Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 153–158
Bioorganic & Medicinal Chemistry Letters

Design and synthesis of *o*-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles as inhibitors of farnesyltransferase

Gary T. Wang,* Xilu Wang, Weibo Wang, Lisa A. Hasvold, Gerry Sullivan, Charles W. Hutchins, Steve O'Conner, Robert Gentiles, Thomas Sowin, Jerry Cohen, Wen-Zhen Gu, Haiying Zhang, Saul H. Rosenberg and Hing L. Sham

Global Pharmaceutical Research & Development, Abbott Laboratories, Abbott Park, IL 60064, USA

Received 2 September 2004; revised 5 October 2004; accepted 6 October 2004
Available online 28 October 2004

Abstract—A non-methionine FT inhibitor lead structure (**1**) was designed through computer modeling of the peptidomimetic FT inhibitor ABT839. Optimization of this lead resulted in compounds **2e** and **2g**, with FT IC_{50} values of 1.3 and 1.8 nM, GGT IC_{50} of 1400 nM, and EC_{50} (*Ras* processing) values of 13 and 11 nM, respectively.

Inhibition of farnesyltransferase (FT) has been vigorously pursued as a promising target for the treatment of a broad spectrum of cancers, and several compounds, such as SCH66336 (Sarasar™) and R115777 (tipifarnib or Zarnestra™), are currently in advanced human clinical trials.[1–3] FT catalyzes the transfer of a farnesyl moiety from farnesyl pyrophosphate to a cysteine residue found in the tetrapeptide sequence CAAX (C = Cys, A = an aliphatic amino acid, X is typically Met) in the carboxyl terminal of a group of membrane-bound small G-proteins such as Ras, RhoB, RhoE, lamin A and B, and transducin. This post-translational processing is essential for the signal transduction function of these proteins since the farnesyl moiety is required to anchor these proteins to the cell membrane. In the early days, it was believed that farnesylation of Ras protein was *the* therapeutic target, since oncogenic mutations of Ras have been identified in ~30% of all human malignancies and these mutations result in constitutively active signaling and uncontrolled cell proliferation.[4] However, recent data from several pharmacodynamics studies have revealed a disconnection between Ras farnesylation and anti-neoplastic efficacy, suggesting that Ras farnesylation should be regarded as a surrogate target or a biomarker at the best.[5–7] An enzyme closely related to FT is geranylgeranyl transferase (GGT) type I, which transfers a geranylgeranyl moiety to the CAAX sequence (X is typically Leu) of the substrate proteins. Even though it was initially uncertain whether selective inhibition of FT over GGT was necessary or, perhaps, simultaneous inhibition of FT and GGT was desired, recent in vivo studies using dual active FT–GGT inhibitors have unequivocally established the necessity for selective FT inhibitors, since the dual-active inhibitors were proven to be acutely lethal.[8,9]

Our FT inhibition program initially resulted in the discovery of ABT-839 (Fig. 1), a first generation clinical candidate.[10–12] ABT-839 is a potent FT inhibitor (IC_{50} = 1.1 nM) with good selectivity (GGT/FT = 75,000) and cellular activity (EC_{50} = 16 nM in a Ras processing assay in NIH 3T3 cells), but lacks oral bioavailability. The poor oral bioavailability of ABT-839 was attributed to the methionine moiety. Toward the goal of designing templates devoid of the methionine moiety, the X-ray crystallographic structure of ABT-839 complexed with FT was compared with the computer models of Janssen's R115777 and Merck's *N*-arylpiperazinone series of FT inhibitors.[13,14] These computer-modeling efforts led to the designing and subsequent synthesis of compound **1** (Fig. 1) as our new lead structure.[15] Compound **1**, which retains the signature *o*-tolyl biphenyl core of ABT-839 but has a cyano group on the B ring replacing the acyl methionine moiety, showed FT inhibition IC_{50} of 84 nM, a modest selectivity (GGT IC_{50} = 1300 nM, GGT/FT = 16) and weak cellular activity (EC_{50} = 2700 nM). In this paper, we report the first part of our effort to optimize this lead, which resulted

Keyword: Farnesyltransferase inhibitors.
* Corresponding author. Tel.: +1 8479372489; fax: +1 8479355165; e-mail: gary.t.wang@abbott.com

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.10.014

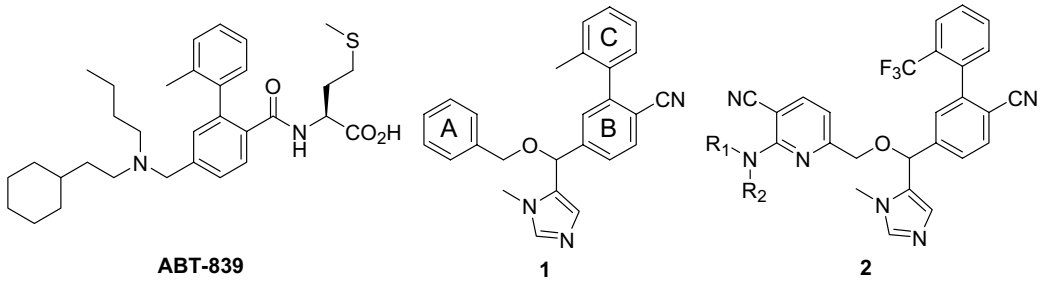
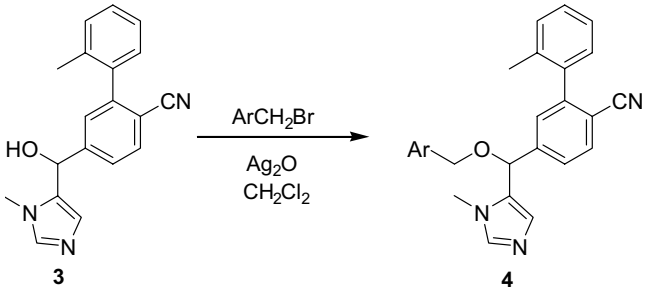


Figure 1.

in the discovery of a series of compounds **2** as potent and selective FT inhibitors with potent activity in cellular assays.

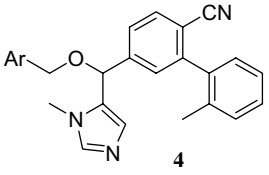
Our attention was first focused on the optimization of the etheral benzyl (A-ring) position. Thus, a library of 80 analogous ethers **4** was prepared from alcohol **3**,[15] by Ag_2O-catalyzed alkylation with commercial available benzyl bromides or benzyl iodides prepared in situ from the benzyl chlorides and NaI (Scheme 1). These compounds were prepared expeditiously using parallel synthesis and were all HPLC-purified and fully characterized.



Scheme 1.

The FT inhibition activity of selected **4** is shown in Table 1. A variety of substituents on the benzyl group was tolerated and result in augmented potency relative to **1**. However, electron-withdrawing substituents generally gave more potent inhibitors in comparison to compounds bearing electron-donating groups (**4a**–**j**). For mono-substituted compounds, there was a clear preference for *para*-substitution, while *ortho*-substitution gave

Table 1. SAR of *o*-tolyl biphenyls **4**



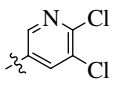
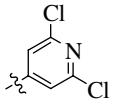
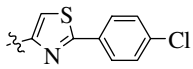
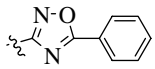
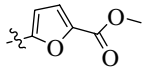
Compd	Ar	FT IC_{50} (nM)[a]	Compd	Ar	FT IC_{50} (nM)[a]
1	Phenyl	84	**4u**	*o*-Cl–phenyl	48
4a	*o*-Tolyl	54	**4v**	*m*-Cl–phenyl	19
4b	*m*-Tolyl	61	**4w**	*p*-Cl–phenyl	11
4c	*p*-Tolyl	54	**4x**	*o*-Br–phenyl	65%[b]
4d	*p*-^{i}Pr–phenyl	51	**4y**	*m*-Br–phenyl	13
4e	*p*-^{t}Bu–phenyl	87	**4z**	*p*-Br–phenyl	12
4f	*p*-Phenyl–phenyl	13	**4aa**	*m*-I–phenyl	20
4g	1-Naphthyl	17	**4ab**	*p*-I–phenyl	13
4h	2-Naphthyl	76%[b]	**4ac**	*o*-NO_2–phenyl	33
4i	8-Quinolyl	59	**4ad**	*p*-NO_2–phenyl	7.5
4j	*p*-Methoxyphenyl	59	**4ae**	*m*-CO_2CH_3–phenyl	61
4k	*m*-F_3CO–phenyl	8.3	**4af**	*p*-CO_2CH_3–phenyl	6.1
4L	*p*-F_3CO–phenyl	16	**4ag**	*p*-CH_3SO_2–phenyl	38
4m	*m*-F_3C–phenyl	8.1	**4ah**	3,4-Cl,Cl–phenyl	27
4n	*p*-F_3C–phenyl	12	**4ai**	3,5-Cl,Cl–phenyl	19
4o	*o*-Cyano-phenyl	62	**4aj**	2,6-Cl,Cl–phenyl	81
4p	*m*-Cyano-phenyl	18	**4ak**		15
4q	*p*-Cyano-phenyl	4	**4al**		13

Table 1 (*continued*)

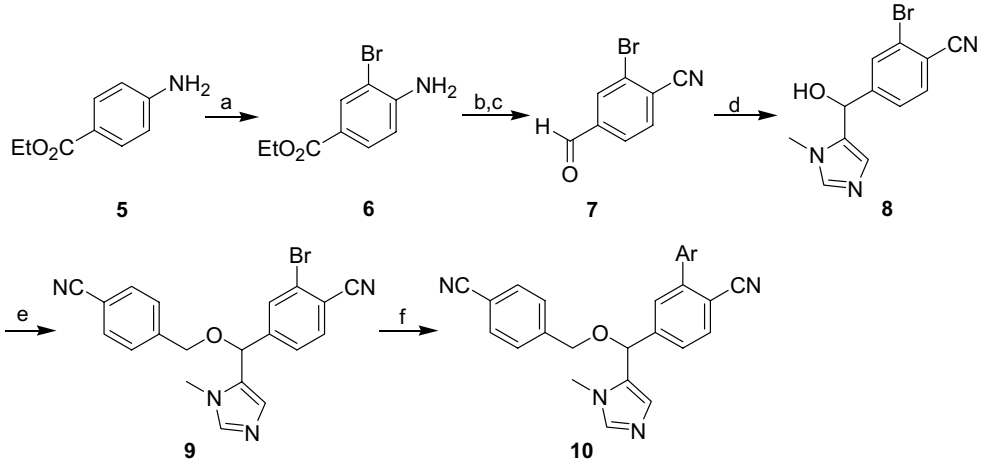
Compd	Ar	FT IC_{50} (nM)[a]	Compd	Ar	FT IC_{50} (nM)[a]
4r	*o*-F–phenyl	70	**4am**		29
4s	*m*-F–phenyl	38	**4an**		56%[b]
4t	*p*-F–phenyl	32	**4ao**		50%[b]

[a] Bovine FT used.
[b] Percentage of inhibition at 100 nM.

the least potent inhibitor (e.g., compare **4o**, **4p**, and **4q**; or **4ac** and **4ad**). Accordingly, the *p*-cyano-benzyl ether **4q**, *p*-nitro-benzyl ether **4ad** and *p*-CO_2CH_3–benzyl ether **4af** are among the most active compounds, being 10–20-fold more potent than **1**. Additional substitution did not result in further enhancement in potency (**4v** vs **4ai**, **4w** vs **4ah**). For heterocyclic ethers, the pyridine ring of **4ak** and **4al** and thiazole ring of **4am** were tolerated while the oxadiazole ring (**4an**) and furan ring (**4ao**) gave less active compounds.

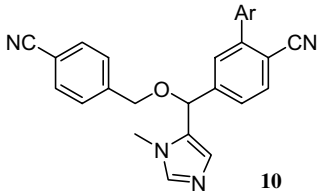
Having established that *p*-cyanobenzyl ether is optimal for A ring, we turned to optimizing the C ring of the biphenyl unit. As shown in Scheme 2, bromination of **5** gave bromide **6**, which was converted to cyano aldehyde **7** through cyanidation via diazonium salt and DIBAL reduction. Addition of the anion generated from 1-methyl-2-triethylsilylimidazole to **7** gave alcohol **8**,[16] which was alkylated with *p*-cyanobenzyl bromide to give bromide **9**, the common intermediate for preparation of **10a**–**j** (Table 2). Previously, during the optimization of the ABT-839 series,[10] it was discovered that the mono-substitution at the *ortho*-position of the C-ring was preferred. Therefore, only a relatively small set of analogs **10** were prepared in the present study. Polar groups at the *ortho*-position (**10d** and **10e**) generally resulted in less potent FT inhibitors. Disubstitution at the 2,4-position seemed to give inferior compounds (**10f**). In contrast, 2,3-disubstitution, as in **10g**, **10h**, and **10j**, gave significantly enhanced activity. In particular, the 2-naphthyl moiety of **10j** led to a 20-fold improvement in FT inhibition and nearly 4-fold improvement in cellular activity relative to **10a**. However, this substitution rendered **10j** also a potent GGT inhibitor (IC_{50} = 18 nM) with no improvement in the FT selectivity as measured by the GGT/FT ratio.[16–18]

The *ortho*-trifluoromethyl substituted **10b** stood out as an attractive compound, with a 6-fold improvement in FT inhibition and 5-fold improvement in cellular activity over **10a**, as well as a 10-fold improvement in selectivity (GGT/FT ratio of 387 for **10b** vs 37.5 for **10a**). Consequently, we decided to combine the *o*-CF_3–biphenyl with other preferred benzyl (A-ring) substitutions from Table 1. Thus, a set of bromo ethers **11** were prepared from alcohol **8** by alkylation with a selected set of benzylic bromides. Suzuki coupling of **11** with *o*-trifluoromethylbenzene boronic acid gave the desired biphenyls **12a**–**d** (Scheme 3). Among these compounds (Table 3), **12d** provided the best profile. Even though the FT IC_{50} decreased by about 3-fold relative to **10b**, **12d** showed similar (albeit insufficient) cellular activity and further improvement in selectivity with a GGT IC_{50} of 1500 nM and GGT/FT ratio of 555.

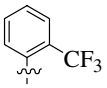
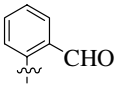
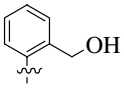
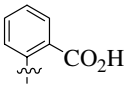
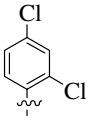
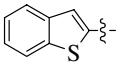
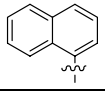


Scheme 2. Reagents and conditions: (a) Br_2, DCM/pyridine, −10 °C to rt, 24 h, 38%. (b) (i) $BF_3{\cdot}Et_2O$, ^{t}BuONO, DCM; (ii) CuCN, NaCN, H_2O/toluene, 48%. (c) DIBAL, DCM, −100 °C, 74%. (d) 1-Methyl-2-triethylsilyl-imidazole, *t*-BuLi, −78 °C, 86%. (e) 4-Cyano-benzyl bromide, Ag_2O, DCM, rt, 24 h, 58%. (f) $ArB(OH)_2$, $Pd(OAc)_2$, Ph_3P, Na_2CO_3, *n*-PrOH, H_2O, 100 °C, 50–80%.

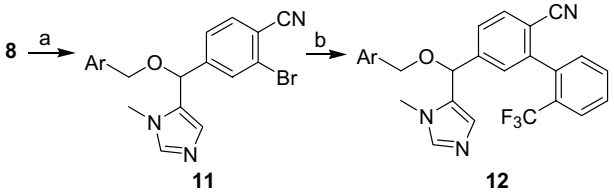
Table 2. SAR of *p*-cyanobenzyl ethers **10**



10

Compound	AR	IC_{50} (nM)		EC_{50} (nM)
		FT[a]	GGT[b]	*Ras* processing[c]
10a (4q)		4.8	180	420
10b		0.8	310	85
10c		1.9	NT	110
10d		5.5	480	89% @ 1 μm
10e		14	NT	>1000
10f		47	NT	>1000
10g		1.5	85	240
10h		2.1	130	>1000
10i		160	NT	NT
10j		0.2	18	110

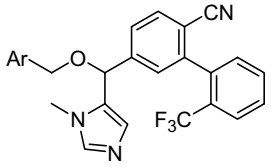
[a] Bovine FT used.
[b] Bovine GGT used.
[c] *H*-ras processing in NIH 3T3 cells.



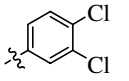
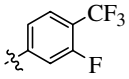
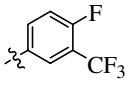
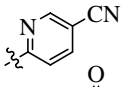
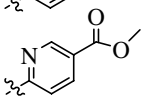
11 **12**

Scheme 3. Reagents and conditions: (a) $ArCH_2Br$, Ag_2O, DCM, rt, 24 h, 40–60%. (b) *o*-$F_3CPhB(OH)_2$, $Pd(OAc)_2$, Ph_3P, Na_2CO_3, *n*-PrOH, H_2O, 100 °C, 40–70%.

Table 3. SAR of *o*-trifluoromethyl biphenyls **12**



12

Compound	AR	IC_{50} (nM)		EC_{50} (nM)
		FT[a]	GGT[b]	*Ras* processing[c]
12a		1.7	72	NT
12b		6.1	160	>1000
12c		4.1	120	100
12d		2.7	1500	90
12d		9	3900	83% @ 100 nM

[a] Bovine FT used.
[b] Bovine GGT used.
[c] *H*-ras processing in NIH 3T3 cells.

In order to further improve the cellular activity of **12d**, we sought to add amino substituents to the 3-cyano-6-pyridyl ring, leading to structure **2**. This idea was based on the structure of SCH66336, which has a 1-piperidinecarboxamide interacting with a remote binding pocket of the FT active site.[1,19] Superimposition of the computer model of a hypothetical (2-dimethylamino-3-cyano-6-pyridyl)methyl ether with the X-ray structure of SCH66336 suggested that the R_1R_2N-residue of **2** can potentially occupy the same binding site as the terminal piperidine moiety of SCH66336 (Fig. 2), offering an opportunity to alter the physical properties of these molecules.

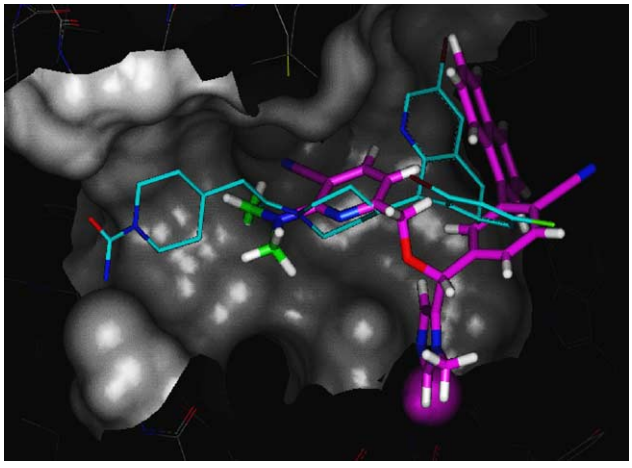
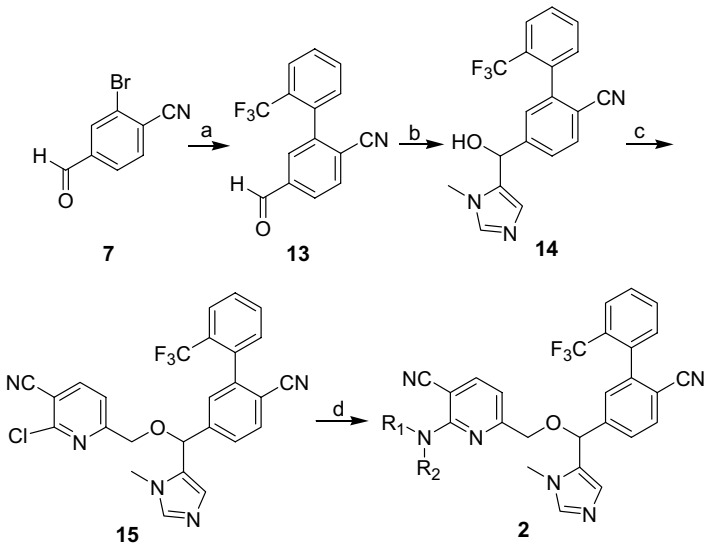


Figure 2. Superimposition of the computer model of a hypothetical (2-dimethylamino-3-cyano-6-pyridyl)methyl ether (in purple) with the X-ray structure of SCH66336 (in blue).[19]



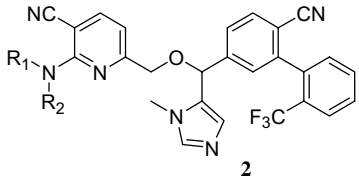
Scheme 4. Reagents and conditions: (a) *o*-$F_3CPhB(OH)_2$, CsF, $Pd(PPh_3)_4$, DME, MeOH, 100 °C, 73%. (b) 1-Methyl-2-triethylsilyl-imidazole, *t*-BuLi, −78 °C, 62%. (c) (3-Chloro-4-cyano-6-pyridyl)methyl bromide, Ag_2O, DCM, rt, 24 h, 40%. (d) R_1R_2NH, DMSO, 80 °C, 5 h. 20–60%.

The synthesis of **2** was shown in Scheme 4. Bromoaldehyde **7** reacted with *o*-trifluoromethylbenzene boronic acid to give **13**. Addition of the anion from 1-methyl-2-triethylsilyl imidazole afforded alcohol **14**. Alkylation of **14** with 2-chloro-3-cyano-6-bromomethyl pyridine, prepared from bromination of 2-chloro-3-cyano-6-methyl pyridine, then furnished the key intermediate **15**. Displacement of the chloride of **15** with a set of amines was accomplished by heating in DMSO, leading to the desired compounds **12a**–**n** (Table 4).

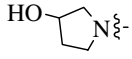
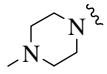
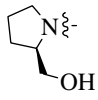
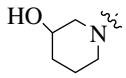
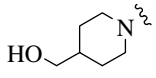
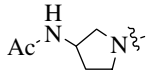
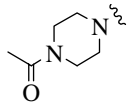
The data in Table 4 indicated that compounds **2** with an aliphatic cyclic amino substitution (**2a**–**j**) all retained the FT inhibitory potency of **12d**, while compounds with primary amino substituents (**2k**–**n**) were 2–3-fold less potent. In terms of selectivity, the compounds with six-membered ring substituents (morpholinyl of **2b**, piperidinyl of **2e** and **2g**, piperazinyl of **2c**, **2i**, and **2j**) were all more selective than the pyrrolidinyl-substituted **2a**, **2d**, and **2f**. The compounds with six-membered ring substituents also showed better cellular activity. Particularly, compounds with a six-membered ring cyclic amino substituents bearing a hydroxy group, such as **2e**,**g**,**j**, showed outstanding cellular activity. Most noticeable is compound **2e**, which is a 1.2 nM FT inhibitor with a selectivity over 1000-fold and 13 nM cellular activity. This is likely due to favorable cellular penetration of this subset of compounds.

In summary, we have succeeded in the transition from ABT-839 to non-methionine FT inhibitors through computer-modeling and medicinal chemistry efforts. Starting from lead compound **1**, placing electron-withdrawing substituents such as cyano group at the *para*-position of the A-ring increased the FT inhibition potency by 15–20-fold. Replacing the *o*-tolyl of the C-ring with bicyclic aryl groups such as 1-naphthyl resulted in very potent FT inhibitors but with very poor selectivity, indicating very similar volume in this part of the active

Table 4. SAR of (2-amino-3-cyano-6-pyridyl)methyl ethers **2**

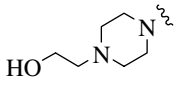
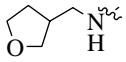
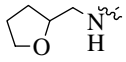
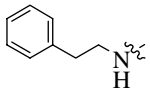
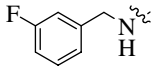


2

Compd	R_1R_2N–	IC_{50} (nM)		EC_{50} (nM)
		FT[a]	GGT[b]	*Ras* processing[c]
2a		3.5	970	120
2b		1.3	1200	89
2c		1.2	2600	53
2d		2.0	920	170
2e		1.3	1400	13
2f		3.6	680	210
2g		1.8	1400	11
2h		1.7	1600	330
2i		2.6	1800	130

(*continued on next page*)

Table 4 (*continued*)

Compd	R_1R_2N–	IC_{50} (nM)		EC_{50} (nM)
		FT[a]	GGT[b]	*Ras* processing[c]
2j		1.3	2000	30
2k		7.7	2200	201
2l		7.5	2400	285
2m		9.1	2300	>1000
2n		10	750	>1000

[a] Bovine FT used.
[b] Bovine GGT used.
[c] *H*-ras processing in NIH 3T3 cells.

sites of FT and GGT. Replacing the C-ring with *o*-trifluoromethylphenyl represents an acceptable compromise. Finally, changing the A-ring into 2-amino-3-cyano-6-pyridyl resulted in further improvement in selectivity and cellular activity, leading to compounds such as **2e** and **2g** with desirable properties.

References and notes

1. Bell, I. M. *J. Med. Chem.* **2004**, *47*, 1869.
2. Ayral-Kaloustian, S.; Salaski, E. *Curr. Med. Chem.* **2002**, *9*, 1003.
3. Adjei, A. A. *Drugs Future* **2000**, *25*, 1069.
4. Bos, J. L. *Cancer Res.* **1989**, *49*, 4682.
5. Lebowitz, P. F.; Prendergast, G. C. *Oncogene* **1998**, *17*, 1439.
6. Prendergast, G. C.; Davide, J. P.; deSolms, S. J.; Giulianin, E. A.; Graham, S. L.; Gibbs, J. B.; Oliff, A.; Kohl, N. E. *Mol. Cell. Biol.* **1994**, *14*, 4183.
7. Prendergast, G. C.; Rane, N. *Expert Opin. Invest. Drugs* **2001**, *10*, 2105.
8. deSolms, S. J.; Ciccarone, T. M.; MacTough, S. C.; Shaw, A. W.; Buser, C. A.; Ellis-Hutchings, M.; Fernandes, C.; Hamilton, K. A.; Huber, H. E.; Kohl, N. E.; Lobell, R. B.; Robinson, R. G.; Tsou, N. N.; Graham, S. L.; Beese, L. S.; Taylor, J. S. *J. Med. Chem.* **2003**, *46*, 2973.
9. Lobell, R. B.; Omer, C. A.; Abrams, M. T.; Bhimnathwala, H. G.; Brucker, M. J.; Buser, C. A.; Davide, J. P.; deSolms, S. J.; Dinsmore, C. J.; Ellis-Hutchings, M. S.; Kral, A. M.; Liu, D.; Lumma, W. C.; Machotka, S. V.; Rands, E.; Williams, T. M.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Heimbrook, D. C.; Kohl, N. F. *Cancer Res.* **2001**, *61*, 8758.
10. Augeri, D. J.; O'Conner, S. J.; Janowick, D.; Szczepankiewicz, B.; Sullivan, G.; Larsen, J.; Kalvin, D.; Cohen, J.; Devine, E.; Zhang, H.; Cherian, S.; Saeed, B.; Ng, S.-C.; Rosenberg, S. *J. Med. Chem.* **1998**, *41*, 4288.
11. O'Conner, S. J.; Barr, K. J.; Wang, L.; Sorensen, B. K.; Tasker, A. S.; Sham, H. L.; Ng, S.-C.; Cohen, J.; Devine, E.; Cherian, S.; Saeed, B.; Zhang, H.; Lee, J. Y.; Warner, R.; Tahir, S.; Kovar, P.; Ewing, P.; Alder, J.; Mitten, M.; Leal, J.; Marsh, K.; Bauch, J.; Hoffman, D. J.; Sebti, S. M.; Rosenberg, S. H. *J. Med. Chem.* **1999**, *42*, 3701.
12. Henry, K. J., Jr.; Wasical, J.; Tasker, A. S.; Cohen, J.; Ewing, P.; Mitten, M.; Larsen, J. J.; Kalvin, D. M.; Swenson, R.; Ng, S.-C.; Saeed, B.; Cherian, S.; Sham, H. L.; Rosenberg, S. H. *J. Med. Chem.* **1999**, *42*, 4844.
13. Venet, M. G.; Angibaud, P. R.; Muller, P.; Sanz, G. C.; W.O. patent 97/21701, 1997.
14. 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, B.; Bogusky, M. J.; Culberson, 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.; Bibbs, J. B.; Graham, S. L.; Heimbrook, D. C.; Hartman, G. D.; Oliff, A. I.; Huff, J. R. *J. Med. Chem.* **1999**, *42*, 3779.
15. Hutchins, C., et al. *Bioorg. Med. Chem. Lett.*, in preparation.
16. Wang, L.; Wang, G. T.; Wang, X.; Tong, Y.; Sullivan, G.; Park, D.; Leonard, N. M.; Li, Q.; Cohen, J.; Gu, W.-Z.; Zhang, H.; Bauch, J. L.; Jakob, C. G.; Hutchins, C. W.; Stoll, V. S.; March, K.; Rosenberg, S. H.; Sham, H. L.; Lin, N.-H. *J. Med. Chem.* **2004**, *47*, 612.
17. We have undertaken an effort to further optimize **10j**, primarily by introducing nitrogen into various rings. Wang, W.-B., et al., in preparation.
18. Hasvold, L. A.; Wang, W.-B.; Gwaltney, S. L.; Rockway, T. W.; Nelson, L. T. J.; Mantei, R. A.; Fakhoury, S. A.; Sullivan, G. M.; Li, Q.; Lin, N.-H.; Wang; Le; Zhang, H.; Cohen, J.; Gu, W.-Z.; Marsh, K.; Bauch, J.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4001.
19. Strickland, C. L.; Weber, P. C.; Windsor, W. T.; Wu, Z.; Le, H. V.; Albanese, M. M.; Alvarez, C. S.; Cesarz, D.; Rosario, J.; Deskus, J.; Mallams, A. K.; Njorge, F. G.; Piwinski, J. J.; Reminszewski, S.; Rossman, R. R.; Taveras, A. G.; Vibulbhan, B.; Doll, R. J.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Med. Chem.* **1999**, *42*, 2125.