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An Investigation Into the Activities of 1,2,3 & 1,2,4 Triazoles in Biological and Catalytic Systems

David John Schneider
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by David John Schneider entitled "An Investigation Into the Activities of 1,2,3 & 1,2,4 Triazoles in Biological and Catalytic Systems." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

Shane Foister, Major Professor

We have read this thesis and recommend its acceptance:

David C. Baker, Zi-ling (Ben) Xue

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

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An Investigation into the Activities of 1,2,3 and 1,2,4-Triazoles in Biological and Catalytic Systems

A Thesis Presented for
the Master of Science
Degree
The University of Tennessee, Knoxville

David John Schneider
December 2009

Abstract

Selective epigenetic control of the cellular machinery is a grail of drug development. The balance between HAT's and HDAC's activities is one way the cell controls what, and at when during the cellular lifecycle a gene is expressed. Having the ability to lock chromatin down to the histone is a powerful tool for the treatment of disease states like cancer. Presented here is a preliminary exploration of the synthesis, and basic testing of novel compounds that use a triazole motif as a zinc binding group in an attempt to gain further selectivity in inhibition over HDAC's.

Interest in the development of organic ligands to promote a metals activity as a catalyst is a broad, important field within organic chemistry. The synthesis of select bidentate 1,2,4-triazole- based ligands was carried out with the intent to study and to direct their catalytic activities once bound to a transition-metal center.

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1.0 Triazole based HDAC inhibition

1.1 Introduction

Histones are the protein scaffold that binds the DNA of a eukaryotic cell into the chromatin structure present in the nucleus. The DNA is wound around the protein octomer in a left handed helical fashion. How tightly the DNA is, or is not bound to the chromatin is a chief tool that the cell uses to regulate gene expression.[1,2] If the DNA is tightly bound to the histone structure it is impossible for the cascading process of genetic expression to take place as there is no room for promoter molecules to bind to the DNA helix.[3]

On the molecular level the genetic material is held to the protein via non covalent interactions between the amine functionality of lysine residues and the base pairs within the DNA itself.[4] In a normal functioning cell how tightly the DNA is bound to the histone is controlled by the balanced interaction between histone deacetylases (HDAC) and histone acetyltransferase (HAT), these two classes of enzymes deacylate or acylate the side chain amine respectively. (Figure 1)

This chemical transformation dictates the ability of the amine to hydrogen bond with the DNA. If the HDAC is inhibited from performing its normal cellular function DNA transcription is up regulated in the cell. This up regulation speeds up cellular processes and triggers apoptosis. This cascade effect is one of the focuses of the cancer related HDAC inhibition (HDACi) research that has been, is being performed.[5-8]

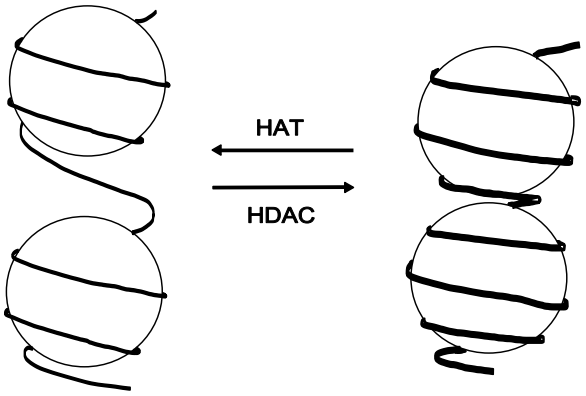

Figure 1. Cartoon of histone DNA interaction macro and micro scale

The aim of this project was to build upon the success of previous histone HDACi drugs. These drugs though they are effective suffer from being easily metabolized and eliminated from the body.[5] Along with this obvious obstacle there is a second issue of these compounds having cross activity for all of the classes of HDAC's [5,8-12] the problem of selectivity has previously been approached from the hydrophobic head element of the molecule. It was thought that by changing the head element of the molecule, the ligand would be selective for one particular HDAC pocket versus another. This appears to be a valid approach due to the fact that all HDAC's active sites contain the same zinc II cation. Unfortunately this approach has neglected the differences in the linings of the wall inside the actual catalytic pocket. This current successful generation of HDACi drugs contains a similar overall structure. (Figure 2) This structure is made up of three

parts. These are the hydrophobic head, or recognition element, the linker arm, and finally, the zinc binding unit.[10,13]

The development of the compounds in this project focused on improving the stability and selectivity in vitro of the zinc binding group[14] (ZBG), through the use of various triazoles. It was hoped that by varying the substituent on the triazole, and the nitrogen placement within the triazole itself the binding affinity to the zinc ion in the HDAC pocket could not only be improved but also made selective.

To limit the focus of this study and the scope of the synthesis, SAHA was chosen as a template molecule. This was done as SAHA has passed clinical trials and is currently in use as a cancer treatment. SAHA is well documented and offered a stable easily accessible scaffold structure to build from. Keeping the phenyl group as a head group and a straight chain alkane as the linker arm allowed for comparison of the different ZBG's not only with each other but also with known molecules.

The varied linker lengths were used to accommodate the differences in the triazole moiety and the hydroxamic acid moiety as a ZBG. As well as leading to a possible differentiation of action on different classes of HDAC's. Although the HDAC's have a recurring structural motif, they are not all identical, and differing depths of active-site pockets may lead to better control of drug specificity.[8,15]

Figure 2. Typical HDAC inhibitor structures

1.2 Synthesis of 1,2,3-Triazole SAHA analogues

The retrosynthetic analysis of the first triazole HDACI molecules begins with the triazole formation that employs the azide alkyne "click" reaction, a Huisgen 2+3-dipolar cycloaddition.[16] (Figure 3) This click reaction's placement within the synthesis allowed for the parallel synthesis of all analogs up until the last step. Placing the diversity element step at the end of the synthesis provided for the rapid development of a compound library. The balance of the retrosynthetic analysis was based upon standard amide bonds.

Synthesis was carried out for two initial target molecules. Compounds numbered 2 and 8. (Figure 4) The synthesis was started with 1-aminohexanoic acid and 1-aminobutanoic acid, respectively. After the preparation of triflic azide by reported methods, this was used to perform the transformation of the primary amine to an azide in a high-yielding clean fashion.[17,18] This crude product was then coupled to aniline using standard amide coupling conditions.[19] Compounds **2** and **8** were then purified by column chromatography, characterized and stored. Aliquots of each respective compound were then combined under standard aqueous click conditions and mild heat resulting in the products, compounds **3**, **4**, **6** and **9**, **10**, and **12**, in high yield and excellent purity.

Compounds **5** and **11** failed to form in any useful amount under these particular click conditions. This is believed to be because of the primary amines ability to coordinate the copper(I) catalyst or its copper(II) precursor. This chelation could then be leading to multiple side products and a very poor reaction quality overall. An alternate synthetic pathway was used to complete these two remaining compounds using common carbamate protection chemistry on the propargyl amine. (Figure 5)

Figure 3. Retro synthesis of 1,2,3-trizole SAHA analogues.

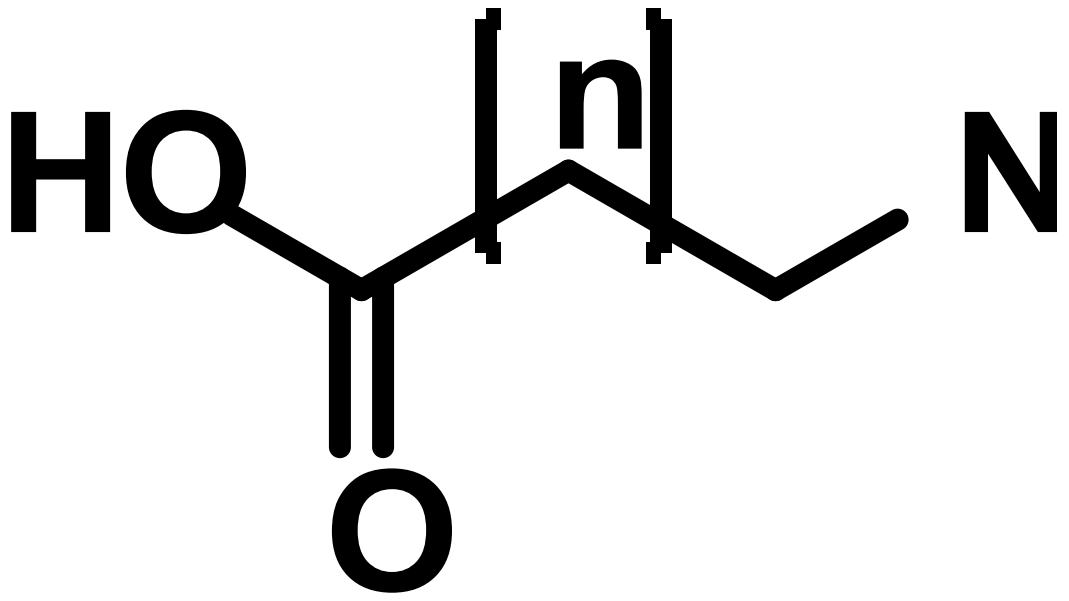

Figure 4. Synthetic scheme of 1,2,3-triazole SAHA analogues

Figure 8. Alternate pathway for propargyl amine based triazoles

All products were then purified using flash chromatography. The TMS protecting groups on compounds **3** and **9** were removed using TBAF, followed by another purification step. Compounds **5** and **11** were finally synthesized after the Boc protection group was removed from compounds **13** and **14**, respectively, in 25% TFA DCM this deprotection also resulted in a similar purification step being required

1.3 Preliminary biological results

The compounds were first screened using a fluor de lys HELA cellular extract kit purchased from Biomol. These assays were set using TSA as a standard and assay quencher. The preliminary biological results pointed to the benefit of having a longer alkyl linker as well as a heteroatom connected via a methelyne or ethylene group to the 4 position in the 1,2,3-triazole. With this knowledge further synthesis was started immediately before the biological results could be duplicated.

1.4 Further analogue development/screening

Based upon the results that were received, a further lengthening of the alkyl linker chain was required to improve activity. Therefore the synthesis of the two most active triazoles was undertaken based upon 7-aminoheptanoic acid. This synthesis followed the same basic scheme as presented earlier (Figure 6)

Once triazoles **15** and **16** were purified, they were screened along with the more active compounds of the previous iteration to see if there was any indication of the type of selectivity in target enzymes that had been sought after. The compounds were screened not only against the HELA extract but also against HDAC 1 and HDAC 6. These assays were chosen to represent nuclear and cytosolic HDAC's respectively. The completion of these screens and biological results of the testing of these compounds is eagerly awaited..

Figure 9. Synthesis of 7-aminoheptanoic acid based analogues

1.5 Current Ongoing Work

The manner in which the triazole can be best utilized as a ZBG requires not only that a variety of triazoles be tested, but also a variety of substitution patterns on the triazole ring itself must be explored. By varying not only the region chemistry of the triazole ring, but also the substituent placed upon it, greater control of both the selectivity and efficacy should be gained. This theory led to the adaptation of the chemistry that allowed for the installation of a 1,2,4-triazole via a condensation reaction with a free amine and a hydrazide.[20] (Figure 7). This approach was pursued but in the end was terminated due to sluggish (48 - 72 hours), harsh (100 - 110 °C) reaction conditions and poor overall yield (less than 50% monitored by HPLC), with a difficult separation following the final step.

These difficulties led to the current investigation of the synthetic pathway displayed in Figure 8.[21,22] This work is ongoing and should prove fruitful in defining the role that a triazole can play in the selectivity and activity of a HDAC inhibitor as the chelation group.

Along with the bench-top chemistry the effort to build a functioning model of the HDAC pocket and the ligand interaction therein has begun. Using Comparative Molecular Field Analysis (COMFA) do develop a predictive tool, it is believed that a helpful guide for further synthesis will be had, but also a tool that can assist in explaining results already gathered.[14,23-25]

Figure 10. Attempted 1,2,4-triazole formation

Figure 8. Current 1,2,4-triazole synthetic scheme

1.6 Future work

Future investigation's should focus on bringing the activity and selectivity of the inhibitors up by further decoration of the triazole coupled with modification to both linker length and hydrophobic head recognition units. Investigation into coupling the triazole ZBG to the linker group via amide bond formation or click chemistry may be avenues worthy of investigation.

This work coupled with an investigation into a model that more closely mimics the structure of the natural substrate of HDAC's could lead to a better drug scaffold candidate. The natural substrate, being of course, the side chain located on a lysine residue. The side chain amine could be easily converted to an azide and then transformed to a 1,2,3-triazole once this unnatural amino acid is placed in polypeptide compound on a solid phase support. This could be done using known chemistry that has already been exploited within our laboratory.[26,27] This approach may also lend itself to the installation of interesting active cyclic polypeptides for the hydrophobic head unit. (Figure 9)

Figure 9. Proposed synthetic pathways for "natural" 1,2,3-triazole-based HDACi molecules

2.0 1,2,4-Triazole-based ligands for catalysis

2.1 Introduction

1,2,3-Triazole metal complexes have been studied at length by inorganic, and organic chemists alike. Biologically these compounds have been known to possess antifungal activity since the early part of the 20th century.[28] Meanwhile the investigations of inorganic chemists have focused mainly on the structure and crystal formation of the metal ligand complexes followed with some attention in the carbene formation and insertion chemistry of these compounds.[29,30] It must be noted though that very little attention has been applied to the possible catalytic activity of these complexes in other arenas.[31]

Based upon results of the studies in our group on the activity of 1,2,4-triazole monodentate triazole metal center complexes the investigation of a series of bidentate ligands was undertaken. This study was begun in the hopes of either providing a more robust oxidative system or finding a selectivity of activity for the ligand metal complex. The basic bidentate structure was synthesized from two readily available straightchain amino acids, as well as one representative biphenyl system. A relatively fast synthetic approach was taken so as to lay a possible foundation for the direction of a more thorough directed approach to the synthesis of a tunable ligand set.

2.2 Synthesis

The primary amine of an alkyl or aryl compound can be condensed with a hydrazide and other carbon source to form a 1,2,4-triazole substituted on the 4 position.

The alkyl amino acid was condensed with the prepared phenyl hydrazide and n, n-dimethylformamide dimethyl acetal (dmfdma). Then the acid was converted to and ester using Fisher esterification followed directly by the formation of the hydrazide.[32,33] This product was then condensed in the same manner as the first step to yield the final product after purification. This synthetic sequence was carried out in a linear stepwise manner with minimal purification until the final step. (Figure 10) The overall yields were low, but this was of little interest at this time due to the focus on characterization of the ligand's activity once it was complexed with a metal center.

The biphenyl system was constructed in a very similar end product focused manner. The esterification and hydrazide formation and triazole condensation took place in a single pot with only the solvent being stripped off in between steps. The mono triazole compound was crashed out of solution using hot ethyl acetate. This solid was pure enough to move on to the third step which was a Suzuki coupling. This synthetic scheme hinges upon the Suzuki coupling of the two aromatic rings. This key step to the synthesis was found to not be as robust while varying ring placement of the already installed triazole as compared to the halogen. The coupling of the meta and ortho halogen with the boronic acid stalled with very little product formation. This could not be overcome by prolonged reaction time, up to 7 days, elevated temperature, reflux, or a change in the ligation of the palladium catalyst bid(dibenzylideneacetone) palladium (II), ($Pd(dba)_2$) to Palladium tetrakis ($Pd(PPh_3)_4$), and a combination of the two catalysts. It is the authors belief that the combination of electronic effect of the triazole ring placement along with the steric restrictions of the bulky 4-substitued triazole ring that are causing the failure of the normally reliable Suzuki coupling reaction.

Complexations of these compounds were carried out in THF at elevated temperature overnight, with copper (II) nitrate, and iron (III) chloride. The equivalencies of metals were varied from a 1:1 ratio to a 2:1 ratio of metal: ligand respectively. This was done due to the fact it was unknown at the time if the ligand's two triazole centers would bind a single metal center or possibly bridge two metal centers. (Figure 3.3) The qualitative analysis of the supernatant after the complexed ligand/metal structure crashed out showed that the ligand preferentially bound one metal center. The metal ligand complex once filtered from the supernatant was dried and screened for oxidative properties. The ligands were also chelated and studied directly for their ability to act as catalysts for azide/alkyne click chemistry.

Figure 10. Synthetic route to alkyl bidentate triazole ligands

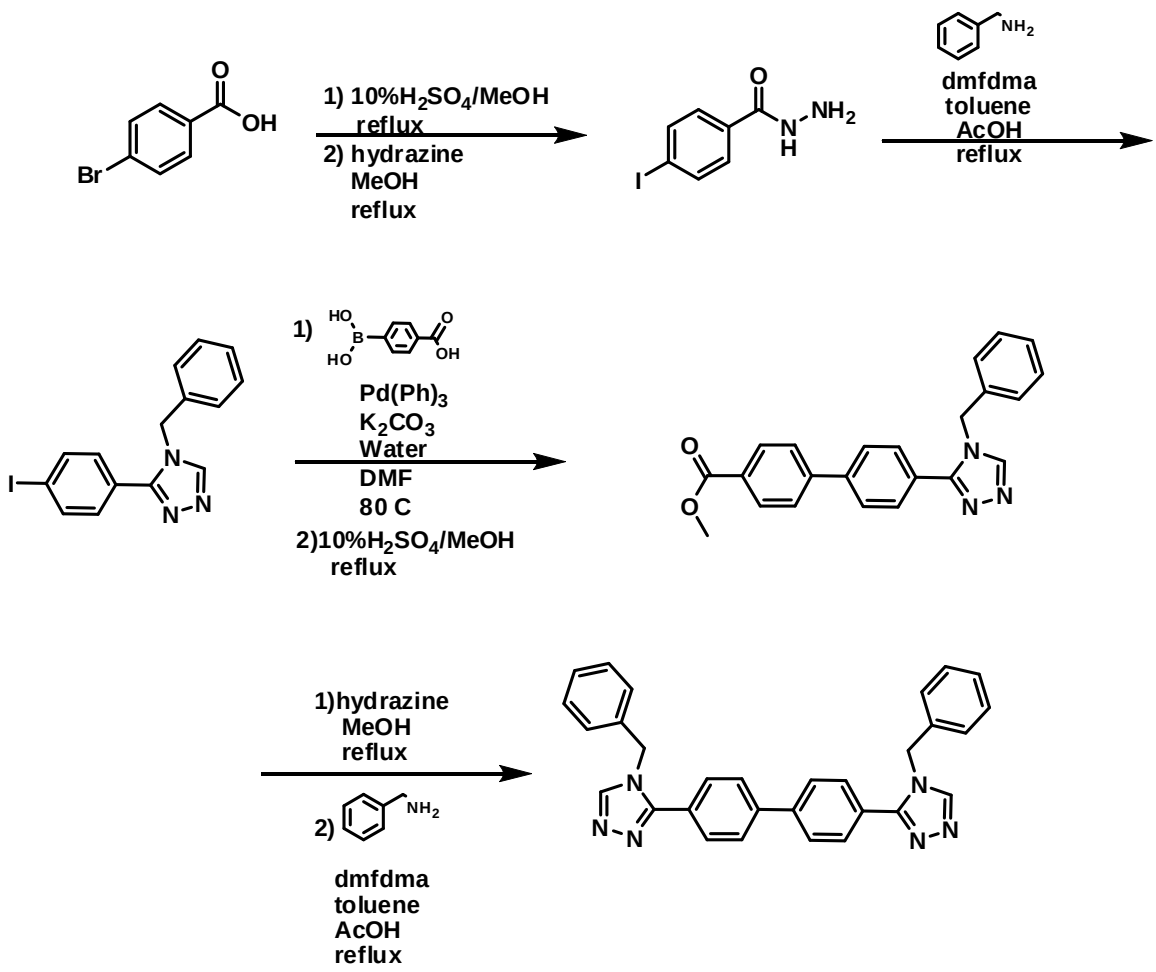

Figure 11. Biphenyl ligand synthetic scheme

Figure 12. Probable metal chelation structures.

2.3 Screening and Data collection

The bidentate ligands were screened against cyclooctane in the presence of hydrogen peroxide to judge their oxidative activity. The ligandmetal complex was combined with solvent, substrate and oxidant. This reaction then was monitored by gas chromatography mass spectrometry (GCMS) at two time points using method 2. Each experiment was run in duplicate using standardized conditions and the average conversion to the ketone is reported here. The reaction conditions and order of addition are listed in Table 1. The collected date is shown in Table 2.

Table 1 Standard catalyst screening reaction conditions

Catalyst : Substrate : Peroxide	0.05 : 1 : 5
Morality	0.4 M
Solvent	CH_3CN
Time	1 h /12 h
Percent conversion was measured vs. an internal standard.	

This data is not entirely unexpected nor is it terribly encouraging as far as the pursuit of this particular family of ligands for oxidative chemistry. The small discrepancy between the complex that was exposed to excess metal, and those exposed to an equimolar amount of metal could be explained by the fact that not all of the excess metal was washed away when the complex was filtered from the complexation solution.

The next set of reactions that these ligands were tested for activity in was the 2 + 3 cycloaddition between and azide and alkyne referred to as click chemistry. The ligands were compared to other known ligands that expedite this reaction[34,35]. The reactions were run at optimized conditions developed in our lab (Figure 10), and conversion was monitored via gcms using method 1 at three time points or 10 minutes, 30 minutes and 1 hour. The percent yields are being reported based upon the observation of unreacted starting material.

Table 2. Bidentate ligand oxidative activity test.

Ligand	Metal	Substrate	% cyclooctanone
	$Cu(NO_3)_2$ 1 eq.	cyclooctane	6.92
	$Cu(NO_3)_2$ 2 eq.	cyclooctane	7.07
	$FeCl_3$ 1 eq.	cyclooctane	12.86
	$FeCl_3$ 2 eq.	cyclooctane	13.54
	$Cu(NO_3)_2$ 1 eq.	cyclooctane	9.64
	$Cu(NO_3)_2$ 2 eq.	cyclooctane	16.06
	$FeCl_3$ 1 eq.	cyclooctane	12.17
	$FeCl_3$ 2 eq.	cyclooctane	15.82
	$Cu(NO_3)_2$ 1 eq.	cyclooctane	3.99
	$Cu(NO_3)_2$ 2 eq.	cyclooctane	4.98

Figure 13. Standard click reaction conditions

Table 3. Bidentate ligand click chemistry activity

Ligand	% conversion	
	10 min	66.18
	30 min	83.71
	1 h.	85.63
	10 min	61.05
	30 min	>95
	1 h.	>95
	10 min	21.49
	30 min	53.04
	1 h.	66.92
No ligand (control)	10 min	<5
	30 min	14.19
	1 h.	72.74

2.4 Conclusion and proposed work

The small library of bidentate ligands that have been synthesized above show some promise as reaction direction catalysts and as a possible addition to speed hindered or sluggish click reactions. The lack of oxidative activity may prove a benefit as this type of ligand/catalyst could be used in a reaction that is typically tolerant of many functional groups.

It should be noted that typical click reaction conditions are also conducive to the formation of Glaser products. Both reactions require a base, a copper(I) salt, and an alkyne in a slightly oxidative environment.[36] These ligands should be screened to see if they support or impede Glaser reactions under conditions that have been optimized for the alkyne alkyne coupling.

The affect of the length of the alkyl linker between triazoles could be investigated. If the linker is made longer will the ligand become bridging? Or if the linker length is set much shorter will the ligand become monodentate? Finally, to truly answer these questions and the structure of the active complex a crystal structure may be needed.

With the work that has been done, is ongoing, and has been proposed on the synthesis and characterization of the bidentate 1,2,4 triazoles it is this authors belief that a useful first-generation catalyst for synthetic purposes can be developed in a rather efficient manner.

Appendix

List of Abbreviations

ACN: acetonitrile

MeCN: acetonitrile

DMF: N, N-dimethylformamide

DMFDMA: N, N-dimethylformamide dimethyl acetal

TFA: trifluroacetic acid

HDAC: histone deacetylase

HAT: histone acetyltransferase

GCMS: gas chromatography mass spectrometry

EtOAc: ethyl acetate

EDTA: ethylenediaminetetraacetic acid

AcOH: acetic acid

DCM: dichloromethane

BOC: tert-butyl carbamate

FMOC: 9-Fluorenylmethyl carbamate

MeOH: methanol

TMS: trimethylsilane

SAHA: suberoylanilide hydroxamic acid

Tf: trifluoromethanesulfonyl

HOBT: N-hydroxybenzotriazole-H_2O

HBTU: O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate

Experimental

Standard characterizations

HPLC purity was measured using Beckman Coulter HPLC System Sold series 126 solvent module and System Sold 168 detector, fitted with Varian Microsorb MV 100-5 C8 250 x 4.6mm column.

Method 1: Mobile phase: A= 0.1%TFA water, B=MeCN, 0 - 1min 5%B; 1 - 5.5min 5%B→95%B; 5.5min - 10min 95%B; 10min - 12min 95%B→5%B, flow rate = 1mL/min.; run time = 12 min.

All NMR spectra were collected on a Varian Mercury 300 MHz instrument. The spectra were then worked up using Mestrenova software. Infrared spectroscopy taken on a Win Bomen FTIR instrument.

All mass spectrometry was perfomed on a Jeoll AccuTOF DART instrument.

6-azidohexanoic acid (1)

6-Aminohexanoic acid (1.08g, 9.195 mmol) was combined with sodium bicarbonate (2.75 g, 32.8 mmol), and copper(II)sulfate pentahydrate (161 mg, 0.656 mmol) then dissolved in 100 mL of water. The reaction was cooled to 0 ºC. Triflic azide (24.5 mL, 24.5mmol) was slowly added along with 15 mL of MeOH. The reaction was allowed to warm to room temperature slowly and then run for 18 h. MeOH was removed under vacuum, EtOAc (15 mL) was added, and the biphasic solution was then brought to a pH of 2 with 1M HCl. Organic layer was collected and aqueous layer was then washed and

additional two times with EtOAc. Organic layers were combined, and dried over anhydrous sodium sulfate. Then organics were filtered and solvent was removed. Product was collected as clear crystalline solid

1H NMR (300 MHz, CDCl3) δ 3.18 (t, 2H), 2.22 (t, 2H), 1.52 (m, 4H), 1.3 (m, 2H), IR (neat) 3189, 2944, 2869, 2099, 1699 cm^{-1} LRMS (Accutof/dart) m/e 158.09451 [(M+H) +, calcd for $C_6H_{13}N_3O_2$ 158.09295]

4-azidobutanoic acid (7)

4-Aminobutanoic acid (1.12 g, 10.9 mmol) was prepared in the same manner as 6-azidohexanoic acid. 4-azidobutanoic acid was recovered as a clear crystalline solid. NMR (300 MHz, CDCl3) δ 3.25 (t, 2H), 2.38 (t, 2H), 1.87 (m, 2H), IR (neat) 3068, 2944, 2103, 1709 cm^{-1} LRMS (Accutof/dart) m/e 130.05929 [(M+H) +, calcd for $C_4H_8N_3O_2$ 129.05383]

6-azido-N-phenylhexanamide (2)

6-Azidohexanoic acid (353 mg, 2.25 mmol), DCC (463mg, 2.25 mmol), and HOBT monohydrate (346 mg, 2.25 mmol) dissolved in DMF (3 mL), and DCM (10 mL). This solution was stirred at room temperature for 2 h. The resulting suspension was then filtered into a solution of aniline (0.205 mL, 2.25 mmol), triethylamine (0.630 mL, 4.49 mmol) and DCM (10 mL). The reaction was then allowed to stir for 8 h. at room

temperature. DCM was removed under vacuum the resultant heavy oil was diluted with EtOAc (10 mL). The organic was washed with saturated sodium bicarbonate solution. The organics were then collected, combined and dried with anhydrous sodium sulfate. The solvent was removed and the crude product was loaded on silica gel. The column was eluted with 7:1 hexanes: EtOAc. 6-Azido-N-phenylhexanamide (348 mg, 1.50 mmol) was collected as a white solid for a 66.7% yield.

4-azido-N-phenylbutanamide (8)

4-Azidobutanoic acid (429 mg, 3.32 mmol) was prepared in the same way as 6-azido-n-phenylhexanamide. After flash column chromatography, 4:1 hexanes: EtOAc eluent 4-azido-n-phenylbutanamide (363 mg, 1.78 mmol) 53.5% yield was recovered as a white solid.

Standard Aqueous Click Conditions for formation of 1,2,3 triazole compounds.

A single equivalent of the azido compound was weighed into a vessel. 1.0 eq. of 1 M sodium ascorbate was added followed by 0.1 eq. of 0.5 M copper sulfate pentahydrate, and 2.0 eq. 2.5 M ammonium carbonate. An equal volume of THF was then added to the vessel followed by 1.1 eq of alkyne. A magnetic stir bar was added and the reaction

mixture was capped and warmed to 60 ºC overnight while stirring. The reaction was then cooled to room temperature, and filtered through celite. The filtrate was then diluted with equal volumes of water and EtOAc. The aqueous layer was with EtOAc. The organic layers were collected and dried over anhydrous sodium sulfate. The extract was then filtered and solvent was stripped under vacuum. The resultant crude product was TLC'd and if further purification was required it was done so via flash chromatography, over silica gel.

N-phenyl-6-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)hexanamide (3)

6-azido-N-phenylhexanamide (100 mg, 0.431 mmol) was combined with TMS-alkyne (0.067 mL, 0.474 mmol) under standard click conditions. The crude product extract was taken up in THF, followed by the addition of 1 M TBAF solution in THF. This solution was allowed to stir for 2 h. After the removal of the TMS group was confirmed by TLC, the solvent was stripped under vacuum. This crude oil was then columned clean over silica gel with 100% EtOAc as eluent.

H^1 NMR (300 MHz, CD_3OD) δ 8.29 (s, *1*H), 7.53 (m, *3*H), 7.27 (m, 2H), 7.03 (m, 1H), 4.32 (m, 2H) 2.31 (m,2H) 1.87 (m, 4H) 1.97 (m, 2H).1.32 (m, 2H) HRMS: (AccuTOF/dart) m/e 259.15596 [(M+H)+, calcd for $C_{14}H_{19}N_4O_1$ 259.15589] HPLC: (Method 1): retention time 7.989 min

N-phenyl-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl) butanamide (9)

4-Azido-N-phenylbutanamide (100 mg, 0.490 mmol) was combined with TMS-alkyne (0.072 mL, 0.539 mmol) under standard click conditions the crude product extract was taken up in THF, followed by the addition of 1 M TBAF solution in THF. This solution was allowed to stir for 2 h. After the removal of the TMS group was confirmed by TLC, the solvent was stripped under vacuum. This crude oil was then columned clean over silica gel this crude oil was then columned clean over silica gel with 100% EtOAc as eluent. H^1 NMR (300 MHz, CD_3OD) δ 7.8 (m, *7*H), 4.48 (s, *2*H), 2.29 (m, 2H), 1.19 (m, 4H), HRMS: (AccuTOF/dart) m/e 231.12453 [(M+H) +, calcd for $C_{12}H_{15}N_4O_1$ 231.12459] HPLC: (Method 1): retention time 7.989 min

6-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-phenylhexanamide (4)

6-Azido-N-phenylhexanamide (100mg, 0.431 mmol) was combined with propargyl alcohol (0.028 mL 0.474 mmol) under standard click conditions. Crude product was purified via flash chromatography through silica gel. Solvent gradient was taken from 8:1 EtOAc: MeOH to 4:1 EtOAc: MeOH

H^1 NMR (300 MHz, CD_3OD) δ 7.90 (s, *1*H), 7.53 (d, 2H), 7.26 (m, 2H), 7.08 (m, 1H), 4.65 (s, 2H) 4.42 (t, 2H) 2.37 (t, 2H) 1.97 (m, 2H) 1.75 (m, 2H) 1.41 (m, 2H) HRMS: (AccuTOF/dart) m/e 289.16475 [(M+H)+, calcd for $C_{15}H_{21}N_4O_2$ 289.16645] HPLC: (Method 1) retention time 7.519 min.

4-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-phenylbutanamide (10)

4-Azido-N-phenylbutanamide (100mg, 0.490 mmol) was combined with propargyl alcohol (0.032 mL, 0.539 mmol) under standard click conditions. Crude product was purified via flash chromatography through silica gel. Solvent gradient was taken from 8:1 EtOAc: MeOH to 4:1 EtOAc: MeOH. 91 mg of the product was collected as an off white solid, 71% yield. H^1 NMR (300 MHz, CD_3OD) δ 8.29 (s, *1*H), 7.38 (m, 5H), 4.32 (s, 2H), 2.31 (m, 2H), 1.33 (m, 4H) HPLC (Method 1) retention time 7.519 min. HRMS: (AccuTOF/dart) m/e 261.13632 [(M+H) +, calcd for $C_{13}H_{17}N_4O_2$ 261.13515]

6-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)-N-phenylhexanamide (5)

6-Azido-N-phenylhexanamide (100 mg, 0.431 mmol) was combined with tert-butyl prop-2-ynylcarbamate (84mg, 0.474 mmol) under standard click conditions. The crude extract

was taken up in DCM/TFA and allowed to stir until the removal of the Boc protecting group was verified via TLC. This compound required no further purification, 101 mg of product was collected as brown heavy oil giving an 82% yield. H^1 NMR (300 MHz, CD_3OD) δ 7.83 (s, *1*H), 7.51 (d, 2H), 7.26 (m, 2H), 7.07 (t, 1H), 4.40 (s, 2H) 3.85 (b, 2H) 2.36 (t, 2H) 1.97 (m, 2H) 1.75 (m, 2H) 1.40 (m, 2H) HPLC **(**Method 1) retention time 7.748min HRMS (AccuTOF/dart) m/e 288.18221 [(M+H)+, calcd for $C_{15}H_{22}N_5O_1$ 288.18243]

4-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)-N-phenylbutanamide (11)

4-azido-N-phenylbutanamide (100 mg, 0.490 mmol) was combined with propargyl alcohol (0.032 mL, 0.539 mmol) under standard click conditions. The Boc protected intermediate was purified via flash chromatography over silica gel using a combination of EtOAc: MeOH. The intermediate was then taken up in DCM/TFA and allowed to stir until the removal of the Boc protecting group was verified via TLC. The solvent was stripped resulting in the 61 mg, 34% yield of the product being recovered as heavy brown oil. (300 MHz, CD_3OD) δ 8.07 (s, *1*H), 7.51 (m, 2H), 7.27 (t, 2H), 7.07 (d, 1H), 4.50 (t, 2H) 4.21 (d, 2H) 3.31 (e, 2H) 2.32 (m, 4H) HPLC(Method 1) retention time 6.953min HRMS: (AccuTOF/dart) m/e 260.15093 [(M+H)+, calcd for $C_{13}H_{18}N_5O_1$ 260.15113]

6-(4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-N-phenylhexanamide (6)

6-Azido-N-phenylhexanamide (100 mg, 0.431 mmol) was combined with but-3-yn-1-ol (0.036 mL, 0.474 mmol) under standard click conditions. This product required no further purification after extraction. (300 MHz, CD_3OD) δ 7.76 (s, 1H) 7.52 (d, 2H) 7.27 (m 2H) 7.08 (m, 1H) 4.36 (t, 2H) 3.78 (t, 2H) 2.87 (t, 2H) 2.35 (t, 2H) 1.94 (m, 2H) 1.72 (m, 2H) 1.38 (m, 2H) HPLC (Method 1) retention time 7.511min
HRMS (AccuTOF/dart) m/e 303.18143 [(M+H) +, calcd for $C_{16}H_{23}N_4O_2$ 303.18210]

Tert-butyl prop-2-ynylcarbamate (Boc-propargyl amine)

Propargyl amine (0.300 mL, 4.37 mmol) was dissolved in a flask with EtOAc (30 mL). Boc-anhydride (1.05 g, 4.81 mmol) was added to reaction along with a magnetic stir bar. Then 2.5 M NaOH (30mL) was poured into the reaction and it was allowed to stir for 6 hours at room temperature while being monitored via TLC. When completed, the reaction was cooled to 0 ºC in and ice water bath, and the pH was adjusted to 2 with 1 M HCl. The reaction was extracted with EtOAc. The organics were dried over anhydrous sodium sulfate, filtered and solvent stripped under vacuum. The product was used without further purification. LRMS (AccuTOF/dart) m/e 156.10436 [(M+H) +, calcd for $C_8H_{14}NO_2$ 156.10245]

trifluoromethanesulfonyl azide (triflic azide)

Sodium azide (6.23 g, 95.8 mmol) was dissolved in 100 mL of water while stirring. This solution was cooled to 0 ºC. Trifluoromethanesulfonic anhydride (8.00 mL, 63.9 mmol) was diluted in toluene (30 mL). This was then dripped slowly into stirring azide solution. The biphasic reaction mixture was allowed to stir vigorously for 3 h. The organic layer was extracted from the reaction mixture and diluted further with toluene to give an approximate molarity of 1. The product was used as was with out further purification or characterization.

(9H-fluoren-9-yl) methyl 7-oxo-7-(phenylamino)heptylcarbamate

Fmocaminoheptanoic acid (521 mg, 1.40mmol) coupled with aniline (0.127 mL, 1.40 mmol) under standard DCC amide coupling conditions. The reaction was allowed to run for 8 h. then diluted with DCM (20 mL) the organic layer was extracted 2 times with 2 M NaOH, followed by 1 1 M HCl wash. LRMS (AccuTOF/dart) m/e 443.23682 [(M+H) +, calcd for $C_{28}H_{31}N_2O_3$ 443.23347]

7-azido-N-phenylheptanamide

(9H-Fluoren-9-yl)methyl7-oxo-7-(phenylamino)heptylcarbamate crude was taken up in dmf (10 ml). Piperdine (0.5 mL) added and stirred for 2 hours. The solvent was stripped under vacuum. The remaining residue was prepared in the same way as 6-azido-N-phenylhexanamide. This product was used without further purification or characterization.

7-(4-(2-hydroxyethyl)-1H-1, 2, 3-triazol-1-yl)-N-phenylheptanamide (16)

7-Azido-N-phenylheptanamide, (70 mg, 0.284 mmol) was reacted with but-3-yn-1-ol (20 mg, 0.285 mmol) under standard click conditions. The extract was purified via flash chromatography. Product was collected as a white solid 50 mg, 55.7% yield. (300 MHz, CD_3OD) δ 7.74 (s, 1H) 7.52 (d, 2H) 7.39 (s, 1H) 7.27 (m, 2H) 7.07 (t, 1H) 4.30 (t, 2H) 3.93 (s, 2H) 2.94 (dd, 2H) 2.30 (t, 2H) 1.87 (m, 2H) 1.69 (m, 2H) 1.34 (m, 4H) HPLC (Method 1) retention time 7.943min

7-(4-(hydroxymethyl)-1H-1, 2, 3-triazol-1-yl)-N-phenylheptanamide

7-Azido-N-phenylheptanamide, (70 mg, 0.28 mmol) was reacted with propargyl alcohol (16 mg, 0.29 mmol) under standard click conditions. The extract was treated with flash column chromatography which resulted in the product as a white solid, 35 mg, 40.8% yield. (300 MHz, CD_3OD) δ 7.97 (s, 1H) 7.54 (m, 2H) 7.29 (t, 2H) 7.08 (m, 1H) 4.70 (b, 1H) 4.41 (t, 2H) 3.32 (m, 2H) 2.36 (t, 2H) 2.20 (m, 2H) 2.03 (m, 2H) 1.39 (m, 4H) HPLC (Method 1) retention time 7.653min

methyl 4-iodobenzoate

4-Iodobenzoic acid (2.00 g, 8.06 mmol) dissolved in 10% H_2SO_4 / MeOH, reflux condenser was affixed and reaction was brought to reflux for 8 h. The MeOH was stripped off under vacuum and the residue was brought back up in EtOAc (25 mL). This solution was washed 2 times with 1 M NaOH (15 mL). The organic layer was collected, dried over anhydrous sodium sulfate, filtered and then concentrated, 1.89g 89.6% yield All spectra match those found in literature.[37]

4-iodobenzohydrazide

Methyl 4-iodobenzoate (1.89 g, 7.22 mmol) taken up in MeOH, hydrazine monohydrate added (18.05 mmol). Reaction fitted with condenser and brought to reflux. Reaction allowed to stir for 24 hours, then cooled to room temperature and solvent stripped. Product was recovered as a white solid and used without further purification. All spectra collected matched those reported in literature.[38]

4-benzyl-3-(4-iodophenyl)-4H-1,2,4-triazole

4-Iodobenzohydrazide (656.4 mg, 2.504 mmol) combined with dmfdma (0.332 mL, 2.504 mmol) in toluene (30 mL) and brought to 80 °C for 2 h. Then benzyl amine (0.274 mL, 2.504 mmol) added along with 0.1 mL AcOH. The reaction was allowed to stir at elevated temperature for a total reaction time of 24 h. The toluene was removed under vacuum and then the resultant oil was taken up in EtOAc. This solution was chilled to -30 °C and then filtered. The solid was washed with cold EtOAc and hexanes. No further purification was required 471.2 mg of white solid was recovered for a 54.0% yield. (300 MHz, CD_3OD) δ 8.19(s, 1H) 7.31 (m, 9H) 5.19 (s, 2H). HRMS (Accutof/dart) m/e 362.01546 [(M+H) +, calcd for $C_{15}H_{13}IN_3$ 362.01542]

Methyl 4'-(4-benzyl-4H-1,2,4-triazol-3-yl) biphenyl-4-carboxylate

4-Benzyl-3-(4-iodophenyl)-4H-1,2,4-triazole (200mg, 0.554 mmol) combined with 4-boronobenzoic acid (101 mg, .609 mmol), potassium carbonate (153 mg, 1.11 mmol) and $Pd(DBA)_2$ (32 mg, .055 mmol) in dmf (6 ml) and water (1 mL). The reaction was then warmed to 90°C for 24 h. At this time TLC showed complete conversion. The solvent was removed under vacuum and then immediately placed under standard Fischer esterification conditions to form the methyl ester. The MeOH was removed under vacuum and product was purified via flash column chromatography. 100 mg of white solid was recovered providing a 49.0% yield over both steps. Alternatively, product was collected in reasonable purity by crashing the product out of hot DCM by layering it with cold hexanes, after the esterification reaction was extracted with 1 M NaOH. LRMS (AccuTOF/dart) m/e 370.14566 [(M+H) +, calcd for $C_{23}H_{20}N_3O_2$ 370.15555]

4, 4'-bis (4-benzyl-4H-1,2,4-triazol-3-yl) biphenyl

Methyl 4'-(4-benzyl-4H-1,2,4-triazol-3-yl)biphenyl-4-carboxylate (370 mg, 1.00 mmol) taken up in MeOH, then hydrazine monohydrate (0.121 mL, 2.50 mmol) added and

reaction brought to reflux for 24 h. MeOH stripped off of reaction and then residue purified via flash chromatography using 6:1 EtOAc: Hexanes as eluent. The product was taken on without further characterization beyond TLC. Hydrazide (277 mg) combined with dmfdma (0.108 mL, 0.899 mmol) in toluene (10 mL) then brought to 80 °C for 2 h. Benzyl amine (0.109 mL, 0.899 mmol) and AcOH (0.10 mL) added to the reaction mixture. The reaction was then allowed to run for an additional 24 h. Solvent was removed from reaction and the residue was purified via column chromatography yielding 159 mg of off white solid (45% yield). . (300 MHz, CD_3OD) δ 8.18 (s, 1H) 8.04 (s, 1H) 7.82 (m 2H) 7.57 (m, 6H) 7.30 (m, 6H) 7.09 (m, 2H) 2.93 (s, 4H) HRMS (AccuTOF/dart) m/e 469.21428 [(M+H) +, calcd for $C_{30}H_{25}N_6$ 469.21407]

Benzohydrazide

Methyl benzoate (17.54 g, 128.82 mmol) taken up in MeOH (35mL). Hydrazine monohydrate (15.60 ml, 322.1 mmol) added over 5 minutes. Reaction fixed with reflux condenser and brought to reflux for 48 h. The reaction was stripped of solvent and then re-dissolved in MeOH and brought to dryness under vacuum 3 more times. The resultant 17.44 g of white powder 99.4% yield, required no further purification and all spectra matched those reported in literature.[39]

Methyl 4-(3-phenyl-4H-1, 2, 4-triazol-4-yl) butanoate

Benzohydrazide (467 mg, 3.45 mmol) combined with dmfdma (0.515 mL, 4.31 mmol) in toluene (10 mL). The reaction was then warmed to 80 °C for 2 h. Then 4-aminobutanoic acid (566 mg, 4.31 mmol) was added along with AcOH (0.10 mL) and the reaction allowed to run for another 24 h. The solvent was removed from the reaction and the crude was taken up in 10% H_2SO_4 / MeOH (15 mL) and refluxed for 12 h. The MeOH was stripped off of the reaction, and crude was dissolved in DCM and washed with saturated sodium bicarbonate solution. The organic was collected and dried over anhydrous sodium sulfate, filtered and solvent removed leaving light brown oil. LRMS (AccuTOF/dart) m/e 246.13103 [(M+H) +, calcd for $C_{13}H_{16}N_3O_2$ 246.12425]

Methyl 6-(3-phenyl-4H-1,2,4-triazol-4-yl) hexanoate

Benzohydrazide (754 mg, 5.54 mmol) combined with dmfdma (0.794 mL, 6.65 mmol) in toluene (10 mL). The reaction was then warmed to 80 °C for 2 h. Then 6-aminohexanoic acid (871 mg, 6.65 mmol) was added along with AcOH (0.10 mL) and the reaction allowed to run for another 24 h. The solvent was removed from the reaction and the crude was taken up in 10% H_2SO_4 / MeOH (15 mL) and refluxed for 12 h. The

MeOH was stripped off of the reaction, and crude was dissolved in DCM and washed with saturated sodium bicarbonate solution. The organic was collected and dried over anhydrous sodium sulfate, filtered and solvent removed leaving light brown oil. LRMS (AccuTOF/dart) m/e 274.16029 [(M+H) +, calcd for $C_{15}H_{20}N_3O_2$ 274.15555]

4-benzyl-3-(3-(3-phenyl-4H-1,2,4-triazol-4-yl) propyl)-4H-1,2,4-triazole

Methyl 4-(3-phenyl-4H-1,2,4-triazol-4-yl) butanoate crude (500 mg,) dissolved in 3% hydrazine/MeOH (15 mL) and brought to a reflux for 24 h. Reaction monitored until found complete by TLC. The solvent was then stripped from the reaction. The crude residue was dissolved in toluene (10 mL) followed by the addition of dmfdma (0.10 mL). The reaction was then warmed to 80°C for 2 h. Then benzyl amine (0.10mL) was added along with AcOH (0.10 mL) and reaction was allowed to reflux for a total of 24 h. The solvent was removed under vacuum and the crude oil was purified via flash chromatography. Product collected as light brown oil (433 mg, 36.4% yield over all steps). (300 MHz, CD_3OD) δ 8.50 (m, 2H) 7.33 (m, 10H) 5.20 (s, 2H) 4.13 (t, 2H) 2.43 (t, 2H) 2.14 (m, 2H)

4-benzyl-3-(5-(3-phenyl-4H-1,2,4-triazol-4-yl) pentyl)-4H-1,2,4-triazole

Methyl 6-(3-phenyl-4H-1,2,4-triazol-4-yl) hexanoate crude (675 mg,) dissolved in 3% hydrazine/MeOH (15 mL) and brought to a reflux for 24 h. Reaction monitored until found complete by TLC. The solvent was then stripped from the reaction. The crude residue was dissolved in toluene (10 mL) followed by the addition of dmfdma (0.10 mL). The reaction was then warmed to 80 °C for 2 h. Then benzyl amine (0.10 mL) was added along with AcOH (0.10 mL) and reaction was allowed to reflux for a total of 24 h. The solvent was removed under vacuum and the crude oil was purified via flash chromatography. Product collected as light brown oil (412 mg, 16.6% yield over all steps). (300 MHz, CD_3OD) δ 8.50 (m, 2H) 7.32 (m, 10H) 5.18 (s, 2H) 4.02 (d, 2H) 2.57 (d, 2H) 1.34 (m, 4H)

Standard Ligand Complexation Procedure

Ligand (1 eq.) dissolved in THF (0.08 M). Metal added to solution (1 eq.) and solution warmed to 60 °C for a minimum of 8 h. Once all ligand was consumed via TLC the reaction was cooled to room temperature and transferred to centrifuge tube. The reaction was centrifuged for 5 minutes. Then supernatant was removed and the pellet was rinsed with aliquots of THF followed by subsequent centrifugation. The solid metal complex was collected and dried. For the qualitative test for bridging of ligands the same procedure was followed exchanging the 1 equivalent of metal for 2 equivalents.

GCMS Methods

All GCMS data collected on a Hewlett Packard 6890 series GC system fitted with a Agilent 19091S-433E column, coupled to a Hewlett Packard 5973 mass selective detector.

Method 1 split injection, gas flow of 0.8mL/min. Initial temperature of 35° C, ramp 5° C/min to 75 °C, ramp 25° C/min to 250 °C hold 2 min.

Method 2 split injection, gas flow of 0.8 mL/ min. Initial temperature of 35 °C. ramp 1 °C/ min to 40 °C, ramp 5 °C/ min to 55° C, ramp 1 °C/ min to 60 ° C, ramp 5 °C/ min to 75 °C, ramp 25 °C/min to 250 °C hold for 2 min.

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Vita

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