Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 5537–5543
Bioorganic & Medicinal Chemistry Letters

Surfing the piperazine core of tricyclic farnesyltransferase inhibitors

Laura L. Rokosz,[a,*] Chia-Yu Huang,[a] John C. Reader,[a] Tara M. Stauffer,[a] Daniel Chelsky,[a] Nolan H. Sigal,[a] Ashit K. Ganguly[b] and John J. Baldwin[a]

[a]*Pharmacopeia, PO Box 5350, Princeton, NJ 08543-5350, USA*
[b]*Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1300, USA*

Received 28 June 2005; revised 22 August 2005; accepted 25 August 2005
Available online 3 October 2005

Abstract—In order to fully explore structure–activity relationships at the 1- and 2-positions of the piperazine core of tricyclic farnesyltransferase inhibitors, an 11,718-member ECLiPS® library was synthesized and screened in a farnesyltransferase scintillation proximity assay. A detailed description of the library and analyses of the screening data will be provided.

Farnesyltransferase (FTase) is a heterodimeric protein that transfers the isoprenoid moiety of farnesyl pyrophosphate (FPP) to C-terminal CAAX box sequences.[1] Since CAAX prenylation is required for activation of oncogenic Ras proteins,[2] it had long been thought that Ras activity could be tempered through FTase inhibition. However, numerous studies show that FTase inhibitors (FTIs) can suppress the growth of transformed cells and tumors regardless of Ras activation status.[3] Despite these ambiguities, FTIs promote clinical regression of a number of solid tumor types and hematological malignancies with a modest toxicity profile when used as single agents or in combination with cytotoxic agents.[3d,4]

SCH 66336 (lonafarnib, Sarasar®, Fig. 1) is a FTI from the Schering-Plough Research Institute (SPRI) currently in phase III clinical trials.[3d,4g] This compound, (+)-4-[2-[4-(8-chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11 (*R*)-yl)-1-piperidinyl]-2-oxo-ethyl]-1-piperidinecarboxamide, is derived from the SPRI compound collection.[5] Since its discovery SPRI has continued to develop analogs with an improved therapeutic index.[6] Structure–activity relationships (SARs) targeting the N-1 position of the piperidine core of **SCH 66336** have been vigorously explored.[7] A large proportion of the reported analogs, however, produce IC_{50s} in the micromolar range. Several studies have established that piperazine is a suitable replacement for the piperidine core, producing compounds with comparable potency and pharmacokinetic (PK) profiles.[5a,7c] X-ray crystallographic analyses of inhibited complexes show that the two substructures are superimposible.[7d] Chemical development of tricyclic FTIs containing a piperazine core has been largely limited to substitution with either pyridine or piperidine functionalities. In order to more thoroughly define the SAR at the piperazine core, we chose to evaluate 63 distinctly different substituents at N-1 (R^3) in conjunction with 31 substituents at the C-2 (R^1) position, a site that had never previously been modified. In this paper, we describe the synthesis of an 11,718-member ECLiPS® (Encoded Combinatorial Library on Polymeric Support) library and the results of the ensuing screen.

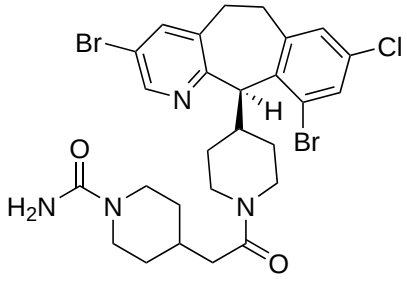
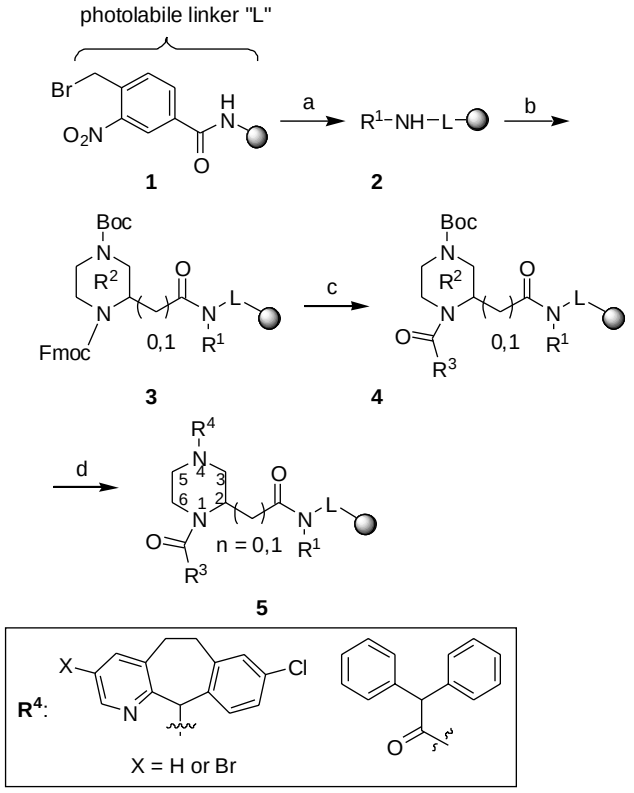


Figure 1. SCH 66336, Sarasar®.

Keywords: Farnesyltransferase inhibitors; Anti-cancer; Scintillation proximity assay (SPA); Combinatorial chemistry; ECLiPS®; High-throughput screening.
* Corresponding author. Tel.: +1 609 452 3718; fax: +1 609 655 4187; e-mail: rock@pcop.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.08.074

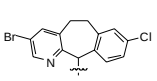
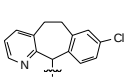
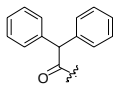


Scheme 1. Solid phase synthesis of ECLiPS® FT-1. Reagents: (a) R^1NH_2 (31), THF; (b) R^2CO_2H (2), HATU, DIEA, CH_2Cl_2; (c) i—piperidine, DMF; ii—R^3CO_2H (63), HATU, DIEA; (d) i—TFA, CH_2Cl_2; ii—Et_3N, MeOH; iii—R^4Cl (2), 1,2,2,6,6-pentamethylpiperidine, DMA or R^4CO_2H (1), HATU, DIEA.

The library, FT-1 (Scheme 1), is based on a piperazine core containing a 3-bromo-8-chloro-substituted tricyclic- (sublibrary 1), an 8-chloro-substituted tricyclic- (sublibrary 2) or a novel phenylbenzyl-top piece (sublibrary 3). The library was prepared on TentaGel™ resin derivatized with 4-bromomethyl-3-nitrobenzamide, a photolabile linker. As shown in Scheme 1, the resin **1** was reacted with 31 primary amines R^1NH_2 to generate the resin bound secondary amine **2**. After a pool and split step, **2** was coupled with two different R^2, either piperazine carboxylic acid or piperazine acetic acid to produce amide **3**. Amide **3** was pooled, split, and treated with piperidine in DMF to remove the Fmoc group. The resulting amine was coupled with 63 different R^3 pieces, including 56 carboxylic acids and 7 sulfonyl chlorides to produce **4**. After a third pool and split step, the resin **4** was divided into three parts. For each part, the Boc group on R^2 was removed, and the corresponding amine was derivatized with a different R^4 chloride or acid to produce **5**. The 31 R^1, 2 R^2, and 63 R^3 synthons were encoded, prior to each pool and split step, by haloaromatic alcohol tags that can be decrypted using electron spray gas chromatography.[8] R^4 was not encoded. Instead, resin **5** was kept as three separate sublibraries (as defined above), each containing 3906 compounds. Thus, a focused ECLiPS library containing 11,718 compounds was prepared. It should be noted that the tricyclic compounds were not resolved at the carbon center attached to the piperazine nitrogen (N-4) since the stereochemistry at this position, for compounds in the mono- and dihalogenated series, does not have a significant impact on FTase activity.[7d] The average compound yield, as quantified by LC–MS of a random set of library beads, was 100 pmol.

FT-1 was screened using a scintillation proximity assay (SPA) as described.[9,10] The library beads were partially eluted and screened initially at an approximate density of ten compounds per well. Each sublibrary was screened separately at a final concentration of 500 nM per bead eluate. The cut-off for decode submission was set at 70% of control (30% inhibition). The beads from the active wells were then re-arrayed, eluted in a second step, and tested at a screening density of one compound per well. Four-and-one-half or more equivalents[11] of each sublibrary produced a total of 507 wells that were re-arrayed, which subsequently produced 405 decoded structures (Table 1). Since the sublibraries are arrayed in a random fashion, statistics assume that if three or more equivalents of each sublibrary are screened then at least 95% of the library will be assayed once and at least 80% will be assayed two or more times. Consequently, many compounds are decoded multiple times. Greater than 50% of the decodes from sublibraries 1 and 2 were observed two or more times, producing 188 and 41 unique structures, respectively. Far fewer decodes were retrieved from sublibrary 3, despite surveying a greater percentage of that sublibrary, and just one compound was decoded two times. The decode repetition observed from sublibraries 1 and 2 is evidence of a preferred SAR. The distinct lack of decode repetition from sublibrary 3 suggests that the compounds decoded

Table 1. FT-1 screening summary

	Sublibrary 1	Sublibrary 2	Sublibrary 3
Sublibrary definition			
Number of bead eluates screened (equivalents)	17,600 (4.5)	22,880 (5.9)	33,440 (8.6)
Number of wells submitted for re-array	294	116	97
Number of beads decoded[a]	302	64	39
Percentage of compounds decoded two or more times	57	53	5
Number of unique structures decoded	188	41	38

[a] The cut-off for decode submission was set at 70% of control which corresponds to 30% inhibition.

from this sublibrary are either very weak or are false positives. This is consistent with the findings of Mallams et al.[7c] which acknowledged the importance of the tricyclic moiety in binding to a hydrophobic cavity in the FTase active site. The data in Table 1 also show that each re-arrayed well from sublibrary 1 produced at least one decoded structure (294 re-arrays and 302 decodes).

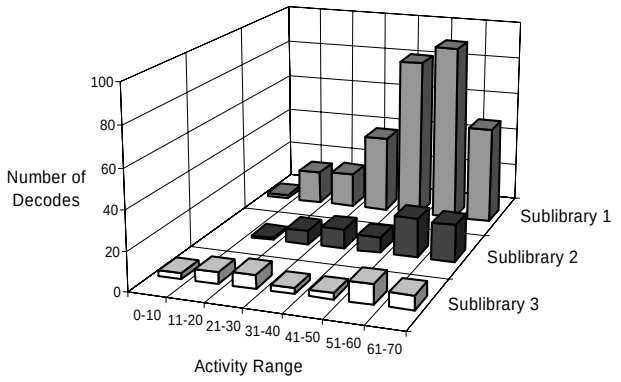


Figure 2. FTase activity (percentage of control) of the FT-1 decodes. All compounds were screened at a final concentration of 500 nM.

This correlation drops to approximately 2:1 for sublibrary 2 (116 re-arrays and 64 decodes) and to nearly 3:1 for sublibrary 3 (97 re-arrays and 39 decodes). We hypothesize that this result may be due to the additive effects of multiple weak actives in the sublibraries 2 and 3 primary screens. The screening activity of the decoded structures from each sublibrary is shown in Figure 2. The activity of the decoded compounds ranged from 10% of control (90% inhibition) to 70% of control (30% inhibition) with the largest percentage spanning 40–60% of control.

Synthon frequency plots (Fig. 3) are used to depict the SAR of the decoded structures at positions N-1 (R^3) and C-2 (R^1) of the piperazine core. Distinct SAR patterns (Table 2) were readily apparent among the sublibraries 1 and 2 decodes. No pattern could be seen for the sublibrary 3 decodes (data not shown). The synthon plots show that the structures decoded from sublibrary 1 have a preference for (cf. Table 2) alkyl amides (s2–s10, s17, s18) and 3-pyridylmethylamide (s25) at R^1, while all other aromatic substituents, including 2-pyridylmethylamide (R^1s20) and 4-pyridylmethylamide (R^1s24), were not frequently tolerated. 4-Pyridylacetamide (s37) and

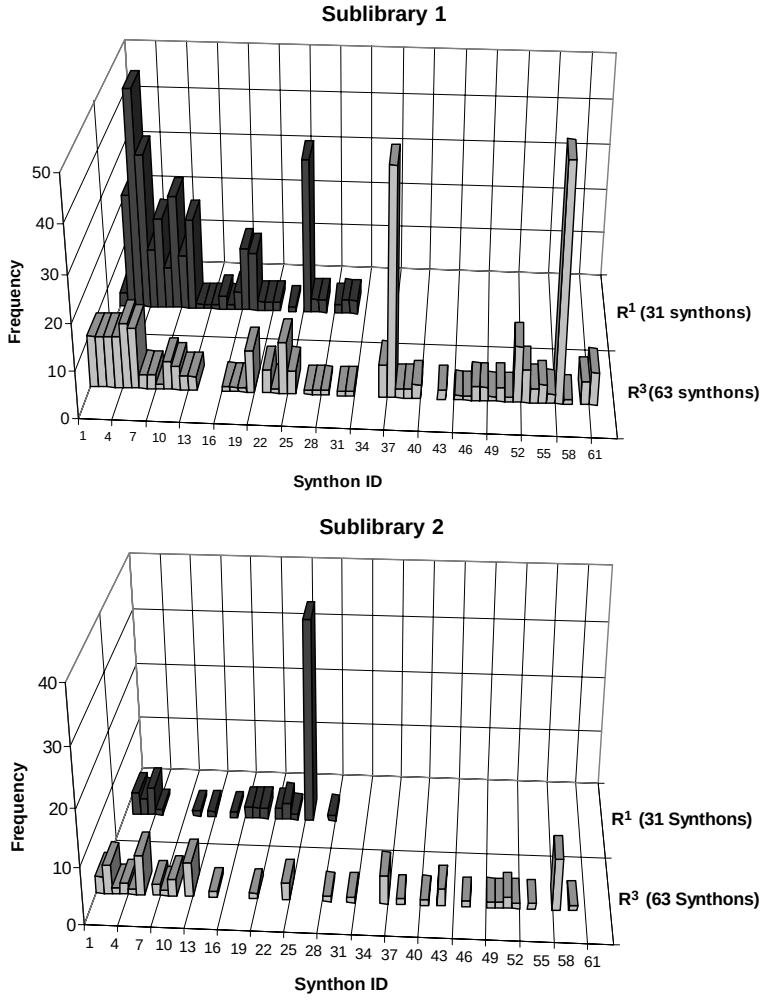
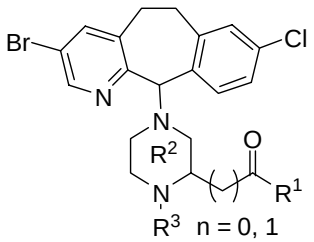
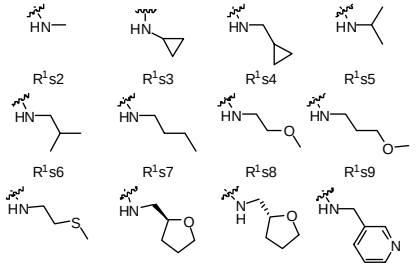
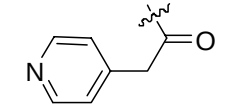
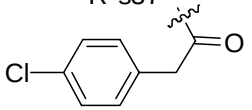
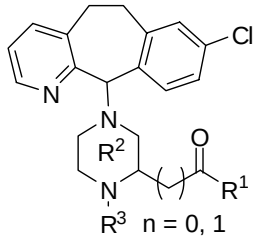
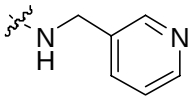
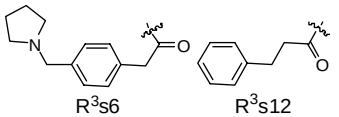
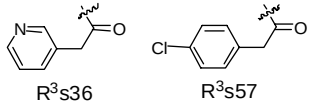


Figure 3. Frequency of decoded synthons from FT-1. The *x*-axis represents the synthon ID. The *y*-axis represents the substituent position. The *z*-axis represents how frequently each synthon was decoded.

Table 2. Preferred synthons of the FT-1 decodes

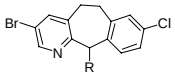
Sublibrary	R^1	R^2	R^3
 Sublibrary 1	 R^1s2 R^1s3 R^1s4 R^1s5 R^1s6 R^1s7 R^1s8 R^1s9 R^1s10 R^1s17 R^1s18 R^1s25	n = 0 256 of 302 decodes	 R^3s37  R^3s57
 Sublibrary 2	 R^1s25	n = 0 55 of 64 decodes	 R^3s6 R^3s12  R^3s36 R^3s57

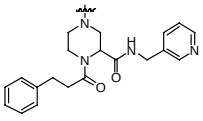
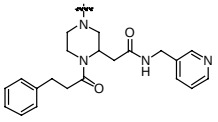
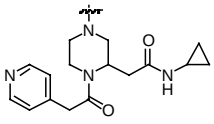
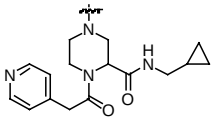
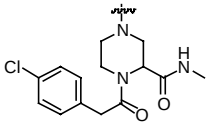
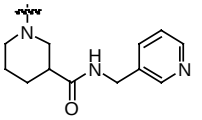
4-chlorophenylacetamide (s57) predominate at R^3. The structures decoded from sublibrary 2 (Fig. 3 and Table 2) show a strict preference for 3-pyridylmethylamide (s25) at R^1 and a modest preference for 2-(4-(pyrrolidin-1-ylmethyl)phenyl)acetamide (s6), 3-phenylpropanamide (s12), 3-pyridylacetamide (s36), and 4-chlorophenylacetamide (s57) at R^3. Both the sublibraries 1 and 2 decodes clearly show that piperazine carboxamide is preferred over piperazine acetamide (Scheme 1 and Table 2) at R^2. The preferred synthons are a prominent feature of the replicate decodes and are used to guide the selection of compounds chosen for re-synthesis. The screening activity and the number of times decoded are considered as well.

Four replicate decodes from sublibrary 1 were resynthesized in order to confirm the level of activity seen in the screen (Table 3). These compounds indeed confirmed the expected activity with enzyme IC_{50}s of 0.03–0.10 μM. To test for cell-based activity, these compounds were also evaluated in a COS cell Ha-Ras processing assay.[12] The cellular IC_{50}s ranged from 0.10 to 0.20 μM. This level of enzyme and cell-based activity is consistent with that of the most potent dihalogenated tricyclic FTIs containing a piperazine core.[7c] Compound **6**, which contains 3-pyridylmethylamide at R^1 and phenylpropanamide at R^3, was the most potent re-synthesized decode. Addition of a methylene unit between the piperazine core and the R^1 substituent, to produce **7** (IC_{50} = 0.96 ± 0.04 μM), reduced the potency by more than 30-fold. Compound **7** was contained in the library but was not decoded. Given the theoretical screening concentration (500 nM), the weak potency confirms that it should not have been decoded. This finding is also consistent with the fact that far fewer compounds containing the piperazine acetamide core were decoded compared to those containing the piperazine carboxamide core (cf. Table 2). Nonetheless, the piperazine acetamide core is well tolerated when R^1 is a small aliphatic substituent and R^3 is 4-pyridylacetamide, as in **8** (IC_{50} = 0.07 ± 0.00 μM). The 4-pyridylacetamide was also a preferred R^3 substructure reported by Mallams et al.[7c] Converting 4-pyridylacetamide at R^3 to 4-chlorophenylacetamide and removal of the cyclopropyl unit at R^1 of **9** (IC_{50} = 0.05 ± 0.00 μM) to produce **10** (IC_{50} = 0.10 ± 0.01 μM) reduced the potency twofold.

3-Pyridylmethylamide (s25) is a R^1 substituent that was frequently decoded from sublibraries 1 and 2. Prior to this work, substitution at the 2-position had not been explored. In order to assess the importance of this modification in an unhindered environment, a 3-pyridylmethylamide derivative without any substitution at R^3

Table 3. FTase activity of FT-1 re-synthesized compounds



Compound	R	Decode frequency	Screening activity (% of control)	FTase IC_{50} (μM) ± SD	COS IC_{50} (μM)
6		2	32 ± 9	0.03 ± 0.01	0.15, 0.20
7		Not decoded		0.96 ± 0.04	2.0, 2.0
8		2	33 ± 5	0.07 ± 0.00	0.10, 0.20
9		3	23 ± 5	0.05 ± 0.00	0.10, 0.20
10		4	28 ± 13	0.10 ± 0.01	0.15, 0.20
11		Decode analog		0.12 ± 0.02	2.0, 2.0

was synthesized. This decode analog, **11**, generated an enzyme IC_{50} of 0.12 ± 0.03 μM, which is just fourfold less potent than the most potent re-synthesized compound **6**. The COS assay IC_{50} was much higher (2.0 μM), suggesting that the R^3 substituent facilitates cell penetration.

No decoded structures from sublibrary 2 were re-synthesized since the screening results suggested that the compounds from this sublibrary would be considerably weaker than those from sublibrary 1. This finding is consistent with data showing that the addition of bromine at the 3-position of the tricycle makes a tangible contribution in potency when paired with chlorine at the 8-position.[7c,13]

These data produced 229 unique inhibitors from sublibraries 1 and 2 with screening activities of greater than 30% inhibition at 500 nM. In addition, we showed for the first time that substitution at R^1 was tolerated and that 16 of the 31 synthons paneled at this position were frequently decoded in the dihalogenated series. This finding is remarkable since it identifies a new site that can be exploited to incorporate additional, pharmaceutically important properties. As a result, these data enabled the identification of the potent (IC_{50} = pM) imidazole-tethered compounds discovered in our laboratory and subsequently described by Taveras et al.[6b] The screening data were also used to develop the zinc-liganded structures reported by Njoroge et al.[6d] The library synthesis and screening campaign thus also provide an important historical perspective of how a number of previously published FTIs were originally developed.

Acknowledgment

We would like to express our sincere appreciation to Dr. Matthew Sills for critical review of the manuscript.

References and notes

1. (a) Reiss, Y.; Stradley, S. J.; Gierasch, L. M.; Brown, M. S.; Goldstein, J. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 732; (b) Casey, P. J.; Thissen, J. A.; Moomaw, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8631.
2. Kato, K.; Cox, A. D.; Hisaka, M. M.; Graham, S. M.; Buss, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 6403.
3. (a) Cox, A. D.; Der, C. J. *Biochim. Biophys. Acta* **1997**, *1333*, F51; (b) Kohl, N. E. *Ann. NY Acad. Sci.* **1999**, *886*, 91; (c) Sebti, S. M.; Hamilton, A. D. *Expert Opin. Invest. Drugs* **2000**, *9*, 2767; (d) Bishop, W. B.; Kirschmeier, P.; Baum, C. *Cancer Biol. Ther.* **2003**, *2*, 73.
4. (a) Haluska, P.; Dy, G. K.; Adjei, A. A. *Eur. J. Cancer* **2002**, *38*, 1685; (b) Caponigro, F.; Casale, M.; Bryce, J. *Expert Opin. Invest. Drugs* **2003**, *12*, 943; (c) Head, J. E.; Johnston, S. R. *Expert Opin. Emerg. Drugs* **2003**, *8*, 163; (d) Kelland, L. R. *Expert Opin. Invest. Drugs* **2003**, *12*, 413; (e) Mazieres, J.; Pradines, A.; Gilles, F. *Cancer Lett.* **2004**, *206*, 159; (f) O'Regan, R. M.; Khuri, F. R. *Endocr. Relat. Cancer* **2004**, *11*, 191; (g) Doll, R. J.; Kirschmeier, P.; Bishop, W. B. *Curr. Opin. Drug Discov. Dev.* **2004**, *7*, 478.
5. (a) Njoroge, F. G.; Taveras, A. G.; Kelly, J.; Remiszewski, S.; Mallams, A. K.; Wolin, R.; Afonso, A.; Cooper, A. B.; Rane, D. F.; Liu, Y. T.; Wong, J.; Vibulbhan, B.; Pinto, P.; Deskus, J.; Alvarez, C. S.; del Rosario, J.; Connolly, M.; Wang, J.; Desai, J.; Rossman, R. R.; Bishop, W. R.; Patton, R.; Wang, L.; Kirschmeier, P.; Ganguly, A. K. *J. Med. Chem.* **1998**, *41*, 4890; (b) Njoroge, F. G.; Girijavallabhan, V. M. *Curr. Med. Chem.—Imm. Endocr. & Metab. Agents* **2001**, *1*, 185.
6. (a) Doll, R. J. *IDrugs* **2001**, *4*, 1382; (b) Taveras, A. G.; Kirchsmeier, P.; Baum, C. M. *Curr. Top. Med. Chem.* **2003**, *3*, 1103; (c) Huang, C.-Y.; Rokosz, L. *Expert Opin. Ther. Pat.* **2004**, *14*, 175; (d) Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Strickland, C.; Kirschmeier, P.; Bishop, W. R.; Girijavallabhan, V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5877.
7. (a) Njoroge, F. G.; Vibulbhan, B.; Alvarez, C. S.; Bishop, W. R.; Petrin, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2977; (b) Njoroge, F. G.; Doll, R. J.; Vibulbhan, B.; Alvarez, C. S.; Bishop, W. R.; Petrin, J.; Kirschmeier, P.; Carruthers, N. I.; Wong, J. K.; Albanese, M. M.; Piwinski, J. J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 101; (c) Mallams, A. K.; Rossman, R. R.; Doll, R. J.; Girijavallabhan, V. M.; Ganguly, A. K.; Petrin, J.; Wang, L.; Patton, R.; Bishop, W. R.; Carr, D. M.; Kirschmeier, P.; Catino, J. J.; Bryant, M. S.; Chen, K. J.; Korfmacher, W. A.; Nardo, C.; Wang, S.; Nomeir, A. A.; Lin, C. C.; Li, Z.; Chen, J.; Lee, S.; Dell, J.; Lipari, P.; Liu, M., et al. *J. Med. Chem.* **1998**, *41*, 877; (d) Strickland, C. L.; Weber, P. C.; Windsor, W. T.; Wu, Z.; Le, H. V.; Albanese, M. M.; Alvarez, C. S.; Cesarz, D.; del Rosario, J.; Deskus, J.; Mallams, A. K.; Njoroge, F. G.; Piwinski, J. J.; Remiszewski, S.; Rossman, R. R.; Taveras, A. G.; Vibulbhan, B.; Doll, R. J.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Med. Chem.* **1999**, *42*, 2125.
8. (a) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922; (b) Nestler, H. P.; Bartlett, P. A.; Still, W. C. *J. Org. Chem.* **1994**, *59*, 4723.
9. Library beads from FT-1 were arrayed into polypropylene 96-well, filter-bottomed microtiter plates (Millipore Corp, Medford, MA) at an average density of 10 beads per well and were photoeluted for 30 min in 97% ethanol containing 3.0% TFA. These conditions yield approximately 50% (50 pmol) of the total bead eluate. The eluted compounds were extracted directly from the filter plate to polypropylene U-bottomed plates. The beads corresponding to the active wells from the primary screen were re-arrayed at a density of one bead per well and the remaining compound on the bead was photoeluted in the same solvent for 2 h. Both the primary and re-arrayed bead eluates were dried overnight in a convection oven at 37 °C and then re-suspended directly in the standard FTase radiochemical assay mix.[10] The beads corresponding to the active wells in the re-array screen were then submitted for decoding.
10. FTase assays were conducted using a SPA kit following the protocol described by the manufacturer (Amersham Biosciences, Piscataway, NJ), substituting a biotinylated substrate peptide containing the Ki-Ras carboxyl-terminal sequence (biotin–KKSKTKCVIM, obtained from SPRI). Typical reaction mixtures (50 μl total) contained 40 mM HEPES, pH 7.5, 20 mM $MgCl_2$, 5 mM DTT, 0.01% (v/v) Igepal detergent (Sigma, St. Louis, MO), 20 nM [^{3}H]FPP (Perkin Elmer Life Sciences, Boston, MA; 20 Ci/mmol), 68 nM FPP (Sigma), 12.5 ng (approximately 2.8 nM) of purified recombinant human FTase enzyme, the indicated

concentration of inhibitor or dimethylsulfoxide (DMSO) vehicle control (5% v/v, final) and 2.5 ng (approximately 75 nM) Ki-Ras peptide. After a 20 min incubation at room temperature, reactions were quenched with 75 μl of a cold suspension containing 250 mM EDTA (Digene, Gaithersburg, MD), pH 8.0, 0.5% bovine serum albumin (Sigma), and 100 μg SPA beads. Radioactivity was measured in a Perkin Elmer–Wallac Microbeta 1450 liquid scintillation counter. Percent inhibition was calculated relative to the DMSO vehicle control. IC_{50} values were calculated by fitting the data to the Michaelis–Menten equation using the non-linear regression analysis program Kaleidagraph (Synergy Software, Essex Junction, VT). All compounds were tested in triplicate at least two times. The IC_{50} data are reported as the average of multiple determinations ± standard deviation.

11. One equivalent corresponds to the number of compounds in each sublibrary which, in the case of FT-1, is 3906.
12. Ha-Ras processing in COS-7 African, green monkey kidney cells was conducted as described in Bishop, W. B.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, G.; Catino, J.; Schwartz, J.; Windsor, W.; Syto, R.; Schwartz, J.; Carr, D.; James, L.; Kirschmeier, P. *J. Biol. Chem.* **1995**, *270*, 30611. Ras proteins were visualized using AttoPhos (JBL Scientific, Inc., San Luis Obispo, CA) and quantified on a STORM phosphorimaging device (Molecular Devices, Sunnyvale, CA). IC_{50} values were calculated as previously described.[10] All compounds were tested at least two times and both values are reported.
13. Njoroge, F. G.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K. J.; Nomeir, A. A.; Lin, C. C.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1997**, *40*, 4290.