no Sr analogue is known. Hydrogenation of $SrMg_2$ yields the phase $Sr_2Mg_3H_{10}$[10] to which no corresponding compound in the Eu-Mg-H system could be found (see Experimental Section).

The structure data of $EuMg_2D_6$ and $EuMgD_4$ provide the first refined Eu–D distances. The values for the various coordination numbers are 266 (Eu[12]-D[6]), 254 (Eu[12]-D[4]), and 252 pm (Eu[9]-D[4]). The collection of these data became possible through the development of advanced neutron diffractometers and detectors with a high flux neutron source. This underlines the importance of instrumental developments on such sources for solid-state research.

Experimental Section

$EuMg_2$ and EuMg, prepared by arc-melting of the elements (Eu 99.9 %, Mg 99.95 %) at the nominal composition 1:3 and 1:1.3, respectively, were hydrogenated (deuterated) in an autoclave at 600 K and 50 bar $H(D)_2$ pressure. The excess of Mg compensated the sublimation losses in the arc furnace. Owing to their moisture sensitivity $EuMg_2H_6$ and $EuMgH_4$ were handled in an argon-filled glove box. Both hydrides decompose at 800 K and 5 bar H_2 pressure into EuH_2 and Mg metal. Variations of the sample composition and synthesis conditions gave no evidence for the existence of further ternary phases in the Eu-Mg-H system.

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Design, Synthesis, and Evaluation of Novel Modular Bisubstrate Analogue Inhibitors of Farnesyltransferase**

Martin Schlitzer* and Isabel Sattler

The ras signal transduction pathway plays a decisive role in cell growth and differentiation. Point mutations in the *ras* gene can lead to *ras* proteins of constitutive activity, that is, they are unable to return to an inactive form after activation. These mutant variants deliver constant signals to the nucleus, which result in growth stimulation. Such ras mutations have been found in nearly 30 % of all tumors; the incidence can be as high as 90 % in certain tumor types.[1] Ras proteins must be post-translationally modified for localization at the inner cell membrane. The first such modification, crucial to the function of both normal and mutant ras proteins, is catalyzed by farnesyltransferase (FTase), which transfers a farnesyl residue from farnesylpyrophosphate (FPP) to the side chain SH group of cysteine in the C-terminal sequence CAAX (C: cysteine, A: aliphatic amino acid, X: C-terminal methionine or serine).[1] Both FPP and the CAAX tetrapeptide serve as suitable templates for FTase inhibitors. Bisubstrate analogue inhibitors, which contain elements from both peptide and farnesyl moieties, represent a further class of FTase inhibitors.[1a, 2] Such bisubstrate inhibitors are of particular interest as they can circumvent the need for the free SH function present in almost all CAAX peptidomimetics.[3] Such free SH groups are unfavorable both as a result of their inherent chemical sensitivity and, more importantly, because they are a source of serious side effects as seen, for example, with the antihypertensive drug Captopril.[4] In addition, recent kinetic studies show that FTase has an unusually high affinity for its product, the farnesylated ras protein, which is only released upon binding of a further FPP molecule.[5]

Bisubstrate inhibitors, which represent product analogues, should therefore be particularly good FTase inhibitors.[5] Few bisubstrate or product analogues have been reported to date. Recently, Waldmann et al. synthesized the natural product pepticinnamin E (**1**, Scheme 1) in multiple step reaction sequence and showed it to be a suitable model for bisubstrate FTase inhibitors.[6]

Herein we present a novel class of fully synthetic modular bisubstrate inhibitors. Our aim was to develop a bisubstrate inhibitor containing a peptidomimetic (corresponding to CAAX) and a non-prenyl lipophilic group (corresponding to farnesyl). In a series of *N*-acylaspartates, for example, **2** (Scheme 1) we have identified the benzyloxycinnamoyl moiety as a suitable farnesyl mimetic.[7] The FPP analogue,

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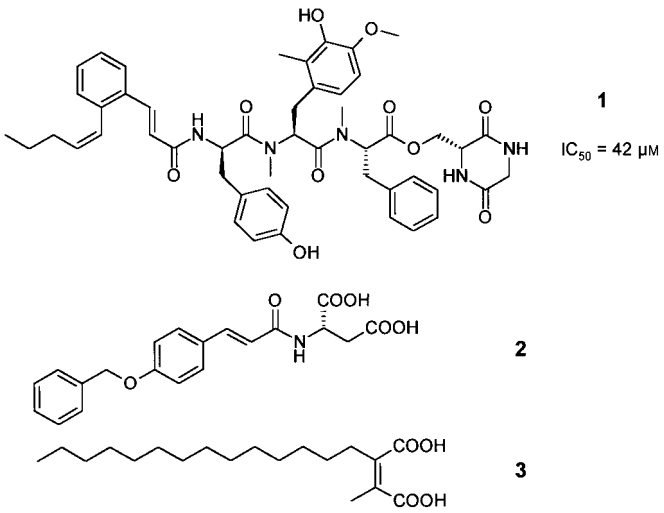
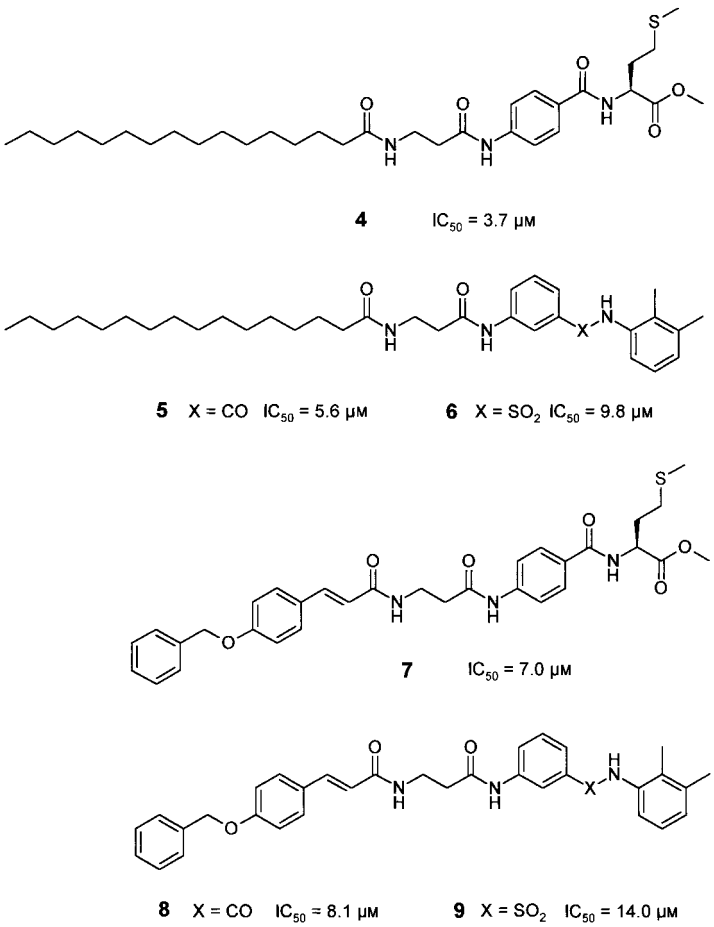


Scheme 1. Pepticinnamin E (**1**) and the non-prenyl FPP-analogue farnesyltransferase inhibitors **2** and **3**.

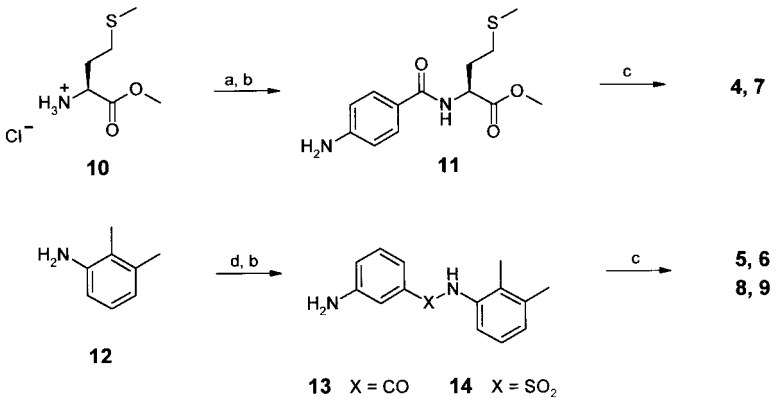
natural product chaetomellic acid (**3**, Scheme 1),[8] suggests that long-chain alkyl residues may be substituted for the farnesyl group. We have therefore fused palmitic- or 4-benzyloxycinnaminic acid through a β-alanine linker to the AAM or AA-mimetic partial structures of known[9] or our own[10] CAAX-analogue FTase inhibitors to form the novel bisubstrate product analogues **4**–**9** (Scheme 2). β-Alanine was chosen as the distance between its amide nitrogen and carbonyl carbon atoms is closest to that between the cysteine SH group and the C-1 atom.

Synthesis of compounds **4**–**9** was achieved by reaction of methionine methyl ester **10** with 4-nitrobenzoyl chloride or 2,3-dimethylaniline (**12**) with 3-nitrobenzoyl chloride or 3-nitrobenzenesulfonyl chloride. The nitro group of the resulting amide was reduced to an amino group with zinc(II) chloride.[11] The intermediates **11**, **13**, and **14** were linked through *N*-acyl-β-alanine, obtained by reaction of β-alanine with carboxylic acid chloride in aqueous alkaline solution,[12] to form the final products **4**–**9** (Scheme 3).

The inhibitory potency of the compounds was measured by using the same fluorescence enhancement assay used by Waldmann et al.[6] to determine the activity of **1**. The FTase reaction rate was measured at different concentrations of test substance through the increase in fluorescence at 505 nm that occurs upon farnesylation of a dansyl-labeled pentapeptide (Ds-GlyCysValIleSer).[13] Recombinant *Saccaromyces cerevisiae* FTase was expressed as a GST-fusion protein in *E. coli* and isolated by GST-affinity chromatography (GST = glutathione-S-transferase).[14]



Scheme 2. Modular non-prenyl and non-peptidyl bisubstrate or product-analogue FTase inhibitors **4**–**9**.



Scheme 3. Synthesis of **4**–**9**. a) 4-Nitrobenzoyl chloride, CH_2Cl_2, *N*-methylmorpholine (NMM), 12 h, 0 °C, 90 %; b) $SnCl_2 \cdot 2H_2O$, EtOAc, 2 h, reflux, **11** 88 %, **13** 81 %, **14** 80 %; c) *N*-palmitoyl- or *N*-(4-benzyloxycinnamoyl)-β-alanine, *i*BuOCOCl, NMM, DMF, −15 °C → RT, 16 h, **4** 78 %, **5** 82 %, **6** 68 %, **7** 53 %, **8** 77 %, **9** 13 %; d) 3-nitrobenzoyl chloride or 3-nitrobenzolsulfonyl chloride, CH_2Cl_2, NMM, 12 h, 0 °C, 86 % and 95 %, respectively.

The novel bisubstrate (product) analogues (Scheme 2) inhibit FTase at a lower concentration (IC_{50}) than the natural product pepticinnamin E (**1**, Scheme 1). In addition to their lack of labile prenyl or peptidyl substructures, these synthetic bisubstrate inhibitors are particularly attractive for their modular construction. The synthesis and linkage of the three building blocks—AA(X) mimetic, linker, and farnesyl mimetic—is a relatively straightforward procedure. This facilitates the synthesis of structural variants with advantageous pharmacological profiles, as well as the production of tailored "chemical" tools to further investigate the ras signal transduction pathway.[6, 15]

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$Rb_{10}Mo_{36}S_{38}$: A Novel Reduced Molybdenum Sulfide Containing the Highest Nuclearity Metal Transition Cluster in a Solid-State Compound

Soazig Picard, Michel Potel, and Patrick Gougeon*

Reduced molybdenum chalcogenides are characterized by Mo–Mo bonds that lead to the formation of clusters with different geometries and nuclearities. The most frequently observed cluster is the octahedral Mo_6, which is present in the Chevrel – Sergent ternary compounds MMo_6X_8 (M = Na, K, Ca, Sr, Ba, rare-earth metals, Sn, Pb…).[1] Clusters with higher nuclearities result essentially from the uniaxial *trans* face sharing of octahedral Mo_6 units. This condensation process is well exemplified by the series of compounds $M_{2n-2}Mo_{6n}X_{6n+2}$ (M = Rb, Cs; X = S, Se, Te)[2] where n ranges between 2 to 5 and infinity. The first member ($n = 1$) corresponds to the binary Mo_6X_8,[3] which constitutes the host structure of the MMo_6X_8 compounds. The final member is the one-dimensional compound $M_2Mo_6X_6$,[4] containing infinite chains of *trans*-face-sharing Mo_6 octahedra $|Mo_{6/2}|^{1}_{\infty}$. In addition to their novel interesting structures, Mo condensed cluster compounds also show unusual physical properties. Indeed, the sulfides and selenides generally present superconducting or metal – insulator transitions at low temperature. Thus, studies of the normal and superconducting states of $Cs_2Mo_{12}Se_{14}$ ($n = 2$)[2b] and $Rb_4Mo_{18}Se_{20}$ ($n = 3$)[2c] by measuring the conductivity and magnetization of single crystals and powder samples have shown that these compounds can be classified among the "exotic" superconductors.[5] The quasi-one-dimensional superconductor $Tl_2Mo_6Se_6$ presents extreme type II and non-Bardeen – Cooper – Schrieffer behavior. On the other hand, the anisotropy of the electronic properties in the latter compound is one of the largest ever observed in a superconductor, with a ratio of the conductivities parallel and perpendicular to the infinite chains ($\sigma_{\parallel}/\sigma_{\perp}$) of about 1000, and a ratio of the upper critical fields ($H_{c2\parallel}/H_{c2\perp}$) of about 26.[5]

We present here the crystal structure of the sixth member of the $M_{2n-2}Mo_{6n}X_{6n+2}$ family: $Rb_{10}Mo_{36}S_{38}$. The Mo_{36} cluster present in this new compound constitutes the largest observed in solid-state chemistry to date.

The new Mo_{36} cluster is shown in Figure 1 with the 44 sulfur atoms of its environment, the whole forming a $Mo_{36}S_{44}$ cluster unit. Of these 44 sulfur atoms, 38 are inner ligands and the remaining 6 are outer ligands. The local symmetry of the $Mo_{36}S_{44}$ cluster unit is the same ($\bar{3}$ or S_6) as that of the monomeric Mo_6S_8 unit. The Mo_{36} core can be seen as the result of the uniaxial *trans* face sharing of 11 octahedral Mo_6 clusters.[6] It can alternatively be described as a stack of 12 staggered Mo_3 triangles.

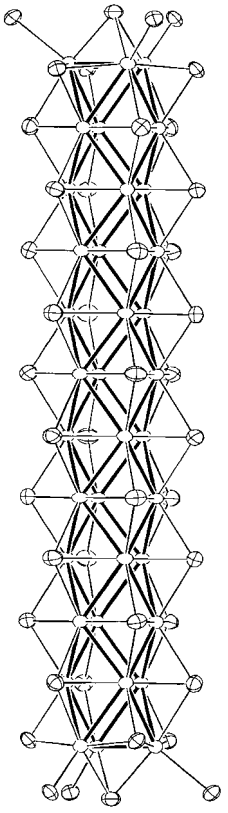

Figure 1. Schematic representation of the $Mo_{36}S_{44}$ cluster unit (ORTEP drawing).

The metal – metal distances lie between 2.637(1) and 2.744(1) Å, and the metal – chalcogen distances between 2.394(2) and 2.602(2) Å. As noticed previously for all phases containing $Mo_{6n}S_{6n+2}$ entities,[2] Mo–Mo bonds between Mo_3 triangles spread over a larger range (2.662(1) – 2.744(1) Å) than those within triangles (2.637(1) – 2.662(1) Å). In average, both types of distances tend to those found in the infinite chains of the $M_2Mo_6S_6$ sulfides. This trend is also reflected by the average distance between the Mo_3 triangles of 2.22 Å in $Rb_{10}Mo_{36}S_{38}$, compared to 2.402 and 2.213 Å for the first member Mo_6S_8 and the final member $M_2Mo_6S_6$, respectively.

Each cluster shares six outer sulfur atoms (*a* type) with six neighboring clusters to form the three-dimen-

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