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3-Aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)methylpyrrole, a Novel Class of Farnesyltransferase Inhibitors

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Abstract—Design, synthesis and structure–activity relationship of a class of 3-aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)methylpyrroles as farnesyltransferase inhibitors are described. Compound **7** inhibits farnesyltransferase with an IC_{50} value of 4.6 nM.

Mutated versions of three human *ras* genes are frequently found in many human cancers, most notably cancers of the pancreas, colon, and lung, implying an important role for aberrant Ras function in human tumor growth.[1–4] The p21 Ras oncogenic products are synthesized as cytosolic proteins, which undergo posttranslational modifications for attachment of the normal as well as mutated Ras proteins to the membrane.[5,6] A key step in a series of posttranslational modifications of the oncogenic product Ras is farnesylation of the thiol group of cystein located at the C-terminal CAAX sequence in Ras proteins, which is catalyzed by farnesyltransferase (FTase).[7,8] Farnesyltransferase inhibitors (FTIs) would therefore have potential as anticancer agents for tumors in which a *ras* gene is oncogenically mutated.[9–11] In fact, the efficacy of FTIs in murine models has been demonstrated by their ability to inhibit tumor growth in nude mice and to induce tumor regression in transgenic mice.[12–14]

Numerous structurally diverse classes of FTIs that mimic tetrapeptide of Ras C-terminal CAAX motif have been reported.[15–18] Avenues toward improving the biological and pharmacokinetic properties of peptidomimetic inhibitors have included the use of nonpeptide surrogates for the central AA portion, deletion of carboxyl containing terminus, and replacement of cystein moiety. Notable examples have featured the substitution of 4-aminobenzoic acid for central hydrophobic dipeptide (e.g., **1**, $IC_{50} = 0.5$ nM), and the use of an imidazole ring as an alternative to the cystein thiol group (e.g., **2**, $IC_{50} = 1.4$ nM) which is believed to be involved in an important binding interaction with Zn++ of FTase (Fig. 1).[16,17] Although they are potent, inhibitors with carboxylic acid moiety showed poor cell membrane permeability and poor oral bioavailibility.[17] Our efforts focused on the design of inhibitors, without carboxylic acid and thiol moiety, based on non-petidic template with the putative zinc binding capacity. In our search for a suitable template, we have investigated pyrrole series as a hypothetical pharmacophore featuring an aromatic binding interaction, the spacer for the central hydrophobic dipeptide, an H-bond acceptor, and zinc binding ligand. 3-Aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)-methylpyrroles were designed to satisfy those above requirements by attaching the aryl ring, the central pyrrole ring, the ketone oxygen carbonyl group and imidazole, respectively.

A general synthesis of the 3-aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)methylpyrroles is illustrated in Scheme 1. Synthesis of pyrroles are very well known in the chemistry literature.[19] We prepared pyrroles by reacting toluene-4-sulfonylmethyl isocyanide (TosMIC) with appropriate chalcones in anhydrous THF in the presence of potassium *t*-butoxide. Chalcones were obtained by the condensation of an aldehyde derivative with an acetophenone derivative in ethanol with sodium hydroxide as catalyst.[19] 5-chloromethyl imidazole hydrochloride was prepared from 5-hydroxymethyl imidazole by the literature procedure.[20] Compound **3** was coupled with chloromethyl imidazole to give the

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compound **4** in the presence of NaH. Deprotection of trityl protecting group of the imidazole provided **5b**. Compounds **5a**, **c**–**i** (Table 1) were synthesized analogously by coupling the corresponding pyrroles with chloromethyl imidazole. Compound **6** was prepared by reduction of **5b** in the presence of sodium borohydride. Compound **7** was synthesized by coupling the corresponding pyrrole with 5-chloromethyl-1*H*-1-methylimidazole.

The structure–activity relationships are presented in Table 1. Initial lead compound **5a** inhibited FTase with modest activity with IC_{50} value of 5 μM. The dramatic boost of inhibitory activity from **5a** to **5b** is clearly noteworthy, indicating the hydrophobic aromatic substituent at C-3 of the pyrrole is critical to the inhibitory potency of the imidazole-containing pyrrole. We utilized the arylcarbonyl group at C-4 of the pyrrole to supply the hydrophobic group as well as the hydrogen bond-accepting group. Substitutions in the region of ortho or para position of the aryl group led to moderate increase in activity. The potent inhibitor (**5g**) contained a hydrophobic phenoxy to the *para* position. Reduction of ketone in compound **5b** to alcohol (**6**) led to 10-fold active loss than the parent compound, suggesting the ketone group plays roles both as a hydrogen bonding acceptor and as a geometric restrictor. The methylation at N-1 of the imidazole ring in compound **7** increased the potency, suggesting N-3 of imidazole be involved in binding with Zn++ of Ftase.

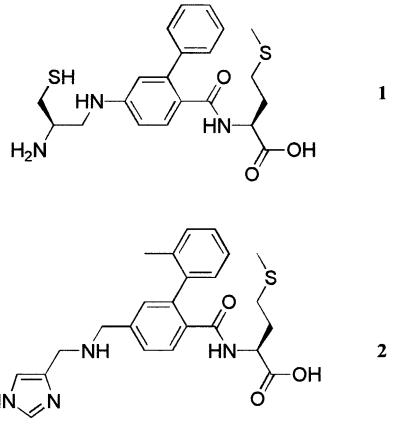
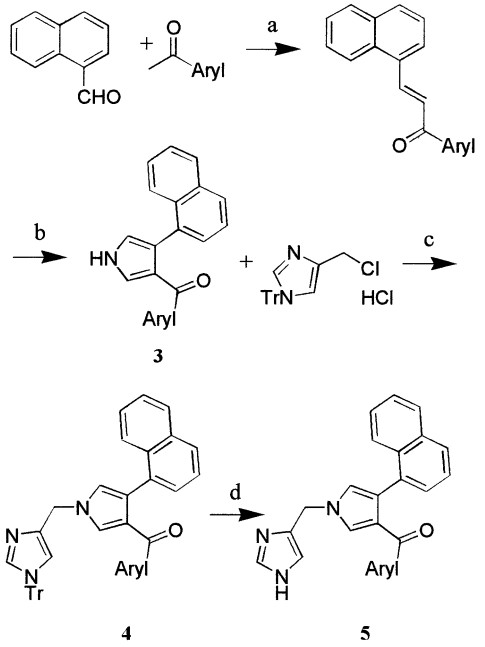


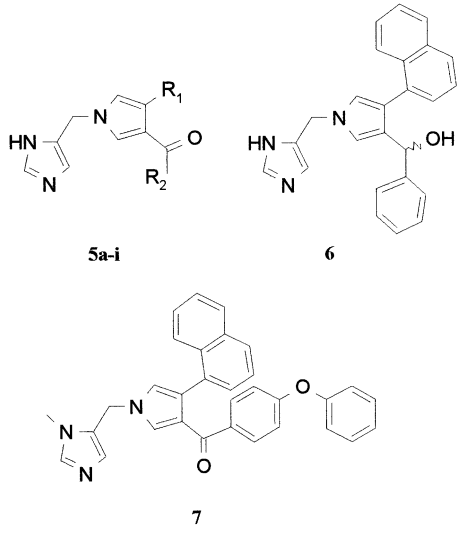
Figure 1. Structure of compounds **1** and **2**.



Scheme 1. General synthesis of 3-aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)methylpyrroles for compounds **5a**–**i**. (a) Ethanol, NaOH; (b) tosylmethylisocyanide (TosMIC), *t*-BuOK/THF (c) NaH (2.5 equiv)/DMF, 0 °C; (d) trifluoroacetic acid, triethylsilylhydride.

In summary, a series of 3-aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)methylpyrroles **5** were designed and synthesized as small molecular FTIs. These series of compounds inhibit farnesyltransferase at concentration as low as IC_{50} of 4.6 nM. Structure–activity relationship studies were focused primarily on pyrrole derivatives. Although further studies are required to ascertain the utility of pyrrole ring system as a template for the attachment of pharmacophores, it represents a novel class of FTIs that do not have the problematic thiol and carboxylate functional groups. This new pharmacophore would be valuable for the development of farnesyltransferase inhibitor as a clinically useful anticancer agent.

Table 1. Farnesyltransferase inhibitory activities of compound **5a**–**i**,**6** and **7**.[a]



Compd	R1	R2	Ftase IC_{50}, nM[b]
5a	Phenyl	Phenyl	5000
5b	1-Naphthyl	Phenyl	115
5c	1-Naphthyl	2-bromophenyl	88
5d	1-Naphthyl	3-bromophenyl	150
5e	1-Naphthyl	4-bromophenyl	32
5f	1-Naphthyl	4-methylphenyl	65
5g	1-Naphthyl	4-phenoxyphenyl	16
5h	2-Naphthyl	4-methylphenyl	2300
5i	9-anthracenyl	4-methylphenyl	470
6	—	—	1350
7	—	—	4.6

[a]The farnesyltransferase inhibitory assays were performed as described in ref 21.
[b]Values are means of three experiments.

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21. The assay was done by a modification of the procedure described by Moores et al. (Moores, S.L.; Schaber, M. D.; Mosser, S.D.; Rands, E.; O'Hara, M. B.; Garsky, V. M., Marchall, M. S.; Pompliano, D. L., Gibbs; J. B. *J. Biol. Chem.* **1991** *266*, 14603). Briefly, ras protein (20 μM) was incubated for 30 min at 37 °C with FTase enzyme (16.6 nM), [^{3}H]-farnesylpyrophosphate(FPP) (0.3 μM, 20 Ci/mmol, Dupont NEN) and serially diluted test compounds at given concentration in the buffer containing 50 mM HEPES, pH 7.4, 250 mM $MgCl_2$, 25 mM KCl, 0.5% *N*-octylglucoside, 50 μM $ZnCl_2$, and 10 mM DTT. The enzyme reactions were then quenched by adding the solution containing 10% HCl in absolute ethanol. The [^{3}H] FPP-incorporated Ras was collected by filter binding (25 mm Glass fiber filter, Whatman) and quantitated by scintillation counter.

FT IC_{50}: the concentration of compound required to reduce the FTase-catalyzed incorporation of [^{3}H]FPP into H-Ras protein by 50%.