Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 273–275

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

3-Imidazolylmethylaminophenylsulfonyltetrahydroquinolines, a Novel Series of Farnesyltransferase Inhibitors

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Received 29 October 1999; accepted 29 November 1999

Abstract—Design, synthesis and structure–activity relationship of a series of 3-imidazolylmethylaminophenylsulfonyltetrahydroquinolines as farnesyltransferase inhibitors are presented. A working pharmacophore of inhibiting farnesyltransferase by this series of inhibitors is proposed.

Mutated ras oncogenes are frequently found in many human cancers, most notably cancers of the pancreas (90%), colon (50%) and lung (30%).[1–6] The p21 Ras oncogenic products are synthesized as cytosolic proteins, which undergo post-translational modifications before assuming their proliferative functions. The first and obligatory step is farnesylation. The enzyme farnesyltransferase (FT) catalyzes this reaction.[2–9] Farnesyltransferase inhibitors (FTIs) could serve to downregulate the ras activities; therefore, FTIs have the potential to be anticancer chemotherapeutics.[10–12] In fact, FTIs have been shown to inhibit tumor growth in transgenic mice and mice bearing human tumor xenografts (for representative publications, see refs 13 and 14).

Numerous structurally diverse classes of FTIs have been reported in the literatures (for recent representative publications, see refs 15–20). Pseudopeptidic FTIs based on the Ras C-terminal CAAX motif contain a thiol and a carboxylate residue, with both being necessary for high inhibitory potency in vitro (for recent representative publications, see refs 21 and 22). In order to obtain small molecule FTIs which would have the appropriate pharmacokinetic properties to be potential chemotherapeutics, it was sought to design a series of small molecule FTIs that contain neither a thiol nor a carboxylate group. The starting point was a reported piperazine series of farnesyltransferase inhibitors (e.g. compound **1** of Fig. 1, FT IC_{50}: 3 nM).[23] These inhibitors are non-peptidic, do not contain a carboxylate essential for potent in vitro activity, but they contain a labile thiol group.

Earlier studies have shown that a thiol group could be replaced by an imidazole ring with retention of high farnesyltransferase inhibitory activity in a pseudopeptide series.[24] For example, the thiol of compound **2** (FT IC_{50}: 0.6 nM) was replaced by an imidazole ring giving compound **3** (FT IC_{50}: 0.8 nM) without a detrimental change in FT inhibitory activity. This retention of activity was speculatively attributed to the capability of the imidazole to serve as an alternative zinc ligand.[25,26] The potent FT inhibitory activity of the piperazine series led us to believe that this series of inhibitors bind to the FT active site with the thiol group serving as a zinc ligand. Our working knowledge in the FT area linked together with the general chemical structure of the piperazine series enabled us to formulate a working pharmacophore model for inhibition of the enzyme. This hypothetical pharmacophore model features an aromatic binding interaction, an H-bond acceptor, a lipophilic spacer, and a zinc-binding ligand. Satisfying this pharmacophore, 3-imidazolylmethylaminophenylsulfonyltetrahydroquinolines (Table 1) were designed such that the fused tetrahydroquinoline aryl ring satisfied the aromatic binding interaction, the sulfonamide oxygens provided the H-bond acceptor, the central phenyl ring provided the lipophilic spacer, and the imidazole served as the putative zinc ligand.

A general synthesis of the 3-imidazolylmethylaminophenylsulfonyltetrahydroquinolines is depicted in Scheme 1. Reaction of 3-nitrobenzenesulfonyl chloride **4** with tetrahydroquinoline gave sulfonamide **5**. The

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0960-894X/00/$ - see front matter
PII: S0960-894X(99)00686-1

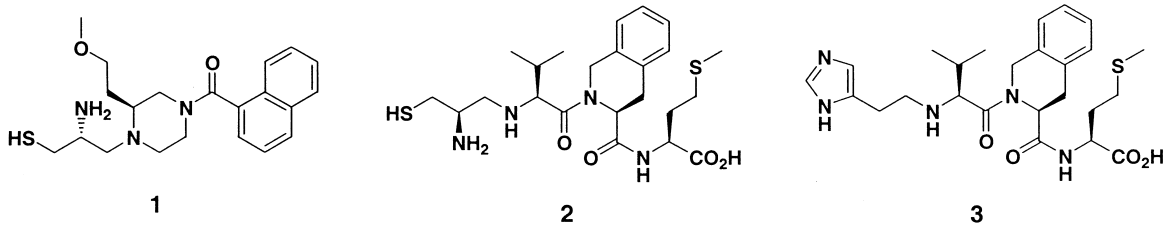
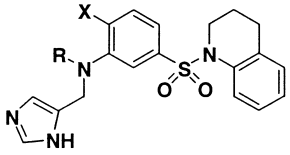


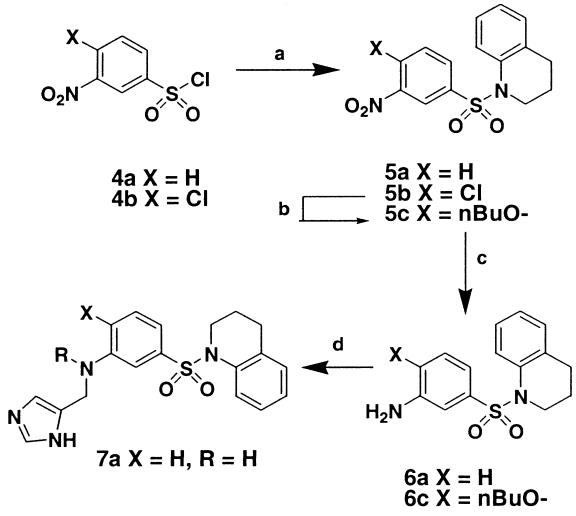
Figure 1. Structures of compounds **1**–**3**.

Table 1. Farnesyltransferase inhibitory activities of compound **7a**–**d**.[a]



Compounds	R	X	$FTIC_{50}$ (μM)[b]
7a	H	H	15
7b	4-(5)-Imidazolylmethyl	H	0.13
7c	4-(5)-Imidazolylmethyl	*n*-BuO-	0.48
7d	3-Cyanophenylmethyl	H	0.57

[a]The farnesyltransferase inhibitory assays were performed as described in ref 27.
[b]$FTIC_{50}$ values are the means of three measurements.



Scheme 1. General synthesis of 3-imidazolylmethylaminophenylsulfonyl-tetrahydroquinolines. (a) Tetrahydroquinaline, Py, CH_2Cl_2. (b) *n*-BuOH, NaH. (c) $SnCl_2$, EtOAc. (d) 3-Cyanobenzaldehyde, $Na(OAc)_3BH$ and/or excess 4-formylimidazole, $Na(OAc)_3BH$.

butoxy analogue **5c** was prepared by displacing the chlorine of the corresponding chlorobenzenesulfonamide **5b** (prepared from **4b**) in butanol in the presence of NaH. Reduction of the nitro group in **5** with stannous chloride produced aniline derivatives **6.** Compound **7a** was prepared from **6a** by reductive alkylation using one equivalent of 4-formylimidazole in the presence of sodium triacetoxyborohydride. Compounds **7b** and **7c** were prepared similarly except excesses of both 4-formylimidazole and the reducing agent were used. Compound **7d** was prepared by reductive alkylation of **6a** using 3-cyanobenzaldehyde first, followed by 4-formylimidazole in the presence of the reducing agent.

The structure–activity relationships are presented in Table 1.[27] Compound **7a** inhibited FT with modest activity. The bis-imidazole derivative **7b** displayed a more than two order of magnitude increase in inhibitory potency over **7a**. Modification of the linker region by addition of a *n*-butoxyl group (i.e. compound **7c**) was aimed at mimicking the methoxyethyl side chain of compounds such as **1**. Although an extensive SAR study was not conducted, the addition of a butoxy side chain slightly reduced potency. The dramatic boost of inhibitory activity from **7a** to **7b** is clearly noteworthy and the importance of the second imidazole was further studied. Replacing one of the imidazole rings with a 3-cyanophenyl group gave compound **7d**. This compound exhibited similar inhibitory activity of **7b**, indicating that the presence of two imidazoles was not necessary. It is possible that one imidazole binds to the active site zinc, and the other binds to an unexpected pocket. This binding pocket is tolerant since it can accommodate a more lipophilic 3-cyanophenyl group to give similar activity. Comparable binding pockets were also described in other series of FTIs,[28–30] which reaffirms our discovery.

In summary, we proposed a pharmacophore of inhibiting farnesyltransferase with consideration of a known piperazine series of FTIs. Based on this, we designed and synthesized 3-imidazolylmethylaminophenylsulfonyltetrahydroquinolines as small molecule FTIs. This series of compounds inhibits farnesyltransferase with good potency. Although further studies are required to ascertain the utilities of this series of compounds, they represent a novel series of FTIs that do not have the problematic thiol and carboxylate functional groups. The limited set of structure–activity relationship presented here further refines our working pharmacophore model of inhibiting farnesyltransferase. We found that there was a binding pocket that can accommodate aryls (e.g. 3-cyanophenyl) or heteroaryls (e.g. imidazole) in the vicinity of zinc binding site. Taking advantage of this pocket can lead to substantial increases in inhibitory activity.

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