Carborane-Containing α -Sulfone Hydroxamate MMP Inhibitors for Boron Neutron Capture Therapy (BNCT) in Cancer Treatment

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Abstract

The design and synthesis of a new series of agents for use in boron neutron capture therapy (BNCT) is described that target gelatinases MMP-2 and MMP-9, wherein the MMP inhibitor structure bears a boron-rich icosahedral carborane cluster. To understand the binding of the analogs, the Molecular Operating Environment (MOE) was utilized for docking with gelatinase enzyme MMP-2 (PDB 1HOV), and to enable the docking experiments to be performed, the carborane cluster in each analog was replaced with a phenyl group. Docking suggests that the hydroxamate chelates the active site zinc atom, and the diaryl ether occupies the S_1' pocket. The syntheses of the two isomeric triazole targets **18** and **19** are presented in detail.

Introduction

Boron neutron capture therapy (BNCT) is a binary radiotherapeutic cancer treatment that has shown great promise in clinical trials, in which a drug containing ^{10}B atoms is selectively transported into tumor cells and then irradiated with thermal neutrons.¹ It is well known that MMP enzymes including gelatinases MMP-2 and MMP-9 are upregulated in tumors, and these MMPs are responsible for remodeling, angiogenesis, and metastasis, therefore MMPs have been targeted as tumoristatic agents that show excellent efficacy in animal models and have been explored in the clinic for the treatment of cancer.^{2,3} We selected to append a borane-rich carborane cluster onto an MMP-targeting pharmacophore to enable delivery of ^{10}B atoms into a tumor. The piperidine α -sulfone hydroxamate pharmacophore of MMP inhibitors SC-76276, SC-78080, and SC-77964 (Table 1) described by Pharmacia was selected, as this series of compounds is potent for the desired target MMP enzymes and sparing of MMP-1, and also display excellent pharmacokinetic properties.^{4,5} This scaffold has been used for the delivery of fluorescent dyes into tumor cells for visualization.⁶ As for the fluorescent tumor markers previously described, where the large fluorescent tag was well tolerated on the piperidine scaffold by appending the fluorophore on the piperidines nitrogen that extends into solvent, we tethered the boron-rich carborane cluster on the piperidine nitrogen, which was supported by modeling studies described herein.

Potent and Selective α -Sulfone Hydroxamates MMP Inhibitors

MMP Inhibitor	Enzyme Potency IC ₅₀ (nM)						
	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13
SC-77964	4,000	<0.1	22.0	7,000	1.2	0.1	0.1
SC-76276	9,000	0.2	13.0	>10K	1.8	1.5	0.4
SC-78080	>10K	<0.1	28.7	7,000	1.7	0.2	<0.1

Table 1. Previously reported potent and selective α -piperidines sulfone hydroxamate MMP inhibitors.

Molecular Docking of 1,4-Click and 1,5-Click Compounds Bearing Phenyl As a Surrogate For the Carborane

Figure 1. MMP inhibitor **20** (SC-74020) used as a model for docking. The ionized form of model 1,4-triazole isomer **21** and the ionized forms of model 1,5-triazole isomer **22** were used for docking experiments using Molecular Operating Environment (MOE) software.

Figure 2. Hydrogen bonds and metal (green sphere) coordination is depicted as dotted lines. **(A)** Modeled complex of 1,4-Click Isomer **21** bound at the MMP-2 active site (PDB accession code: 1HOV). **(B)** Modeled complex of 1,5-Click isomer **22** bound at the MMP-2 active site (PDB accession code: 1HOV).

The docking results of isomers **21** and **22** (Figure 2) show both compounds forming an intricate web of contacts to the catalytic zinc ion and surrounding amino acids in similar ways (Figure 2A and 2B). In compound **21**, important coordination between oxygen atom of the hydroxamate and the metal is observed, and supplementary interactions are formed with side chains of His120 and His130, respectively. Two hydrogen bonds are made between sulfone moiety and Leu83 on the protein backbone, as well as hydrogen on carbon atom adjacent to the nitrogen on the piperidine substituent (Figure 2A). An additional close interaction (2.4 Å) is observed between another hydrogen atom within piperidine substituent and Ala83 residue. The diphenyl ether tail protrudes deeply into the S_1' subsite, which is an open conformation. The piperidine N-substituent extends into the solvent and generally has little or no impact on potency at MMP-2. The capacity of the P_1' pocket to accommodate such large moieties as the biphenyloxyphenylsulfonate is rather remarkable, and demonstrates that the pocket is both flexible an open at the bottom. The trifluoromethoxy substituent at the terminus of the biphenyl ring in P_1' is surrounded by the hydroxyl of Thr143, hydrophobic chain of Leu137, and guanidine group of Arg149. Docking of hydroxamate **22** shows all of the same interactions with MMP-2, as compound **21**, with the exception of generating two hydrogen bonds between sulfone moiety and Leu83, as well as Leu82 residues.

Synthesis

The synthesis of the analogs commences with N-BOC ethyl isonipecotate **1** as described in Scheme 1 yielding ultimately the THP-protected intermediate **9**. The carborane cluster **15** with the linker to the azide to employ in Click chemistry is summarized in Scheme 2. The acetylene moiety of intermediate **9** was then reacted with azide **15** in a thermal Click reaction was provided the two separable triazoles **16** and **17**, which were each converted to the final hydroxamate inhibitors **18** and **19**.

Scheme 1. Synthesis of THP-Protected Hydroxamate

Scheme 2. Preparation of TBDMS-Protected Propyl Azido Carborane

Thermal [3+2] Click Reaction for Triazole Synthesis

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