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A novel inhibitor of farnesyltransferase with a zinc site recognition moiety and a farnesyl group

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ABSTRACT

Protein prenylation such as farnesylation and geranylgeranylation is associated with various diseases. Thus, many inhibitors of prenyltransferase have been developed. We report novel inhibitors of farnesyltransferase with a zinc-site recognition moiety and a farnesyl/dodecyl group. Molecular docking analysis showed that both parts of the inhibitor fit well into the catalytic domain of farnesyltransferase. The synthesized inhibitors showed activity against farnesyltransferase *in vitro* and inhibited proliferation of the pancreatic cell line AsPC-1. Among the compounds with farnesyl and dodecyl groups, the inhibitor with a farnesyl group was found to have stronger and more selective activity.

Modification of proteins by prenyl lipids, e.g., farnesyl (15-carbon) or geranylgeranyl (20-carbon) isoprenoid lipid, is often crucial for protein function in a cell.[1,2] The first step of prenylation is catalyzed by a zinc-containing farnesyltransferase or geranylgeranyltransferase, which conjugates a farnesyl/geranylgeranyl group of farnesyl/geranylgeranyl pyrophosphate to a cysteine residue of the C-terminal CAAX motif (X: aliphatic amino acid; A: any amino acid) of the substrate protein. Subsequently, the terminal AAX tripeptide is removed by endoprotease digestion and the resulting carboxyl of the prenylated cysteine is methylated by methyltransferase. The attached prenyl group, with its hydrophobic character, facilitates the translocation of the prenylated protein to the membrane.

Protein prenylation is associated with various diseases, such as cancer, progeria, infectious diseases, glaucoma and neurological diseases.[1,3] Thus, many inhibitors of farnesyltransferase/geranylgeranyltransferase have been developed, including some under clinical investigation.[1–4] Most of the inhibitors are CAAX analogues, farnesyl/geranylgeranyl pyrophosphate analogues and screened library compounds. However, the zinc site of these transferases has yet to be a major inhibitory target.

We developed previously a dithiol compound SN-1 (Fig. 1) and showed that SN-1 inhibits the function of zinc proteins[5–7] via a zinc-binding mechanism.[8] In particular, we successfully endowed SN-1 with farnesyltransferase specificity by introducing a protein-recognizing naphthyl group, i.e., naphthyl-SN-1 (Fig. 1).[9] This compound inhibited farnesyltransferase, which is known to farnesylate the Ras oncoprotein to cause cancer.[10–12] We herein report novel SN-1 derivatives with a farnesyl/dodecyl group that bind into the farnesyl pyrophosphate-binding pocket of farnesyltransferase.

Analogous to the case of naphthyl-SN-1, we placed a farnesyl group at the 4-position of pyridine, i.e., farnesyl-SN-1 (Fig. 1). The structure of farnesyl-SN-1 seemed rational, as indicated by the docking study using the Molecular Operating Environment (MOE) 2014.09. As a template for docking, we selected the X-ray crystal structure (PDB ID: 1SA4) of human farnesyltransferase complexed with farnesyl pyrophosphate and an inhibitor Tipifarnib, which binds to the catalytic domain with high affinity.[3,13]

Abbreviations: DTT, dithiothreitol.

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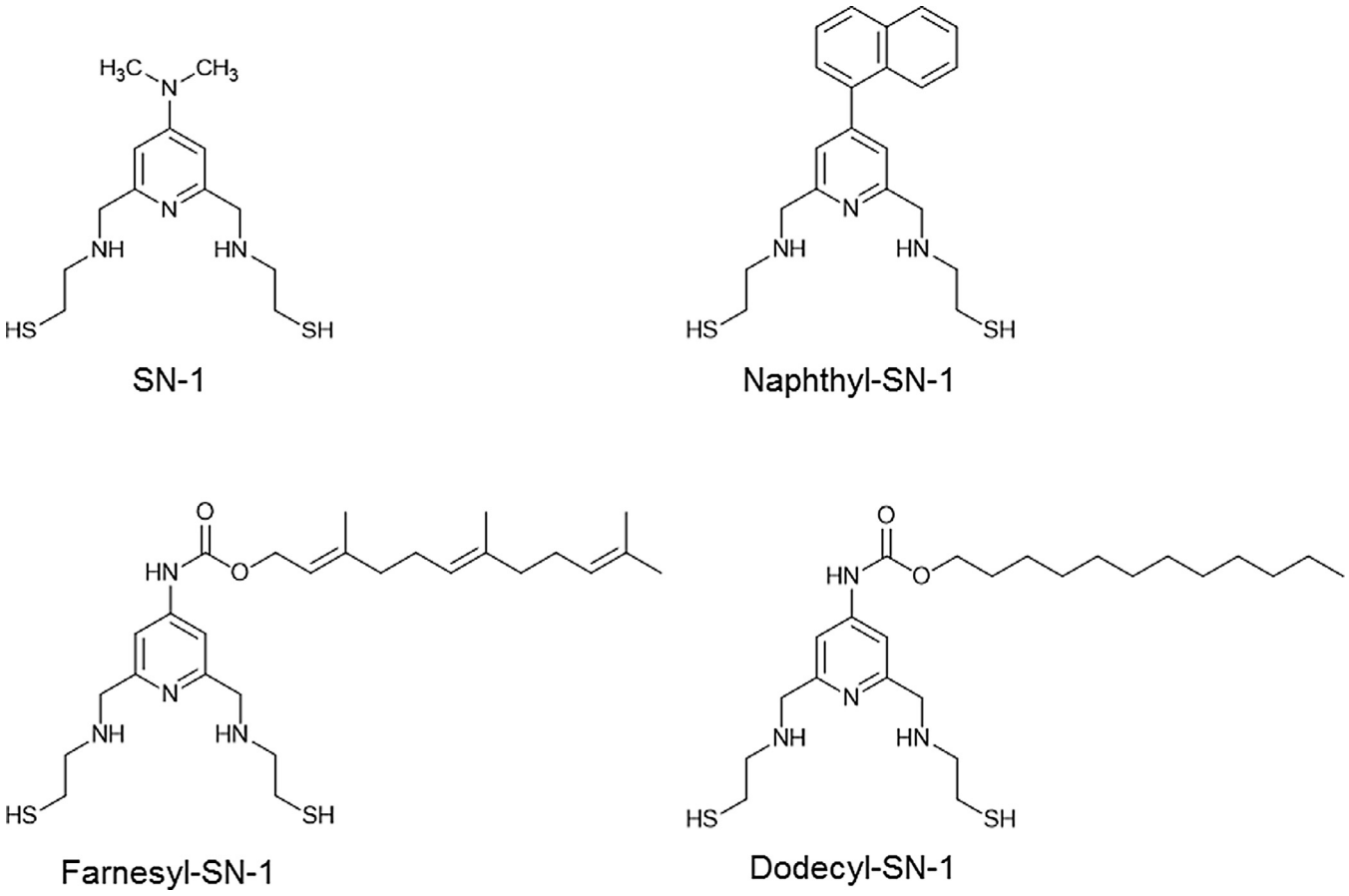

Fig. 1. Structures of SN-1[7] and its derivatives with naphthyl,[9] farnesyl and dodecyl groups.

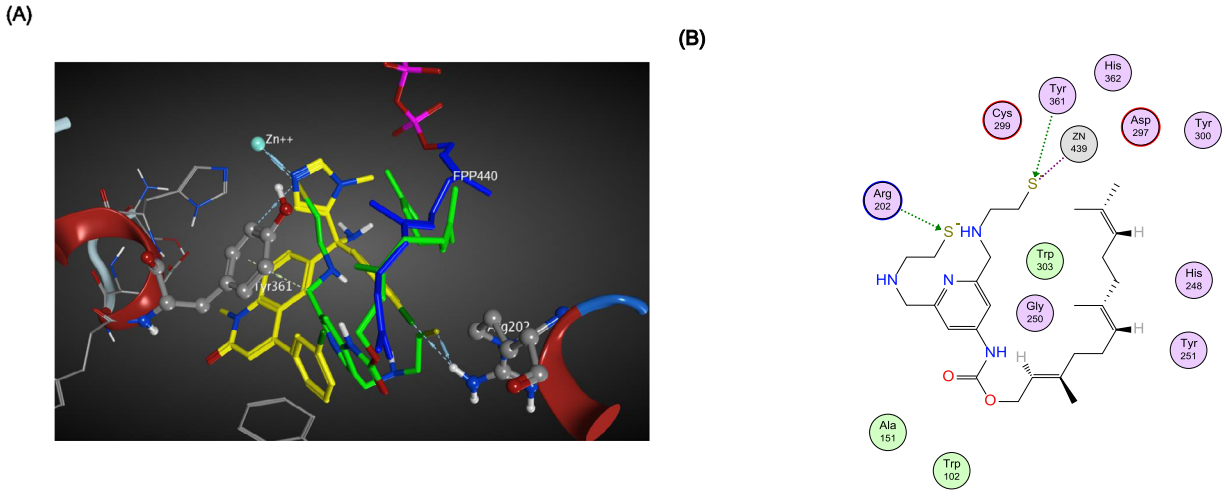

Fig. 2. Binding mode of farnesyl-SN-1 into farnesyltransferase catalytic domain as predicted by the MOE 2014.09 using human farnesyltransferase complexed with the inhibitor Tipifarnib and farnesyl pyrophosphate (PDB ID: 1SA4).[13] Structural refinement, protonation, removal of water molecules and energy minimization were carried out using MOE LigX function. Farnesyl-SN-1 was created, energy minimized, and then docked by the default docking protocol implemented in MOE.[8] (A) 3D depiction. Farnesyl-SN-1 (green), Tipifarnib (yellow) and farnesyl pyrophosphate (FPP, blue) are shown. Farnesyl-SN-1 binds to Zn^{2+}, Arg^{202} and Tyr^{361} residues. (B) 2D depiction. Proximal amino acids and settled interactions (dashed lines and arrows) are shown.

As shown in Fig. 2, the docking result revealed that both the SN-1 moiety and the farnesyl group of farnesyl-SN-1 fit the catalytic domain of farnesyltransferase well with a binding score of −8.1 kcal/mol. One thiol group of farnesyl-SN-1 binds to zinc and Tyr^{361}, whereas the other thiol interacts with Arg^{202}. Interestingly, the farnesyl group of farnesyl-SN-1 is accommodated in the farnesyl pyrophosphate pocket.

In addition to farnesyl-SN-1, we also designed dodecyl-SN-1 with a saturated straight-chain dodecyl group (Fig. 1). We also synthesized the corresponding disulfides, farnesyl-SN-1 disulfide