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Synthesis of Conformationally Constrained 5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridine Inhibitors of Farnesyltransferase

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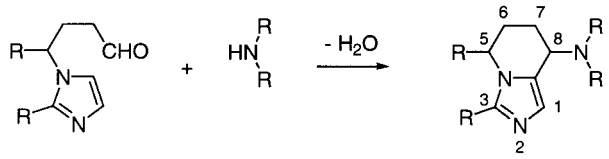
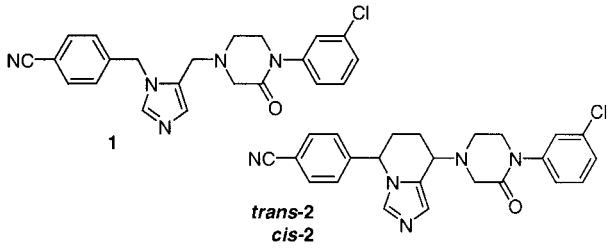
ABSTRACT



Synthesis of the 8-amino-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine ring system was accomplished by intramolecular cyclization of an iminium ion, derived from condensation of an amine and a substituted γ-(1-imidazolyl)butyraldehyde. The reaction was used to produce conformationally restricted farnesyltransferase inhibitor analogues which exhibit improved in vivo metabolic stability.

Farnesyltransferase (FTase) is an important posttranslational processing enzyme that prenylates proteins and enables their participation in signal transduction during cell proliferation.[1] Inhibitors of this enzyme (FTIs) are promising antitumor agents, and several are currently being evaluated in human clinical trials.[2] During our efforts to improve the properties of the clinical candidate **1**,[3] we sought to understand



structural aspects of its enzyme-bound conformation and address the compound's metabolic liabilities. We anticipated that both goals could be accomplished simultaneously by constraining the imidazole substituents in a ring. On the basis of these considerations, the disubstituted 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine **2** was selected as a target for synthesis. Evaluation of this ring system would afford opportunities to assess the binding of *cis* and *trans* isomers to the enzyme, as well as the merits of adding substituents at key positions of **1** to block oxidative metabolism and enhance in vivo pharmacokinetic behavior.[4] We report herein

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(1) (a) Kato, K.; Cox, A. D.; Hisaka, M. M.; Graham, S. M.; Buss, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 6403−6407. (b) Rowinsky, E. K.; Windle, J. L.; Von Hoff, D. D. *J. Clin. Oncol.* **1999**, *17*, 3631−3652.

(2) (a) Oliff, A. *Biochim. Biophys. Acta* **1999**, *1423*, C19−C30. (b) End, D. W. *Invest. New Drugs* **1999**, *17*, 241−258. (c) Gibbs, J. B. *J. Clin. Invest.* **2000**, *105*, 9−13.

(3) (a) Williams, T. M.; Dinsmore, C. J.; Bergman, J. M.; Hutchinson, J. H.; MacTough, S. C.; Stump, C. S.; Wei, D. D.; Zartman, C. B.; Bogusky, M. J.; Chen, I.-W.; Culberson, J. C.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Motzel, S. L.; Salata, J. J.; Gibbs, J. B.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Huff, J. R. *Abstracts of Papers*, 216th National Meeting of the American Chemical Society, Boston, MA, 1998, American Chemical Society: Washington, DC, 1998; MEDI 309. (b) Manuscript in preparation.

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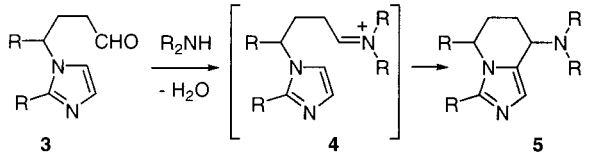
a new synthesis of this fused 5,6-ring system and discuss the biological characterization of **2** and related analogues.

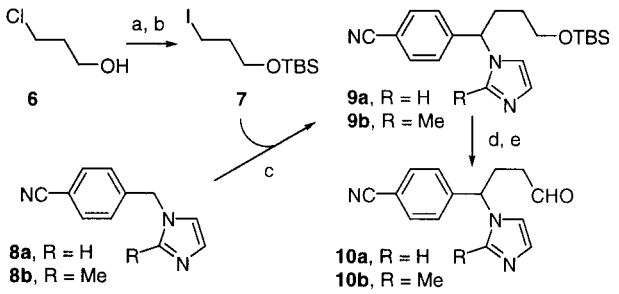
Although tetrahydroimidazo[1,5-*a*]pyridine fragments have been evaluated in numerous medicinal chemistry programs,[5] relatively few methods to prepare them are known. These include S_N2 ring closure of activated 4-(3*H*-imidazol-4-yl)-1-butanol derivatives,[5c,e] functionalization of the olefin in 5,6-dihydroimidazo[1,5-*a*]pyridines,[5b,d,6] and hydrogenation of imidazo[1,5-*a*]pyridines.[5a,f] Only one example featuring an amino substituent at the 8-position has been reported, in which treatment of a 5,6-dihydroimidazo[1,5-*a*]pyridine with NBS provided the derived bromosuccinimide.[5d] We hypothesized that a direct approach to 8-amino-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridines such as **2** might result from the cyclocondensation of two easily prepared synthons. Thus, a γ-(1-imidazolyl)butyraldehyde derivative, **3**, could be combined with an amine to produce the iminium ion intermediate **4**, which would undergo intramolecular electrophilic aromatic substitution to provide the desired product **5** (Scheme 1).[7]

Scheme 1



The requisite aldehydes used in this study were prepared by the addition of a three-carbon unit to the benzylic carbon of the 1-(4-cyanobenzyl)imidazoles **8a** and **8b**[8] (Scheme 2).

Scheme 2[a]

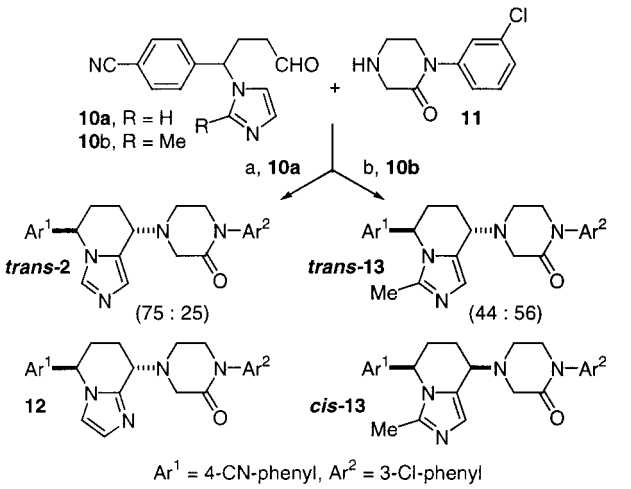


[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 18 h, 95%; (b) NaI, acetone, reflux, 24 h, 78%; (c) LiHMDS (1.1), THF, −78 °C, 1 h; add **7**, −78 to 0 °C, 6 h, 57% for **9a**, 87% for **9b**; (d) TBAF, THF, 0 °C, 45 min; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 30 min, 57% for **10a**, 77% for **10b** over two steps.

3-Chloropropanol **6** was protected and activated as the corresponding iodide **7**, which was used to alkylate the Li-anions of **8a** and **8b**. Deprotection of the silyl ethers **9a** and **9b** with tetrabutylammonium fluoride was followed by Swern oxidation[9] to give the aldehydes **10a** and **10b**.

In the key transformation, treatment of the γ-(1-imidazolyl)butyraldehyde derivative **10a** with 1-(3-chlorophenyl)-2-piperazinone **11**[10] and magnesium sulfate in refluxing chlorobenzene gave a 50% combined yield of a 75:25 ratio of the 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine *trans*-**2** and the undesired *trans*-[1,2-*a*] regioisomer **12** (Scheme 3).[11a,b]

Scheme 3[a]



[a] Reagents and conditions: (a) $MgSO_4$, PhCl, reflux, 1.5 h, 31% for *trans*-**2**, 19% for **12**; (b) $MgSO_4$, PhCl, reflux, 3 h, 18% for *trans*-**13**, 25% for *cis*-**13**.

No *cis*-**2** was detected in the reaction mixture. The reaction of 2-methylimidazole derivative **10b** was evaluated next in an effort to block formation of the undesired 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine isomer. Interestingly, the diastereoselectivity in this case was degraded almost com-

(4) In liver microsome incubation studies, **1** suffers *N*-dealkylations of the imidazole and piperazinone rings (unpublished results, ref 3b).

(5) (a) H2 antagonists: Durant, G. J.; Loynes, J. M.; Wright, S. H. B. *J. Med. Chem.* **1973**, *16*, 1272−1276. (b) Cardiotonics: Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337−1342. (c) Aromatase inhibitors: Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E.; Bhatnager, A. *J. Med. Chem.* **1991**, *34*, 725−736. (d) A-II antagonists: Huang, H.-C.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; Chen, S. T.; McMahon, E. G.; Palomo, M. A.; Blaine, E. H.; Manning, R. E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2591−2596. (e) Glycosidase inhibitors: Frankowski, A.; Deredas, D.; Nouen, D. L.; Tschamber, T.; Streith, J. *Helv. Chim. Acta* **1995**, *78*, 1837−1842. (f) 5-HT3 antagonists: Ohta, M.; Suzuki, T.; Koide, T.; Matsuhisa, A.; Furuya, T.; Miyata, K.; Yanagisawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 991−999.

(6) Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863−1867.

(7) For the related Pictet−Spengler cyclization of histamine derivatives with aldehydes, see: (a) Heyl, D.; Luz, E.; Harris, S. S.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3669. (b) Jouanisson, A.; Chavignon, O.; Couquelet, J.; Teulade, J.-C.; Chabard, J.-L.; Dauphin, G. *Heterocycles* **1995**, *41*, 21−28. (c) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4865−4868.

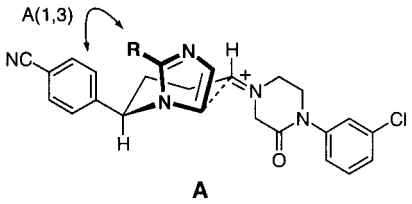
(8) Compounds **8a** and **8b** were prepared from α-bromo-*p*-tolunitrile (1.0 equiv), imidazole or 2-methylimidazole (1.1 equiv), and K_2CO_3 (1.5 equiv) in DMF at room temperature for 4 h (62% for **8b**).

(9) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(10) Weissman, S. A.; Lewis, S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 7459−7462.

pletely to afford a 44:56 mixture of *trans*-**13** and *cis*-**13** in 43% combined yield.[11b]

The influence of the methyl group at the 2-position of the imidazole ring on the *cis*/*trans* distribution in the products can be rationalized by consideration of transition states for the iminium ion cylization. The favored transition state **A** (Figure 1), which would lead to *trans*-products, is preferred



A

Figure 1. Chair transition state for the formation of *trans*-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridines showing A(1,3)-strain interaction for R ≠ H.

relative to alternative boat conformers and chair conformers with axial substituents. However, the addition of a methyl group to the imidazole ring (**13**, R = Me) exerts a significant conformational bias due to an A(1,3)-strain interaction[12] with the 4-cyanophenyl group. Consequently, alternative transition states would be favored.

The conformationally constrained FTIs were found to have diminished FTase inhibitory activity[13] relative to that of the unconstrained compound **1** (Table 1). One possible explanation for this is that the required enzyme-bound conformation is precluded by the *trans* and *cis* ring constraints.[14] That both *trans*-**13** (presumably a diequatorial half-chair)[15] and *cis*-**13** (presumably an axial−equatorial half-chair) are considerably less potent than the unconstrained system **1** implies that the cyanophenyl and piperazinone groups of **1** are required to align themselves perpandicular to the imidazole ring, in either an *anti* relative orientation or a *syn* orientation, on binding to the enzyme active site. These putative bound conformations of **1** would correspond to the higher energy *trans*-**13** diaxial half-chair and *cis*-**13** diaxial boat, respectively.[15] Alternatively, the ethano-bridge may experience destabilizing intermolecular interactions with residues in the enzyme active site. It is also possible that both intramolecular conformational and intermolecular steric effects may contribute simultaneously to the decrease in inhibitory activity. In contrast, the pharmacokinetic behavior of compounds after oral dosing to dogs was significantly improved by the presence of the tetrahydroimidazo[1,5-*a*]pyridine ring constraint.[14,16] Although FTI **1** had less than a 1 h half-life, compounds *trans*-**2** and *trans*-**13** exhibited half-lives greater than 10 h and were well absorbed (Table 1). This may be the result of a steric blockade of potential metabolic sites in the parent molecule **1**.[4,17]

In summary, the cyclocondensation method described herein for the synthesis of amino-substituted 5,6,7,8-tetrahy-

Table 1. FTase Inhibition Data[a] and Pharmacokinetic Data[b] in Dogs Following Combination Oral Dosing at 1 mpk

compd	IC_{50} (nM)[a]	$t_{1/2}$ (h)	C_{max} (μM)	AUC rel **1**[d]
1	2	0.79 ± 0.2[c]	2.98 ± 1.3[c]	1.00
trans-**2**	8440	10.6	1.59	4.16
trans-**13**	3840	13.3	1.34	2.43
cis-**13**	3800	5.5	0.93	0.76

[a] Concentration of compound required to reduce the FTase-catalyzed incorporation of [^{3}H]FPP into recombinant human K-Ras by 50% (see ref 13). [b] Compounds were administered orally to two dogs as mixtures with 10 other compounds, each at 1 mg/kg, with compound **1** included as an internal reference. Plasma extracts were analyzed by LC/MS/MS, and reported data are the average of two dogs unless otherwise indicated (see ref 16). [c] Mean data from 19 experiments, in good agreement with single compound administration data. [d] The ratio of the compound's average AUC to that of the internal standard **1** from the same experiment.

(11) (a) **Representative procedure**: To a solution of aldehyde **10a** (824 mg, 3.45 mmol) and amine **11** (726 mg, 3.45 mmol) in 10 mL of anhydrous chlorobenzene under argon was added $MgSO_4$ (1.00 g, 8.3 mmol). The reaction was heated to reflux for 1.5 h, cooled to room temperature, diluted with dichloromethane (300 mL), filtered, and concentrated in vacuo. Purification by flash chromatography (6 × 15 cm silica gel, 40 → 80% acetone/dichloromethane) provided **12** (276 mg, 19%) and *trans*-**2** (455 mg, 31%), both as pale yellow foams. (b) Data for compounds: *trans*-**2**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.1 Hz, 2H), 7.32−7.37 (m, 2H), 7.22−7.28 (m, 3H), 7.22 (d, J = 7 Hz, 2H), 7.14 (d, J = 3.3 Hz, 1H), 5.20 (dd, J = 7.9 and 4.4 Hz, 1H), 4.09 (dd, J = 8.6 and 5.1 Hz, 1H), 3.73 (m, 1H), 3.63 (m, 1H), 3.63 (d, J = 16.2 Hz, 1H), 3.49 (d, J = 16.2 Hz, 1 H), 3.03 (m, 1H), 2.94 (m, 1H), 2.52 (m, 1H), 2.07 (m, 1H), 1.80−1.96 (m, 2H); *m*/*z* (FAB$^+$) 432.3 (MH$^+$). **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 2H), 7.30−7.36 (m, 2H), 7.21−7.25 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 1.3 Hz, 1H), 6.50 (d, J = 1.3 Hz, 1H), 5.21 (dd, J = 7.8 and 5.1 Hz, 1H), 4.07 (dd, J = 7.9 and 5.1 Hz, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.60 (s, 2H), 3.46 (m, 1H), 3.07 (m, 1H), 2.58 (m, 1H), 2.13 (m, 1H), 1.90−2.05 (m, 2H); *m*/*z* (FAB$^+$) 432.3 (MH$^+$). ***trans*-13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.84 (m, 3H), 7.42−7.46 (m, 2H), 7.34−7.37 (m, 3H), 7.32 (bd, J = 8 Hz, 1H), 5.76 (m, 1H), 4.57 (m, 1H), 3.83−3.95 (m, 2H), 3.81 (bd, J = 16 Hz, 1H), 3.73 (bd, J = 16 Hz, 1H), 3.35−3.43 (m, 2H), 2.78 (m, 1H), 2.19 (s, 3H), 2.09−2.18 (m, 3H); HRMS (ES) exact mass calcd for $C_{25}H_{25}N_5OCl$ (M + H$^+$) 446.1742, found 446.1746. ***cis*-13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (bs, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.42−7.47 (m, 2H), 7.35 (m, 1H), 7.30 (m, 1H), 7.26 (d, J = 8.3 Hz, 2H), 5.89 (dd, J = 5.7 and 2.7 Hz, 1H), 4.54 (m, 1H), 3.82−3.92 (m, 2H), 3.78 (d, J = 16.1 Hz, 1H), 3.65 (d, J = 16.1 Hz, 1H), 3.36 (m, 1H), 3.22 (m, 1H), 2.55 (m, 1H), 2.46 (m, 1H), 2.33 (s, 3H), 2.09 (m, 1H), 1.75 (m, 1H); HRMS (ES) exact mass calcd for $C_{25}H_{25}N_5OCl$ (M + H$^+$) 446.1742, found 446.1732.

(12) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124 and references therein.

(13) For assay conditions, see: Graham, S. L.; deSolms, S. J.; Kohl, N. E.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Breslin, M. J.; Deanna, A. A.; Garsky, V. M.; Scholz, T. H.; Gibbs, J. B.; Smith, R. L. *J. Med. Chem.* **1994**, *37*, 725−737.

(14) The FTase inhibitory activity and dog pharmacokinetic (PK) properties of **1** and the corresponding 2-methylimidazole analogue of **1** are very similar, suggesting that the methyl groups in *trans*-**13** and *cis*-**13** contribute little to their inhibitory and PK activities (Merck Research Laboratories, unpublished results).

(15) (a) Molecular modeling results, with relative energies in kcal/mol shown in parentheses: *trans*-**13** diequatorial half-chair (0.00); *trans*-**13** diaxial half-chair (1.56); *cis*-**13** equatorial-(ArCN)−axial-(piperazinone) half-chair (0.18); *cis*-**13** axial-(ArCN)−equatorial-(piperazinone) half-chair (0.59); *cis*-**13** diaxial boat (5.46). Conformations were generated using the metric matrix distance geometry algorithm JG (S. Kearsley, Merck Research Laboratories, unpublished). The structures were subjected to energy-minimization within Macromodel (ref 15b) using the MMFF force field. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(16) For the protocol for PK analysis, see: Olah, T. V.; McLoughlin, D. A.; Gilbert, J. D. *Rapid Commun. Mass Spectrom.* **1997**, *11*, 17−23.

(17) Consistent with this hypothesis, metabolic clearance in dogs after an intravenous dose was significantly reduced for *trans*-**2** (1 mpk: CL = 1.40 mL/min/kg, $t_{1/2}$ 10.3 h) relative to **1** (2 mpk: CL = 10.6 mL/min/kg).

droimidazo[1,5-*a*]pyridines was used to prepare constrained analogues of the clinical candidate, FTI **1**, to assess conformational preferences of the enzyme-bound ligands and to improve in vivo pharmacokinetic properties. This study provided compounds with diminished enzyme inhibitory activity but significantly improved pharmacokinetic properties.

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