7-27-2020

Carborane-Containing Matrix Metalloprotease (MMP) Ligands as Candidates for Boron Neutron-Capture Therapy (BNCT)

Marlon R. Lutz Jr
Biosynthetic Technologies

Sebastian Flieger
Loyola University Chicago

Andre Colorina
Regis Technologies

John Wozny
Northern Illinois University

Narayan S. Hosmane
Northern Illinois University

Recommended Citation

Lutz, Marlon R. Jr; Flieger, Sebastian; Colorina, Andre; Wozny, John; Hosmane, Narayan S.; and Becker, Daniel P. Ph.D.. Carborane-Containing Matrix Metalloprotease (MMP) Ligands as Candidates for Boron Neutron-Capture Therapy (BNCT). ChemMedChem, , : , 2020. Retrieved from Loyola eCommons, Chemistry: Faculty Publications and Other Works, http://dx.doi.org/10.1002/cmdc.202000470

Carborane-containing Matrix Metalloprotease (MMP) Ligands as Candidates for Boron Neutron Capture Therapy (BNCT)

Marlon R. Lutz, Jr.[a], Sebastian Flieger[b], Andre Colorina[c], John Wozny[d] , Narayan S. Hosmane[d], and Daniel P. Becker[b]

[a] Dr. M. Lutz

Biosynthetic Technologies

6320 Intech Way, Indianapolis, IN 46278, (USA)

[b] S. Flieger, Prof. Dr. D Becker

Department of Chemistry and Biochemistry

Loyola University Chicago, Chicago, IL 60660, (USA)

E-mail: dbecke3@luc.edu

[c] A. Colorina

Regis Technologies, Inc.

8210 Austin Ave., Morton Grove, Illinois 60053, (USA)

[d] J. Wozny, Prof. Dr. N. Hosmane

Abstract: Based on previously reported potent and selective sulfone hydroxamate inhibitors SC-76276, SC-78080 (SD-2590), and SC-77964, potent MMP inhibitors have been designed and synthesized to append a boron-rich carborane cluster employing click chemistry for targeting tumor cells that are known to upregulate gelatinases. Docking against MMP-2 suggests binding involving the hydroxamate zinc-binding group, key H-bonds by the sulfone moiety with the peptide backbone residues Leu 82 and Leu 83, and a hydrophobic interaction with the deep P1' pocket. The more potent of the two triazole regioisomers exhibits and IC50 of 3.7 nM versus MMP-2 and and IC50 of 46 nM versus MMP-9.

Introduction

Boron neutron capture therapy (BNCT) is a binary radiotherapeutic cancer treatment that has shown great promise in clinical trials against glioblastoma, glioblastoma multiforme, melanoma, malignant gliomas, and glioblastomas as reviewed recently.[1] In BNCT, a drug containing 10B

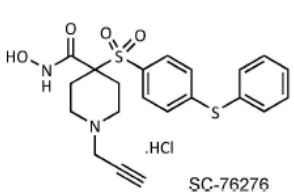
atoms is transported into tumor cells and then irradiated with thermal neutrons.[2] Thereupon, a 10B nucleus absorbs a neutron to form an excited 11B nucleus that undergoes decay via fission, emitting an α-particle (4He2+) as well as a 7Li3+ ion, both with high kinetic energy. The highly charged particles have a range of only about one cell diameter (5-9 μm) which limits the radiation damage to the cancer cell in which they arise, thus avoiding damage to the surrounding healthy tissue.[3] The ultimate success of BNCT depends upon the availability of neutron sources, and the advent of accelerator based neutron sources (ABNS) is encouraging, as well as the need for new and more effective boron delivery agents.[4] Currently, the clinically investigated[1] BNCT drugs include boronophenylalanine and sodium borocaptate that are neither tumor-specific nor do they accumulate in tumor cells. Carboranes including borocaptate are icosahedral boron cage molecules that have found use in the treatment of diseases including various cancers and rheumatoid arthritis most notably through BCNT, and also are distinguished with a rich and diverse synthetic chemistry.[5] Yet even these agents have demonstrated therapeutic efficacy in patients with high grade gliomas, recurrent tumors of the head and neck region, and a much smaller number with cutaneous and extra-cutaneous melanomas.[6] There is a critical need for boron-containing therapeutics that both contain a higher density of boron atoms with a high neutron-capture cross section, and which are selectively taken up in tumor cells. Agents similarly are needed for boron neutron capture synovectomy for the treatment of severe cases of rheumatoid arthritis, which works through the same principle and mechanism as BNCT.[5] Boron-containing agents designed for neutron capture therapy have recently been reviewed.[1] Boron agents have played an increasingly important role in medical applications,[7] and recent literature reports of BNCT agents include a membrane-permeable boron cluster that was developed using the cell-penetrating lipopeptide pepducin as the vehicle for intracellular delivery of boron clusters.[8] Cellular uptake has been evaluated for pentagamaboronon-0 (PGB-0) to treat breast cancer with BNCT.[9] A receptor-mediated uptake of boron-rich Neuropeptide Y analogues has recently been described for BNCT.[10] Relying on the accumulation of folate in fast-growing cancer cells, a folate receptor-targeted novel boron compound for BNCT has been investigated in F98 glioma-bearing rats.[11] Very recent reports include selectively targeting tumor cells via transportation by the membrane transport protein LAT1[12] and the synthesis and evaluation of tris-carborane α-D-mannopyranoside derivatives prepared using click chemistry.[13]

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the remodeling and degradation of all components of the extracellular matrix (ECM).[14] MMP enzymes play a key role in normal development, morphogenesis, bone remodeling, wound healing, and angiogenesis, yet inappropriately high MMP activity has been implicated in a number of disease states including tumor growth and metastasis and in the degradation of articular cartilage in arthritis.[15] MMPs in particular gelatinases MMP-2 and MMP-9 are known to be overexpressed in tumors as well as in articular cartilage in patients suffering from rheumatoid and osteoarthritis. [16] In order to halt disease progression resulting from exaggerated matrix remodeling mediated by MMPs, MMP inhibitors (MMPi's) have been extensively explored.[17] Elegant EGFR inhibitor[18] and kinase inhibitor[19,20] target-directed BNCT agents have recently been reported by Viñas and colleagues. Importantly, MMP inhibitors bearing fluorescent dyes have also been used in imaging of cancer cells by binding

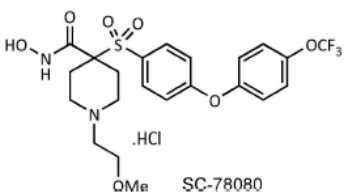
tightly to MMP enzymes,[21] and a hydrogel-based delivery system to treat glioblastoma multiforme using upregulated MMP-2 and MMP-9 to deliver chemotherapeutics has been described.[22]

We have previously described[23,24] α-sulfone hydroxamate MMP inhibitors that are highly potent for MMPs that are over-expressed in tumors and are critically involved in tumor growth and accompanying angiogenesis, and in metastasis. Clinical candidates arising from these efforts are illustrated in Table 1 including SC-276 (SC-76276),[23] SC-78080/SD-2590, and SC-77964,[24] shown with their respective potencies at various MMP enzymes. These α-sulfone MMP inhibitors exhibited high levels of selectivity versus MMP-1, which has been implicated in the musculoskeletal syndrome (MSS) side effect in patients treated clinically with broad-spectrum MMP inhibitors, and also exhibited oral bioavailability and efficacy in several in vivo models of cancer and congestive heart failure. Because the piperidine-N-substituent is directed into solvent and is outside of the enzyme active site, very large groups may be placed in this position without a significant loss of potency[21] and it is this position where we intended to install a carborane moiety. Utilizing this approach, we now report MMP inhibitors employing the pharmacophore of these clinical candidates that bind with high potency to gelatinase enzymes MMP-2 and MMP-9 that are overexpressed[16] in tumors and in arthritic tissues that should be capable of delivering a high density of boron atoms to tumor and/or arthritic tissue, thus enabling a high neutron-capture cross section and binary treatment of tumors utilizing BNCT as well as the treatment of RA with neutron therapy. In addition, these potent inhibitors exhibit a much lower potency at MMP-1, which has been implicated in the muscular skeletal syndrome. The trifluoromethoxyphenyl ether moiety in SC-78080 and SC-77964 contains fluorine (19F) atoms that will enable the use of magnetic resonance spectroscopy for the detection and localization of fluorinated drugs in tumors, which is essential to demonstrating the localization of drug in target tissues.[25] For example, 4-10B-borono-2-18F-fluoro-l-phenylalanine (18F-FBPA) was developed for monitoring the pharmacokinetics of 4-10B-boronol-phenylalanine (10B-BPA) used in BNCT with positron emission tomography (PET).[26] For these reasons we have selected to pursue analogs that contain the trifluoromethoxy ether linkage, in addition to the fact that these analogs were among the most potent and selective among the α-sulfone hydroxamates that were previously described.[23,24]

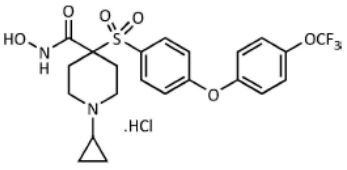
Table 1. Previously reported potent and selective α-sulfone hydroxamate MMP inhibitors



SC-76276



SC-78080

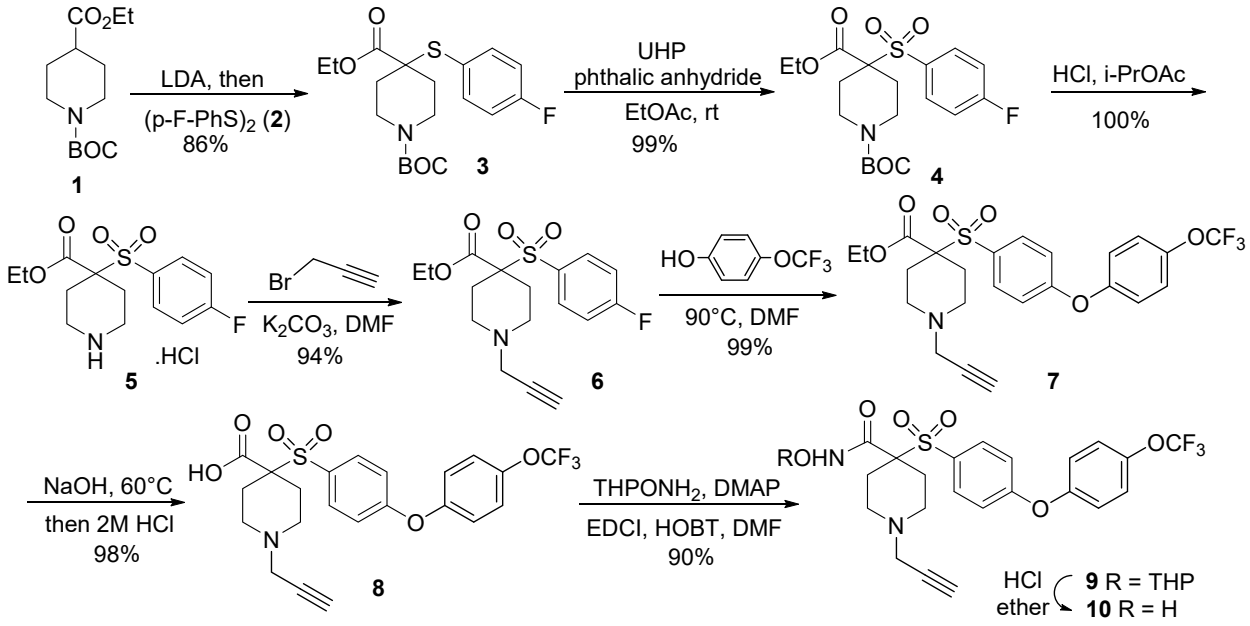


SC-77964

MMP Inhibitor	Enzyme Inhibitory Potency, IC_{50} (nM)						
	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13
SC-76276	9000	0.2	13.0	>10000	1.8	1.5	0.4
SC-78080	>10000	<0.1	28.7	7000	1.7	0.2	<0.1
SC-77964	4000	<0.1	22.0	7000	1.2	0.1	0.1

Results and Discussion

The synthetic route to these carborane-bearing MMP inhibitors for BNCT is an extension of our earlier procedures[23,24] and the route was improved during process development. The preparation of key intermediate 9 as the THP-protected hydroxamate is illustrated in Scheme 1. Ethyl N-Boc-piperidine-4-carboxylate (1) was treated with LDA under cryogenic conditions to produce the enolate anion that subsequently reacts with disulfide 2 to produce the sulfide adduct 3. The preparation of disulfide 2 was accomplished by the reaction of 4-fluorothiophenol in DMSO in markedly improved yields by isolating the disulfide at 0-5°C providing crystalline material as a low melting solid. The sulfide adduct 3 was reported to have been oxidized to sulfone 4 using MCPBA which required chromatographic purification. Utilization of the use of the recently-described safe, efficient, and scalable conditions using urea hydrogen peroxide (UHP)/phthalic anhydride system[27] in ethyl acetate enabled this oxidation to be carried out on a 180 g scale with facile isolation of highly pure sulfone 4 via an extractive workup without chromatography. The N-Boc sulfone 4 was deprotected with hydrogen chloride gas in isopropyl acetate to produce the piperidine hydrochloride salt 5, which was then alkylated with propargyl bromide and potassium carbonate in DMF to cleanly produce the propargylamine adduct 6 in high yield. SNAr reaction of propargylamine 6 with 4-(trifluoromethoxy)phenol and potassium carbonate in DMF produced the diphenyl ether adduct 7 in high yield. Alkaline hydrolysis of ethyl ester 7 in ethanol with an excess of NaOH and overnight heating to achieve 98% yield of ester to carboxylic acid 8. Lastly, the reaction of carboxylic acid 8 with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine using EDC and HOBt with DMAP as base in DMF afforded pure THP-hydroxamate 9 in 90% yield after normal phase chromatographic purification.

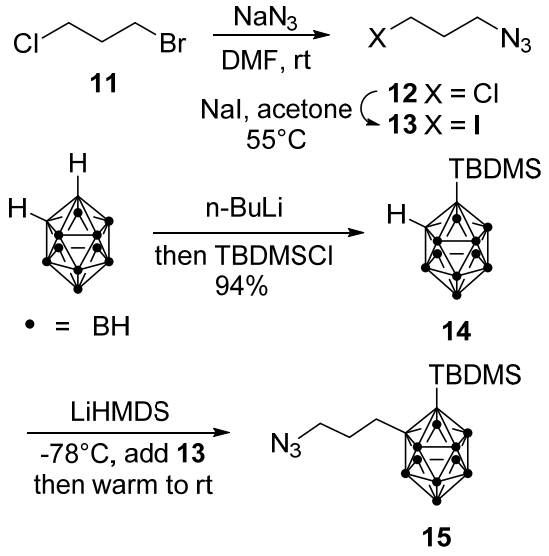


Scheme 1. Synthesis of THP-protected hydroxamate 9.

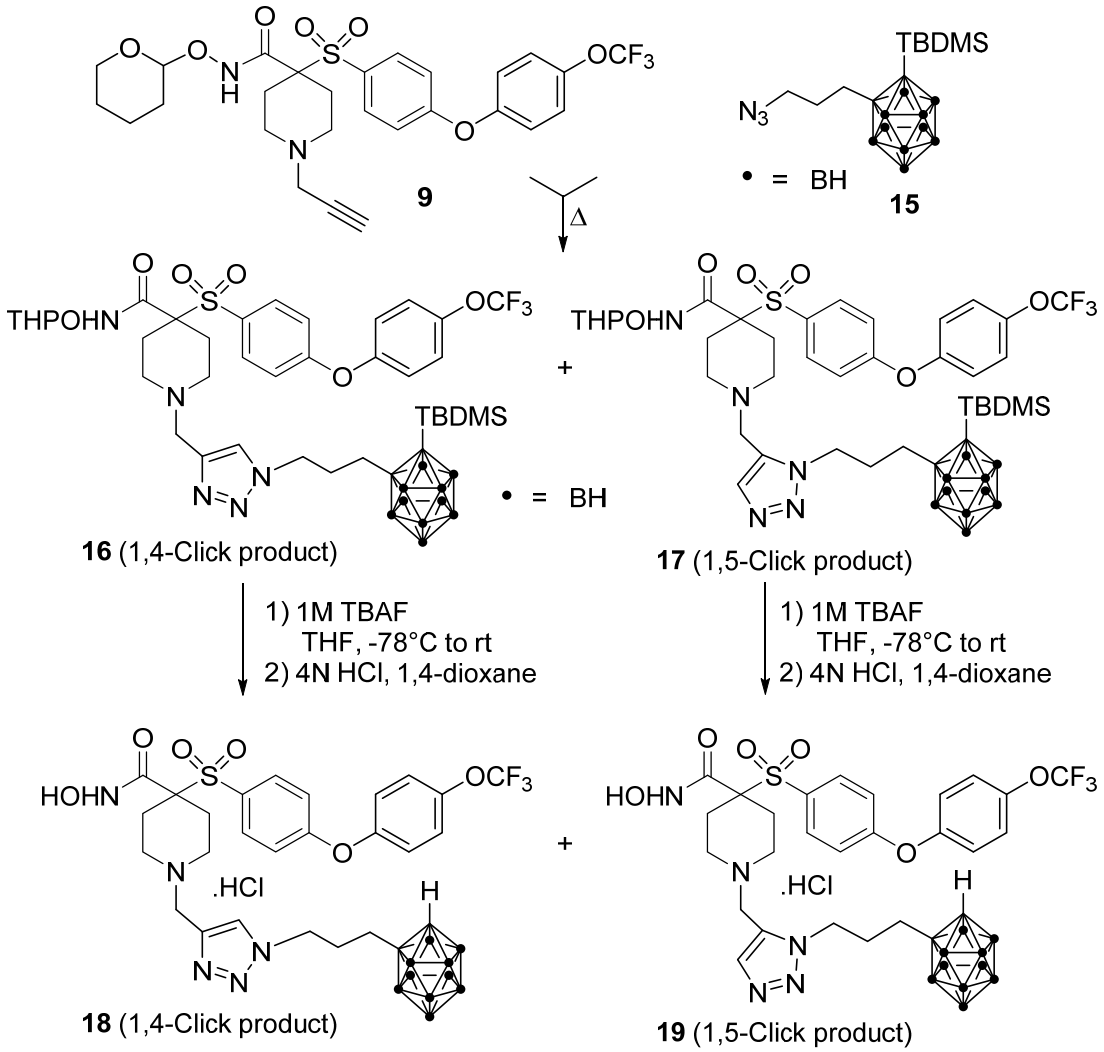
Reactions involving alkynes and decaborane have been a useful method of covalently attaching boron clusters to carrier molecules[28] for a wide range of chemical including electronics,

nanomaterials, and medicine. It was envisioned that direct reaction of the alkyne moiety of N-propargyl piperidine 9 with B¬10H12(MeCN)2[28] would furnish the corresponding closo-carborane for BNCT after deprotection of the hydroxamate. Many sets of conditions were evaluated including variations in temperature, solvent, in situ generation of the B10H12(MeCN)2 complex, stoichiometry of B¬10H12(MeCN)2, and catalytic addition of silver nitrate,[29] but reactions with either THP-protected derivative 9 or free hydroxamate 10, formed[24] by deprotection of 9 yielded complex mixtures. We postulate that the hydroxamate moiety was undergoing chelation with decaborane or the corresponding decaborane activated complex. Indeed, THP removal by decaborane has been previously reported.[30]

We therefore elected to employ [3+2] click chemistry to attach boron clusters to the alkyne moiety of 9.[31,32] Others have employed click chemistry to append carboranes toward the preparation of new BNCT agents.[13,33] The preparation of the requisite carboranyl propyl azide is shown below in Scheme 2. Formation of 1-azido-iodopropane was accomplished based on literature precedent[34] which entailed SN2 reaction of sodium azide and 1-bromo-3-chloropropane in DMF providing a 95% mass balance of 1-azido-3-chloropropane as the major product along with 1H NMR showing a 85/15 mixture of chloro/bromo which was taken forward without further purification. The crude 1-azido-3-halopropane was subjected to Finkelstein conditions using sodium iodide in acetone that generated pure 1-azido-3-iodopropane in 81% isolated yield after filtration through a plug of silica gel. The next reaction involved preparation of the tert-butyldimethylsilyl (TBDMS)-carborane derivative 14 which entailed deprotonation of commercially-available o-carborane with n-butyllithium generating the carborane anion that subsequently attacks TBDMSCl affording highly pure TBDMS carborane 14 in 94% isolated yield. The last step was accomplished using lithium hexamethyldisilazide (LiHMDS) to generate the carboranyl anion that sequentially attacks 1-azido-3-iodo-propane to furnish pure TBDMS propyl azido carborane 15 in 98% isolated yield.



Scheme 2. Preparation of TBDMS propyl azido carborane 15.



Scheme 3. Thermal click reaction of propargyl piperidine **9** with carboranyl propylazide **15**.

There are a number of methods of employing click chemistry[13,32,33] coupling azides to alkynes either thermally or via copper or ruthenium catalysis (CuAAC or RuAAC, respectively). We initially performed a thermal click reaction to obtain both triazole regioisomers, thus the thermal click reaction without metal catalysis was used to prepare both the 1,4-disubstituted and 1,5-disubstitued triazole click products for evaluation. Scheme 3 outlines the preparation of the 1,4-disubstituted and 1,5-disubstitued triazole click products was accomplished by preparation of protected carboranyl propyl azide and subsequent click reaction with 9 in toluene at elevated temperatures (120-140°C). The thermal heating of an azide and an alkyne without copper and ruthenium agents generates a mixture of 1,4-disubstituted and 1,5-disubstituted triazole products. Executing the click chemistry on TBDMS propyl azido carborane 15 and propargyl piperidine 9 confirmed formation of 1,4-disubstituted triazole and 1,5-disubstituted triazole products. Two separate reactions were carried out using copper to facilitate the selective formation of the 1,4-disubstiuted triazole click product and ruthenium catalysis to promote selective formation of the 1,5-disubstituted click product. Carrying out the CuAAC reaction using stoichiometric copper

sulfate and excess sodium ascorbate in aqueous THF at room temperature produced solely the 1,4-disubstituted triazole. Performing the RuAAC reaction generated the 1,5-disubstitued triazole with only trace amounts (<2% AUC) of the 1,4-triazole when performing the reaction at ambient temperature.

Given the work to identify which component was either 1,4-triazole or 1,5-triazole, the next phase was to optimize the thermal click reaction in toluene as the solvent medium. The temperatures screened for the thermal click reaction were 100°C, 120°C, and 140°C. The click reaction at 100°C is significantly slower compared to the reactions at 120°C and 140°C. The reaction at 120°C was capable of progressing to 62% conversion (sum of both triazole regioisomers) after 42 hours whereas the reaction at 140 °C for 19 hours performed slightly better with a total conversion of 69% (sum of both triazole regioisomers) and contained less starting material alkyne (22%). The formation of presumed nido complex, based on high polarity since the nido complex would be negatively charged, was lower at 120°C even after 42 hours and slightly elevated at 140°C after 19 hours, however heating the mixture for longer periods of time at 140°C does consume more starting material alkyne, but at the expense of forming significantly higher amount of nido-like components.

Batch preparation of the click regioisomers was executed on a gram scale using batch-type pressure vessels at 120°C for 58 hours. HPLC analysis of the reaction after 58 hours showed ~65% conversion (sum of click regioisomers) with ~20% unreacted alkyne. HPLC analysis confirmed that the thermal Huisgen 1,3-dipolar cycloaddition reaction gives 1,4-triazole and 1,5-triazole products with a ratio of 1.6 to 1, respectively, which agrees with Sharpless' study[35] of the component ratio of the triazole regioisiomers. Cleavage of the TBDMS group was accomplished using 1M tetrabutylammonium fluoride (TBAF) in THF for the 1,4-triazole regioisomer and for the 1,5-triazole regioisomer. Lastly, deprotection of the THP protecting group was executed using 4N HCl in 1,4-dioxane/methanol at room temperature. Once the reaction was complete, the reaction mixture was concentrated, redissolved in dichloromethane, and subsequently precipitated using diethyl ether to furnish both carborane containing regioisomers as hydrochloride salts.

The MMP inhibitory potencies of click isomers 18 and 19 were evaluated with IC50 data tabulated in Table 2. Gelatinases MMP-2 and MMP-9 were selected as target enzymes because these enzymes are upregulated in a number of tumor types. MMP-1 was selected because its inhibition in broad-spectrum MMP inhibitors has been suggested to be involved in causing the musculoskeletal syndrome (MSS).[24] These data give an indication of the potency of binding of these BNCT agents to MMP enzymes that are upregulated in tumor cells. Deptrotected alkyne 10 was assayed as a direct comparator lacking the carborane cluster, and NNGH (BML-205) was employed as a standard. Both 1,4-triazole 18 and 1,5-triazole 19 exhibited low nM potency at MMP-2 (37 nM and 9.8 nM) as well as at MMP-9 (46 uM and 13 nM, respectively), while neither compound showed any significant inhibition of MMP-1, as expected. 1,5-Triazole 19 was ~3X more potent than triazole 18. Triazole 19 was 49X less potent than propargyl piperidine 10 at MMP-2, and 43X less potent than propargyl piperidine 10 at MMP-9. The loss in potency of the carboranes relative to the simple propargyl piperidine 10 may be due to a physicochemical

effect such as hydrophobic collapse, nevertheless both triazoles exhibit very good, low nM potency.

Table 2. MMP-2 and MMP-9 inhibitory potency and selectivity vs. MMP-1

Compounds	IC_{50} [nM] or % inhibition		
	MMP-1	MMP-2	MMP-9
N-propargyl piperidine **10**	860 ± 48	0.24 ± 0.025	0.30 ± 0.06
1,4-triazole **18**	> 10 000 *NI at 10 000 nM	37 ± 1.3	46 ± 4.6
1,5-triazole **19**	> 10 000 20 % at 10 000 nM	9.8 ± 0.96	13 ± 1.2
NNGH	120 ± 4.0	2.7 ± 0.51	5.1 ± 0.65

*NI: no significant Inhibition. IC50 values were determined in duplicate. Reported[24] IC50 values for N-propargyl piperidine 10, MMP-1 IC50= 2,600 nM, MMP-2 IC50= <0.1 nM, MMP-9 IC50=0.1 nM. NNGH (BML-205)[36] is N-isobutyl-N-(4-methoxyphenylsulfonyl)glycyl hydroxamic acid used as a standard MMP inhibitor in the assay with reported IC50 values, MMP-1=220 nM, MMP-2=6.9 nM and MMP-9=2.9 nM.

Carboranes, which are icosahedral boron-rich clusters, are exceptionally difficult to model computationally in the same way as organic moieties due to their unique electronic properties, different hydrogen bonding patterns, hexacoordinate carbon and boron atoms, and different properties for ionic forms.[28] As a consequence of its non-classical bonding interactions, molecular modeling of carboranes is extremely difficult. Many currently available software packages for molecular modeling, do not have inbuilt parameters or empirical potential energy functions for various types of boron-atoms, yet alone for structure/ligand-based drug design.[28,29] While there is an urgent need to develop accurate force field parameters for the entire carborane cluster, in order for the molecular modeling/docking to work successfully, several strategies have been implemented including substitution of boron atoms within the carborane, with hexa-coordinated carbon atoms defined with special force field parameters using PyMOL, AutoDock, Glide, FlexX and Surfflex softwares.[29-35] Such strategy leads to forced simplifications that result in approximate calculations, which have limitations in the design of new molecules due to lack of accuracy. Nevertheless, computational methods are often useful for predicting or explaining experimentally observed results.[28] Carboranes can act as a bioisosteric replacement for phenyl rings, as can adamantane, due to their similarity in size and lipophilicity, which has been extremely useful in medicinal chemistry.[36,37] There are many examples of closo-carboranes having been used as bioisosteric replacements for heteroaromatic or heteroaliphatic rings.[38-47] Due to the complexity of substituting each individual boron atom within the carborane cluster with carbon atoms, we considered an alternative approach, where the entire carborane cluster is replaced with a simple phenyl ring for molecular docking experiments, given the similar 3-dimensional sweep volume and high lipophilicity of both moieties.

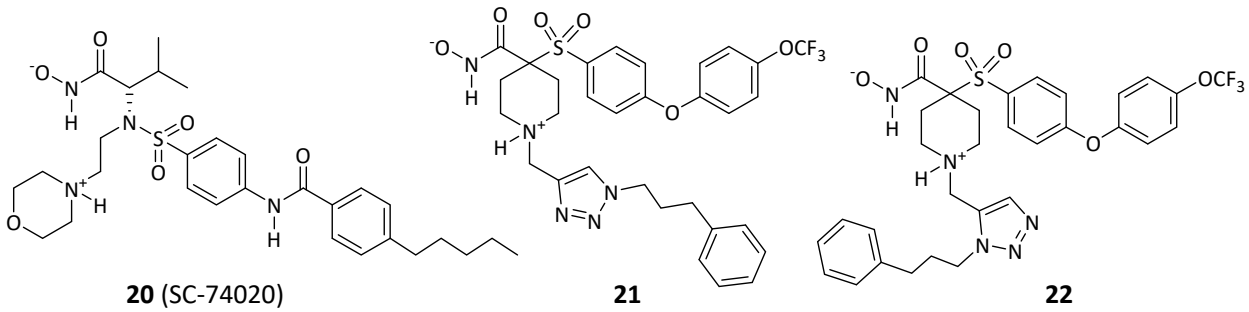


Figure 1. MMP inhibitor 20 (SC-74020) constructed for use as a model for docking; ionized form of model 1,4-triazole isomer 21 used in docking experiments, ionized forms of model 1,5-triazole isomer 22 used for docking experiments.

The reported solution structure of the known hydroxamate MMP inhibitor 20 (SC-74020, Figure 1) bound to MMP-2 (PDB accession code: 1HOV)[56] was used as a model for the docking experiments. Molecular models of compounds 21 and 22 were developed using the Molecular Operating Environment (MOE) computational suite's Builder utility as the ionized species 21 and 22 as specified in Figure 1.

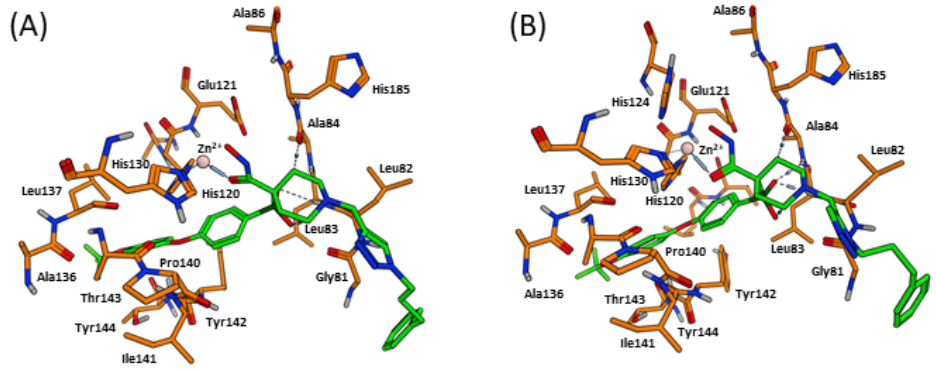


Figure 2. Modeled complexes of A) the 1,4-triazole regioisomer 21 and B) the 1,5-triazole regioisomer 22 bound at the MMP-2 active site (PDB ID: 1HOV). Hydrogen bonds and metal (pink sphere) coordination are depicted as dotted lines.

The docking results of isomers 21 and 22 suggest that both compounds form a similar intricate web of contacts to the catalytic zinc ion and surrounding amino acids (Figure 2A and 2B). In 1,4-triazole 21, important coordination between oxygen atom of the hydroxamate and the metal is observed, and supplementary interactions are formed with side chains of His 120 and His 130, respectively. Two hydrogen bonds are made between sulfone moiety and Leu 83 on the protein backbone (Figure 2A). An additional close interaction (2.4 Å) is observed between another hydrogen atom within piperidine substituent and Ala 83 residue. The diphenyl ether tail protrudes deeply into the S1' subsite. The piperidine N-substituent extends into the solvent and typically has little or no impact on potency at MMP-2. The capacity of the P1' pocket to accommodate such large moieties as the phenyloxyphenylsulfonate is rather remarkable, and demonstrates that the pocket is both flexible and open at the bottom. The trifluoromethoxy

substituent at the terminus of the biphenyl ring in the P1' pocket is surrounded by the hydroxyl of Thr 143, hydrophobic chain of Leu 137, and guanidine group of Arg 149. Docking of hydroxamate 22 shows all of the same interactions with MMP-2, displayed by 21, with the exception of generating two hydrogen bonds between the sulfone moiety and Leu 83, as well as with Leu 82, residues (Figure 2).

Conclusion

In summary we report the synthesis of potent gelatinase (MMP-2 and MMP-9) ligands bearing isosahedral carborane clusters to enable the delivery a high cross-section of boron atoms to tumor cells through click attachment of the carborane moiety to the previously-described MMP inhibitors SC-78080 and SC-77964. The presence of fluorine (19F) atoms will enable the use of magnetic resonance spectroscopy for the detection and localization of these fluorinated drugs in tumors.[25] Evaluation of in vivo efficacy of these derivatives is in progress and will be reported in due course..

Experimental Section

Experimental All solvents were distilled prior to use and all reagents were used without further purification unless otherwise noted. All synthetic reactions were conducted under an atmosphere of nitrogen. Silica gel 60A, 40−75 μm (200 × 400 mesh), was used for column chromatography. Aluminum-backed silica gel 200 μm plates were used for TLC. 1H NMR spectra were obtained using a 500 MHz spectrometer with trimethylsilane (TMS) as the internal standard. 13C NMR spectra were obtained using a 75 or 125 MHz spectrometer. NMR spectra were processed using the Mnova NMR software program produced by Mestrelab Research. NNGH was purchased from Enzo Life Science. The purity of all compounds was determined to be ≥95% unless otherwise noted by high performance liquid chromatography (HPLC) employing a mobile phase A = 5% acetonitrile B in water and a mobile phase B = 0.1% TFA in acetonitrile with a gradient of 60% B increasing to 95% over 10 min, holding at 95% B for 5 min, then returning to 60% B and holding for 5 min. HRMS spectra were measured on a TOF instrument by electrospray ionization (ESI). HRMS spectra were collected using a Waters Acquity I class UPLC and Xevo G2-XS QTof mass spectrometer with Waters Acquity BEH C18 column (1.7 μm, 2.1x50 mm). Mobile phase A was 0.05% formic acid in water and mobile phase B was 0.05% formic acid in acetonitrile, and a gradient of 5 to 90% B in Mobile phase A over 5 min was applied.

Bis-(4-Florophenyl) disulfide (2)

4-Fluorothiophenol (215.2 g, 1.679 mole) was heated in DMSO (1.4 liters) at 65°C for 8 hours. The mixture was cooled to 15°C and this mixture was added via vacuum transfer using a PTFE transfer line to a separate reactor equipped with an overhead mechanical stirrer and containing 5 kg mixture of ice/USP purified water to afford a white slurry. The slurry was allowed to stir overnight at 0-5°C. The following day, the slurry was filtered and the wetcake solids were washed with cold USP water (1.5 liters), and pulled dry overnight under a stream of nitrogen to provide disulfide 2 as a white crystalline solid (207.4 g, 97.1%). mp = 50-52°C. HPLC purity: 100% AUC. The product was stored in the refrigerator under dry nitrogen. 1H NMR (CDCl3, 400 MHz): δ 7.44 (m, 4H), 7.00 (m, 4H). 13C NMR (CDCl3, 100 MHz): δ 163.96, 161.49,

132.32, 132.29, 131.43, 131.34, 116.51, 116.29, 77.47, 77.16, 76.84. Spectral data were consistent with reported values.[23]

1-tert-Butyl 4-ethyl 4-(4-fluorophenylthio)piperidine-1,4-dicarboxylate (3)

A solution of N-Boc-ethylisonipecotate (1) (150.0 g, 0.583 moles) in anhydrous THF (1.8 L) was cooled to -78°C. To this mixture was slowly added a solution of LDA (2.0 M in THF/ethylbenzene, 350 mL, 0.700 mole) over 22 minutes such that temperature did not exceed -70°C. The resulting mixture was allowed to warm to 0°C, then cooled to -40°C, and subsequently treated with a solution of disulfide 2 (148.75 g, 0.583 mole) in anhydrous THF (600 mL) dropwise over 30 minutes. The mixture was allowed to warm to ambient temperature overnight. The following day, the reaction was deemed complete by HPLC analysis. The reaction mixture was quenched with a solution of acetic acid (7.7 g) in USP water (200 mL), and concentrated under reduced pressure at 35-40°C to yield an aqueous residue that was extracted with ethyl acetate (3 x 450 mL). The combined organic layers were successively washed with USP water (300 mL), brine (500 mL), dried with sodium sulfate, and concentrated under reduced pressure to provide the crude sulfide adduct (232.4 g). Filtration through a silica plug (1.2 kg, 60-200 micron, 5:1 ratio) eluting with ethyl acetate/heptane provided pure sulfide 3 as a light yellow oil (192.26 g, 86.0%). HPLC purity: 99% AUC. 1H NMR (CDCl3, 400 MHz): δ 7.41 (m, 2H), 7.02 (m, 2H), 4.13 (q, 2H, J = 14.4 Hz), 3.80 (bd, 2H), 3.09 (m, 2H), 2.09 (m, 2H), 1.76 (m, 2H), 2.12-2.06 (m, 2H), 1.75 (m, 2H), 1.45 (s, 9H), 1.22 (t, 3H, J = 7.2 Hz). 13C NMR (CDCl3, 100 MHz): δ 171.72, 165.16, 162.67, 154.71, 139.17, 139.08, 125.16, 125.13, 116.12, 115.90, 79.81, 77.48, 77.16, 76.84, 61.33, 53.79, 33.17, 28.48, 14.16. Spectral data were consistent with reported values.[23]

1-tert-Butyl 4-ethyl 4-(4-fluorophenylsulfonyl)piperidine-1,4-dicarboxylate (4)

To a 3-necked 5 liter glass reactor equipped with an overhead mechanical stirrer, J-Kem thermocouple, cooling bath at 15-20°C , nitrogen inlet, and an additional funnel, was charged with ethyl acetate (1.5 liters), urea hydrogen peroxide (UHP, 132.61 g, 1.41 moles), and sulfide 3 (180.00 g, 0.4694 moles). Solid phthalic anhydride (209.16 g, 1.41 moles) was added over 5 minutes and ethyl acetate (700 mL) was used as a rinse. The resulting mixture was allowed to stir overnight while the cooling bath remained in place. After 18 h, HPLC analysis showed complete conversion to sulfone. The reaction slurry was filtered to remove urea and phthalic acid and the filtrate was washed with a solution of aqueous 10% sodium sulfite (1.27 L). The organic layer was digested with aqueous 10% sodium carbonate (800 mL), washed with brine, dried with sodium sulfate, concentrated and finally chased with heptane to provide the sulfone 4 as an off-white solid (193.61 g, 99.3%), HPLC purity: 100% AUC, mp 91-95°C. 1H NMR (CDCl3, 400 MHz): δ 7.81 (m, 2H), 7.25 (m, 2H), 4.20 (m, 4H), 2.63 (vbs, 2H), 2.30 (bs, 2H), 2.04 (td, 2H, J = 12.0, 4.0 Hz), 1.45 (s, 9H), 1.25 (t, 3H, J = 8.0 Hz); 13C NMR (CDCl3, 100 MHz): δ 167.66, 166.7, 165.10, 154.40, 133.26, 133.16, 131.11, 131.08, 116.41, 116.18, 80.26, 77.48, 77.16, 76.84, 72.58, 62.77, 28.41, 27.80, 13.99, 0.05. HRMS (ESI-ToF): m/z calcd for C19H26FNNaO6S+ [M+Na]+: 438.1363, found 438.1361. Spectral data were consistent with reported values.[23]

Ethyl 4-(4-fluorophenylsulfonyl)piperidine-4-carboxylate hydrochloride (5).

Into a solution of sulfone 4 (10.25 g, 24.7 mmol) in isopropylacetate (IPAc, 120 mL) was added HCl gas (10.00 g) via sparge and the reaction was allowed to stir overnight at room temperature. HPLC analysis confirmed that the absence of starting material. The mixture was concentrated under reduced pressure to afford piperidinium hydrochloride salt 5 (8.72 g, 100% yield). HPLC purity: 100% AUC. mp 181-184°C. 1H NMR (DMSO-d6, 400 MHz): δ 9.65 (bs, 1H), 9.42 (bs, 1H), 7.89 (m, 2H), 7.58 (t, 2H, J = 8.8 Hz), 4.13 (q, 2H, J = 14.4 Hz), 3.41 (d, 2H J = 13.2 Hz), 2.76 (bs, 2H), 2.32 (m, 4H), 1.10 (t, 3H, J = 7.2 Hz). 13C NMR (CDCl3, 100 MHz): δ 170.74, 167.94, 165.97, 165.36, 133.46, 133.36, 130.33, 130.30, 116.79, 116.56, 77.47, 77.15, 76.84, 70.05, 67.69, 63.58, 41.32, 25.12, 21.88, 21.50, 13.92, 0.05. HRMS (ESI-ToF): m/z calcd for C14H19FNO4S+ [M+H]+: 316.1019, found 316.1018. Spectral data were consistent with reported values.[23]

Ethyl 4-(4-fluorophenylsulfonyl)-1-(prop-2-ynyl)piperidine-4-carboxylate (6)

A 2-L reactor was charged with hydrochloride salt 5 (30.00 g, 85.27 mmol), anhydrous DMF (600 mL), and potassium carbonate (23.8 g, 172.2 mmol) and the resulting mixture was stirred under mechanical stirring for 10 minutes. Propargylamine (97% purity, 10.35 g, 87.00 mmol) was then added and the reaction was allowed to stir for 23 h at room temperature after which time HPLC analysis revealed 11.75% AUC of unreacted piperidine 5 and 87.3% AUC of propargyl amine 6. The reaction was charged with an additional portion of propargylamine (1.58 g, 1.00 mL, 8.41 mmol) and the reaction was allowed to stir for an additional 1 h at room temperature after which time the reaction was deemed complete by HPLC (2.3% AUC of unreacted piperidine 5 was noted along with 96.3% AUC of propargyl amine 6. The reaction mixture was added dropwise to a 5-L reactor containing ice-cold USP purified water (2.5 L) to initiate crystallization. The resulting slurry was stirred overnight at 0-5°C via mechanical stirring, filtered, washed with USP water (150 mL), and pulled dry under a stream of nitrogen to provide N-propargyl piperidine 6 (28.44 g, 94.4%) as a light beige solid, HPLC analysis: 99.81% AUC, mp 100-102oC. 1H NMR (CDCl3, 400 MHz): δ 7.82 (m, 2H), 7.23 (m, 2H), 4.21 (q, 2H, J = 12.0 Hz), 3.26 (d, 2H, J = 4.0 Hz), 2.90 (m, 2H), 2.39 (m, 2H), 2.20 (m, 5H), 1.25 (t, 3H, J = 12.0 Hz). 13C NMR (CDCl3, 100 MHz): δ 167.5, 166.8, 165.0, 133.2, 133.1, 131.4, 116.3, 116.1, 78.2, 77.4, 77.1, 76.8, 73.5, 71.9, 62.5, 49.1, 46.6, 49.1, 46.6, 28.1, 14.0. HRMS (ESI-ToF): m/z calcd for C17H21FNO4S+ [M+H]+: 354.1175, found 354.1176. Spectral data were consistent with reported values.[23]

Ethyl 1-(prop-2-ynyl)-4-(4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl)piperidine-4-carboxylate (7)

A 500-mL reactor equipped with an overhead mechanical stirrer, J-Kem thermocouple, heating mantle, nitrogen inlet, and an additional funnel was charged with fluorophenyl sulfone 6 (24.86 g, 70.34 mmol), anhydrous DMF (125 mL), milled potassium carbonate (19.54 g, 141.4 mmol), and 4-(trifluoromethoxy)phenol (25.10 g, 140.7 mmol). The reaction was heated at 90°C for 19 h after which time the reaction was deemed complete by HPLC. The reaction mixture was cooled to rt and DMF was removed on a rotary evaporator under reduced pressure at 40-60°C. The

residue was diluted with MTBE/toluene (1:1, 300 mL) and washed with 1M NaOH (2 x 250 mL), USP purified water (250 mL), brine (250 mL), dried with sodium sulfate, filtered, and concentrated to furnish diphenyl ether 7 (36.06 g, 100% yield, yellow oil). HPLC analysis: 98.03% AUC. 1H NMR (CDCl3, 400 MHz): δ 7.76 (m, 2H), 7.27 (m, 2H), 7.10 (m, 2H), 7.06 (m, 2H), 4.23 (m, 2H), 3.25 (s, 2H), 2.90 (bs, 2H), 2.40 (bd, 2H), 2.19 (m, 5H), 1.27 (m, 3H). 13C NMR (CDCl3, 100 MHz): δ 167.0, 162.5, 153.3, 146.1, 132.8, 129.6, 123.0, 121.6, 117.3, 78.3, 77.4, 77.1, 76.7, 73.4, 72.0, 62.4, 49.3, 46.7, 28.3, 14.0. HRMS (ESI-ToF): m/z calcd for C24H25F3NO6S+ [M+H]+: 512.1355, found 512.1353.

Ethyl 1-(prop-2-ynyl)-4-(4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl)piperidine-4-carboxylate (8)

To a 2-L reactor equipped with an overhead mechanical stirrer, J-Kem thermocouple, heating mantle, reflux condenser with nitrogen inlet, and an additional funnel, was charged with a solution of ethyl ester 7 (28.50 g, 55.72 mmol) in EtOH/THF (1:1, 850 mL) and a solution of NaOH (22.30 g, 557.17 mmol) in USP water (425 mL). The reaction mixture was heated to 65°C and allowed to stir for 18 hours which HPLC analysis showed complete consumption of ester 7. The mixture was allowed to cool to ambient temperature, diluted with USP water (300 mL), and concentrated at 45-50°C on a rotary evaporator to remove EtOH and THF. The aqueous residue was diluted with USP water (600 mL) and the pH was adjusted to pH 2.25 using 2M HCl (282 mL) providing a thick white slurry. The slurry was filtered, washed with USP water (750 mL), pulled dry, and dried further in a vacuum oven at 40°C to provide carboxylic acid 8 (26.30 g, 97.6% yield, white solid). HPLC analysis: 94.4% AUC, mp 188-190°C (decomp.). 1H NMR (CDCl3, 400 MHz): δ 7.78 (m, 2H), 7.49 (d, 2H, J = 8.0 Hz), 7.31 (m, 2H), 7.19 (m, 2H), 3.31 (s, 2H), 3.17 (s, 1H), 2.85 (d, 2H, J = 12.0 Hz), 2.19 (d, 2H, J = 12.0 Hz), 2.11 (t, 2H, J = 12.0 Hz), 1.92 (td, 2H, J = 12.0, 4.0 Hz). 13C NMR (CDCl3, 100 MHz): δ 167.5, 161.7, 153.3, 145.03, 145.01, 132.8, 129.2, 123.32, 122.0, 117.4, 78.5, 76.3, 71.0, 48.4, 45.7, 27.5. HRMS (ESI-ToF): m/z calcd for C22H21F3NO6S+ [M+H]+: 484.1042, found 484.1042.

1-Prop-2-ynyl)-N-(tetrahydro-2H-pyran-2-yloxy)-4-(4-(4-(trifluoromethoxy)phenoxy)phenylsulfonyl)piperidine-4-carboxamide (9)

To a 500-mL reactor, equipped with a large magnetic stirring bar, J-Kem thermocouple, cooling Dewer, and nitrogen inlet, was charged with carboxylic acid 8 (20.00 g, 41.37 mmol) and anhydrous DMF (180 mL). The mixture was allowed to stir for 10 minutes at ambient temperature then cooled the mixture to < 5°C. To the cooled mixture was sequentially added O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine (7.50 g, 64.02 mmol), EDCI-HCl (10.00 g, 81.85 mmol), and DMAP (8.00 g, 65.36 mmol). The mixture was allowed to stir overnight and gradually warmed to room temperature while the reactor remained in the cooling bath. After 17 hours, HPLC analysis revealed 16.1% of unreacted carboxylic acid 8. The cooling bath was removed and the reaction mixture was allowed to stir an additional 33 hours at room temperature whereby HPLC analysis confirmed that the reaction was deemed complete. The reaction was quenched with USP water (5 mL) and concentrated under high vacuum at 30°C on a rotovap evaporator to remove DMF. The residue was diluted with ethyl acetate (350 mL) and subsequently washed with saturated aqueous sodium bicarbonate solution (200 mL), brine (200

mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure to provide crude THP-hydroxamate 9 (34.31 g), which was purified by silica gel chromatography using a glass gravity column (24 in x 3 in) and silica gel (680 g, 60-200 micron, Silicycle) and eluted with an EtOAc/heptane gradient (30% to 70%) to provide Compound 9 (21.78 g, 90.4%) as white solids. HPLC analysis: 97% AUC, mp 89-91oC. MS [M+H]+ obs 583.46 m/z. 1H NMR (CDCl3, 400 MHz): δ 9.40 (s, 1H), 7.80 (dd, 2H, J = 6.9, 2.0 Hz), 7.27 (m, 2H), 7.12 (dd, 2H, J = 6.8, 2.3 Hz), 7.05 (dd, 2H, J = 6.9, 2.0 Hz), 5.00 (t, 1H, J = 2.8 Hz), 4.00 (td, 1H, J = 11.2, 2.4 Hz), 3.69 (m, 1H), 3.23 (d, 2H, J = 2.4 Hz), 2.92 (m, 2H), 2.35-2.30 (m, 3H), 2.25-2.20 (m, 4H), 1.88-1.76 (m, 3H), 1.68-1.58 (m, 3H). 13C NMR (CDCl3, 100 MHz): δ 164.0, 162.8, 153.0, 146.1, 146.0, 132.6, 128.0, 123.0, 121.8, 121.7, 119.2, 117.4, 102.0, 78.6, 73.4, 70.3, 62.3, 49.0, 48.9, 46.6, 28.6, 28.4, 27.8, 25.0, 18.3. HRMS (ESI-ToF): m/z calcd for C27H30F3N2O7S+ [M+H]+: 583.1726, found 583.1723.

N-hydroxy-1-(prop-2-yn-1-yl)-4-((4-(4-(trifluoromethoxy)phenoxy)phenyl)sulfonyl)piperidine-4-carboxamide (10)

Hydroxamate 10 was prepared according to the method reported.[24]

1-azido-3-chloropropane (12)

Safety Note on Handling Azido Compounds. Sodium azide is extremely toxic (LC50 Inhalation = 37 mg/m3 for rats, LD50 Dermal = 20mg/kg for rabbits) and very soluble in water (>30 g/100 mL at 0°C). Sodium azide can be easily absorbed dermally and consequently must be handled with appropriate personal protection equipment (PPE). Sodium azide decomposes above 275°C, generating highly reactive sodium metal. Sodium azide is not compatible with any acid as it spontaneously forms highly explosive hydrazoic acid on contact, even in dilute solution. Low molecular weight organic azides are potentially explosive substances that can decompose with a slight input of external energy (heat, friction, pressure etc). Although there has not been any documented explosions on this end of work, any organic azides where the weight attributed to the azido group exceeds 25% of the molecular weight should be handled with significant caution. It is recommended that a blast shield be used during synthesis and avoid of very large-scale reactions when dealing with these substances.[57,58] According to a general precedent,[59] to a 250 mL round bottomed flask was added 100 mL of anhydrous DMF and 10.02 g of 1-bromo-3-chloropropane and then 4.2 g of sodium azide. The reaction was placed in an ambient temperature water bath and stirred overnight (16 h) at room temperature. The reaction mixture was diluted with 50 mL of Et2O and 50 mL USP purified water, stirred 2-3 minutes then separated the organic layer (top). Extracted the bottom aqueous layer with Et2O (2x 60 mL). The combined organic layers were washed with USP purified water (3x 50 mL), dried with sodium sulfate, filtered and concentrated at 25-30°C under reduced pressure to give a colorless oil (7.21g, 95% mass balance) which was taken forward without any further purification to give a mixture of 1-azido-3-chloropropane as the major product (81%) that contained ~15% of 1-azido-3-bromopropane, and which was carried on as such into the next step. 1H NMR (CDCl3, 400 MHz): δ 3.64 (t, 2H, J = 8.0 Hz), 3.51 (t, 3H, J = 8.0 Hz), 2.02 (q, 2H, J = 12.0, 4.0 Hz)

1-Azido-3-iodopropane (13)

According to the general precedent,[34] to a 1000 mL 3-necked round bottomed flask was added 19.35 g of sodium iodide, 7.5 g of crude 1-azido-3-chloropropane and 190 mL of acetone. The vessel was purged with dry nitrogen, covered with aluminum foil, and heated to 52°C. After 40 h, the reaction was allowed reaction to cool to room temperature. The reaction mixture as a yellow slurry was filtered over a pad of Celite, and the funnel and flask were with acetone (~100 mL), then concentrated the yellow filtrate on a rotovap at 25-30°C to remove acetone. After concentration, an orange-yellow residue was obtained (oily solids, 26.2 g). Hexane (50 mL) was added to the oil/solid residue (yellowish-orange) which changed the color to a greenish solid. The slurry was stirred overnight at room temperature then passed over a short silica plug (65 g) packed in n-hexane, then the plug was eluted with n-hexane to collect fractions (each 50-70 mL). Appropriate fractions were combined and concentrated at 25°C to give iodo azide 13 (10.77 g, 81.3%) as a colorless oil. 1H NMR (CDCl3, 400 MHz): δ 3.44 (t, 2H), 3.25 (t, 2H), 2.04 (quintet, 2H).

TBDMS Carborane 14

According to a general procedure[60] was added 3.00 g of o-carborane, 12 mL anhydrous toluene, and 6 mL anhydrous Et2O. Stirred at room temperature until completely dissolved then cooled to < 5°C. Added n-BuLi solution (1.66 M, 13.2 mL) over about 5 minutes to give a murky turbid white mixture. Removed cooling bath after 5 minutes and allowed to store at room temperature. After 2.5 hours, solid TBDMSCl (3.47 g) was added at room temperature as one portion which addition was endothermic. Reaction is a murky white solution. After 22.5 h, the reaction slurry was analyzed by TLC (80% hexane and 20% Et2O) and showed a trace amount of starting material and the reaction was deemed complete. The reaction mixture was quenched with 30 mL of USP purified H2O, then extracted with Et2O (3x30 mL). The combined organic layers were dried with MgSO4, filtered and concentrated to give crude product 7.07 g as a pale yellow oil. The crude oil was purified over silica gel (140 g, 60-200 micron) eluting with n-hexane and 10% Et2O/hexane to give the silyl-protected carborane 14 (5.05 g, 93.9%) as a white crystalline solid, mp 64-66°C. 1H NMR (CDCl3, 400 MHz): δ 3.44 (bs,1H), 2.87-1.54 (m, 10H), 1.02 (s, 9H), 0.23 (s, 6H). 11B NMR (Decoupled, 100 MHz): δ = 0.34, -1.76, -7.02, -10.73, -12.31, -13.26. 11B NMR (Coupled, 100 MHz): δ = 1.01, -0.94, -2.57, -6.29, -7.87, -9.99, -11.62, -12.41, -13.2, -14.26.

TBDMS Propyl Azido Carborane 15

According to a general precedent,[34] to a dry 100 mL round bottomed flask under a nitrogen atmosphere was added anhydrous THF (18 mL) and 1M LiHMDS (9.7 mL). The mixture was cooled to -78°C. A solution of TBDMS carborane (2.00 g) in anhydrous THF (10 mL) was added to the cryogenic mixture via syringe over 5 min such that the temperature was maintained < -65°C. The reaction mixture was allowed to stir an additional 5 minutes at -78°C then allowed to warm to 0°C, stirred an additional 1.25 h at 0°C, and cooled to -78°C. A solution of 1-azido-3-iodopropane (2.15 g) in anhydrous THF (12 mL) was added over 3 minutes at -78°C. The reaction was allowed reaction to stir at -78°C for 10 minutes then allowed to warm to room temperature and stirred an additional 1.25 hours at ambient temperature. The reaction was cooled to 0°C, quenched with USP purified water (5 mL), concentrated under reduced pressure,

extracted with diethyl ether (2x 20mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduce pressure to give a crude yellow oil (3.13 g). The crude oil (3.13 g) was dissolved in DCM/n-hexane (3.5 mL, 25/75, v/v) and passed through a large silica plug (40 g) packed in DCM/n-hexane (25/75, v/v). The silica plug was flushed with DCM/n-hexane (200 mL, 25/75, v/v) to collect 8 fractions (each about 10-15 mL). Fractions 2-6 were combined and concentrated to give carborane azide 15 (2.58 g, 97.7%) as a white solid, mp 41-43°C. 1H NMR (CDCl3, 400 MHz): δ 3.32 (t, 2H), 3.15-1.5 (m, 14H), 1.07 (s, 9H), 0.34 (s, 6H). 13C NMR (CDCl3, 20 MHz): δ 80.6, 76.5, 50.9, 35.3, 29.7, 27.7, 20.5, -2.3. 11B NMR (Decoupled, 100 MHz): δ = 0.29, -3.76, -7.29, -10.18. 11B NMR (Coupled, 100 MHz): δ = 0.99, -0.56, -3.13, -4.62, -6.57, -8.16, -9.48, -11.24.

1,4-Triazole 16 and 1,5-Triazole 17 via Thermal Click Reaction

To a 100 mL round bottomed flask was added carboranyl azide 15 (1.00 g, 3.30 mmol), alkyne 9 (1.54 g, 2.95 mmol) and anhydrous toluene (50 mL). The mixture was stirred for 10 minutes at ambient temperature and the mixture was equally portioned into 6 different pressure vials (ChemGlass, 40 mL) where each vial contained 8.3-8.5 mL of mixture. Each mixture was purged with argon, placed on a heating block at 120°C, and allowed to stir at 120°C for 58 hours. HPLC analysis of each reaction vial indicated that there was ~20% unreacted alkyne and the reaction was taken forward at this point to avoid degradation of product and introduction of impurities that would be difficult to remove downstream. All six reactions after cooling to room temperature were combined and concentrated under reduced pressure to provide a crude oil (2.76 g). The crude oil was dissolved in DCM (30 mL), treated with silica gel (6.9 g, 60-200 micron, Silicycle), and concentrated to dryness to give dry-loaded material on silica which was placed and packed in a 65 g solid loading cartridge. An 80 g RediSep Rf Gold silica gel column cartridge was equilibrated with ethyl acetate/n-hexane (40/60, 2CV), 100% ethyl acetate (1CV), and ethyl acetate/n-hexane (40/60, 2CV). The purification was accomplished using an ethyl acetate/n-hexane step-gradient from ethyl acetate/n-hexane (40/60) to 100% ethyl acetate. The elution of components were in the following order: recovered unreacted starting material 9, 1,5-triazole 17, and lastly 1,4-triazole 16. Appropriate fractions were combined and concentrated to isolate recovered starting material (compound 9, 0.36 g, colorless oil, TLC Rf = 0.51 using 100% EtOAc), 1,5-click product (colorless glass solid, 0.60 g, 32.1% yield, corrected yield for recovered SM, TLC Rf = 0.35 using 100% EtOAc), and 1,4-click product (white solid, 0.90 g, 48.1% yield, corrected yield for recovered SM, TLC Rf = 0.15 using 100% EtOAc).

Characterization data for1,4-triazole click product 16

HPLC purity: 96% AUC (retention time: 26.5 min). 1H NMR (CDCl3, 400 MHz): δ 9.38 (s, 1H), 7.80 (d ,2H, J = 8.0 Hz), 7.41 (s, 1H), 7.28 (d, 2H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.0 Hz), 4.99 (s, 1H), 4.33 (t, 2H, J = 6.4 Hz), 3.99 (t, 1H, J = 10.3 Hz), 3.68 (bd, 1H), 3.59 (s, 2H), 2.93 (bs, 2H), 2.40-1.20 (m, 26H), 0.98 (s, 9H), 0.23 (s, 6H). 13C NMR (CDCl3, 100 MHz): δ 164.1, 162.9, 152.9, 146.1, 145.3, 132.5, 128.5, 123.0, 122.3, 121.8, 117.4, 102.1, 79.8, 77.4, 77.2, 77.0, 76.7, 76.2, 70.5, 62.4, 52.9, 49.8, 49.8, 49.2, 34.9, 30.7, 28.5, 28.3, 27.8, 27.4, 24.9, 20.3, 18.24, -2.60. 11B NMR (Decoupled, 100 MHz): δ = 0.27, -3.86, -

7.47, -10.51.11B NMR (Coupled, 100 MHz): δ = 1.09, -0.59, -3.17, -4.34, -6.64, -8.41, -9.41, -10.81.

HRMS (ESI-ToF): m/z calcd for C38H61B10F3N5O7SSi+ [M+H]+: 926.4944, found 926.5007. FTIR: 2941.1, 2863.3, 2575.8, 1686.5, 1587, 1501.4, 1488.6, 1316.7, 1244.2, 1220.2, 1185.8, 1149.4, 1133.2, 1086.5, 1038.0, 944.4, 896.8, 858.2, 838.3, 752.8, 731.2, 677.0 cm-1.

Characterization data for 1,5-triazole click product 17

HPLC purity: 95% AUC (retention time: 27.4 min). 1H NMR (CDCl3, 400 MHz): δ 9.43 (s, 1H), 7.80 (d, 2H, J = 12.0 Hz), 7.49 (s, 1H), 7.28 (d, 3H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.0Hz), 7.05 (d, 2H, J = 8.0 Hz), 5.01 (bs, 1H), 4.39 (t, 2H, J = 8.0 Hz), 3.99 (t, 1H, J = 8.0 Hz), 3.70 (d, 1H, J = 8.0 Hz), 3.49 (s, 2H), 2.80 (t, 2H, J = 8.0 Hz), 1.58-2.30 (c, 24H), 1.25 (s, 1H), 1.00 (s, 9H). 13C NMR (CDCl3, 100 MHz): δ 164.16, 162.91, 152.91, 1461, 134.74, 132.63, 132.42, 127.82, 123.03, 121.80, 121.71, 117.50, 101.87, 80.13, 77.23, 76.35, 70.15, 62.30, 50.20, 49.93, 49.74, 47.42, 35.04, 30.11, 28.30, 28.10, 27.77, 27.43, 24.92, 20.32, 18.12, -2.59. 11B NMR (Decoupled, 100 MHz): δ = 0.37, -3.85, -7.43, -10.47. 11B NMR (Coupled, 100 MHz): δ = 0.94, -0.47, -4.55, -6.70, -8.43, -10.83. HRMS (ESI-ToF): m/z calcd for C38H61B10F3N5O7SSi+ [M+H]+: 926.4944, found 926.4999. FTIR: 2939.8, 2869.6, 2579.3, 1685.9, 1586.8, 15014, 1488.7, 1319.0, 1295.5, 1220.0, 1243.6, 1185.7, 1149.9, 1134.3, 1086.8, 1037.2, 957.7, 944.6, 896.9, 873.3, 858.7, 838.3, 818.4, 732.1, 677.3 cm-1

Preparation of 1,4-triazole 16 via CuAAC-Catalyzed Click Reaction

To a 100 mL round bottomed flask was added alkyne (690 mg, 1.18 mmole), azide (400 mg, 1.18 mmol), magnetic stir bar, and THF (30 mL). A freshly prepared solution of copper sulfate pentahydrate (303 mg, 1.21 mmole) and sodium ascorbate (234 mg, 1.18 mmole) in deionized water (30 mL) was added to the organic mixture over 4 minutes, and during the addition of aqueous solution the mixture was sparged with nitrogen. The reaction was stirred for 12 hours at room temperature which TLC analysis (eluting with 100% EtOAc on silica gel) indicated full consumption of alkyne starting material. The reaction mixture was concentrated under reduced pressure and the residue was dissolved into ethyl acetate (40 mL). The organic layer was washed with 10% ammonium chloride (40 mL), brine (40 mL), dried with sodium sulfate, filtered, and concentrated to provide crude 1,4-triazole click product. The crude product was dissolved in 5 mL of ethyl acetate and loaded onto two separate preparative thin layer chromatography plates (20 x 20 cm) and eluting with 100% ethyl acetate to give purified 1,4-triazole click product 16 (650 mg, 59.6% yield) as a pale green solid.

Preparation of 1,5-triazole 17 via RuAAC-Catalyzed Click Reaction

To a 20 mL round bottomed flask was added alkyne (750 mg, 1.29 mmol), carboranyl azide 15 (460 mg, 1.35 mmol), Cp*RuCl(cod) (65 mg, 0.17 mmol), magnetic stir bar, and THF (13 mL). The mixture was sparged with nitrogen for 5 minutes, then allowed to stir at room temperature for 24 hours which TLC and HPLC analysis showed complete consumption of alkyne starting material. The reaction mixture was concentrated under reduced pressure to give crude product. The crude product was dissolved in ethyl acetate (6 mL) and loaded onto three separate

preparative thin layer chromatography plates (20 x 20 cm) and eluting with 100% ethyl acetate to give purified 1,5-triazole 17 (665 mg, 55.9% yield) as a light beige solid.

1,4-Triazole Hydroxamate 18

To TBDMS-protected 1,4-triazole 16 (128 mg, 0.139 mmol) was added anhydrous THF (1.25 mL) and the resulting mixture was cooled solution to –78°C. To the cryogenic mixture was added a solution of 1M TBAF in THF (0.17 mL) over approximately 30 seconds. After 5 minutes, the cooling bath was removed and then the reaction was permitted to warm to room temperature. After 30 minutes at room temperature, TLC analysis (100% EtOAc) showed complete consumption of starting material. The reaction mixture was concentrated to a crude oil residue which was dissolved in ethyl acetate (2 mL) and washed with water (1 mL, pH 7-7.5). The aqueous phase was extracted ethyl acetate (1 mL). The combined organic layers were washed with water (pH 7-7.5, 1 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure to give crude product (108 mg). The crude oil (108 mg) was dissolved in ethyl acetate (0.5 mL) and passed through a silica plug (0.27 g) in ethyl acetate. The plug was flushed with ethyl acetate. Appropriate fractions were combined and concentrated to afford desired THP-protected 1,4-triazole (88 mg, 78.6% yield, colorless oil) which was taken forward without any further purification. HPLC purity: 97.4% AUC (retention time: 24.1 min). HRMS (ESI-ToF): m/z calcd for C32H47B10F3N5O7S+ [M+H]+: 812.4079, found 812.4131. FTIR: 2946.6, 2850.4, 2586.7, 1682.0, 1587.0, 1501.5, 1488.4, 1461.3, 1293.7, 1219.9, 1244.5, 1185.9, 1132.6, 1149.0, 1086.1, 1037.5, 1021.5, 956.2, 944.2, 896.0, 873.1, 835.1, 816.0, 754.5, 722.7, 678.9, 645.0 cm-1. To a 10 mL vial containing THP-protected 1,4-triazole (88 mg, 0.109 mmol)) under nitrogen atmosphere was added anhydrous 1,4-dioxane (0.9 mL)/methanol (0.1 mL) and the mixture was allowed to stir until complete dissolution was achieved. To the solution was added 4N HCl in 1,4-dioxane (0.14 mL) and the reaction was allowed to stir for 2 h at room temperature where HPLC analysis revealed that the reaction was deemed complete. The reaction mixture was concentrated under reduced pressure at 30°C to give a crude oil. The crude oil was dissolved in dichloromethane (1 mL) and diethyl ether (3 mL) was added to generate a white slurry. The slurry was allowed to stir at ambient temperature for 1.5 hours, filtered, and the filter cake was washed with diethyl ether (2 mL) and n-heptane (5 mL), pulled dry under nitrogen, and further dried in vacuo at room temperature to provide the title 1,4-triazole carborane hyrdrochloride salt 18 (60 mg, 72.2%) as a white solid. HPLC purity: 97.4% AUC (retention time: 10.4 min), mp 206oC (decomp.). 1H NMR (DMSO-d6, 500 MHz): δ 11.18 (bs, 0.6H), 10.90 (bs, 0.4H), 9.33 (bs, 0.5H), 8.27 (bs, 0.7H), 7.75 (d, 2H, J = 10.0 Hz), 7.48 (d, 2H, J = 10.0 Hz), 7.32 (d, 2H, J = 10.0 Hz), 7.19 (d, 2H, J = 10.0 Hz), 5.25 (bs, 1H), 4.39 (t, 4H), 3.47 (vbs, 2H), 3.16 (m, 2H), 3.01-2.52 (complex, 3H), 2.30-1.40 (complex, 17H). 13C NMR (DMSO-d6, 125 MHz): δ 163.0, 161.9, 153.4, 145.0, 132.9, 123.3, 121.9, 121.1, 119.0, 117.8, 75.5, 63.2, 57.5, 57.5, 57.5, 51.6, 48.4, 33.4, 29.5, 24.9, 23.1, 19.4, 19.2, 13.5. HRMS (ESI-ToF): m/z calcd for C27H39B10F3N5O6S+ [M+H]+: 728.3504, found 728.3540. 11B NMR (Decoupled, 100 MHz): δ = 18.56, -2.94, -6.09, -9.67, -12.20, -13.17. 11B NMR (Coupled, 100 MHz): δ = 18.56, -2.15, -3.64, -5.21, -6.32, -8.91, -11.08, -12.95, -13.86.

1,5-Triazole Hydroxamate HCl Salt 19

To TBDMS-protected 1,5-triazole 17 (71 mg, 0.077 mmol) was added anhydrous THF (0.9 mL) and the resulting mixture was cooled solution to –78ºC. To the cryogenic mixture was added a solution of 1M TBAF in THF (90 µL). After 5 minutes, the cooling bath was removed and then the reaction was allowed to warm to room temperature. After 75 minutes at room temperature, TLC analysis (100% EtOAc) showed complete consumption of starting material. The reaction mixture was concentrated to a crude oil residue which was dissolved in ethyl acetate (2 mL) and washed with water (1 mL, pH 7-7.5). The aqueous phase was extracted ethyl acetate (2 mL). The combined organic layers were washed with water (pH 7-7.5, 1 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure to give crude desired product (82 mg) which was taken forward without any further purification. HPLC purity: 95.2% AUC (retention time: 26.4 min). HRMS (ESI-ToF): m/z calcd for C32H47B10F3N5O7S+ [M+H]+: 812.4079, found 812.4139. To a 10 mL vial containing crude THP-protected 1,5-triazole from the desilylation step (82 mg) under a nitrogen atmosphere was added anhydrous 1,4-dioxane (0.9 mL)/methanol (0.1 mL) and allowed mixture to stir until complete dissolution was achieved. To the solution was added 4N HCl in 1,4-dioxane (0.14 mL) and the reaction was allowed to stir for 2.5 hours at room temperature where HPLC analysis revealed that the reaction was deemed complete. The reaction mixture was concentrated under reduced pressure at 30 + 5°C to give a crude oil. The crude oil was dissolved in dichloromethane (0.5 mL) and diethyl ether (3 mL) was slowly added to generate a white slurry. The slurry was allowed to stir at ambient temperature for 20 min, filtered, and the filter cake was washed with diethyl ether (2.5 mL) and n-hexane (5 mL), concentrated to dryness under nitrogen, and further dried in vacuo at room temperature to provide the title 1,5-triazole carboranyl hydrochloride salt 19 (58 mg, 99%) as a white solid. HPLC purity: 99.1% AUC (retention time: 10.9 min), mp 203°C (decomp.). 1H NMR (DMSO-d6, 500 MHz): δ 11.28-11.20 (complex, 1.8H), 9.38 (bs, 0.6H), 7.98 (bs, 0.8H), 7.75 (d, 2H, J = 10.0 Hz), 7.48 (d, 2H, J = 10.0 Hz), 7.33 (d, 2H, J = 10.0 Hz), 7.19 (d, 2H, J = 10.0 Hz), 5.25 (s, 1H), 4.70-4.40 (complex, 4H), 4.20-3.20 (complex, 6H), 3.16 (m, 0.6H), 3.05-2.70 (complex, 2H), 2.45-2.18 (complex, 7H), 2.10-1.80 (6H), 1.57 (m, 2H). 13C NMR (DMSO-d6, 125 MHz): δ 163.0, 161.8, 153.4, 145.0, 132.9, 123.3, 121.8, 121.1, 119.1, 117.8, 75.6, 62.9, 57.5, 57.5, 57.5, 48.4, 46.7, 46.6, 46.6, 46.6, 46.6, 33.5, 29.4, 23.1, 19.2, 13.5. HRMS (ESI-ToF): m/z calcd for C27H39B10F3N5O6S+ [M+H]+: 728.3504, found 728.3538. 11B NMR (Decoupled, 100 MHz): δ = 18.55, -2.90, -6.26, -9.74, -12.24, -13.14. 11B NMR (Coupled, 100 MHz): δ = 18.58, -2.13, -3.71, -8.99, -11.11, -12.88.

Molecular Docking Protocol

Molecular models of 21 and 22 were developed using the Molecular Operating Environment (MOE) computational suite's Builder utility followed by minimization in the gas phase using the MMFF94X force field. The solution structure of compound 20 bound to MMP-2 was then uploaded into MOE and prepared for docking using MOE's Structure Preparation utility. The hydrogen-bonding network of the docking model was further optimized at pH of 7.4 by automatically sampling different tautomer/protomer states using Protonate3D, which calculates optimal protonation states, including titration, rotamer, and "flips" using a large-scale combinatorial search. The binding pocket of MMP-2 was surveyed using MOE's Site Finder utility, which employs an alpha shape construction algorithm to identify regions of tight atomic

packing in which are filled inactivated dummy atoms that ligand docking can be directed to. Following the preparation of the MMP-2 docking model and inactivation of other atoms, molecular docking using the previously generated ligand conformation database was carried out at the docking site specified by the dummy atoms populating the binding pocket of MMP-2 of the docking active site. Ligand placement employed the Alpha Triangle method with Affinity dG scoring to generate 100 data points per unique ligand that were further refined using the Induced Fit method with GBVI/WSA dG scoring to obtain the top 50 docking poses per ligand. The Amber12:EHT force field was used to perform these calculations.

Enzyme Assays

Enzyme assays were performed under contract by BPS Bioscience of San Diego, CA. For MMP-1, MMP-2, and MMP-9, the substrate employed was 390 MMP FRET and was purchased from Anaspec. NNGH was purchased from Enzo Life science. Enzymes activator APMA (p-aminophenylmercuric acetate) was purchased from Millipore. MMP-1, MMP-2, and MMP-9 enzymes were purchased from Sigma. For MMP-1, 6 ng of enzyme was employed with 5 uM 390 MMP Substrate. For MMP-2, 0.7 ng of enzyme was employed with 2 uM 390 MMP Substrate. For MMP-9, 0.5 ng of enzyme was employed with 1 uM 390 MMP Substrate. A series of dilutions of each compound was prepared with 10% DMSO and 5 µl of the dilution was added to a 50 µl reaction so that the final concentration of DMSO was 1% in all of reactions.

The enzymes were diluted in 50 mM HEPES buffer pH 7.4, 10 mM CaCl2, 0.05% Brij-35, and 1 mM APMA for activation at 37°C for 2 hours. The enzymatic reactions were conducted in duplicate at room temperature for 30 minutes in a 50 µl mixture containing 50 mM HEPES buffer, pH7.4, 10mM CaCl2, 0.05% Brij-35, the MMP substrate, MMP enzyme, and a test compound. Fluorescence intensity was measured at an excitation of 328 nm and an emission of 393 nm using a Tecan Infinite M1000 microplate reader. Phosphatase activity assays were performed in duplicate at each concentration. The fluorescent intensity data were analyzed using the computer software, Graphpad Prism. In the absence of the compound, the fluorescent intensity (Ft) in each data set was defined as 100% activity. In the absence of enzyme, the fluorescent intensity (Fb) in each data set was defined as 0% activity. The percent activity in the presence of each compound was calculated according to the following equation: %activity = (F-Fb)/(Ft-Fb), where F= the fluorescent intensity in the presence of the compound.

The values of % activity versus a series of compound concentrations were then plotted using non-linear regression analysis of Sigmoidal dose-response curve generated with the equation Y=B+(T-B)/1+10((LogEC50-X)×Hill Slope), where Y=percent activity, B=minimum percent activity, T=maximum percent activity, X= logarithm of compound and Hill Slope=slope factor or Hill coefficient. The IC50 value was determined by the concentration causing a half-maximal percent activity..

Acknowledgements

We thank Loyola University Chicago for support of this work.

Keywords: matrix metalloproteinase, MMP, boron neutron capture therapy, BNCT, carborane

[1] K. Hu, Z. Yang, L. Zhang, L. Xie, L. Wang, H. Xu, L. Josephson, S.H. Liang, M. Zhang, Coord. Chem. Rev. 2020, 405, 213139.

[2] R.F. Barth, P. Mi, W. Yang, Cancer Commun. 2018, 38, 35.

[3] S. Gao, R. Fu, N.S. Hosmane, Pure and Applied Chemistry 2015, 87, 123-134.

[4] R.F. Barth, J.C. Grecula, Applied Radiation and Isotopes 2020, 160, 109029.

[5] J.F. Valliant, K.J. Guenther, A.S. King, P. Morel, P. Schaffer, O.O. Sogbein, K.A. Stephenson, Coord. Chem. Rev. 2002, 232, 173-230.

[6] R.F. Barth, Z. Zhang, T. Liu, Cancer Commun. 2018, 38, 36.

[7] F. Ali, N. S Hosmane, Y. Zhu, Molecules 2020, 25, 828.

[8] A. Isono, M. Tsuji, Y. Sanada, A. Matsushita, S. Masunaga, T. Hirayama, H. Nagasawa, ChemMedChem 2019, 14, 823-832.

[9] A. Hermawan, R.A. Susidarti, R.D. Ramadani, L. Qodria, R.Y. Utomo, M. Ishimura, Y. Hattori, Y. Ohta, M. Kirihata, E. Meiyanto, Invest. New Drugs 2019, 1-8.

[10] V.M. Ahrens, R. Frank, S. Boehnke, C.L. Schütz, G. Hampel, D.S. Iffland, N.H. Bings, E. Hey-Hawkins, A.G. Beck-Sickinger, ChemMedChem 2015, 10, 164-172.

[11] T. Kanemitsu, S. Kawabata, M. Fukumura, G. Futamura, R. Hiramatsu, N. Nonoguchi, F. Nakagawa, T. Takata, H. Tanaka, M. Suzuki, Radiat. Environ. Biophys. 2019, 58, 59-67.

[12] R. Li, J. Zhang, J. Guo, Y. Xu, K. Duan, J. Zheng, H. Wan, Z. Yuan, H. Chen, Molecular pharmaceutics 2019, 17, 202-211.

[13] T. Tsurubuchi, M. Shirakawa, W. Kurosawa, K. Matsumoto, R. Ubagai, H. Umishio, Y. Suga, J. Yamazaki, A. Arakawa, Y. Maruyama, Cells 2020, 9, 1277.

[14] H. Birkedal-Hansen, W. Moore, M. Bodden, L. Windsor, B. Birkedal-Hansen, A. DeCarlo, J. Engler, Critical Reviews in Oral Biology & Medicine 1993, 4, 197-250.

[15] J. Martel-Pelletier, D.J. Welsch, J. Pelletier, Best practice & research Clinical rheumatology 2001, 15, 805-829.

[16] M. Raeeszadeh-Sarmazdeh, L.D. Do, B.G. Hritz, Cells 2020, 9, 1313.

[17] J.F. Fisher, S. Mobashery, Cancer Metastasis Rev. 2006, 25, 115-136.

[18] M. Couto, C. Alamón, C. Sánchez, B. Dávila, M. Fernández, N. Lecot, P. Cabral, F. Teixidor, C. Viñas, H. Cerecetto, Future medicinal chemistry 2019, 11, 2273-2285.

[19] M. Couto, I. Mastandrea, M. Cabrera, P. Cabral, F. Teixidor, H. Cerecetto, C. Viñas, Chemistry–A European Journal 2017, 23, 9233-9238.

[20] M. Couto, C. Alamón, M.F. García, M. Kovacs, E. Trias, S. Nievas, E. Pozzi, P. Curotto, S. Thorp, M.A. Dagrosa, Cells 2020, 9, 1408.

[21] J.N. Freskos, B. Asmelash, K.R. Gaston, A. Karwa, T.A. Marzan, M.A. Nickols, T.E. Rogers, T. Schoenstein, C.J. Sympson, B. Vu, Bioorg. Med. Chem. Lett. 2013, 23, 5566-5570.

[22] J.R. Tauro, R.A. Gemeinhart, Bioconjug. Chem. 2005, 16, 1133-1139.

[23] D.P. Becker, C.I. Villamil, T.E. Barta, L.J. Bedell, T.L. Boehm, G.A. DeCrescenzo, J.N. Freskos, D.P. Getman, S. Hockerman, R. Heintz, S.C. Howard, M.H. Li, J.J. McDonald, C.P. Carron, C.L. Funckes-Shippy, P.P. Mehta, G.E. Munie, C.A. Swearingen, J. Med. Chem. 2005, 48, 6713-6730.

[24] D.P. Becker, T.E. Barta, L.J. Bedell, T.L. Boehm, B.R. Bond, J. Carroll, C.P. Carron, G.A. De Crescenzo, A.M. Easton, J.N. Freskos, C.L. Funckes-Shippy, M. Heron, S. Hockerman, C.P. Howard, J.R. Kiefer, M.H. Li, K.J. Mathis, J.J. McDonald, P.P. Mehta, G.E. Munie, T. Sunyer, C.A. Swearingen, C.I. Villamil, D. Welsch, J.M. Williams, Y. Yu, J. Yao, J. Med. Chem. 2010, 53, 6653-6680.

[25] D.W. Klomp, H.W. van Laarhoven, A.P. Kentgens, A. Heerschap, Magnetic resonance in medicine 2003, 50, 303-308.

[26] K. Ishiwata, Ann. Nucl. Med. 2019, 33, 223-236.

[27] M. Lutz, M. Wenzler, I. Likhotvorik, Synthesis 2018.

[28] G.B. Giovenzana, L. Lay, D. Monti, G. Palmisano, L. Panza, Tetrahedron 1999, 55, 14123-14136.

[29] A. Toppino, A.R. Genady, M.E. El-Zaria, J. Reeve, F. Mostofian, J. Kent, J.F. Valliant, Inorg. Chem. 2013, 52, 8743-8749.

[30] J. Gigg, R. Gigg, Journal of the Chemical Society C: Organic 1967, 431-434.

[31] M. Matuszewski, A. Kiliszek, W. Rypniewski, Z.J. Lesnikowski, A.B. Olejniczak, New Journal of Chemistry 2015, 39, 1202-1221.

[32] B.P. Dash, R. Satapathy, B.P. Bode, C.T. Reidl, J.W. Sawicki, A.J. Mason, J.A. Maguire, N.S. Hosmane, Organometallics 2012, 31, 2931-2935.

[33] R. Djeda, J. Ruiz, D. Astruc, R. Satapathy, B.P. Dash, N.S. Hosmane, Inorg. Chem. 2010, 49, 10702-10709.

[34] H. Choi, H.J. Shirley, P.A. Hume, M.A. Brimble, D.P. Furkert, Angewandte Chemie 2017, 129, 7528-7532.

[35] V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angewandte Chemie 2002, 114, 2708-2711.

[36] A. Rossello, E. Nuti, E. Orlandini, P. Carelli, S. Rapposelli, M. Macchia, F. Minutolo, L. Carbonaro, A. Albini, R. Benelli, Bioorg. Med. Chem. 2004, 12, 2441-2450.

[37] Z.J. Lesnikowski, J. Med. Chem. 2016, 59, 7738-7758.

[38] R. Tiwari, K. Mahasenan, R. Pavlovicz, C. Li, W. Tjarks, Journal of chemical information and modeling 2009, 49, 1581-1589.

[39] J. Johnsamuel, Y. Byun, T.P. Jones, Y. Endo, W. Tjarks, Journal of organometallic chemistry 2003, 680, 223-231.

[40] V. Martichonok, J.B. Jones, Bioorg. Med. Chem. 1997, 5, 679-684.

[41] A. Minkkila, S.M. Saario, H. Käsnänen, J. Leppänen, A. Poso, T. Nevalainen, J. Med. Chem. 2008, 51, 7057-7060.

[42] S. Narayanasamy, B. Thirumamagal, J. Johnsamuel, Y. Byun, A.S. Al-Madhoun, E. Usova, G.Y. Cosquer, J. Yan, A.K. Bandyopadhyaya, R. Tiwari, Bioorg. Med. Chem. 2006, 14, 6886-6899.

[43] W. Neumann, S. Xu, M.B. Sárosi, M.S. Scholz, B.C. Crews, K. Ghebreselasie, S. Banerjee, L.J. Marnett, E. Hey-Hawkins, ChemMedChem 2016, 11, 175-178.

[44] J. Brynda, P. Mader, V. Šícha, M. Fábry, K. Poncová, M. Bakardiev, B. Grüner, P. Cígler, P. Řezáčová, Angewandte Chemie International Edition 2013, 52, 13760-13763.

[45] F. Issa, M. Kassiou, L.M. Rendina, Chem. Rev. 2011, 111, 5701-5722.

[46] S.M. Wilkinson, H. Gunosewoyo, M.L. Barron, A. Boucher, M. McDonnell, P. Turner, D.E. Morrison, M.R. Bennett, I.S. McGregor, L.M. Rendina, ACS chemical neuroscience 2014, 5, 335-339.

[47] P. Stockmann, M. Gozzi, R. Kuhnert, M.B. Sárosi, E. Hey-Hawkins, Chem. Soc. Rev. 2019.

[48] N.A. Meanwell, J. Med. Chem. 2011, 54, 2529-2591.

[49] W. Eberhardt, B. Crawford Jr, W.N. Lipscomb, J. Chem. Phys. 1954, 22, 989-1001.

[50] M.W. Lee Jr, Y.V. Sevryugina, A. Khan, S.Q. Ye, J. Med. Chem. 2012, 55, 7290-7294.

[51] Y. Endo, T. Iijima, K. Yaguchi, E. Kawachi, N. Inoue, H. Kagechika, A. Kubo, A. Itai, Bioorg. Med. Chem. Lett. 2001, 11, 1307-1311.

[52] T. Ogawa, K. Ohta, T. Yoshimi, H. Yamazaki, T. Suzuki, S. Ohta, Y. Endo, Bioorg. Med. Chem. Lett. 2006, 16, 3943-3946.

[53] T. Goto, K. Ohta, T. Suzuki, S. Ohta, Y. Endo, Bioorg. Med. Chem. 2005, 13, 6414-6424.

[54] R.L. Julius, O.K. Farha, J. Chiang, L.J. Perry, M.F. Hawthorne, Proc. Natl. Acad. Sci. U. S. A. 2007, 104, 4808-4813.

[55] M.F. Page, S.S. Jalisatgi, A. Maderna, M.F. Hawthorne, Synthesis 2008, 2008, 555-563.

[56] R.C. Reynolds, S.R. Campbell, R.G. Fairchild, R.L. Kisliuk, P.L. Micca, S.F. Queener, J.M. Riordan, W.D. Sedwick, W.R. Waud, A.K. Leung, J. Med. Chem. 2007, 50, 3283-3289.

[57] Y. Feng, J.J. Likos, L. Zhu, H. Woodward, G. Munie, J.J. McDonald, A.M. Stevens, C.P. Howard, G.A. De Crescenzo, D. Welsch, Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics 2002, 1598, 10-23.

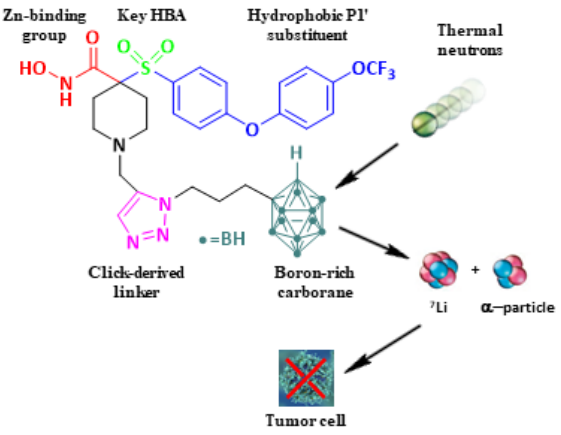
[58] T. Archibald in Strategies for Safely Handling Industrial Azide Reactions: The Three Traps, ACS Publications2014, pp. 87-109.

[59] T. Keicher, S. Löbbecke, S. Bräse, K. Banert), Bräse, K.Banert, H NMR spectru 2010.

[60] L. Yao, B.T. Smith, J. Aubé, J. Org. Chem. 2004, 69, 1720-1722.

[61] V.M. Ahrens, R. Frank, S. Stadlbauer, A.G. Beck-Sickinger, E. Hey-Hawkins, J. Med. Chem. 2011, 54, 2368-2377.

Graphic Abstract:



Boron delivery: Potent gelatinase (MMP-2 and MMP-9) ligands that spare MMP-1 have been prepared for use in BNCT. Click chemistry was used to install the carborane moiety yielding two triazole regioisomers. Molecular docking against MMP-2 using MOE was performed with phenyl as a bioisostere for the carborane moiety suggesting active site binding similar to the SC-model compounds.