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Aryl Tetrahydropyridine Inhibitors of Farnesyltransferase: Bioavailable Analogues with Improved Cellular Potency

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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 bioavailable aryl tetrahydropyridines that are potent in cell culture. The design, synthesis, SAR and biological properties of these compounds will be discussed.

In the preceding paper, we described the discovery of a novel class of farnesyltransferase inhibitors (FTIs) that contain a tetrahydropyridine (THP) core. In this letter, we disclose further examples from this series, many of which are potent in a cellular assay and several of which are bioavailable. As explained before, 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).[1] Selected compounds were then tested for pharmacokinetics.[2]

The best compound identified in the previous work is the histidine derivative **1** (Fig. 1). This compound is potent and selective for FT, but suffers loss of potency in the cellular assay.

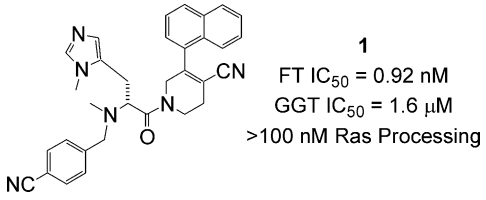

Figure 1. Compound **1**.

In an effort to improve upon this compound, we examined several other series of tetrahydropyridine containing FTIs. One series related to the previously described glycine derivatives is represented by the ureas in Scheme 1. The synthesis of these analogues begins with the known compounds **2** and **3**. Reductive amination provided secondary amine **4**. In situ formation of the carbamoyl chloride followed by addition of the tetrahydropyridine core gave the urea. These lower homologues of the glycine derivatives show markedly improved potency for FT inhibition. These compounds are also selective for FT over the related enzyme geranylgeranyltransferase-I (GGT-I). Unfortunately, none of these compounds was sufficiently potent in the cellular assay.

We next prepared an analogue with a one carbon linker attaching the imidazole and cyanophenyl pharmacophores to the tetrahydropyridine core. This compound was prepared by alkylating the THP with the secondary chloride derived from **11**. **12** demonstrated excellent potency for farnesyltransferase and was also potent in the cellular assay, but was not as selective as previous compounds (Scheme 2).

To examine a homologue of compound **12**, we found it convenient to install a hydrazine unit in our inhibitor. The synthesis of this compound is shown in Scheme 3 and makes use of the method developed for the

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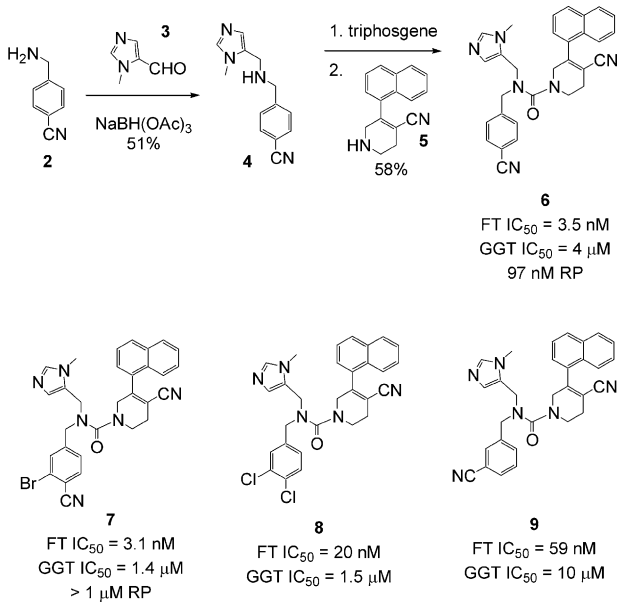
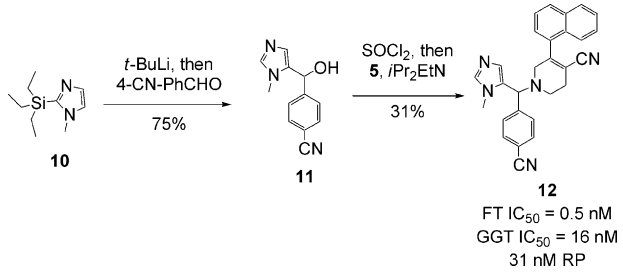


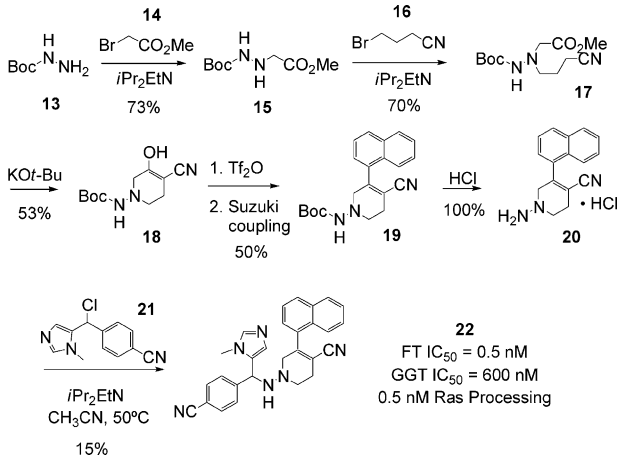
Scheme 1. Urea derivatives.



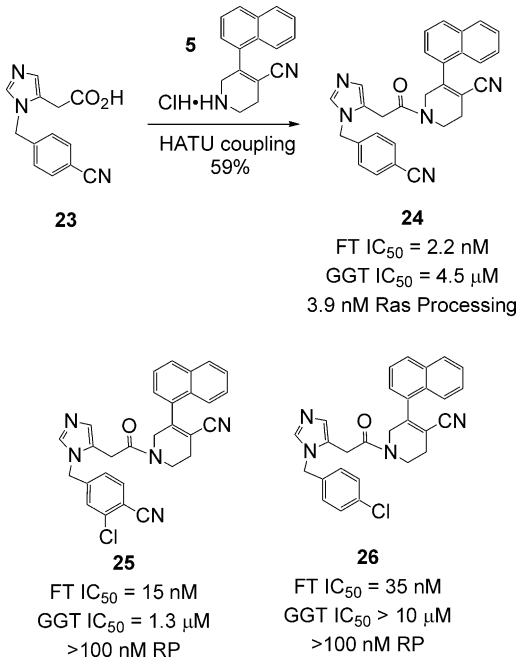
Scheme 2. Methine linked inhibitor **12**.

tetrahydropyridine core described in the preceding article. Compound **22** demonstrated excellent potency both in enzymatic and in cellular assays and showed good selectivity for FT. In addition, this compound is orally bioavailable in dogs ($F = 27\%$) with a half-life of 1.2 h.

We also examined analogues based on imidazoleacetic acid, as shown in Scheme 4. The known acid **23**[3] was coupled to the THP core using HATU to provide **24**.



Scheme 3. Hydrazine containing FTI **22**.



Scheme 4. Imidazoleacetic acid derivatives.

Compound **24** showed excellent potency both in enzymatic and in cellular assays and was selective for FT. However, the compound has poor pharmacokinetics with an oral bioavailablility of 10% and a half-life of 0.7 h in dogs.

A crystal structure of **24** bound to FT was obtained (Fig. 2).[4] Surprisingly, this compound binds in a markedly different manner from ABT-839 and other THP inhibitors examined. While the imidazole is still bound to zinc, the tetrahydropyridine core and the cyanobenzyl unit have switched places in the active site.

The crystallography and biological results for **24** led us to prepare the homologue with another carbon in the

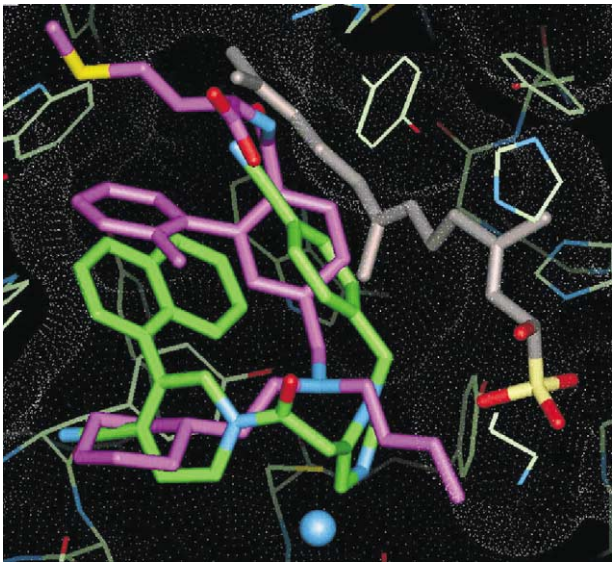
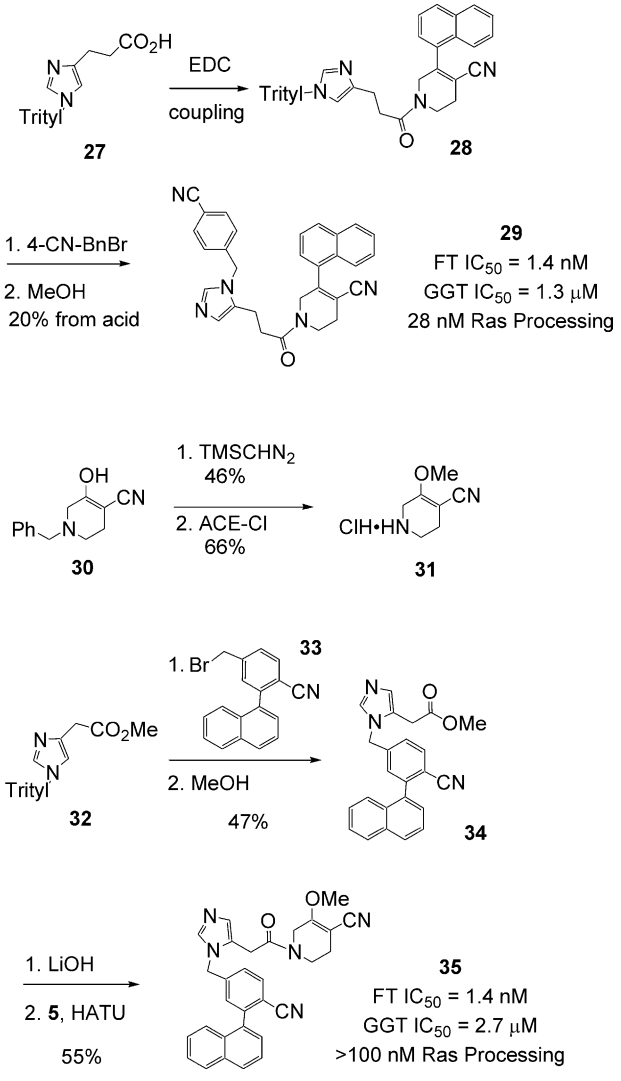


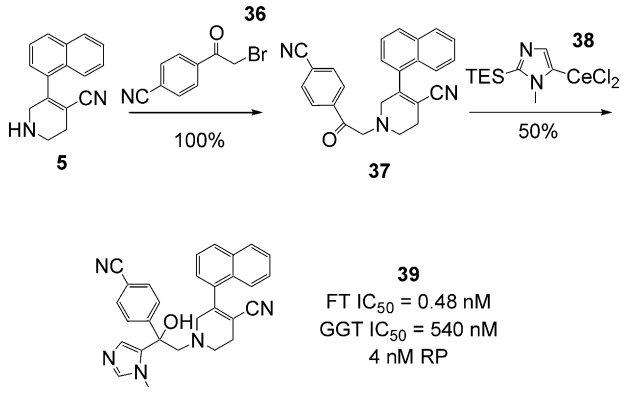
Figure 2. Superimposed X-ray crystal structures of ABT-839 and **24** in the FT active site.

linker and an analogue where the naphthyl unit was moved to the cyanobenzyl group. The synthesis of these compounds is shown in Scheme 5. The known acid **27**[5] was coupled to the THP core using EDC. This amide was then treated with 4-cyanobenzyl bromide to affect quaternization of the imidazole nucleus. Methanolysis of this salt led to **29**. The preparation of **35** begins with the enol intermediate from the THP core synthesis described in the preceding paper. Treatment of **30** with trimethylsilyldiazomethane gave the methyl ether, which could be converted to the amine salt using ACE-Cl as before. To prepare the coupling partner for this amine, the known ester **32** was first alkylated with bromide **33**.[6] Methanolysis and saponification gave the imidazoleacetic acid which was then coupled to the THP using HATU. Gratifyingly, both **29** and **35** were potent and selective for FT; however, neither realized improvement over **24** in cellular potency.

Upon examination of the SAR for the compounds thus far, one notes that compounds **12** and **22** are two of the best. With this in mind, we sought to prepare a hybrid of these compounds by using an ethylene linker. This was accomplished by preparing the tertiary alcohol **39**



Scheme 5. Analogues of **24**.



Scheme 6. Tertiary alcohol **39**.

as shown in Scheme 6. Alkylation of the THP core with the commercially available **36** gave ketone **37**. Addition of the cerium reagent **38** led to production of the tertiary alcohol **39**. This compound showed impressive potency in enzymatic and cellular assays and is approximately 1000 fold selective for FT over GGT-I. This compound also demonstrates reasonably good pharmacokinetics with an oral bioavailability of 57% and a half-life of 1.7 h in dogs.

In summary, the aryl tetrahydropyridine containing farnesyltransferase inhibitors described here[7] represent a significant improvement over previous compounds. Many are potent and selective inhibitors of FT. Several also possess good cellular activity and oral bioavailability. X-ray crystallography proved valuable for understanding the interactions of these inhibitors with FT and for the design of new analogues.

Acknowledgements

Crystallographic data were collected at beamline 17-ID in the facilities of the Industrial Macromolecular Crystallograpy 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

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7. All compounds reported have physical data consistent with the assigned structures.