Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1895–1899
Bioorganic & Medicinal Chemistry Letters

Design, synthesis, and structure–activity relationships of tetrahydroquinoline-based farnesyltransferase inhibitors

Louis J. Lombardo,* Amy Camuso, John Clark, Krista Fager, Johnni Gullo-Brown, John T. Hunt, Ivan Inigo, David Kan, Barry Koplowitz, Francis Lee, Kelly McGlinchey, Ligang Qian, Carolyn Ricca, George Rovnyak, Sarah Traeger, John Tokarski, David K. Williams, Laurence I. Wu, Yufen Zhao, Veeraswamy Manne and Rajeev S. Bhide

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, United States

Received 12 January 2005; revised 31 January 2005; accepted 1 February 2005

Abstract—Tetrahydroquinoline-based small molecule inhibitors of farnesyltransferase (FT) have been identified. Lead compounds were shown to have nanomolar to sub-nanomolar activity in biochemical assays with excellent potency in a Ras-mutated cellular reversion assay. BMS-316810 (**9e**), a 0.7 nM FT inhibitor, was orally-active in a nude mouse tumor allograft efficacy study.

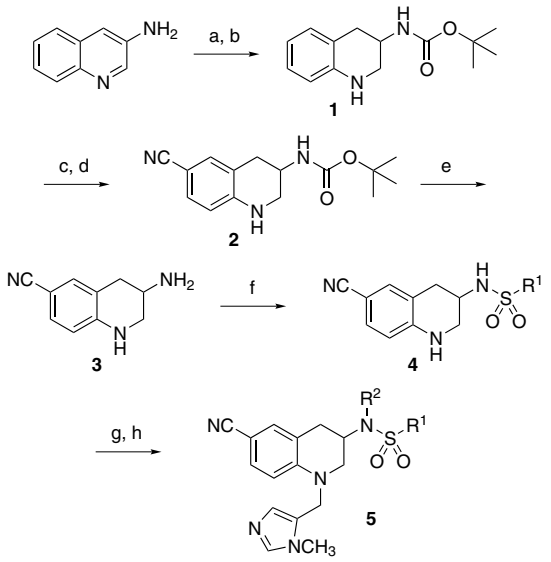
Ras proteins are a family of GTP-binding proteins involved in cellular signal transduction and cell proliferation. Oncogenic mutations of the Ras protein cause disruption of its GTPase activity and prevent interaction with GTPase activating protein, resulting in constitutive activation of the Ras signaling cascade.[1,2] Oncogenic *ras* thereby promotes unregulated cell growth and is estimated to occur in 30–50% of colon, 30% of lung, and 90% of pancreatic tumors in humans.[3] The signaling functions of both normal and oncogenic Ras are contingent upon their association with the cell membrane, which is accomplished by a series of post-translational modifications of the newly synthesized protein.[4] Farnesylation of the C-terminal cysteine residue of p21 ras protein, which is catalyzed by the zinc metalloenzyme farnesyltransferase (FT), is critical for its ability to associate with the membrane. Thus, disruption of farnesyltransferase enzymatic activity is an attractive pharmacological target for controlling *ras* dependent tumor growth.[5]

The activity of benzodiazepine-based farnesyltransferase inhibitors has been described.[6] Motivated by the potent in vitro activity and excellent in vivo efficacy of these leads, tetrahydroquinoline-based inhibitors were proposed as a second-generation series. Herein, we describe the synthesis, structure–activity relationships, and in vivo activity of novel tetrahydroquinoline farnesyltransferase inhibitors in mutant Ras cancer models.

Compounds were prepared following the synthetic sequence illustrated in Scheme 1. Boc-protected 3-amino-1,2,3,4-tetrahydroquinoline **1** was prepared by reaction of the sodium salt of commercially available 3-aminoquinoline with di-*tert*-butyldicarbonate, followed by catalytic hydrogenation over palladium in acidic methanol. Bromination with pyridinium tribromide proceeded regioselectively to afford the 6-bromo analog, which was converted to the corresponding 6-cyano derivative **2** by treatment with zinc cyanide and tetrakis(triphenylphosphine)palladium in dimethylformamide. Removal of the Boc group with trifluoroacetic acid in dichloromethane afforded the key intermediate 3-amino-6-cyano-1,2,3,4-tetrahydroquinoline **3** as a racemate in 27% overall yield. Completion of the target molecules (**5**) was accomplished following a three step sequence of sulfonamide formation, reductive amination, and alkylation. In general, reaction of amine **3** with a variety of sulfonyl chlorides under standard conditions gave the corresponding sulfonamides (**4**) in good to excellent yield. Installation of the imidazole using previously described reductive amination conditions,[7] followed by alkylation of the sulfonamide nitrogen with an

Keywords: Farnesyltransferase inhibitor; BMS-316810.
* Corresponding author. Tel.: +1 609 252 4265; fax: +1 609 252 4710; e-mail: louis.lombardo@bms.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.02.004

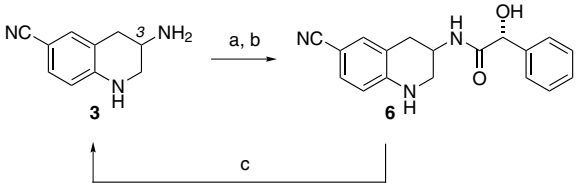


Scheme 1. Synthesis of tetrahydroquinoline-derived farnesyltransferase inhibitors. (a) NaHMDS, $(Boc)_2O$, THF, 100%; (b) H_2, Pd/C, HOAC, CH_3OH, 46%; (c) PBr_3, THF, 75%; (d) $ZnCN_2$, $Pd(PPh_3)_4$, DMF, 81%; (e) 50% CF_3CO_2H, CH_2Cl_2, 100%; (f) R^1SO_2Cl, Et_3N, CH_2Cl_2, 60–95%; (g) 1-methyl-5-formylimidazole, Et_3SiH, CF_3CO_2H, CH_2Cl_2, 75–90%; (h) R^2Br, base, DMF, 50–80%.

appropriate alkyl halide under basic conditions (NaHMDS or Cs_2CO_3) afforded final compounds in high yield.

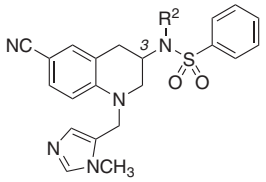
Multigram quantities of enantiomerically-pure **3** could be obtained using the covalent resolution process outlined in Scheme 2. Carbodiimide coupling of racemic **3** with *S*-(+)-mandelic acid proceeded in quantitative yield to afford diastereomeric amides (**6**), which could subsequently be separated by flash chromatography on silica gel or fractional crystallization. Hydrolysis of the diastereomerically-pure amides in refluxing acidic ethanol afforded the corresponding enantiomerically-pure amines (**3**) in high overall yield. Each enantiomer of **3** was converted to the target compounds as described in Scheme 1. The absolute configuration at the C-3 position of the tetrahydroquinoline ring was assigned by single crystal X-ray crystallography of one diastereomer of compound **6**, which was determined to be of the (*S*,*S*)-configuration.

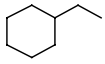
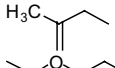
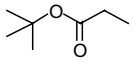
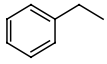
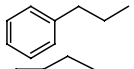
Initial structure–activity relationship (SAR) studies focused on assessing the effect of alkyl group substitution (R^2) on the C-3 nitrogen of a benzenesulfonamide-derivatized tetrahydroquinoline scaffold (Table 1). Consistent with the defined pharmacophore for benzodiazepine FT inhibitors, the 6-cyano and 1-(1-methylimidazolylmeth-5-yl) groups were held constant in the tetrahydroquinoline series of compounds.[6] Generally, the R^2 position was tolerant of a broad range of substituents (compounds **7b**; **7d–f**; **7h**), with lower alkyl-, alkenyl-, carboxymethyl-, and aralkyl-substituted analogues all demonstrating excellent potency in a human recombinant farnesyltransferase inhibition biochemical assay. Good enzyme inhibitory activity was also observed with the unsubstituted derivative **7a**, but a reduction in potency was measured with the bulkier cyclohexylmethyl (**7c**) and homologated phenethyl (**7g**) analogues.



Scheme 2. Covalent resolution of the racemic 3-aminotetrahydroquinoline intermediate **3**. (a) *S*-(+)-mandelic acid, EDAC, HOBT, DMF, 100%; (b) flash chromatography (SiO_2; 2:1 EtOAc–hexanes) or fractional crystallization (acetone–hexanes), 66–78% of theoretical; (c) 15% H_2SO_4, EtOH, reflux, 72%.

Table 1. Effect of alkyl group substitution on the C-3 exocyclic nitrogen



Compd	R^2	FT[a,b] IC_{50}, nM	Cellular reversion[a] % @ 100 nM
7a	H	10	0% (30% @ 10 μM)
7b	CH_3	3.5	45%
7c		48	0% (90% @ 1 μM)
7d		0.9	95%
7e		4.0	75%
7f		3.0	85%
7g		>5000	0%
7h (racemic)		2.5	90%
7i (*S*)-		1.1	85%
7j (*R*)-		2.8	80%

[a] Experimental details for all in vitro assays are contained in Ref. 8.
[b] IC_{50} values are the mean of at least two determinations. Standard deviations are typically within 30% of the IC_{50} value.

The cellular activity of tetrahydroquinoline FT inhibitors was evaluated in mutant H-*ras* transfected Rat-1 cells. This transformed cell line is characterized by unchecked proliferation in culture, with the cells no longer displaying contact-inhibited growth properties and possessing a distinctive, rounded and elongated phenotype. The activity of compounds under evaluation is reported as the percentage of cells no longer displaying this mutant Ras phenotype at the screening concentration of 100 nM, unless otherwise noted. Activity in the cellular reversion assay correlated well with biochemical potency through the series, with two notable exceptions. The