Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 1359–1362

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Aryl Tetrahydropyridine Inhibitors of Farnesyltransferase: Glycine, Phenylalanine and Histidine Derivatives

Stephen L. Gwaltney, II,* Stephen J. O'Connor, Lissa T. J. Nelson, Gerard M. Sullivan, Hovis Imade, Weibo Wang, Lisa Hasvold, Qun Li, Jerome Cohen, Wen-Zhen Gu, Stephen K. Tahir, Joy Bauch, Kennan Marsh, Shi-Chung Ng, David J. Frost, Haiying Zhang, Steve Muchmore, Clarissa G. Jakob, Vincent Stoll, Charles Hutchins, Saul H. Rosenberg and Hing L. Sham

Pharmaceutical Discovery, R47B, Building AP-10, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

Received 12 August 2002; accepted 2 January 2003

Abstract—Inhibitors of farnesyltransferase are effective against a variety of tumors in mouse models of cancer. Clinical trials to evaluate these agents in humans are ongoing. In our effort to develop new farnesyltransferase inhibitors, we have discovered a series of aryl tetrahydropyridines that incorporate substituted glycine, phenylalanine and histidine residues. The design, synthesis, SAR and biological properties of these compounds will be discussed.

Ras oncogene mutations are the most frequently identified in human tumors, especially those of the pancreas, colon, lung and bladder. Mutations in *ras* genes lead to uncontrolled cell growth. Post-translational farnesylation of Ras (alkylation of the protein by a C-15 isoprenoid) is required for the association of mature proteins with the cell membrane. This association allows for the transmission of extracellular signals to the nucleus and leads to cell proliferation. Farnesylation is catalyzed by protein farnesyltransferase (FT). A related enzyme, geranylgeranyltransferase-I (GGT-I) carries out geranylgeranylation (alkylation of the protein by a C-20 isoprenoid).[1]

Farnesyltransferase inhibitors (FTIs) were designed to exploit the requirement of post-translational farnesylation of Ras in oncogenesis. It is now recognized that protein targets other than Ras, such as Rho B, are important for the antitumor effects of farnesyltransferase inhibitors (FTIs).[1] While the mechanism of action of these agents is still debated, the compounds have shown impressive efficacy in preclinical models of human cancer. Clinical trials of these agents have also shown that they possess activity alone and in combination with cytotoxic agents.[2]

Since GGT-I is responsible for the majority of protein prenylations and it has been shown that concomitant inhibition of FT and GGT-I in vivo leads to substantial toxicity,[3] we sought a selective inhibitor of FT. Initially, all our compounds were tested for their ability to inhibit FT and GGT-I in vitro. Potent compounds were then tested in a cellular assay that measured inhibition of the farnesylation of Ras (Ras processing, RP).[4]

Abbott's first generation FTI, ABT-839, is shown in Figure 1. This compound is a potent inhibitor of FT ($IC_{50} = 1.1$ nM) and is selective for FT over GGT-I (75,000 fold). The compound also demonstrates good cellular activity (Ras processing $EC_{50} = 16$ nM) and in vivo efficacy. However, the compound suffers from poor pharmacokinetics.

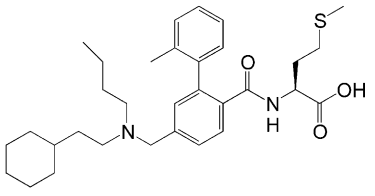


Figure 1. ABT-839.

*Corresponding author. Tel.: +1-858-731-3562; fax: +1-858-550-0526; e-mail: stephen.gwaltney@syrrx.com

0960-894X/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00095-7

The crystal structure of ABT-839 bound to FT is shown in Figure 2.[5] Note that the compound does not interact strongly with the active site zinc.

In an effort to discover new FTIs, a tetrahydropyridine core was used to replace the biphenyl core of ABT-839. This provided for easy substitution on nitrogen and increased hydrophilicity. The synthesis of the tetrahydropyridine core is shown in Scheme 1. Esterification of acid **1** followed by diazotization and iodination gave the known iodoester **2**.[6] Suzuki coupling utilizing *o*-tolylboronic acid led to tolylpyridine **3** in 98% yield. Quaternization of the pyridine followed by reduction gave the benzyltetrahydropyridine **4**.

This core was then used to prepare the methionine containing tetrahydropyridines as shown in Scheme 2. Treatment of **4** with 1-chloroethylchloroformate (ACE-Cl) in the presence of di-t-butyldicarbonate led to the Boc-protected amine with concomitant cleavage of the methyl ester. EDC coupling of **5** to methionine methyl ester followed by removal of the Boc group gave **6**. Treatment of **6** with chloroacetylchloride followed by addition of **7**[7] gave the methyl ester which was saponified to FTI **8**.

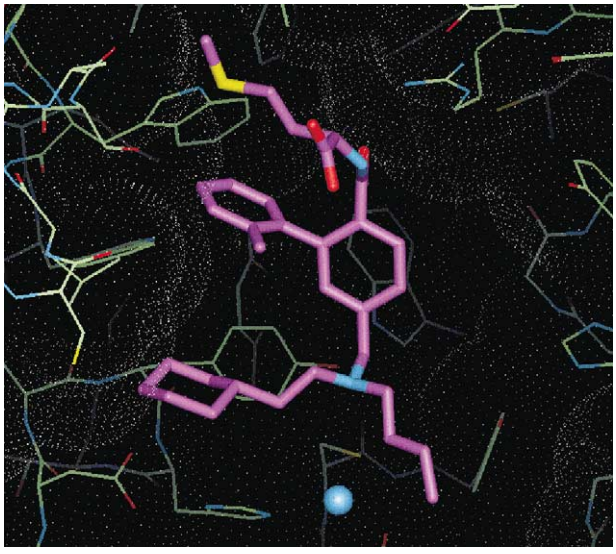
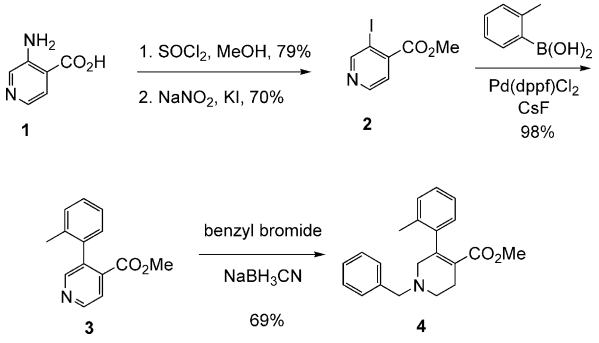


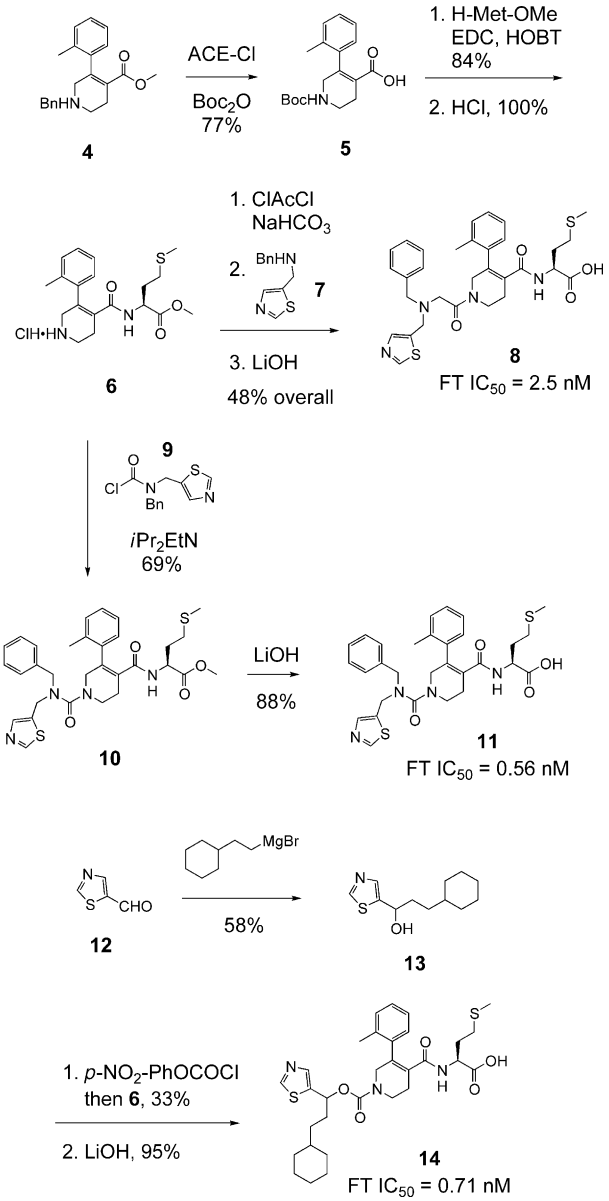
Figure 2. ABT-839 bound to farnesyltransferase.



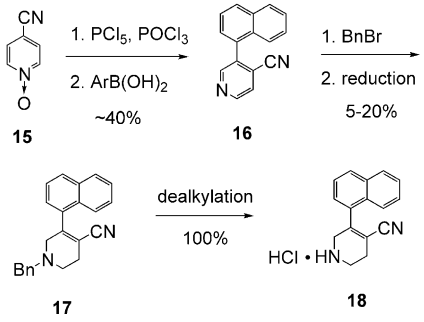
Scheme 1. Synthesis of compound **4**.

Intermediate **6** was also used in the preparation of FTIs **11** and **14**. Acylation of **6** with the carbamoyl chloride **9**[7] gave ester **10**. Saponification then provided the target compound. The synthesis of **14** began with known thiazolyl aldehyde **12**.[8] Treatment with cyclohexylethyl Grignard gave alcohol **13**, which was activated and coupled to **6**. Saponification then gave **14**.

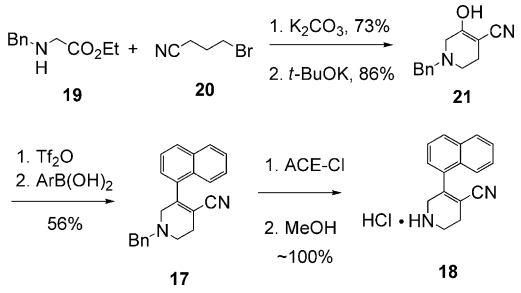
While these compounds were potent, they suffered from poor pharmacokinetics. The methionine residue proved to be a metabolic liability, suffering oxidation on sulfur. After substantial work in another series of FTIs at Abbott, it was discovered that a nitrile could serve as a suitable replacement for the methionine. Armed with this knowledge, we set out to prepare a cyano-substituted tetrahydropyridine core. Syntheses of the cyano substituted tetrahydropyridine core are shown in Schemes 3 and 4.



Scheme 2. Synthesis of methionine containing tetrahydropyridine FTIs.



Scheme 3. Synthesis of compound **18**.



Scheme 4. Improved synthesis of compound **18**.

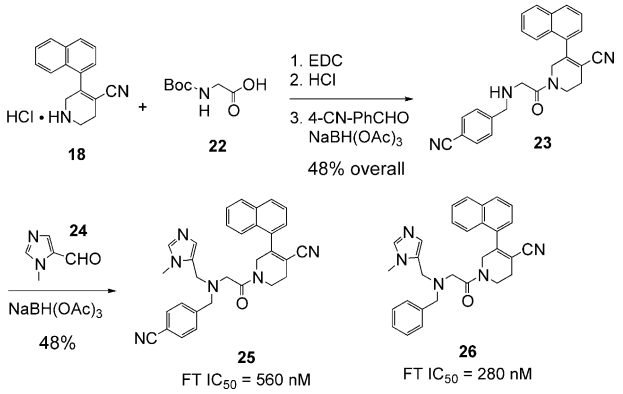
Chlorination[9] of **15** followed by a Suzuki coupling gave aryl pyridine **16**. Quaternization and reduction as described in Scheme 1 gave the protected tetrahydropyridine, which was deprotected using ACE-Cl.

While the method shown in Scheme 3 provided the target, it was found to be inconvenient. Workup of the chlorination proved tedious and this difficult isolation led to lowered yields. In addition, the reduction of the pyridinium salt proceeded in low yield and led to regioisomeric by-products. The overall yield for this sequence is 2–8%. In an effort to improve on this method, the sequence shown in Scheme 4 was adopted. Alkylation of the commercially available **19** with **20** was followed by a Dieckmann cyclization to give enol **21**. Triflation followed by Suzuki coupling then provided the protected tetrahydropyridine. Cleavage of the benzyl group was then accomplished as shown earlier. This method proceeds in approximately 35% overall yield, can be carried out on large scale easily and allows for variation of the aryl group.

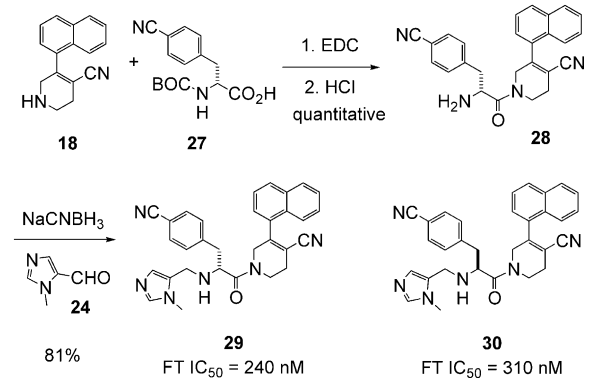
With the core tetrahydropyridine in hand, various series of derivatives were prepared. We first examined the *N*,*N*-disubstituted glycine derivatives shown in Scheme 5. These were prepared from the tetrahydropyridine by first carrying out an EDC coupling with a protected glycine followed by deprotection. Reductive amination then installed the benzyl and imidazolyl methyl groups.

These compounds did not possess the potency required and were not evaluated further.

We next examined inhibitors containing para-cyanophenylalanine derived substituents on the tetrahydropyridine (Scheme 6). These compounds were prepared in the same way as the glycine derivatives and were of similar potency. We noted little difference in potency between the L- and D-phenylalanine derivatives.



Scheme 5. Glycine derivatives.



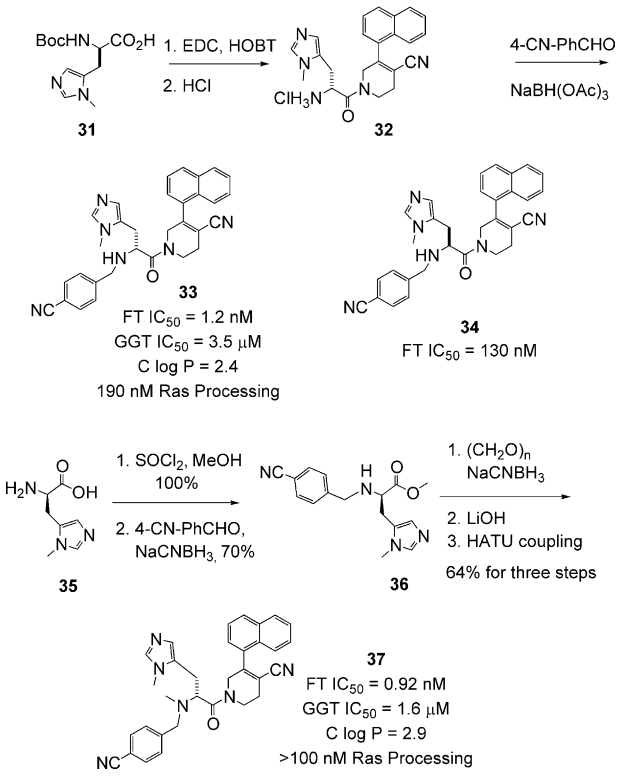
Scheme 6. Phenylalanine derivatives.

We then examined analogues derived from histidine (Scheme 7). Again, much the same chemistry was used for this work. We found it convenient to install both the *N*-benzyl and *N*-methyl groups using reductive amination. The first two compounds in this series showed surprisingly different potency based on the stereochemistry at the alpha carbon, with the D-histidine derivative proving 100 times more potent than the L-histidine derivative. This result is in sharp contrast with that seen in the phenylalanine containing compounds discussed above.

A crystal structure of compound **33** was obtained and shows that this inhibitor overlays well with ABT-839 in the FT active site (Fig. 3).[10] In contrast to the binding of ABT-839, compound **33** makes a good interaction with the zinc atom.

Compound **33**, while potent and selective for FT was markedly less potent in the cellular assay. In an effort to modulate the polarity[11] of the compound and improve cellular activity, we prepared the N-methyl derivative, **37**. This compound was of similar in vitro potency as the parent, but did not realize a significant gain in potency in the cellular assay.

The farnesyltransferase inhibitors described here,[12] while potent in vitro, did not possess the cellular activity



Scheme 7. Histidine derivatives.

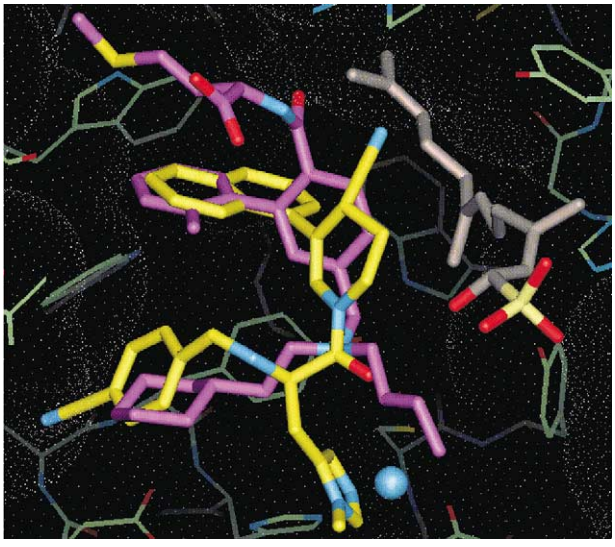


Figure 3. Superimposed X-ray crystal structures of ABT-839 and compound **33**.

required. However, the efficient synthesis of the tetrahydropyridine core provided a useful template that can be easily modified to give potent FTIs. In the following paper, we describe further efforts to improve the cellular activity of these inhibitors and to discover compounds with good pharmacokinetics.

Acknowledgements

Crystallographic data were collected at beamline 17-ID in the facilities of the Industrial Macromolecular Crystallography Association Collaborative Access Team (IMCA-CAT) at the Advanced Photon Source. These facilities are supported by the companies of the Industrial Macromolecular Crystallography Association through a contract with Illinois Institute of Technology (IIT), executed through IIT's Center for Synchrotron Radiation Research and Instrumentation. Use of the Advanced Photon Source was supported by the US Department of Energy, Basic Energy Sciences, Office of Science, under Contract No. W-31-109-Eng-38.

References and Notes

1. Prendergast, G. C.; Rane, N. *Exp. Opin. Investig. Drugs* **2001**, *10*, 2105.
2. Bell, I. M. *Exp. Opin. Ther. Patents* **2000**, *10*, 1813.
3. 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-Hutchins, 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. E. *Cancer Res.* **2001**, *61*, 8758.
4. 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.
5. Coordinates deposited (PDB ID 1N94).
6. Epsztajn, J.; Plotka, M. W.; Grabowska, A. *Synth. Comm.* **1997**, *27*, 1075.
7. O'Connor, S. J.; Nelson, L. T. J. U.S. Patent 6,277,871, 2001; *Chem Abstr.* **2001**, *135*, 180945.
8. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, *11*, 998.
9. Rokach, J.; Girard, Y. *J. Het. Chem.* **1978**, *15*, 683.
10. Coordinates deposited (PDB ID 1N95).
11. C log *P* calculations were performed with Biobyte 1.5.
12. All compounds reported have physical data consistent with the assigned structures.