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Identification of potent and selective MMP-13 inhibitors

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Abstract—A potent, selective series of MMP-13 inhibitors has been derived from a weak (3.2 μM) inhibitor that did not bear a zinc chelator. Structure-based drug design strategies were employed to append a Zn-chelating group to one end of the molecule and functionality to enhance selectivity to the other. A compound from this series demonstrated rat oral bioavailability and efficacy in a bovine articular cartilage explant model.

MMP-13 (collagenase 3), a member of the matrix metalloproteinase family of zinc dependent enzymes, has been identified as an important target for the treatment of osteoarthritis (OA).[1,2] This enzyme is known to efficiently degrade type II collagen, the enzyme's preferred substrate and the main structural component in cartilage. Its expression has been shown to be upregulated in OA.[3,4] In addition, small molecule inhibitors of MMP-13 have been found to inhibit the degradation of type II collagen in articular cartilage explants.[5] The potential for orally bioavailable MMP-13 inhibitors to slow the progression of OA, for which there are at present only agents that provide symptomatic relief, has led to several clinical trials. Unfortunately, many broad spectrum MMP inhibitors have been found to have dose-limiting toxicity in the form of musculoskeletal side effects including joint stiffness and inflammation.[6,7] While the inhibition of specific MMPs such as MMP-1[8–10] or MMP-14[11,12] has been postulated to be responsible for musculoskeletal syndrome (MSS) the exact cause of this pathology is not yet clear.[13,14] Therefore, in an effort to reduce the likelihood of MSS in an effective therapeutic for OA, we sought a potent inhibitor of MMP-13 with a high degree of selectivity over other MMPs.

Our design of a selective, orally bioavailable MMP-13 inhibitor began with CL-82198, a high-throughput screening (HTS) hit that had an IC_{50} of 3.2 μM against MMP-13 and was selective over MMP-1 and MMP-9. We demonstrated earlier that a potent, selective, hydroxamate-containing inhibitor could be realized by using structure-based methods to hybridize the benzofuran carboxamide portion of CL-82198 directly to a hydroxamate head piece (see Scheme 1).[15] We now disclose the design, synthesis, and biological activity of a series of carboxylic acid inhibitors with a rigid linker to the benzofuran carboxamide P1′ terminus along with additional functionalities that impart selectivity over a broader range of MMPs.

The design of these rigid P1′ analogs was the result of a detailed, structure-based computational analysis,[16] where the replacement of the ubiquitous hydroxamic acid group as the chelator of the MMP-13 active site zinc with a carboxylate group was specifically explored. Since the carboxylate group is a less effective Zn-chelator[17] than the hydroxamate (note that the carboxylate analog of WAY-170523 is not active at 10 μM[18]), several features of the scaffold of WAY-170523 that were believed to contribute negatively to its free energy of binding needed to be optimized. These included entropic penalties resulting from the conformationally mobile $–O–CH_2–CH_2–$ linker, the positioning of the amide group, and minimal enthalpic interactions beyond the hydroxamate moiety. This analysis led us to utilize

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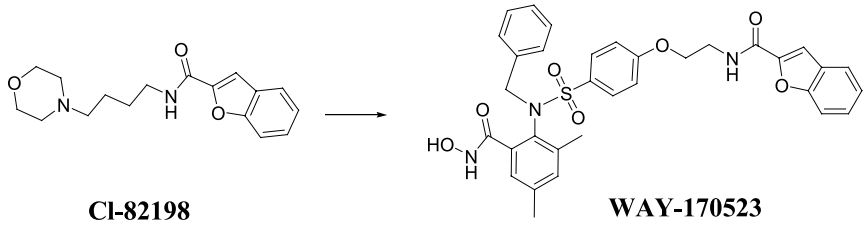


Scheme 1. Evolution of potent, selective inhibitor WAY-170523 from HTS hit CL-82198.

a scaffold exemplified by compound **1**, with a carboxylate zinc chelator and a sulfonamide group to H-bond to LEU185 and ALA186. To correctly position the benzofuran moiety of the P1′ group, a biphenyl P1′ linker was installed to rigidify the molecule, fill the hydrophobic S1′ tunnel, and to π-stack with HIS222. Most importantly, it places the terminal benzofuran carboxamide in a manner that retains the selectivity and binding features of CL-82198. An overlay illustrating these features is shown in Figure 1.

Following the chemistry outlined in Scheme 2[19] the compounds in Table 1[20] were prepared, wherein the carboxylic acid was connected to the benzofuran via a biphenyl sulfonamide spacer, resulting in a series of rigid and potent inhibitors of MMP-13. These analogs were evaluated for selectivity for MMP-13 over MMP-14 and MMP-2. As MMP-2 is highly homologous to MMP-13 in and around the S1′ pocket, it was hoped that compounds that demonstrated selectivity over MMP-2 would also possess enhanced levels of selectivity over a wide variety of other MMPs.

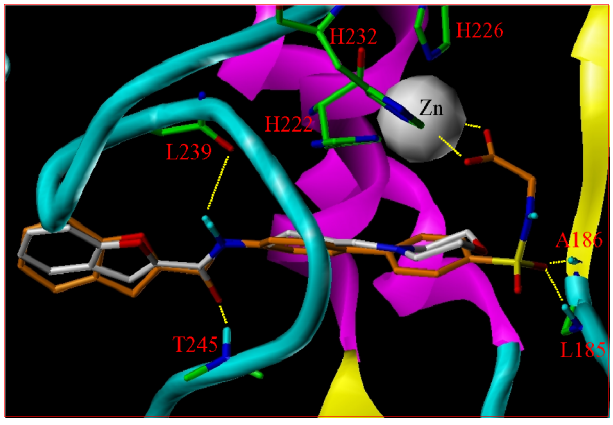
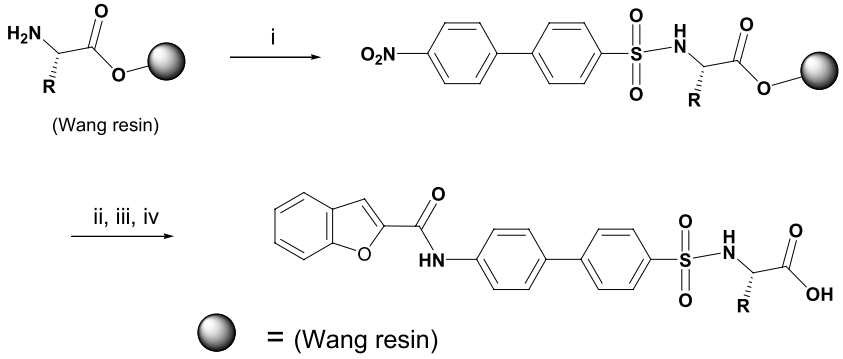


Figure 1. Overlay of CL-82198 and compound **1**.

While the glycine-based compound **1** was reasonably potent, a 17-fold improvement in activity was obtained for compound **2**, with the isopropyl group derived from valine. The increased potency of compound **2** is attributed to both the restricted conformational flexibility of the amino acid portion of the molecule due to its bulky isopropyl group, and the increased burial, or shielding of the sulfonamide H-bond with ALA186. The rigidity and length of the P1′ moiety also provide selectivity for MMP-13 over MMP-1 ($IC_{50} > 16$ μM), MMP-9 ($IC_{50} = 1.1$ μM), and MMP-14 ($IC_{50} = 2.2$ μM) (Table 4). As can be seen in Table 1, MMP-13 activity is retained for both hydrophobic (compounds **2** and **4**) and hydrophilic (compounds **3**, **5**, and **6**) α-substituents. This is not surprising given the solvent exposed nature of this region.[21] Having identified compound **2** with excellent MMP-13 potency and promising selectivity, the activity of this analog in a bovine articular cartilage explant model,[22] and its pharmacokinetic properties were assessed. We were gratified to find that compound **2** demonstrated low clearance in rats (2 mL/min/kg at 2 mg/kg iv), reasonable half-life on both iv (3.7 h) and oral dosing (3 h at 5 mg/kg po), as well as bioavailability of 24%. It was also a potent inhibitor of cartilage degradation in the explant assay with an EC_{50} of 4 nM.

With compound **2** as a promising lead, the role of the benzofuran and the amide linker in providing potency and selectivity was examined. Following the chemistry shown in Scheme 3 the compounds in Table 2 were



Scheme 2. Reagents: (i) 4′-nitrobiphenyl-4-sulfonyl chloride, iPr$_2$NEt, CH_2Cl_2; (ii) $SnCl_2$, DMF; (iii) R′COCl, iPr$_2$NEt, CH_2Cl_2; (iv) TFA.