, tipifarnib (R-115777, **1**)[3] is perhaps the most potent and selective non-thiol FTase inhibitor.[2,4] In the preceding papers, we demonstrated that the 2-quinolone core of **1** could be replaced by 4-quinolones and other heterocycles.[5a] We also detailed how the scaffold of tipifarnib could be rearranged to give simpler inhibitors of FTase while maintaining potency.[5b,c] In this paper, we report on further efforts to utilize tipifarnib as a template in designing a novel class of FTase inhibitors.

The X-ray structure of tipifarnib[5a,6] in complex with FTase revealed that the chlorophenyl group (C-ring) is indispensable for the overall potent interaction of tipifarnib with the enzyme. By occupying the tryptophan-rich hydrophobic pocket, the C-ring is nearly parallel to the D-ring. Shrinkage of the A-ring to five-membered heterocycles would not significantly alter the orientation of the D-ring, while yielding a new template (as represented by **2**) that has not previously been explored.[4d] The benzimidazolone core in **2** is relatively easy to synthesize and retains the carbonyl group of the parent quinolone, which is important for activity (Fig. 1).

Our initial approach to the target molecules is illustrated in Scheme 1. 2-Fluoronitrobenzene **3** was converted to phenylaniline **4** in 97% yield by nucleophilic displacement of the fluorine by 3-chloroaniline.[7] Reduction of the nitro group with $SnCl_2$ followed by cyclization with carbonyl-diimidazole gave benzimidazolone **5**. Compound **5** underwent Friedel–Crafts 4-chlorobenzoylation to produce two regioisomers **6** and **7**[8] both of which were converted to the final compounds **2a** and

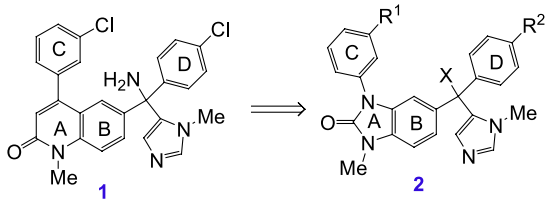
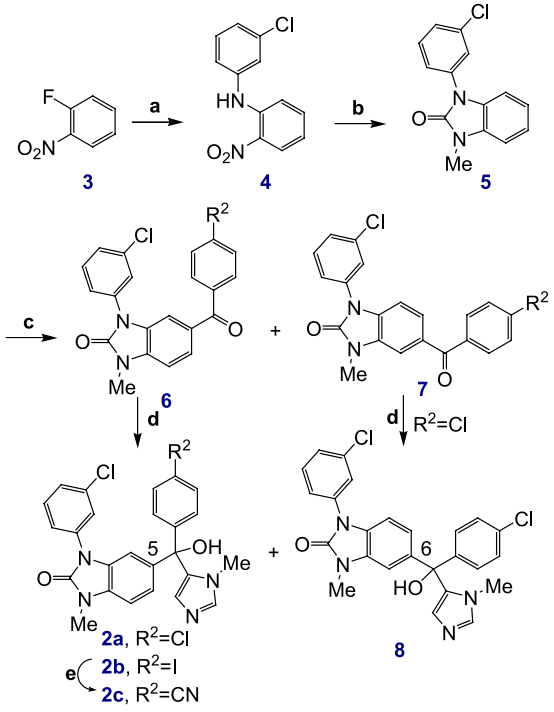


Figure 1. Modifications of tipifarnib (**1**) lead to novel inhibitors (**2**) of FTase.

* Corresponding author. Tel.: +1 847 937 7125; fax: +1 847 936 1550; e-mail: qun.li@abbott.com

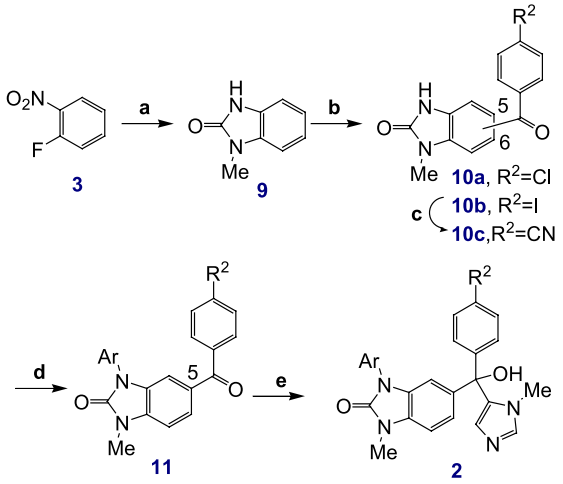
0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.03.049



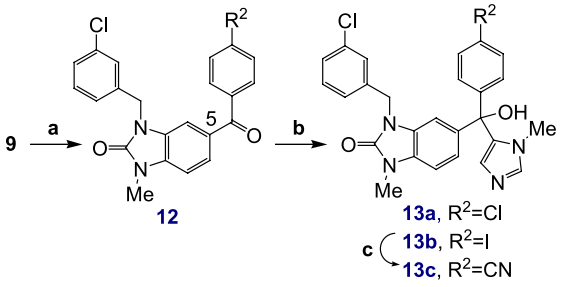
Scheme 1. Reagents and conditions: (a) 3-chloroaniline, KF, 180 °C, 44 h, 97%; (b) (i) $SnCl_2{\cdot}2H_2O$, HCl, EtOH, 0 °C–rt, overnight, 97%; (ii) CDI, CH_2Cl_2, reflux, 2 h, then EtOH, reflux, 2 h, 73%; (iii) MeI, NaH, DMF, rt, 1 h, 94%; (c) 4-halobenzoyl chloride (excess), $AlCl_3$, neat, 150 °C, overnight, 17–40% (**6**), 21% (**7**, X = Cl); (d) (i) 1-methyl-2-TES-imidazole, *tert*-BuLi, THF, −78 °C, 0.5 h, then **6** or **7**, −78 °C to rt, 4 h; (ii) MeOH, 10% HCl, rt, 0.5 h, 62–87% (**2**), 42% (**8**); (e) $Zn(CN)_2$, $Pd(P(Ph)_3)_4$, DMF, 80 °C, 3 h, 71%.

8, respectively, by addition of 1-methyl-2-triethylsilyl-5-imidazolyl lithium[9] and subsequent removal of the triethylsilyl protecting group with HCl in methanol. Repeating the same sequence with 4-iodobenzoyl chloride in place of the 4-chloro gave iodo analog **2b**, which was reacted with zinc cyanide catalyzed by tetrakis(triphenylphosphine)palladium to furnish cyano analog **2c** in 71% yield.

A more convergent synthetic approach that allows for modifications of the C- and D-rings is shown in Scheme 2. Fluoronitrobenzene (**3**) was converted to *N*-methylbenzimidazolone **9** in a three-step sequence including nucleophilic substitution by methylamine, hydrogenation catalyzed by palladium on carbon and cyclization with carbonyldiimidazole. Benzimidazolone **9** underwent Friedel–Crafts reaction with 4-halobenzoyl chloride to provide compounds **10** as a 1:1 mixture of the 5-ketone and the 6-ketone in 46–73% yield. As before, cyano analog **10c** was prepared in 98% yield from the iodo compound (**10b**). Without separation, **10**, as a mixture was reacted with arylboronic acids in the presence of cupric acetate utilizing a condition developed by Chan et al.[10] to yield the desired ketones **11** in 12–43% yield and the other regioisomers after chromatographic separation. Addition of the imidazolyl lithium to ketones **11** utilizing the same conditions used previously for **2a** furnished the final products.



Scheme 2. Reagents and conditions: (a) (i) $MeNH_2$, $MeOH/H_2O$, reflux, overnight, 98%; (ii) H_2, 10% Pd–C, MeOH, rt, 30 min, 98%; (iii) CDI, CH_2Cl_2, reflux, 3 h, 73%; (b) 4-halobenzoyl chloride (excess), $AlCl_3$, neat, 150 °C, overnight, 46–73%, 1:1 mixture of 5- and 6-isomers; (c) $Zn(CN)_2$, $Pd(P(Ph)_3)_4$, DMF, 80 °C, 3 h, 98%; (d) $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, CH_2Cl_2, rt, 3 days, 12–43%; (e) 1-methyl-2-TES-imidazole, *tert*-BuLi, THF, −78 °C, 0.5 h, then **11**, −78 °C to rt, 4 h; (ii) MeOH, 10% HCl, rt, 0.5 h, 19–87%.

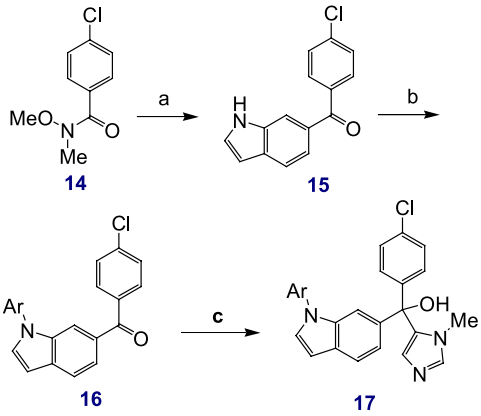


Scheme 3. Reagents and conditions: (a) (i) 3-chlorobenzyl chloride, NaH, DMF, rt, 1 h, 95%; (ii) 4-halobenzoyl chloride (excess), $AlCl_3$, neat, 100 °C, overnight, 31–34%; (b) 1-methyl-2-TES-imidazole, *tert*-BuLi, THF, −78 °C, 0.5 h, then **12**, −78 °C to rt, 4 h; (ii) MeOH, 10% HCl, rt, 0.5 h, 85–94%; (c) $Zn(CN)_2$, $Pd(P(Ph)_3)_4$, DMF, 80 °C, 3 h, 62%.

The *N*-benzyl analogs (**13**) were prepared similarly from **9** by *N*-chlorobenzylation, Friedel–Crafts acylation and subsequent addition of the imidazolyl lithium as depicted in Scheme 3. Formation of cyano analog **13c** was achieved in 62% yield from the corresponding iodide (**13b**) with zinc cyanide in the presence of $Pd(PPh_3)_4$.

The synthesis of the indole analogs (**17**) is illustrated in Scheme 4. Reaction of Weinreb amide **14**[11] with 5-indolyllithium[12] provided ketone **15** in 43% yield. Ullmann arylation of **15** with the aryliodides gave *N*-arylindole **16** in 27–30% yield. Addition of the imidazolyl lithium as described previously furnished the desired compounds **17** in 49–73% yield.

The compounds were evaluated for their inhibitory activities against bovine FTase[13] and cellular Ras pro-



Scheme 4. Reagents and conditions: (a) 5-Bromoindazole, KH/*tert*-BuLi, ether, −78 °C, 10 min, then **16**, −78 °C to rt, 1 h, 43%; (b) 3-iodochlorobenzene, CuBr, Na_2CO_3, NMP, 170 °C, overnight, 27–30%; (c) 1-methyl-2-TES-imidazole, *tert*-BuLi, THF, −78 °C, 0.5 h, then **16**, −78 °C to rt, 4 h; (ii) MeOH, 10% HCl, rt, 0.5 h, 49–73%.

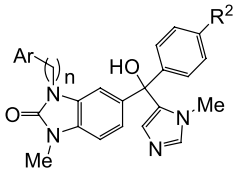
cessing in H-*ras* transformed cells.[13] The results are summarized in Table 1. Also included in Table 1 is the selectivity data against type I geranylgeranyltransferase (GGTase I), a closely related enzyme that is not targeted.

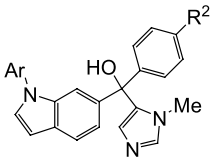
Compound **2a** is a potent FTase inhibitor with an IC_{50} of 16 nM. This represents an approximately 20-fold drop in activity as a result of the A-ring contraction of tipifarnib. Please note that **2a** lacks a tertiary amino group as seen in **1**. Because the hydroxy analog[2c] of the tipifarnib is only 2-fold less active against FTase than tipifarnib, the hydroxy analogs were used in this study. Compared to **2a**, activity is reduced ~100-fold for regioisomer **8**, in which the tertiary carbon is attached to C-6 of the benzimidazolone.

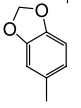
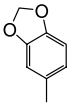
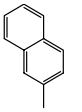
Further modifications of the C- and D-rings were undertaken in an attempt to improve the activity (Table 1). Substituting iodine for the chlorine in the D-ring (**2b**) is deleterious. On the other hand, the 4-cyanophenyl analog (**2c**) demonstrates excellent activities in both enzymatic and cellular assays, with IC_{50} and EC_{50} values of 1.4 and 18.1 nM, respectively. The activity of **2c** is close to that of tipifarnib, exhibiting only 2-fold and about 10-fold reduced potent against FTase and Ras processing, respectively. These potency-enhancing effects of the cyanophenyl group have been known in the literature[14] as well as from our previous work.[5,15] Although its role is not clear, the X-ray structure and the modeling (Fig. 2) show that the D-ring cyano group fits into a small pocket and accepts H-bonds from the main chain NH of both Tyr361 and Phe360 of the β-subunit.[5a]

Taking advantage of the convergent synthesis, several compounds with various C-rings were prepared. Replacing the 3-chloro with methoxyl (**2d**) or ethoxyl (**2f**) groups imparted modest increases in activity against FTase. Compound **2f** also displays improved cellular potency, with an EC_{50} of 22 nM. The bicyclic replacements

Table 1. Activity of benzimidazolone and indole farnesyltransferase inhibitors[13]





Compd	Ar	R^2	*n*	IC_{50} (nM) FT[a]	IC_{50} (nM) GGT[b]	EC_{50} (nM) Ras[c] processing
2a		Cl	0	16	11,000	26%[d]
2b		I	0	24	1200	2%[d]
2c		CN	0	1.4	1800	18.1
2d		Cl	0	6.7	>10,000	24%[d]
2e		CN	0	5.1	>10,000	NT[e]
2f		Cl	0	6.6	7500	22
2g		CN	0	0.5	>10,000	47%[d]
2h		Cl	0	150	NT[e]	NT[e]
2i		CN	0	8	>10,000	0%[d]
2j		Cl	0	21	2900	0%[d]
13a		Cl	1	150	NT[e]	NT[e]
13b		I	1	71	NT[e]	NT[e]
13c		CN	1	5.2	5600	51%[d]
17a		—	—	36	NT[e]	13%[f]
17b		—	—	200	NT[e]	NT[e]
8	—	—	—	1100	NT[e]	NT[e]

(*continued on next page*)

Table 1 (*continued*)

Compd	Ar	R^2	*n*	IC_{50} (nM)		EC_{50} (nM)
				FT[a]	GGT[b]	Ras[c] processing
1	Tipifarnib[g]			0.65	1100	1.6
	Lonafarnib[g,16]			8.3	>10,000	100

[a] Bovine farnesyltransferase.
[b] Bovine geranylgeranyltransferase.
[c] In H-*ras* NIH-3T3 cells.
[d] Inhibition at 100 nM.
[e] Not tested.
[f] Inhibition at 1000 nM.
[g] Data from racemic mixtures.

including the benzodioxolanes (**2h**,**i**) and the naphthalene (**2j**) are less favorable. The most potent compound in vitro in this series is **2g**, which combines the 3-ethoxyphenyl and 4-cyanophenyl structural motifs. Compound **2g** displays an IC_{50} of 0.5 nM, which is comparable to that of tipifarnib (IC_{50} 0.65 nM). Unfortunately, **2g** was found to have poor cellular activity in the Ras processing assay. Compared with tipifarnib, the C-ring attached to the benzimidazolones is tilted away from the D-ring, resulting an altered conformation of which may not be optimal. To compensate for this effect, several compounds with a carbon inserted between the A- and the C-rings were designed and synthesized. With the exception of **13c**, in general, the benzyl analogs (**13**) display sharply reduced activity in comparison with the phenyl analogs (**2**).

Finally, a more drastic modification that involved substituting the indole for the benzimidazolone was explored. The resulting compounds (**17**) lack the carbonyl group believed to be important for binding to FTase. Surprisingly, the activity of **17a** is better than expected with an IC_{50} of 36 nM, which is merely 2-fold less active than the similar benzimidazolone (**2a**). The activity of the 1-naphthyl analog (**17b**) declines sharply.

All compounds in Table 1 exhibit good selectivity against GGTase I with IC_{50} values equal to or greater than 1.2 μM.

Stereo view of an overlay of a model of **2a**, which was modeled based on the X-ray crystal structure of a close chemical analog[15] as well as the X-ray crystal structure of tipifarnib (**1**)[5a,6] is shown in Figure 2. The model of **2a** superimposes very well with tipifarnib, in which the imidazole is interacting closely with the Zn^{2+} in the active site. The A-ring extends out over the loop of residues Asp359-Phe360 forming 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 farnesylpyrophosphate (HFP). The C- and D-rings also stack together forming a strong π/π interaction.

In summary, a series of analogs of tipifarnib have been synthesized as inhibitors of FTase by substituting benzimidazolone and indole for the 2-quinolone moiety of tipifarnib. The novel benzimidazolones are potent and selective inhibitors of FTase. The best compounds of this series exhibits IC_{50} values close to those of tipifarnib. The current series demonstrate good cellular activity as measured by their Ras processing inhibitory activity in NIH-3T3 cells. Even with the tertiary hydroxy group, rather than the known cellular potency-enhancing amino group,[2b] compounds **2c** and **2f** display EC_{50} values of 18 and 22 nM, respectively. These encouraging results warrant further investigation in order to optimize the desirable properties of these molecules and to extend further in the achiral series as described in our previous paper.[5b]

References and notes

1. For a recent reviews on FTIs see: (a) Sebti, S. M.; Adjei, A. A. *Semin. Oncol.* **2004**, *31*(Suppl. I), 28–39; (b) Mazieres, J.; Pradines, A.; Favre, G. *Cancer Lett.* **2004**, *206*, 159–167; (c) Doll, R. J.; Kirschmeier, P.; Bishop, W. R. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 478–486; (d) Bell, I. M. *J. Med. Chem.* **2004**, *47*, 1869–1878.
2. (a) van Cutsem, E.; van de Velde, H.; Karasek, P.; Oettle, H.; Vervenne, W. L.; Szawlowski, A.; Schoffski, P.; Post, S.; Verslype, C.; Neumann, H.; Safran, H.; Humblet, Y.; Perez Ruixo, J.; Ma, Y.; von Hoff, D. *J. Clin. Oncol.* **2004**, *22*, 1430–1438; (b) Venet, M.; End, D.; Angibaud, P. *Curr. Top. Med. Chem.* **2003**, *3*, 1095–1102; (c) Caponigro, F.; Casale, M.; Bryce, J. *Expert Opin. Invest. Drugs* **2003**, *12*, 943–954; (d) Norman, P. *Curr. Opin. Invest. Drugs* **2002**, *3*, 313–319.
3. Angibaud, P. R.; Venet, M. G.; Filliers, W.; Broeckx, R.; Ligny, Y. A.; Muller, P.; Poncelet, V. S.; End, D. W. *Eur. J. Org. Chem.* **2004**, 479–486.
4. Relevant studies using tipifarnib as a template: (a) Angibaud, P.; Bourdrez, X.; End, D. W.; Freyne, E.; Janicot, M.; Lezouret, P.; Ligny, Y.; Mannens, G.;

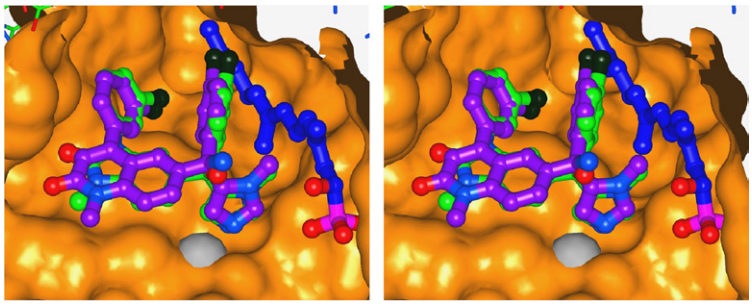


Figure 2. Stereo view of an overlay of a model of compound **2a** (in green) over the X-ray crystal structure of tipifarnib (**1**)[5] (in purple) in complex with FTase in the active site. Zn^{2+} is in shown in gray and hydroxy farnesylpyrophosphate in blue.

Daqmsch, S.; Mevellec, L.; Meyer, C.; Muller, P.; Pilatte, I.; Poncelet, V.; Roux, B.; Smets, G.; Dun, J. V.; Remoortere, P. V.; Venet, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4365–4369; (b) Angibaud, P.; Saha, A. K.; Bourdrez, X.; End, D. W.; Freyne, E.; Lezouret, P.; Mannens, G.; Mevellec, L.; Meyer, C.; Muller, P.; Pilatte, I.; Poncelet, V.; Roux, B.; Smets, G.; Dun, J. V.; Remoortere, P. V.; Venet, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4361–4364; (c) Angibaud, P.; Bourdrez, X.; Devine, A.; End, D. W.; Freyne, E.; Ligny, Y.; Muller, P.; Mannens, G.; Pilatte, I.; Poncelet, V.; Skrzat, S.; Smets, G.; Dun, J. V.; Remoortere, P. V.; Venet, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1543–1547; (d) Dong, Z. X.; Shen, Y. WO 9965898, 1999; *Chem. Abstr.* **1999**, *132*, 35705.

5. (a) Li, Q.; Claiborne, A.; Li, T.; Hasvold, L.; Stoll, S. V.; Muchmore, S.; Jakob, C. G.; Gu, W.; Cohen, J.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5367–5370; (b) Li, Q.; Wang, G. T.; Li, T.; Gwaltney, S. L., II; Woods, K. W.; Claiborne, A.; Wang, X.; Gu, W.; Cohen, J.; Stoll, S. V.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett* **2004**, *14*, 5371–5376; (c) Li, Q.; Woods, K. W.; Wang, W.; Lin, N.-H.; Claiborne, A.; Gu, W.-Z.; Cohen, J.; Stoll, S. V.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2033–2039.
6. Reid, T. S.; Beese, L. S. *Biochemistry* **2004**, *43*, 6877–6884.
7. Kulagowski, J. J.; Rees, C. W. *Synthesis* **1980**, 215–216.
8. The structures of the two regioisomers **6** and **7** were determined by NOE.
9. Molina, P.; Fresneda, P. M.; Garcia-Zafra, S. *Tetrahedron Lett.* **1996**, *37*, 9353–9356.
10. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
11. Gallagher, T. F.; Seibel, G. L.; Kassis, S.; Laydon, J. T.; Blumenthal, M. J.; Lee, J. C.; Lee, D.; Boehm, J. C.; Fier-Thompson, S. M.; Abt, J. W.; Soreson, M. E.; Smietana, J. M.; Hall, R. F.; Garigipati, R. S.; Bender, P. E.; Erhard, K. F.; Krog, A. J.; Hofmann, G. A.; Sheldrake, P. L.; McDonnell, P. C.; Kumar, S.; Young, P. R.; Adams, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 49–64.
12. Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110.
13. Assay methods described in: Vogt, A.; Qian, Y.; Blaskovich, M. A.; Fossum, R. D.; Hamilton, A. D.; Sebti, S. M. *J. Biol. Chem.* **1995**, *270*, 660–664.
14. (a) Anthony, N. J.; Gomez, R. P.; Schaber, M. D.; Mosser, S. D.; Hamilton, K. A.; O'Neil, T. J.; Koblan, K. S.; Graham, S. L.; Hartman, G. D.; Shah, D.; Rands, E.; Kohl, N. E.; Gibbs, J. B.; Oliff, A. I. *J. Med. Chem.* **1999**, *42*, 3356–3368; (b) 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.
15. Wang, L.; Wang, G. T.; Wang, X.; Tong, Y.; Sullivan, G.; Park, D.; Leonard, N.; Li, Q.; Cohen, J.; Gu, W.-Z.; Zhang, H.; Bauch, J.; Jacob, C. G.; Hutchins, C. W.; Stoll, S. V.; Marsh, K.; Rosenberg, S. H.; Sham, H.; Lin, N.-H. *J. Med. Chem.* **2004**, *47*, 612–626.
16. Wang, E.; Johnson, W. W. *Chemotherapy* **2003**, *49*, 303–308.