SYNTHESIS AND CONFORMATIONAL STUDY OF TRIAZOLYLCYCLOHEXANOLS
AND TRANS-2-(AZAARYLSULFANYL)-CYCLOHEXANOLS

By

Mulinde Ronnie Goodman Ruyonga

A Dissertation Submitted to the
Graduate School
In Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Thomas J. Long School of Pharmacy and Health Sciences
Pharmaceutical and Chemical Sciences

University of the Pacific
Stockton, California

2021
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SYNTHESIS AND CONFORMATIONAL STUDY OF TRIAZOLYL CYCLOHEXANOLS AND TRANS-2-(AZAARYLSULFANYL)-CYCLOHEXANOL S

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By

Mulinde Ronnie Goodman Ruyonga
DEDICATION

This dissertation is dedicated to my lifelong mentor and friend Dr. Hashim Ali. I am grateful for your guidance as I grow into the scientist I am today.

This dissertation is also dedicated to the memory of Dr. Nataliya Samoshina. Your kindness and warm encouragement will resonate with me forever.
ACKNOWLEDGEMENTS

I would like to deeply thank my research advisor Dr. Vyacheslav Samoshin for his guidance, inspiration, persistence and patience during my journey as a graduate student. He is an outstanding teacher and scientist, and his insight, knowledge and bright ideas inspired me through my research. I am grateful for the opportunity to explore these research projects under his direct supervision. My time as a graduate student has been an uplifting experience and has made me a better scientist.

I would also like to give special appreciation to Dr. Nataliya Samoshina who is no longer with us. Your mentorship on the glycosidase activity project and the day to day advice on improving as a scientist are greatly appreciated. Thank you for being for everything you did for me from my settling in as a graduate student to the entire project you guided me on.

I sincerely thank Dr. Andreas Franz, Dr. Liang Xue, Dr. Jerry Tsai and Dr. Sven Hachbusch for being my committee members and overseeing my dissertation defense. Their participation and expertise are greatly appreciated. I would like to thank Dr. Dmitriy Gremyachinskiy, Dr. Pete Crusali and Dr. Meng Taing for their guidance and supervision during my internship experience with Roche Sequencing Solutions Santa Clara. I learnt a lot under your tutelage and that experience has prepared me for industrial work.

Finally, I would like to thank Prof. David Sparkman, Dr. Patrick Batoon, Dr. Michael Pastor and Chao Feng for their help with mass-spectrometric analysis. Thanks to my lab mates Carim Van Beek and Marcos Beltran-Sanchez for their help as we interacted to grow into better scientists.
SYNTHESIS AND CONFORMATIONAL STUDY OF TRIAZOYLICYCLOHEXANOLS AND TRANS-2-(AZAARYLSULFANYL)-CYCLOHEXANOL S

Abstract

By Mulinde Ronnie Goodman Ruyonga

University of the Pacific
2021

Amino-cyclohexanol derivatives have been successful models for pH-triggered conformational switches. By changing the groups on the amine nitrogen, these models provide a wide pH-range in which a switch can occur. The pH-induced switch of conformation can be monitored by \(^1\)H NMR.

In this work, structurally similar trans-2-(azaarylsulfanyl)-cyclohexanol derivatives and trans-2-triazolylcyclohexanol derivatives have been explored for the first time as compounds with a potential for the analogous pH-induced conformational switch. The azaarylsulfanyl groups showed selective conformational flexibility while the triazolyl group showed a strong preference for the equatorial position. Further, conformational studies were done on a series of trans-2-triazolylcyclohexanols and triazolycyclohexanes to determine the previously unknown conformational energy of the triazolyl group. In addition, a series of carbasugar analogues based on trans-2-(1,2,3-triazolyl)-cyclohexanol moiety was synthesized and tested for activity (inhibition or activation) towards fungal glycosidases from Aspergillus and Penicillium sp due to the growing use of triazoles in the pharmaceutical industry.
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<td>A</td>
<td>axial position of a substituent</td>
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<tr>
<td>AA</td>
<td>diaxial position of substituents</td>
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<tr>
<td>Borax</td>
<td>Sodium tetraborate</td>
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<tr>
<td>COSY</td>
<td>Correlated Spectroscopy</td>
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<td>CuAAC</td>
<td>Copper (I) catalyzed alkyne-azide cycloaddition</td>
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<td>Dart</td>
<td>Direct Annalysis in Real Time</td>
</tr>
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<td>Dichloromethane / Methylene chloride</td>
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<td>E</td>
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<td>Nuclear Magnetic Reasonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl group</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating-frame Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofurane</td>
</tr>
<tr>
<td>TACH</td>
<td>trans-amino cyclohexanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total Correlation Spectroscopy</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Molecular Switches

Molecular switches are molecules whose properties, shape or conformation, can be altered reversibly. The requirements for a molecule to be classified as a molecular switch include: two or more stable or meta-stable states, reversibility of switching within the given states and activation of switching by external stimuli\textsuperscript{1}. These switches are triggered by metal complexation, electric fields, light at specific wavelength, pH changes etc. On exposure to these external stimuli, some molecules exhibit a conformational change, hence the term mechanical or conformational switch. Molecular switches are useful in designing controllable compounds with variety of functionality, which may include drug release, information storage and information transmission.\textsuperscript{1-6}

Allosteric systems are among the most studied conformationally switchable systems. The presence of two or more binding sites on the allosteric system (e.g. enzyme molecules) enables the switching capability of the molecule to be monitored. The binding of an allosteric activator, in a form of another molecule or ion, results in the mechanical transmission of a signal thought the allosteric system leading to a conformational change at the active site (Figure 1.1). This same approach can be used for allosteric inhibition. The principle of allosteric activity is well studied and the effects of small molecules as inhibitors or activators is also well known.\textsuperscript{7,8}
Figure 1.1. Allosteric effect. (a) Binding of the allosteric inhibitor to one end of the system changes the conformation enabling inhibition at the active site and blocking the binding of the substrate. (b) Binding of the allosteric activator to one end of the system changes the conformation enabling the active site to accommodate for the binding of the substrate.  

Cyclohexane-Based Conformational Switches

The cyclohexane-based molecular systems provide an efficient model for conformational switches in relation to allosteric systems. The conformational switches in cyclohexanes are elucidated by monitoring the chair-chair conformational transition in relation to the positioning of the protons. A negative cooperativity within the cyclohexane switches can be observed by the position of the protons on the molecule when a switch occurs upon interaction with external stimuli. The effect of interacting with external stimuli on one end of the cyclohexane is transferred through the ring. While switching, the position of all protons and substituents will change from axial to equatorial and vice versa depending on their initial positioning.

Trans and cis-cyclohexane derivatives (Scheme 1.1 and 1.2) have been well studied due to the simplicity of their structures. Trans-1,4- and cis-1,4-cyclohexane derivatives help to
explore the interaction of the substituents with the ring and the ability for one of the substituents to act as a “counterbalance.” The diequatorial conformer B for trans-1,4-cyclohexane derivative (Scheme 1.1) is more stable than the diaxial conformer A due to the steric repulsion between the substituents and the ring. *Trans* and *cis*-1,2-cyclohexane derivatives (Scheme 1.2) help to compare the gauche repulsion for the substituents in conformer B and the steric repulsion of the axial substituents in conformer A. The latter repulsion usually causes more strain on the ring leading to a preference for conformer B. However, interactions like hydrogen bonding and ionic attraction may also lead to the stabilization of conformer B. Other factors that may affect this equilibrium include; shape, size, polarity, intra- and intermolecular interactions, temperature, solvent interactions etc. Several illustrated examples of the cyclohexane-based conformation-switching structures are considered below.
Scheme 1.1. Conformational Chair-Chair Switch in trans and cis-1,4-Cyclohexane Derivatives.

\[ \text{Structural Effects on Conformation Switches} \]

Given the unfavorable conditions with substituents in the axial position experiencing steric repulsion in structures 1-4, the same trend is expected in the conformational behavior of trans-cyclohexano-15-crown-5 and trans-cyclohexano-18-crown-6 structures (Scheme 1.3).\(^9\)

Therefore with no counterbalance \((R = H)\) there is a conformational preference for structures 5E,
as compared to 5A. The conformational preference can be determined by the free energy difference $\Delta G_{E-A}$ as measured from $^1$H-NMR parameters.$^{13}$

\[ \text{Scheme 1.3. Cyclohexane-Based Crown Ethers with Counterbalances R.} \]

Introduction of bulky substituents or attractive/repulsive interactions on a cyclohexane ring can affect the conformational equilibrium and the preference for conformer A or E. These bulky substituents can act as counterbalances and transmit conformational change through the cyclohexane ring. The presence of small counterbalances, like $R = \text{CH}_3$, on $\text{trans}$-cyclohexano-15-crown-5 and $\text{trans}$-cyclohexano-18-crown-6 structures (Scheme 1.3) shows a considerable shift in equilibrium towards conformation A. The axial methyl group in conformer 5E destabilizes the structure by at least 8 kJ/mol. A similar effect is seen with the presence of axial cyano group ($R = \text{CN}$). Therefore, the presence of counterbalances in these crown ethers shifts equilibrium towards conformer 5A.$^{14-16}$
Scheme 1.4. Sulfur-Containing Cyclohexane-Based Crown Ethers.\textsuperscript{9}

The preference for the equatorial position on a cyclohexane is dependent on the size and rigidity of the substituents. For example, the sulfur-containing cyclohexane-based crown ethers 6 and 7 (Scheme 1.4), that are more flexible, have a substantially less predominance for the equatorial conformation E as compared to analogous cyclohexane-based crown ethers.\textsuperscript{9}

Scheme 1.5. Cyclohexane-Based Podands with Counterbalances.\textsuperscript{9}

Podands (Scheme 1.5), noncyclic structural analogs of crown ethers (\textbf{Scheme 1.3}), have less rigidity due to their noncyclic ether chains that allow for movement and structural flexibility. In the absence of a counterbalance (\(R = H\)) podand 8 has a higher population of conformer A compared to the analogous crown ether 5. In the presence of counterbalances, \(R = CH_3\),
CH(OCH$_2$CH$_2$O) or COCH$_3$, podand 8 shows even greater increase in population of conformer A as compared to analogous crown ethers.$^{9,17,18}$

![Scheme 1.6. Sulfur-Containing Cyclohexane Macrocycles](image)

In the presence of more than one substituent attached to the cyclohexane ring, the equilibrium can be shifted based on the interaction of the substituents with each other and with the cyclohexane ring. For example, two axial ethoxycarbonyl groups of the sulfur-containing cyclohexane macrocycles destabilize the conformer 10E by 7-10 kJ/mol as compared to 9E (Scheme 1.6).$^{9,17,19,20}$

![Scheme 1.7. Cyclohexane Podands with Chemically Adjustable Levers](image)

$^{14,15}$
If a bulky group can be chemically modified into a smaller group, then the relative stability of the conformers can be varied. For example, the presence of an acetal group, a bulky substituent, on podand 11 gives complete preference for conformer 11A (Scheme 1.7). Upon the hydrolysis of the acetal group to a smaller acetyl group in podand 12, there is now a complete change in conformational orientation to favor 12E. This interaction is used to control the complexation of podands with alkali metals which is possible for only 12E.16

Scheme 1.8. Conformational-Locked Cyclohexane Podands. 16

An alternative approach can be locking the sterically unfavorable conformer A by chemically inserting a five-member cyclic acetal on the cyclohexane ring 13A. The bridge forces the polyether groups to stay in axial positions. However, the conformer E favorable for complexation can be achieved by hydrolysis of the acetal group to diols (Scheme 1.8). 16 The resulting structure has the polyether groups in energetically preferred equatorial positions (14 E) Cyclohexane Complexation-Induced Conformational Switch

Complexation is an avenue for altering the conformational preference. Given that the interaction during complexation is powerful in terms of energy and can be transmitted through the molecule by the mechanics of the cyclohexane ring, the bulky substituents can move from the equatorial to axial position. The only constraint for these systems is that their conformational
energy cannot exceed the energy needed to screw the ring into a twist form (23–26 kJ/mol).\textsuperscript{9,10} Consequently, complexation can be used as a conformational trigger based on the interactions at the complexation site.\textsuperscript{18} This complexation usually involves the interactions of the compounds with cations from sodium, potassium, copper, zinc, and others metals. For instance, the shift of dipodand 15E from diequatorial orientation to diaxial orientation, 16A, occurs due to complexation with sodium (Scheme 1.9).\textsuperscript{21}

Scheme 1.9. Complexation of Cyclohexane-Based System with Sodium. \textsuperscript{21}

Compounds with the structure 17, podands with $R = \text{CH}_2\text{CH}_3$ and $R' = \text{CH}_2\text{CH}_3$, and crown ethers with $R = \text{CH}_3$ or CN and $R' = \text{CH}_2\text{CH}_3$, have an initial preference for
conformation A (Scheme 1.10). These compounds adopt conformation E upon the complexation with KSCN. Crown ethers and podands of this nature are potential sensor materials in PVC-matrix membranes of ion-selective electrodes.9

The same interaction is seen between copper cations and cis-1,3diaminocyclohexane 18. Before complexation, 18E is the predominant conformer. Upon interaction with a copper ligand, its conformation changes from diequatorial, 18E, to diaxial 18A, due to the attraction of both amino groups to the copper ion (Scheme 1.11)9.

Scheme 1.11. Complexation of Cyclohexane-Based Systems with Copper. 9

Scheme 1.12. Complexation of Pyranose-Based Systems with Zinc.22,23
Similar to cyclohexane-based systems, pyranose-based systems, saccharides made of six-membered ring consisting of five carbon atoms and one oxygen atom, are known to complex with metals. This particular system was designed to be part of the bilayers of liposomes, spherical vesicles comprising of a lipid bilayer that can be disrupted by stimuli to release its load.\textsuperscript{24} This liposome, containing 2,4-diaminoxylopyranoside, is able to release its cargo upon interaction with zinc. The Zinc cation binds to the amino groups and holds them in diaxial positions resulting into the hydrophobic alkoxy groups switching to diaxial positions; thus the conformational preference form \textbf{19E} to \textbf{19A} (Scheme 1.12).\textsuperscript{22,23}

**pH-Induced Conformational Switch**

Cyclohexanes are also good potential models for pH-controlled molecular switches. The two adjacent carboxylic groups in compounds \textbf{20} and \textbf{21} energetically favor conformer \textbf{E} due to the intra-molecular hydrogen bonding between these two groups. Upon addition of base, these two carboxylic groups are converted to carboxylate ions that experience strong electrostatic gauche repulsion. This shifts the conformational preference from \textbf{E} to \textbf{A}. However, the preference for \textbf{E} can be restored by addition of acid. The energy of this conformational switch was experimentally estimated ($^1$H-NMR) to be $\geq 10 \text{ kJ/mol}$ for both compounds (Scheme 1.13).\textsuperscript{9,19}

![Scheme 1.13. Conformational pH-Induced Switch of trans-1,2-Diacidic Systems.\textsuperscript{19}](image-url)
The interactions due to intramolecular and intermolecular forces can also function as counterbalances in the conformational preferences of trans-2-aminocyclohexanols. This functionality can be monitored by analyzing the conformational behavior in different solvents. In CDCl₃, conformer 22A is more stabilized due to the formation of intramolecular hydrogen bonding of the type OH...N between vicinal substituents. In CD₃OD or CD₃CN, the conformational equilibrium shifted towards conformer 22E. This is because the intramolecular hydrogen bonding is disrupted and replaced by an intermolecular hydrogen bonding with solvent (Scheme 1.14). Other trans-2-amino-cyclohexanol showed the same characteristics.

Scheme 1.14. Conformational Chair-Chair Switches Due to Solvent Effect.

An adaptable way of altering the conformational equilibrium of trans-aminocyclohexanols is the use of acid to protonate the amino group and create a strong intramolecular hydrogen bond between the proton on the protonated amine and the hydroxyl group’s lone pair electrons (O...H-N⁺ type) as seen in 23AH⁺ (Scheme 1.15).

Upon protonation, the trans-aminocyclohexanol’s hydroxyl and protonated amino groups adopt a strong attraction due to the hydrogen bond. This attraction, whose energy may exceed 20 kJ/mol, is transmitted mechanically through the cyclohexane ring and is able to alter the position.
of the substituents on the other end of the ring. This translation alters the interactions of
substituents across the ring. Hence, the vicinal OH/NR₂ groups are a plausible target due to their
specificity in binding to protons in allosteric systems with high negative cooperativity, bringing
\textit{trans}-2-aminocyclohexanols potential applications in aspects of pH-sensitive membrane
transport and targeted drug delivery to importance.⁹,³¹,³²

\textit{Scheme 1.15.} pH-Induced Conformational Switches of \textit{trans}-Aminocyclohexanols (TACH). ²⁵
The effect of protonation and complexation can be merged in controlling the conformational equilibrium of \textit{trans}-aminocyclohexanols. By adding acid, that can protonate the amine group and avail the hydrogen for intramolecular bonding, the crown ether’s and podand’s affinity for metal ions can be regulated.

For instance, crown compounds 24 and 25 (Scheme 1.16) have two different sites that alter the conformation of the cyclohexane; HO\ldotsHN^+R_2 groups’ interactions and complexation of potassium ions with ether tails of podands or crown ethers respectively. Diequatorial arrangement of the ether tails in conformer E is necessary to aid in cation complexation, as discussed in Scheme 1.10, and further strengthens the equatorial positioning in conformer EK^+.\textsuperscript{9,18,30}

\textit{Scheme 1.16.} pH-Controlled Allosteric TACHs System for Cation Complexation.\textsuperscript{30}
Scheme 1.17. Allosteric Enhancement of Ion-Transport Through an Organic Membrane.\textsuperscript{33}

The effect of complexation and protonation can also be used in ion transport with \textit{trans}-2-cyclohexanols as the carrier.\textsuperscript{34} For instance, compound 26 transports potassium cations in membranes between phases of different pH (Scheme 1.17). In a low pH environment, the crown ether undergoes a conformational change from 26E.3K\textsuperscript{+}, which is able to complex with potassium cations, to 26AK\textsuperscript{+}, which is not able to undergo complexation. During this process, potassium ion can be transferred more effectively from the source phase (higher pH) to the receiving phase (lower pH).\textsuperscript{33}
Double Conformational Switch

Scheme 1.18. Double Conformational Switch of cis-1,3-Diamine Derivatives of Fluorescent Moieties.\textsuperscript{35}

Amino compounds 27 undergo a more complex protonation-induced conformational switching. The neutral, monocationic and dicationic states of the molecule all play roles in the conformational preference. These three amine protonation states are formed with the stepwise addition of acid. The amino groups 27E (Scheme 1.18) were initially in diequatorial orientation to ease repulsion. Upon protonation by a low concentration of acid, one of the amino groups is protonated and interacts with the other to form a bridge hydrogen bond which fixes the ring in a tetra-axial conformation 27AD\textsuperscript{+}. Consequent to the addition of more acid, the second amino group is protonated. This results in the breakage of the hydrogen bond and recreates repulsion due to the positive charges on the amino groups. This results into the stabilization of the tetra-equatorial conformation 27E2D\textsuperscript{+}. Fluorescent substituents were used to follow the stepwise and reversible conformational behavior under the influence of pH. At 395 nm, monomer emissions
of neutral 27E and dication 27E2D⁺ were present. This is because the tetra-equatorial conformation restricts any close proximity of the fluorescent substituents. However, the initiation of 27AD⁺ resulted in a shift in fluorescence emission at 460 nm due tetra-axial locked cyclohexane ring conformation. ⁹,²²,³⁵,³⁶

Scheme 1.19. Double Conformational Flip of trans-3-Hydroxy-4Morpholinopiperidine. ³⁷

Trans-3-hydroxy-4-morpholinopiperidines undergo a more complex conformational system of two consecutive conformational flips or double flips. This flipping is dependent on the initial protonation of the secondary amine in the piperdinyl cycle and a further final protonation of tertiary amine in the morpholinyl cycle. Compound 28 (Scheme 1.19), in hydrochloride form, was used to characterize the pH-induced conformational equilibrium in CD₃OD. It was noticed that both 28E, achieved by adding excess base (DBU), and the double
protonated form $28E2H^+$, achieved by addition of excess acid ($d$-TFA), prefer the diequatorial conformations and are more stable than the diaxial conformations by 1.6 kcal/mol. This double flip was confirmed by monitoring signal width using $^1$H NMR.\textsuperscript{37,38}

**Non-Cyclic Complexation-Induced Conformational Switch**

Complexation of molecules can also happen around non-cyclic bonds. The flexibility of these bonds and the interaction of particular functional groups with ions help to change the molecular structures from one orientation to the other. The ion interactions usually replace or support other intramolecular interactions like hydrogen bonding and weaker ion interactions.

Scheme 1.20. Complexation of Calcium with Diphenoxyethane.\textsuperscript{23,39}

A new application for complexation is the development of designer liposomes that release their contents due to interaction with metal ions that force conformational changes within the lipid layers of the liposome. This phenomenon is plausible as a drug delivery tool in the treatment of malaria due to the increase in concentration of calcium when infected by plasmodia, bacteria that cause malaria.\textsuperscript{40} With molecules of structure 29A (Scheme 1.20) fused in the lipid bilayer, the liposome is loaded with a drug that treats malaria. The drug is released in areas of
high concentration of calcium ion by perturbation of the lipid bilayer through the complexation with calcium to form structure 29B.\textsuperscript{23,39}

\[ \text{Scheme 1.21. Conformational Complexations in Jurczak’s Macrocyclic Polyamides.} \textsuperscript{41} \]

Recently, macrocyclic polyamides, that are primarily folded and unfold in the presence of anions, were tested for conformational change.\textsuperscript{41–43} The pyridine-2,6-dicarboxylate derivative 30 has the most selective binding to chloride and underwent the most noticeable conformational switch 30B (Scheme 1.21). The non-pyridine derivative 31 was less selective, binding to chloride, acetate, benzoate and dihydrogen phosphate, but gave crystal structures that were able to confirm both conformers 31A and 31B. This also confirmed that the intramolecular hydrogen bonding between the amides was not stronger than the ionic interactions for the macrocyclic polyamides.
Diphenylacetylene fragment is commonly used in ion complexation systems because of its rigid structure, low barrier of rotation and electronic ability to interact with cations due to centralization of charge.\textsuperscript{42,44,45} In the interactions of diphenylacetylene derivative 32, absence of external stimulus leads to hydrogen bonding between the lactone and the bidentate urea in 32A (Scheme 1.22). In the presence of chloride ions, complexation stabilizes conformer 32B by ionic interactions with the bidentate urea.

Besides complexation, other non-bonding interactions may include hydrogen bonding and electrostatic interactions. One of the advantages of these non-bonding interactions is they can be manipulated by external influences like solvent and acids/bases. This manipulation can cause a reversible change in the stability of the conformers. For instance, some new pH-responsive lipids, based on a di(methoxyphenyl)pyridine scaffold, exist initially as conformer A (Scheme 1.23). Upon protonation of the pyridine, intramolecular hydrogen bonding between the methoxy and pyridinium groups help stabilize conformer B. The compound 33, 34 and 35 all exhibited a conformational switch when protonated, but at different pK\textsubscript{a}.\textsuperscript{23,46}
Scheme 1.23. Conformational of pH Responsive Di(methoxyphenyl)pyridine Scaffold. 46

Glycosidase Activity

Glycosidases

Glycosidases (also known as glycoside- or glycosyl-hydrolases) are enzymes that are responsible for the breakdown of sugars through the hydrolytic cleavage of the glycosidic bond. These enzymes are found in microorganisms, plants and animals.47 These enzymes play an important role in the digestion of oligosaccharides, glycoproteins, glycolipids and carbohydrates. On a cellular level, glycosidases are involved in the building of cell walls and other components of a cell. They are also involved in a diverse amount of metabolic disorders and diseases, such as diabetes, viral and bacterial infections, HIV and cancer48. With the growing resistance to glycosidase inhibitors by different viruses and bacteria has increased the demand for research into efficient inhibitors, and a better understanding of their structure and activity49.

The stereochemistry of the linkage at the anomeric carbon, α/β linkage, specifies the functionality of these enzymes, α/β glucosidases (Scheme 1.24). Upon recognition, the glycosidic bond is hydrolyzed and the polymer, like a disaccharide, is broken down into
monomers (Table 1). This ability for these enzymes to recognize and target a specific glycosidic bond has made them a viable target to control specific pathways and treat diseases.


Table 1
Some Glycosidases and the Disaccharides They Break Down

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Disaccharide</th>
<th>Glyco-monomers</th>
<th>Glycosidic bond</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-D-Glucosidase</td>
<td>Cellobiose</td>
<td>Glucose, Glucose</td>
<td>β (1 – 4)</td>
</tr>
<tr>
<td>α-D-Glucosidase</td>
<td>Sucrose</td>
<td>Glucose, Fructose</td>
<td>α (1 – 2)</td>
</tr>
<tr>
<td>β-D-Galactosidase</td>
<td>Lactose</td>
<td>Galactose, Glucose</td>
<td>β (1 – 4)</td>
</tr>
<tr>
<td>α-D-Galactosidase</td>
<td>Melibiose</td>
<td>Galactose, Glucose</td>
<td>α (1 – 6)</td>
</tr>
</tbody>
</table>

Mechanism for Enzyme-Catalyzed Hydrolysis by Glycosidases

Glycosidase classification is based on the mechanism by which they break the glycosidic bond of the substrates that they act upon. The two classifications are: the glycosidases that retain the configuration of the glycosidic bond upon hydrolysis and the glycosidases that invert the configuration of the glycosidic bond upon hydrolysis. These two classifications have been
supported experimentally by generation of different substrates designed to study the kinetics of the breaking and reformation of the glycosidic bond.$^{47,50,51}$

Scheme 1.25. Mechanism for Glycosidic Cleavage with Retention of Configuration.$^{50}$

Glycosidases that retain configuration exchange the sugar moiety for water or an alcohol resulting in the conservation of anomeric configuration. The mechanism of these glycosidases involves a double displacement with two consecutive inversions involving the formation and hydrolysis of a covalent glycosyl-enzyme intermediate, both steps proceeding through oxocarbenium ion-based transition state (Scheme 1.25). The carboxylic groups at the active sites act in two different steps. In the first step, as one carboxylic acid protonates the glycosidic
oxygen, the bond cleavage occurs. The second carboxylate performs a nucleophilic attack on the substrate forming a covalently bonded glycosyl-enzyme intermediate. In the second step, as one carboxylate deprotonates the water, the second carboxylate forms a covalent bond to the substrate. The deprotonated water attacks the substrate and replaces the sugar. Both steps occur through oxocarbenium ion-like transition states.\textsuperscript{52}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1}
\caption{Mechanism for Glycosidic Cleavage with Inversion of Configuration.\textsuperscript{52}}
\end{figure}

Glycosidases that invert configuration are shown in Scheme 1.26. The process of this inversion of configuration proceeds through an $S_N2$ like mechanism. The carbonyl groups are important for protonation of the substrate and deprotonation of water, allowing the substrate and water to binding between them. The inversion of configuration occurs through an oxocarbenium ion-like transition state.\textsuperscript{52,53}

Thus, the functionality of these enzymes depends on the ability of the enzyme to recognize the orientation at the anomeric carbon: either retain or alter the conformation of the
substrate depending on the substrate’s interaction with the carboxylic acids residues found in the enzyme’s active site.\textsuperscript{54,55}

**Glycosidase Inhibitors**

The target for inhibition of glycosidases is usually the substrate or transition state.\textsuperscript{56–58} The design of these inhibitors was first envisioned by Baker.\textsuperscript{59} The idea of mimicking substrate with high affinity and specificity for the active site would be important in the discovery of glycosidase inhibitors. The substrate is usually a glycoside of a monomer sugar or a carbohydrate. Many glycoside-based inhibitors, both natural and synthetic, have been discovered as glycosidase inhibitors. By conserving the glycone, sugar residue, and altering the aglycone, non-sugar residue, many inhibitors have been discovered and are now active drugs. The glycone is usually hydrophilic and is recognizable by the enzyme. The aglycone is usually hydrophobic and is designed to interact with the hydrophobic enzyme pocket.\textsuperscript{51,55} Modification to the glycone have been explored to produce notable inhibitors in form of iminosugars\textsuperscript{49,60} like nojirimycin and deoxynojirimycin (Scheme 1.27). Elongation of R group in deoxynojirimycin alters the interaction within the hydrophobic pocket leading to discovery of drugs for cancer and diabetes.\textsuperscript{61}

![Scheme 1.27. Nojirimycin and Deoxynojirimycin as α- and β- Glycosidase Inhibitors.](image-url)

\textsuperscript{54} Substrates depend on the substrate’s interaction with the carboxylic acids residues found in the enzyme’s active site.\textsuperscript{54,55}

\textsuperscript{56}–\textsuperscript{58} The target for inhibition of glycosidases is usually the substrate or transition state.\textsuperscript{56–58} The design of these inhibitors was first envisioned by Baker.\textsuperscript{59} The idea of mimicking substrate with high affinity and specificity for the active site would be important in the discovery of glycosidase inhibitors. The substrate is usually a glycoside of a monomer sugar or a carbohydrate. Many glycoside-based inhibitors, both natural and synthetic, have been discovered as glycosidase inhibitors. By conserving the glycone, sugar residue, and altering the aglycone, non-sugar residue, many inhibitors have been discovered and are now active drugs. The glycone is usually hydrophilic and is recognizable by the enzyme. The aglycone is usually hydrophobic and is designed to interact with the hydrophobic enzyme pocket.\textsuperscript{51,55} Modification to the glycone have been explored to produce notable inhibitors in form of iminosugars\textsuperscript{49,60} like nojirimycin and deoxynojirimycin (Scheme 1.27). Elongation of R group in deoxynojirimycin alters the interaction within the hydrophobic pocket leading to discovery of drugs for cancer and diabetes.\textsuperscript{61}
The growing resistance to glycosidase inhibitors by different viruses and bacteria has increased the demand for research into efficient inhibitors, and a better understanding of their activity. The structural similarity between the inhibitor and substrate, a transition state or a product of enzyme catalysis, is important for the stereospecific interaction between the inhibitors and the enzyme’s active site. Analogous to iminosugar-based glycosidase inhibitors, new pyrrole, imidazole, and tetrazole-based glycosidase inhibitors are emerging drugs (Scheme 1.28) and this has created some interest in other nitrogen-based cyclic substituents, triazoles. Use of the triazolyl substituent would be advantageous due the synthetic ease for both 1,4 and 1,5 triazoles.
CHAPTER 2: RESEARCH GOALS

Molecular Switches

The goal of this project was to synthesize \textit{trans}-2-(azaarylsulfanyl)-cyclohexanol and triazolyl-cyclohexanol derivatives and assess their ability to undergo molecular switching due to change in pH. The aim of the research was as follows:


- Access the influence that counterbalances, ethoxylcarbonyl tails, have on the conformation of the hydrophilic nitrogen-based heterocycle heads for \textit{trans}-2-(azaarylsulfanyl)-cyclohexanol and triazolyl-cyclohexanol derivatives.

- Access the sensitivity of \textit{trans}-2-(azaarylsulfanyl)-cyclohexanol and triazolyl-cyclohexanol derivatives to change in pH.

- Access the change in conformational equilibrium of \textit{trans}-2-(azaarylsulfanyl)-cyclohexanol and triazolyl-cyclohexanol derivatives in response to change in pH.

- Determine the conformational preference, A-value, of the triazolyl group on a cyclohexane.

Glycosidase Inhibitors and Activators

The goal of this project was to synthesize \textit{trans/cis}-2-triazolylycyclohexanol dicarboxylic acids, \textit{trans}-2-triazolylycyclohexanols and hexahydrobenzo-triazolo-oxazinone derivatives, and test their glycosidase activity on α/β-D-glucosidases and α/β-D-galactosidases isolated from fungi \textit{Aspergillus} and β-D-glucosidases and α/β-D-galactosidases isolated from \textit{Penicillium sp.}

The aim of the research was as follows:


- Test the effect of glycosidase activity by \textit{trans/cis}-2-triazolylycyclohexanol dicarboxylic acids, \textit{trans}-2-triazolylycyclohexanols and hexahydrobenzo-triazolo-oxazinone derivatives on
α/β-D-glucosidases and α/β-D-galactosidases isolated from fungi Aspergillus and β-D-glucosidases and α/β-D-galactosidases isolated from Penicillium sp.
Molecular Switches

Previously, TACHs (Schemes 1.19 and 3.1) were found to undergo a pH-induced conformational switch. Addition of acid to these compounds resulted in protonation of the amino group consequentially forming a strong intramolecular hydrogen bond of the type $\text{HO...H-N}^+$ that altered the conformational preference from diaxial to diequatorial for the amino and hydroxyl substituents. A counterbalance of two ethoxylcarbonyl groups was used to confirm the chair-chair flip. These adjacent ethoxylcarbonyl groups, in \textit{trans}-configuration to each other, exhibited the direct opposite orientation to the amino and hydroxyl groups, i.e., when the amino and hydroxyl groups were axil, the adjacent ethyl ester groups were quatorial and vice versa. Alterations of the substituents on the amine nitrogen of \textit{trans}-2-aminocyclohexanols varied the basicity of the amino group, resulting in a wide pH range within which molecular switches were possible (Scheme 3.1).\textsuperscript{25,26,31,38,64}

\textit{Scheme 3.1.} pH-Induced Conformational Switch of TACHs.
Scheme 3.2. pH-Induced Conformational Switch of trans-2-Azaaryl sulfanylcylohexanols.

To expand the existing assortment of potential pH-triggers, we designed analogous trans-
2-(azaaryl sulfanyl)-cylohexanols (Scheme 3.2). The cyclohexanol and two adjacent
ethoxycarbonyls were conserved as in TACHs. The design places sulfur in between the
cyclohexane ring and a nitrogen-heterocyclic ring. The advantage of these models could be an
additional shift of conformational equilibrium towards conformer A due to the gauche repulsion
between the lone pair electrons of oxygen and sulfur. The strong initial bias for A would provide
an opportunity for a wider swing towards conformer BH$^+$ upon protonation.$^{65,66}$
Library of trans-2-Azaaryl sulfanyl cyclohexanol Derivatives


With the design of trans-2-azaaryl sulfanyl cyclohexanols in Scheme 3.2, a library of trans-2-azaaryl sulfanyl cyclohexanols dicarboxylates 3a-m was proposed for synthesis and studied as potential conformational switches (Scheme 3.3). Compounds 3a and 3b were designed as the reference models for the structures 3a-m that can undergo intramolecular
hydrogen bonding and the stabilization of conformer BH$^+$ in acid conditions. They contain azaaryl groups varying in size, number of nitrogen atom and other heteroatoms, and sometimes equipped with additional substituents. Compound 3x, an acetoxy derivative of 3k, was synthesized to compare the interaction of the hydroxyl and acetate substituent with the azaarylsulfanyl group’s nitrogen atoms and hence access the conformational preference due to each substituent. This variety of azaarylsulfanyl groups, with their nitrogens in different positions, would help explore the strength of pH-induced intramolecular hydrogen bonding.

Scheme 3.4. Library of trans-2-(azaarylsulfanyl)-Cylohexanols.

Compounds 5a-m (Scheme 3.4) were synthesized to mirror compounds 3a-m (Scheme 3.3), but with no ethoxylcarbonyl groups as counterbalances. Absence of these ethoxylcarbonyl counterbalances isolates the effect of the gauche interactions between the hydroxyl and thiol or azaarylsulfanyl groups.
Compounds 5a-m were expected to have a very biased conformational equilibrium and thus provide the conformational models with hydroxyl and azaarylsulfanyl groups in the diequatorial positions. Contrasting, compounds 8a-c and 9a-c (Scheme 3.5) were designed with a strong counterbalance of tert-butyl directly across the hydroxyl and the azaarylsulfanyl groups. This would hold the hydroxyl and azaaryl groups in diaxial positions, hence elucidating the conformational limits of these groups in that orientation.

Scheme 3.5. Library of 4/5-tert-Butyl-trans-2-(azaarylsulfanyl)-Cylohexanols.
Synthesis of \textit{trans}-2-(azaarylsulfanyl)-Cylohexanol Derivatives

\textit{Trans}-2-(azaarylsulfanyl)-cyclohexanol dicarboxylates \textbf{3a-m} (Scheme 3.6) were synthesized beginning with diethyl 4-cyclohexene-\textit{trans}-1,2-dicarboxylate \textbf{1}, which was previously synthesized\textsuperscript{19,29,30} through a Diels-Alder reaction between butadiene-sulfone and diethyl fumarate. The synthetic advantage of Diels-Alder reaction is the conservation of stereochemical information of the diene and dienophile. This resulted in the \textit{trans} orientation of the ethoxycarbonyl groups. Epoxidation of alkene \textbf{1} was done with \textit{m}-chloroperoxy benzoic acid (\textit{m}-CBPA) in dichloromethane (DCM). The epoxide, diethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate \textbf{2}, was isolated by column chromatography. The final step of the synthesis
was the cleavage of the epoxide with azaaryl sulfanyl groups. This was done with various solvent ratios of H$_2$O and tetrahydrofuran (THF) depending on the solubility of the azaaryl sulfanyl compounds.$^{57-70}$ The synthesis was done under argon (Ar) to avoid oxidation of the sulfanyl groups, forming disulfide bridges, in the presence of oxygen. The products were isolated by column chromatography and yields of the pure compounds were satisfactory.

Similar to compounds 3a-m (Scheme 3.6), *trans*-2-(azaaryl sulfanyl)-cyclohexanols 5a-m (Scheme 3.7) were synthesized beginning with commercially available cyclohexene oxide 4. Cyclohexene oxide was cleaved with the same conditions for compounds 3a-m and sufficient yields of pure compounds were obtained.

Conformationally biased 4/5-*tert*-butyl-azaaryl sulfanyl cyclohexanols 8a-c and 9a-c (Scheme 3.8) were synthesized to analyze the NMR data for diaxial orientation of the two substituents. Commercially available 4-(*tert*-butyl)cyclohexene 6 underwent epoxidation with *m*-CPBA and DCM to produce 3-(*tert*-butyl)-7-oxabicyclo[4.1.0]heptane 7. Epoxide 7 was cleaved with the same conditions for compounds 3a-m and sufficient yields of pure products were obtained.
Scheme 3.7. Synthesis of trans-2-(azaarylsulfanyl)-Cylohexanols 5a-m.

Scheme 3.8. Synthesis of 4/5-tert-Butyl-trans-(azaarylsulfanyl)-Cyclohexanols 8a-c and 9a-c.

The fast equilibrium $[A + AH^+] \rightleftharpoons [B + BH^+]$ (Scheme 3.9) was examined by $^1$H NMR spectroscopy (600 MHz). The vicinal coupling constants $^3J_{HH}$ between several protons attached to the cyclohexane moiety are strongly conformationally-dependent, which allows an assignment of a predominant conformation and an evaluation of the position of conformational equilibrium:
large vicinal couplings, 9-12 Hz, are observed between the diaxial protons (as \( H^1 \) and \( H^2 \) in A, Scheme 3.9), and small values, 2-5 Hz, are measured for the axial-equatorial and equatorial-equatorial vicinal couplings protons (as \( H^4 \) and \( H^5 \) in A, Scheme 3.9). The observation of a single set of well-resolved multiplets with the averaged NMR parameters attests to high rates of both conformational and acid-base equilibria on the NMR time scale.

The conformer populations \((n_A, n_B)\) in dilute solutions were estimated as described previously using Eliel’s equation applied to the averaged signal width \( W = \Sigma J_{HI} \) (a sum of spin-spin couplings) of the protons geminal to the substituents: \( W_{observed} = W_A \cdot n_A + W_B \cdot n_B \). The parameter \( W \) was measured as a distance between terminal peaks of a multiplet. These signals were usually well resolved and had chemical shifts in a region apart from the signals of other protons (Scheme 3.9).

The limiting parameters \( W_A \) and \( W_B \) for individual conformers were obtained from the measurements for compounds 3c (Scheme 3.6), 5c and 5k (Scheme 3.7) and 9b (Scheme 3.8). \( W_B \) was assumed to equal 25.1 Hz for \( H(O) \) geminal to \( OH \) from 5k (Table 3), 26.7 Hz for \( H(S) \) geminal to \( RS \) from 5c and 5k (Table 3), and \( \sim 10 \) Hz for \( H(COEt) \) geminal to ethoxycarbonyl groups from previous similar structures. The limiting parameters due to conformational bias towards conformation A were obtained from compound 8 and 9 with a tert-butyl conformational anchor which held the hydroxyl and azaarylsulfanyl groups in axial positions. \( W_A \) was set to 8.1 Hz for \( H(O) \) from 9b (Table 7), 9.3 Hz for \( H(S) \) from 9b (Table 7), and 27.7 Hz for \( H(COEt), H^1 \) and \( H^2 \), from 3c (Table 3). Analogous data for other protons was used, when possible, to confirm the conformational assignment.

Prior to protonation, the evaluated share of conformer A \((n_A)\) and conformer B \((n_B)\) includes both the non-protonated form A and the non-protonated form B. Upon protonation, the
evaluated share of conformer A \( (n_A) \) includes both the non-protonated form A and the protonated form \( AH^+ \), and the evaluated share of conformer B \( (n_B) \) includes the non-protonated form B and the protonated form \( BH^+ \). The concentration of acid correlates with the population of conformer \( BH^+ \) \( (n_B) \) in derivatives that are sensitive to acid and undergo conformational changes due to the stabilization by intramolecular hydrogen bonding. In some derivatives of compounds 3, the azaaylsulfanyl and hydroxyl groups’ interactions do not facilitate intramolecular hydrogen bonding, thus stabilizing conformer \( AH^+ \) in an acid environment.

The conformational populations were calculated using the limiting parameters and the signal width from the signals of each proton of interest. Depending on the resolution and clarity of the signals, priority in determining the conformer population was given to protons whose signals showed more attainable and accurate widths. Only these signals contributed to the conformer population through averaging their individual calculated populations to give a percentage of the conformer populations for each compound.

This can be seen in Figure 3.1 where diethyl 4-hydroxy-5-(pyridin-2-ylthio)cyclohexane-1,2-dicarboxylate 3c was monitored for conformational switch through the addition of concentrated deuterated trifluoroacetic acid \( (d\text{-TFA}) \). With the limiting parameters for \( H^4(O) \) geminal to OH as \( 8.1 – 25.1 \) Hz, \( H^5(S) \) geminal to RS as \( 9.3 – 26.7 \) Hz and, \( H^1 \) and \( H^2 \) \( (\text{COOEt}) \) geminal to ethoxycarbonyl groups as \( \sim 10 – 27.7 \) Hz, the conformer population in terms of percentages of conformer A and B was obtained.
Figure 3.1. Acid-induced conformational switch for derivative 3c in CD$_3$OD (0.02M): (I) no acid present (~100% A); (II) 1 equivalent of d-TFA (~70% A+AD$^+$ and ~30% B+BD$^+$); and (III) 2 equivalents (excess) of d-TFA (~50% A+AD$^+$ and ~50% B+BD$^+$).
In the absence of d-TFA, 3c had preference for conformer A. As the amount of d-TFA was increased, the population of conformer BD$^+$ increased until the conformational equilibrium showed equal presence of conformer AD$^+$ ($n_A=50\%$) and conformer BD$^+$ ($n_B=50\%$) in excess d-TFA. The final conformer population was determined by only H$^1$ and H$^2$. This is because the overlap of H$^4$ and H$^5$ made it difficult to measure their signal widths.

The chemical shifts for 3c and all other azaarylsulfanyl cyclohexanols were recorded but not used in the conformational equilibrium estimations. This is because these chemical shifts have a wide range of variation, are generally sensitivity to temperature and are solvent dependent. Considering them would introduce multiple inaccuracies.

In order to monitor the conformational flip due to a change in pD, analogous with pH in deuterated environments, $^1$H NMR titration experiments were done by adding small portions of 1M d-TFA solution in CD$_3$OD to a 0.03 M solution of azaarylsulfanyl compounds in CD$_3$OD solution. The advantage of using d-TFA is the absence of NMR signals from the acid which excludes interference of the titrant’s signals with the signals of the compound of interest. A titration of 3g was performed and the $^1$H NMR parameters were plotted against pD (Table 2, Figure 3.2).
### Table 2

*Titrination \(^1\)H NMR Data and Conformational Parameters for \(3g\).\(^{a)}\)

![Diagram](attachment:image.png)

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\(^{a)}\) 600 MHz; 0.02-0.03 M solutions at 294K; \(d\)-trifluoroacetic acid was added in large excess \((x10^{15})\) to \(CD_3OD\) solution; c) Partially or completely overlapped with other signals; d) Poorly resolved signal.
(Table 2 Continued)

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<sup>a</sup>) 600 MHz; 0.02-0.03 M solutions at 294K; <sup>b</sup>) <i>d</i>-trifluoroacetic acid was added in large excess (x10<sup>-13</sup>) to CD<sub>3</sub>OD solution; <sup>c</sup>) Partially or completely overlapped with other signals; <sup>d</sup>) Poorly resolved signal.
Figure 3.2. Titration curves for 3g monitored by $^1$H NMR in CD$_3$OD with (A) as signal width ($W$) and (B) as chemical shift ($\delta$).
Initially, although the addition of $d$-TFA decreased the pD, the conformational flip of 3g did not occur. This is seen by the constant signal widths and the constant chemical shifts of the signals between pD 7.5-5.0. When the pD was in the buffer zone (pD 5.0-3.0), small additions of $d$-TFA did not change the pD significantly. Consistent with these small additions of $d$-TFA was the slow increase in signal width of H$^4$ (10.9 Hz) and H$^5$ (11.5 Hz) accompanied with the slow decrease in signal width of H$^1$ and H$^2$ (25.1 and 25.3 Hz respectively). This marked the beginning of the conformational flip. The further addition of $d$-TFA shifted the equilibrium towards conformer BD$^+$ with signal width of H$^4$ (18.5 Hz) and H$^5$ (19.9 Hz) and the signal width of H$^1$ and H$^2$ (17.2 and 17.3 Hz respectively). The changes in signal width of all protons on the cyclohexane show that the protonation of the 2-mercapto-1-methylimidazole group consequently changes the conformational equilibrium by stabilizing conformer BD$^+$ through intramolecular hydrogen bonding the type HO...D-N$^+$.

The comparisons of the signal widths to the limiting parameters show that there is a substantial amount of conformer AD$^+$. Evidence of this can be seen in the conformation population $n_B + n_{BH^+}$(%) where the switch ends at ~60% of conformer BD$^+$ (Figure 3.3).

Another confirmation of the conformational flip was seen in the changes in chemical shift (Figure 3.2). Typically, axial protons’ signals are located more upfield as compared to signals of equatorial protons when considering protons geminal to the same substituent. This is confirmed in the chemical shifts of H$^1$, H$^2$ and H$^4$. With the addition of $d$-TFA, the signals for H$^1$ (δ 2.99) and H$^2$ (δ 3.05) in 3g both shifted downfield to δ 3.14 and δ 3.25 respectively. This confirms the axial-equatorial conformational switch. The simultaneously occurring equatorial-axial switch can only be seen in H$^4$. The signal for H$^4$ (δ 3.88) shifted upfield to δ 3.76 with the addition of $d$-TFA. An unexpected reverse trend was seen for signal H$^5$ (δ 3.45) with a downfield shift to δ
3.53 during the equatorial-axial switch. Given that the nitrogen on the imidazole group was protonated and the positioning of the nitrogen close to the geminal proton H⁵ on the cyclohexane ring, the deshielding effect of the positive charge may counteract the effect of the equatorial-axial orientation of the proton. It is also important to note that chemical shifts are sensitive to temperature, types of solvents, complexations with reagents, etc., and this could affect the typical trends of H⁵.

Figure 3.3. Titration curve of 3g in CD₃OD monitoring the signal width of H⁴ corresponding conformer population (nB).

To confirm and follow the conformational flip, the relative population of both conformers (n_A, n_B) in the conformational equilibrium were estimated using the observed signal widths (W_observable). Once the conformer populations were obtained, the Gibbs free energy (∆G_B-A) for the
conformational equilibrium was calculated using the formula: \( \Delta G_{B-A} = -RT\ln(n_B/n_A) \). The results (Table 2) show that the gradual addition of \( d \)-TFA produces a protonation-induced conformational flip of 3g. Compound 3g initially showed significant preference for conformer A (~88% in CD\(_3\)OD) compared to conformer B (~12% in CD\(_3\)OD) (Figure 3.3). The addition of acid resulted in a preference for conformer BD\(^+\) (~60% in CD\(_3\)OD and excess \( d \)-TFA) compared to conformer AD\(^+\) (~40% in CD\(_3\)OD and excess \( d \)-TFA).

Hence, not only can the titration of azaaryl sulfanyl-cyclohexanols be expressed by signal width variation, but it can also be monitored by the equilibrium population of conformers with further insight given by the calculated \( \Delta G_{B-A} \)-values in CD\(_3\)OD from these populations. Prior to addition of \( d \)-TFA, conformation equilibrium was initially biased to conformer A at pH 7.10 (\( \Delta G_{B-A} = 4.3 \) kJ/mol). With the addition of acid, conformation equilibrium became slightly biased to conformer BD\(^+\) at pH 1.14 (\( \Delta G_{B-A} = -1.0 \) kJ/mol). From these \( \Delta G_{B-A} \)-values, the power of this conformational pH-trigger was estimated to be \( \geq 5 \) kJ/mol (Table 2).

**Factors Affecting Conformational Equilibrium of trans-2-(azaaryl sulfanyl)-Cyclohexanol Derivatives**

Given the assortment of substituents used in the synthesis of trans-2-(azaaryl sulfanyl)-cyclohexanol derivatives (Scheme 3.3, 3.4 and 3.5) and the variation in characteristics of media used in the collection of their parameters, for example, addition of \( d \)-TFA, types of solvent and temperature, it is important to assess the factors that affect their conformational equilibrium.

**Effect of azaaryl sulfanyl groups as a polar-head.** The initial conformational studies of azaaryl sulfanyl-cyclohexanol 3g showed similar results to the analogous trans-2-aminocyclohexanols (TACHs) studied previously.\(^{25}\) These TACHs had structural variations in their amino polar-head groups that created variability in conformational switches. The
substituents on the synthesized azaaryl sulfanyl cyclohexanol derivatives 5a-m (Scheme 3.3, 3.4 and 3.5) were of different heterocyclic variety and their conformational behavior was analyzed in different solvents and in the presence of excess d-TFA (Table 3).

Table 3

**1H NMR Data and Conformational Parameters for 5a-m.**

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>H¹ (O)</th>
<th>H² (S)</th>
<th>n_B(nBD)</th>
<th>ΔG_B-A, kJ/mol</th>
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<td>δ W, Hz</td>
<td>δ W, Hz</td>
<td>%</td>
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<td>+ CF₃COOD</td>
<td>3.62</td>
<td>24.7</td>
<td>3.56</td>
<td>26.1</td>
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</table>

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as W_B; e) d-trifluoroacetic acid was added in large excess (x10⁻¹⁵) to CD₂OD solution; f) Poorly resolved signal; g) J_HCOH was subtracted.
(Table 3 Continued)

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<th>solvent, acid</th>
<th>$H'(O)$ $\delta$ $W$, Hz</th>
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<th>$\Delta G_{B-A}$, kJ/mol</th>
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</table>

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) $d$-trifluoroacetic acid was added in large excess ($x10^{15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HOCH}$ was subtracted.
(Table 3 Continued)

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<th>$\Delta G_{B-A}, kJ/mol$</th>
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<td>$\sim24^v$</td>
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<td>3.59</td>
<td>24.7</td>
<td>3.67</td>
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</table>

a) 600 MHz; 0.02-0.03 M solutions at 294 K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) d-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) J$_{HCOH}$ was subtracted
(Table 3 Continued)

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1 (O)$</th>
<th>$H^2 (S)$</th>
<th>$n_B(nB^*)$</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
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<td>$\delta$ W, Hz</td>
<td>$\delta$ W, Hz</td>
<td>%</td>
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<tr>
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<td>3.65 25.6</td>
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<tr>
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<td>3.69 23.6</td>
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<td>-4.3</td>
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<td>3.60 23.5</td>
<td>3.70 25.1</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) $d$-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HC_3OH}$ was subtracted.

All the studied trans-2-azaaryl sulfanylylcyclohexanols 5a-m prefer the diequatorial conformation 5B in all solvents (75-100%, Table 4). In comparison to prior similar models, with $R = CH_3$, Ph, that were studied and found to have total conformational preference for diequatorial orientation 5B regardless of solvent and temperature$^{73}$, the found conformational preference for 5B in compounds 5a-m was significantly smaller.

Also, there is a uniform trend in the interaction of the compounds 5a-m with solvents. Particularly, the preference for conformer 5B is stronger in relatively non-polar CDCl$_3$ than in polar solvents, CD$_3$OD and (CH$_3$)$_2$SO. A plausible explanation for this difference may be the
intramolecular hydrogen bonding which stabilizes 5B in CDCl₃, but is interrupted by
intermolecular hydrogen bonding with CD₃OD and especially with (CD₃)₂SO.

This preference for conformation 5B was useful for comparison with the conformational
equilibrium of dicarboxylate derivatives 3a-m (Table 4) equipped with ethoxycarbonyl
counterbalances that would change the conformation preference.

To explore the possible acid-induced shift of the conformational equilibrium, the CD₃OD
solutions of compound 5a-m were treated with up to a 15-fold excess of d-trifluoroacetic acid.
Despite the already substantial conformational bias, a noticeable additional shift of equilibrium
towards the diequatorial conformer 5BD⁺ was observed, especially for the pyridinyl-derivative
5c (82 → 97%) which was the most sensitive to d-TFA. Expectedly, the equilibrium of phenyl-
derivative 5a and tolyl-derivative 5b remained practically insensitive due to the lack of nitrogen
in their heterocycles.
Table 4

$^1H$ NMR Data and Conformational Parameters for 3a-m.$^a$

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$ (O) $\delta$ W, Hz</th>
<th>$H^5$ (S) $\delta$ W, Hz</th>
<th>$H^1$ $\delta$ W, Hz</th>
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<td>27.0</td>
<td>2.90</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_b$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HCOH}$ was subtracted.
(Table 4 Continued)

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a) 600 MHz; 0.02-0.03 M solutions at 294 K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) $d$-trifluoroacetic acid was added in large excess ($\times 10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HCOH}$ was subtracted.
(Table 4 Continued)

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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) J$_{HCOH}$ was subtracted.
Table 4 Continued

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<th>solvent, acid</th>
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<th>$H^2$ (S) $\delta$ W, Hz</th>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) J$_{HCOH}$ was subtracted.

In comparison to the derivatives 5a-m, which prefer conformation 5B in all solvents, the conformational equilibrium of dicarboxylate derivatives 3a-m in polar solvents, CD$_3$OD and (CD$_3$)$_2$SO, is strongly shifted towards conformation 3A. The conformation 3A has two ethoxylcarbonyl counterbalances in equatorial positions, and the hydroxyl and azaaryl sulfanyl groups in axial positions. Nonetheless, the opposite conformation 3B, with both ethoxylcarbonyl counterbalances in axial positions and the hydroxyl and RS group in equatorial positions, is almost equally populated or even slightly more predominant in non-polar CDCl$_3$. This is apparently due to the stabilization by the intramolecular hydrogen bond that was also seen in compounds 5a-m.

For the dicarboxylate derivatives 3a-m to have a conformational preference for 3A, the ethoxylcarbonyl counterbalances need to have more conformational energy than the hydroxyl and aminothiol group. Previously the destabilizing effect of two axial COOEt groups in
structures similar to 3B was estimated as 7 to 8 kJ/mol in C₆D₁₂ and approximately 10 kJ/mol in CDCl₃ and (CD₃)₂CO.¹⁷ A comparison of the ΔGₐ-ᵦ data in Tables 3 and 4, (5 vs 3), gives similar values: 7.7-8.9 kJ/mol in CDCl₃, 12-15 kJ/mol in (CD₃)₂SO, and 10-14 kJ/mol in CD₃OD.

To explore the possible acid-induced shift of the conformational equilibrium, CD₃OD solutions were treated with up to 15-fold excess of d-TFA. Despite the substantial conformational bias towards conformation 3A for all compounds 3, a significant shift of equilibrium towards the conformer 3BD⁺ was observed for the 2-pyridinyl derivative 3c (8 → 52%), 4-pyridinyl derivative 3d (15 → 42%), imidazolyl derivative 3f (13 → 50%), methyl-imidazolyl derivative 3g (15 → 60%) and benzimidazolyl derivative 3k (9 → 57%). The structural similarity in all these molecules is basic nitrogen on azaarylsulfanyl group that is in proximity with the hydroxyl group and can stabilize the conformation 3BD⁺ upon protonation. This stabilization in the form 3BD⁺ is due to an intramolecular hydrogen bond of the type HO...D-N⁺ and by electrostatic attraction HO...N⁺.

After screening all the compounds 3a-m by treatment with excess d-TFA, the diversity in basicity of the derivatives that showed significant sensitivity to acid was evaluated by titration (Figure 3.4). Previously, it was found that more basic polar head in analogous structures, TACHS, showed noticeable changes in conformation in less acidic pD ranges.²⁵ The azaarylsulfanyl groups appear to undergo conformational changes at more acidic pD ranges (4.8-2.6) with the more basic region for 3f and 3g, and surprisingly with the more acid region for 3c. Although derivative 3k underwent a conformational switch at a lower pD range as compared to other derivatives, the conformational population range span for its switch was the widest (9 → 57%), about 6-times the population increase of conformer 3BD⁺. It is closely followed by 3g (15
→ 60%) whose conformational population increase was four-fold with the highest population limit of 3BD⁺ conformers nB (nBD⁺) at 60 % after the switch.

Figure 3.4. Titration curves of 3c, 3d, 3f, 3g and 3k in CD₃OD monitoring the signal width of H⁴ with its corresponding conformer populations (nB).

Previously, it was found that the basicity of a molecule could be estimated by NMR titrations with acid. As defined in the Henderson-Hasselbalch equation: $pK_a = pH + \log \frac{[HL]}{[L]}$; the pKₐ of a protonated base is equal to pH at equilibrium where equal amounts of unpronotated and protonated base exist ($n_L=n_{HL}$). When obtaining the pKₐ with NMR titrations, the pD is used in place of the pH as deuterated acids are commonly used to avoid signal overlap. As seen in Figure 3.5, the pKₐ of the protonated form of the base can be estimated at the halfway point of the changes of NMR parameters (the chemical shift δ, ppm), which coincides with the middle of the titration curve in terms of pD.
Figure 3.5. Sample estimation of pKₐ based on ¹H NMR Titration curves.⁷⁴

With the use of this method, the basicity of all trans-2-azaaryl sulfanyl cyclohexanol dicarboxylate derivatives that showed significant sensitivity to d-TFA was obtained using mainly the signal width (W), but supported with data from chemical shifts (δ) (Table 5). As previously mentioned, the chemical shift data is not as reliable due to the sensitivity to changes while the data is obtained. However, we observed a good correspondence between the two sets of data.
Table 5
$^1$H NMR Titration-Estimated Basicity$^a$ ($pK_a$) of Dicarboxylate Derivatives 3c, 3d, 3f, 3g and 3k.

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a) 600 MHz; 0.02-0.03 M solutions of CD$_3$OD at 294K

The $pK_a$-values estimated from both signal width ($W$) and chemical shift ($\delta$) were consistent for all trans-2-(azaarylsulfanyl)-cyclohexanol dicarboxylate derivatives that showed significant sensitivity to $d$-TFA.
Effect of the position of nitrogen on azaarylsulfanyl group. The positions of the nitrogen atom on the azaarylsulfanyl groups are important because their proximity to the hydroxyl group helps to stabilize conformers $B$ or $BD^+$ through electrostatic attraction $HO...N^+$ or by intramolecular hydrogen bonding of the type $HO...DN^+$. A comparison of derivatives 3c, 2-pyridinyl, and 3d, 4-pyridinyl, can be used to investigate the influence of nitrogen’s position.

In non-acidic conditions, compounds 3 (Table 4) and 5 (Table 3) with their azaarylsulfanyl groups as 2-pyridine, 3c and 5c, and as 4-pyridine, 3d and 5d, all have similar conformational traits and preferences in different solvents. They all have the highest conformational preference for conformer $B$ in CDCl$_3$, and the highest conformational preference for conformer $A$ in (CD$_3$)$_2$SO.

In acidic conditions, the dicarboxylate derivatives 3c and 3d (Table 4 and Figure 3.4) are more sensitive to acid as compared to non-dicarboxylate derivatives 5c and 5d (Table 3). Both 3c and 3d showed significant response to excess $d$-TFA and were titrated for further investigation (Figure 3.4). Surprisingly, upon titration the conformational switch of 3d happened at a more basic pD than that of 3c although the nitrogen in the 2-pyridinyl group, for 3c, is closer in proximity to the hydroxyl group as compared to the 4-pyridinyl group, for 3d. A possible explanation for this is that the nitrogen in both cycles decreases the basicity of the aromatic rings and makes them more responsive to $d$-TFA (compared to phenyl and tolyl derivatives 3a and 3b respectively (Table 4)). But the closer nitrogen on the azaarylsulfanyl group is to the hydroxyl group, their stronger the stabilization of the intramolecular hydrogen bond. Suggesting that regardless of the amount of $d$-TFA used protonate the nitrogen on the 2-pyridinyl group in 3c, the conformational changes due to hydrogen bonding cannot be compared to the conformational changes in 4-pyridinyl group 3d.
Another plausible explanation for this difference is that the conformational switch could also be facilitated by electrostatic interactions. Once the 4-pyridinyl derivative 3d was protonated, the charge on the pyridinyl group was able to interact with the lone pair of hydroxyl group and form an attraction that aided in the conformational preference for conformer 3BD⁺. It is also reasonable to say that electrostatic interactions may have a significant contribution in other derivatives that were sensitive to acid.

**Effect of R-groups on azaarylsulfanyl groups.** In order to alter the electron density of an aromatic ring, electron donating groups were used. It was possible to see the effect of a mild electron donating group when an azaarylsulfanyl derivative with an alkyl group, methyl, was synthesized and compared to an azaarylsulfanyl derivative without one. This can be seen in the comparison of derivatives 3f and 3g (Table 4 and Figure 3.4) and derivative 5f and 5g (Table 3).

In non-acidic conditions, compounds 3 (Table 4) and 5 (Table 3) with their RS group as imidazole, 3f and 5f, and as 1-methyl-imidazole, 3g and 5g, all have similar conformational traits and preferences in different solvents. They all have the highest conformational preference for conformer B in CDCl₃, and their highest conformational preference for conformer A in (CD₃)₂SO.

In acidic conditions, 3f and 3g (Table 4 and Figure 3.4) are more sensitive to acid as compared to 5f and 5g (Table 3). Both 3f and 3g showed similar response to excess d-TFA and were titrated for further investigation. Upon further inspection, it was evident that the two compounds underwent conformational changes in the same pD range and hence had similar pKₐ-values. The only major difference between 3f and 3g was the conformational population difference that gradually increased between 3.8 – 1.3 (Figure 3.6). The methyl group on 3g uses the inductive donating effect to increase the electron density of the RS group. This leads to a
slight increase in basicity which not only affects the pKₐ but has a greater effect on the conformational switch given the increased pronation ability and hence a stronger intramolecular hydrogen bond of the type HO...D-N⁺ in conformer 3BD⁺.

**Figure 3.6.** Titration curves 3f and 3g in CD₃OD monitoring the signal width of H₄ with their corresponding conformer populations (nB) and show the pKₐ for their conformational switch.

**Effect of t-butyl counterbalance.** In order to explore the limits of the conformational equilibrium, a tert-butyl group was used as a bulky counterbalance. With such a strong anchor directly across the hydroxyl group, in 4-t-butyl-2-azaarylsulfanylcyclohexanol 8, and the RS group, in 5-t-butyl-2-azaarylsulfanylcyclohexanol 9, both of these groups on each type of compound were forced into a diaxial orientation: conformer A. The conformational preference for 8A and 9A provides the limiting parameters for protons adjacent to H¹ (OH) and H² (RS) (Table 6 and 7), hence the limit for Wₐ in all the synthesized azaarylsulfanylcyclohexanol
models. Imidazolyl (8a and 9a), 2-pyridinyl (8b and 9b) and benzimidazole (8c and 9c) derivatives provided models that were most sensitive for estimating the limiting parameter $W_A$.

Table 6

$^1$H NMR Data and Conformational Parameters for 8a-m.$^{a)}$

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<th>$W,\text{Hz}$</th>
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<td>4.08</td>
<td>9.2$^b)$</td>
<td>~0</td>
<td>&gt;10</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_A$; e) $d$-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HCOH}$ was subtracted; h) $^J$-coupling was subtracted
Table 7

$^1$H NMR Data and Conformational Parameters for 9a-m.$^a$)

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<td>b)</td>
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<td>b)</td>
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<td>(~-8)$^g$</td>
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<td>(~10)$^e$</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_A$; e) $d$-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{\text{HCOH}}$ was subtracted; h) $^4$J-coupling was subtracted.

The constitutional isomers 4-t-butyl-2-azaarylsulfanylcylohexanol 8 and 5-t-butyl-2-azaarylsulfanylcylohexanol 9 were separated when possible and analyzed by $^1$H NMR. Only stand-alone well resolved signals were used to determine the limiting parameter $W_A$. Clear
signals of H\(^1\) (OH) for 9b in CD\(_3\)OD (8.1 Hz), and H\(^2\) (RS) for 9b in CDCl\(_3\) (9.3 Hz) (Table 7) were selected as \(W_A\) for other studied models.

The obtained NMR results show a complete preference for conformers 8A and 9A. Even with the presence of \(d\)-TFA that was previously seen to change the conformation preference towards BD\(^+\) and/or the twisted form TD\(^+\) in analogous TACH structures,\(^{25}\) no contribution from 8BD\(^+\) or 8TD\(^+\) in compounds 8a-c and 9BD\(^+\) or 9TD\(^+\) in compounds 9a-c was seen in acid media. This means that the conformational power of the tert-butyl group to remain in the equatorial position supersedes the attraction (HO...D-N\(^+\)) due to intramolecular hydrogen bonding.

Effect of OR

![Diagram of Scheme 3.10](image)

Scheme 3.10. Synthesis of Diethyl 4-((1H-benzoimidazol-2-yl)thio)-5-Acetoxycyclohexane-1,2-Dicarboxylate 3x by Acetylation.

The hydroxyl group is important in the conformational equilibria due to its participation in intramolecular hydrogen bonding. This intramolecular interaction (OH...N) is responsible for the stabilization of conformer B in the absence of \(d\)-TFA, while the intramolecular interaction (HO...D-N\(^+\)) is responsible for the stabilization of conformer BD\(^+\) in the presence of \(d\)-TFA. The influence of this hydroxyl group in both scenarios can be checked by modifying it into an acetate group. Compound 3x was obtained by acetylation using acyl chloride through refluxing in dry chloroform (Scheme 3.10).
The hydroxyl group is important in the conformational equilibria due to its participation in intramolecular hydrogen bonding. This intramolecular interaction (OH...N) is responsible for the stabilization of conformer B in the absence of d-TFA, while the intramolecular interaction (HO...D-N\textsuperscript{+}) is responsible for the stabilization of conformer BD\textsuperscript{+} in the absence of d-TFA. The influence of this hydroxyl group in both scenarios can be checked by modifying it into an acetate group. Compound 3x was obtained by acetylation using acyl chloride through refluxing in dry chloroform (Scheme 3.10).

The conformational equilibrium was estimated as described in previous sections using the parameters from $^1$H-NMR spectra. Unsurprisingly, a significant difference in conformation...
preference was observed between compounds 3k and 3x in CDCl₃. The alcohol 3k demonstrated a slightly higher conformation preference for conformer B than conformer A (H⁴ (OH), W = 18.5 Hz, ~59% B) in CDCl₃. The acetate 3x predominantly adopted a conformation A (H⁴ (OAc), W = 9.2 Hz, ~7% B) in CDCl₃ (Figure 3.7 and Table 8). This highlights the importance of the hydroxyl group in the stabilization of conformer B through intramolecular hydrogen bonding (OH...N), especially in non-polar solvent.

In conjunction with what was mention before, the intermolecular hydrogen bonding with CD₃OD and OH effectively interferes with the diequatorial intramolecular hydrogen bonding (OH...N), hence shifting the conformational equilibrium from conformer B to conformer A. This was consistent with the extracted parameters for 3k, (H⁴ (OH), W = 10.1 Hz, ~11% B), and 3x, (H⁴ (OAc) in CD₃OD (Figure 3.8). Therefore, alcohol 3k and acetate 3x are both stabilized, in the form of conformer A, by the intermolecular hydrogen bonding with CD₃OD. In the case of acetate 3x, there is no stabilization of conformer BD⁺ by d-TFA. But, a difference in sensitivity to d-TFA between alcohol 3k, (H⁴ (OH), W = 18.0 Hz, ~57% B), and acetate 3x, (H⁴ (OAc), W = 14.7 Hz, ~34% B) (Table 8), confirms that conformational preference is dictated by the ability to form a strong intramolecular hydrogen bond (HO...D-N⁺) in acidic media.
Figure 3.8. $^1$H NMR of signal H$^4$ of alcohol 3k and acetate 3x in CD$_3$OD solvent.
Table 8
$^1$H NMR Data and Conformational Parameters for 3k and 3x a)

<table>
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<th>$H^1$(O)</th>
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<th>$H^1$</th>
<th>$H^2$</th>
<th>$nB$ (nn)$^+$,</th>
<th>$\Delta G_{B-A}$,</th>
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<td>3k R=H</td>
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<td>+ CF$_3$COOD e)</td>
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<td>3x R=Ac</td>
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<td>15.7</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as W$_d$; e) d-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) J$_{HCOH}$ was subtracted.

Effect of solvent. Analagous TACHs showed correlation between specific conformers and particular solvents depending on the solvents’ polarity and ability participate in intermolecular hydrogen bonding. The solvents that are not able to undergo intermolecular hydrogen bonding allow the hydroxyl and azaaryl sulfany groups to undergo intramolecular hydrogen bonding. In order to elucidate these concepts further, we evaluated the conformational behavior of dicarboxylate derivative 3h (Figure 3.7) in additional solvents and the $^1$H NMR spectra of 3h were compared and contrasted. The conformer populations ($n_A$, $n_B$) and free energy difference ($\Delta G_{B-A}$) for the conformational equilibrium of 3h was obtained (Table 9).
Table 9
$^1$H NMR Data and Conformational Parameters for 3h in Different Deuterated Solvents.\textsuperscript{a)}

\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
3h, solvent & $H^\prime\,(O)$ & $H^\prime\,(S)$ & $H^\prime$ & $H^2$ & $n_B\,(n_B^*)$, & $\Delta G_{B-A}$, \\
& $\delta$ & $W, \, Hz$ & $\delta$ & $W, \, Hz$ & $\delta$ & $W, \, Hz$ & $\delta$ & $W, \, Hz$ & \% & kJ/mol \\
\hline
CDCl$_3$ & 4.00 & 16.6 & 3.69 & 17.3 & 3.05 & 19.4 & 3.21 & 19.6 & 46 & 0.3 \\
C$_6$D$_6$ & 4.16 & $\sim$15\textsuperscript{c)} & 4.03 & $\sim$16\textsuperscript{c)} & 3.25 & 22.7 & 3.43 & 22.9 & 34 & 1.7 \\
CD$_3$OD & 4.02 & 10.1 & 3.84 & 10.6 & 2.91 & 26.5 & 3.06 & 26.7 & 8 & 6.0 \\
(CD$_3$)$_2$CO & 4.00 & $\sim$12\textsuperscript{b)} & 4.08 & 2.91 & 3.09 & 26.8 & 6 & 6.7 \\
(CD$_3$)$_2$SO & 3.93 & $\sim$9.4\textsuperscript{a)} & 3.86 & 10.2 & 2.75 & 27.5 & 2.92 & 27.5 & 4 & 7.8 \\
\hline
\end{tabular}

\textsuperscript{a)} 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Poorly resolved signal.
Figure 3.9. $^1$H NMR spectra of azaaryl cyclohexanol dicarboxylate 3h in different solvents.
Conformational equilibria of 3h are considerably different in the specific solvents. While the conformational preference for conformer A, \( \Delta G_{B,A} \), decreases, the conformational preference for conformer B increases. This depends on the solvents’ ability to hydrogen bond with the hydroxyl group. This can be seen in the trend below and in Table 9:

\[
(CD_3)_2SO \text{ (7.8 kJ/mol)} > (CD_3)_2CO \text{ (6.7 kJ/mol)} > CD_3OD \text{ (6.0 kJ/mol)} > C_6D_6 \text{ (1.7 kJ/mol)} > CDCl_3 \text{ (0.3 kJ/mol)}.
\]

In polar solvents \((CD_3)_2SO\) and \((CD_3)_2CO\), intermolecular hydrogen bonding obstructs the possibility of intramolecular hydrogen bonding by surrounding the hydroxyl group. The crowding of the hydroxyl due to the intermolecular hydrogen bonding keeps the hydroxyl and azaaryl sulfanyl groups in diaxial positions thus giving conformational preference to conformer A (Scheme 3.11 and Scheme 3.12).

\[\text{Scheme 3.11. Intermolecular Hydrogen Bonding of 3h in (CD}_3)_2\text{SO}.\]
Scheme 3.12. Intermolecular Hydrogen Bonding of 3h in CD3OD.

In nonpolar solvents C6D6 and CDCl3, the intramolecular hydrogen bonding is not hindered by intermolecular hydrogen bonding of solvent with the hydroxyl group. This helps to stabilize conformer B for 3h (Table 9). A possible reason for the stronger conformational preference in CDCl3 as compared to C6D6 is the mild presence of DCl, acid generated due to exposure of CDCl3 to light, that can protonate the azaaryl sulfanyl group and aid in the intramolecular hydrogen bonding (Scheme 3.13). This would stabilize conformer B, with a small contribution from BD+. This same limited influence of DCl probably affects the 1H NMR data in the CDCl3 of all azaarylcylohexanols synthesized (Table 3 and Table 4).

Scheme 3.13. Intramolecular Deuterium Based-Hydrogen Bonding of 3h due to DCl in CDCl3 and the Partial Stabilization of Conformer B.
Library of \textit{trans}-2-Triazolylcyclohexanol/Cyclohexylacetate Dicarboxylate Derivatives

Earlier, it was established that \textit{trans}-2-aminocyclohexanols (TACHs) (Scheme 1.19 and 3.1) successfully underwent pH-induced conformational switches in acidic media and their conformational preference was changed by intramolecular hydrogen bonding. We expanded this concept to include \textit{trans}-2-(azaarylsulfanyl)-cylohexanols (Scheme 3.2) with nitrogen containing heterocycles as the basic amino groups. With these results in consideration, we expanded our assortment of conformational switches by proposing \textit{trans}-2-triazolylcyclohexanols (Scheme 3.14) that are analogous to both TACHs and \textit{trans}-2-(azaarylsulfanyl)-cylohexanols. The conformational switch would be based on protonation of the triazolyl group leading to formation of a strong intramolecular hydrogen bond of the type $\text{HO}...\text{H-N}^+(\text{Tz})$ that alters the conformational preference from diaxial to diequatorial for the triazole and hydroxyl substituents. Similarly, two ethoxycarbonyl groups, in \textit{trans} configuration, were used to counterbalance other substituents.

\begin{center}
\includegraphics[width=\textwidth]{Scheme3.14.pdf}
\end{center}

\textit{Scheme 3.14. Acid-Induced Shift of the Conformational Equilibrium of \textit{trans}-2-Triazolylcyclohexanol Derivatives.}

With this idea, different \textit{trans}-2-triazolylcyclohexanols derivatives were proposed for synthesis (Scheme 3.15 and Scheme 3.16). The hydroxyl and two adjacent ethoxycarbonyls were conserved as in TACHs and \textit{trans}-2-azaarylsulfanylcylohexanols. The design allows for
change of basicity of the triazole ring by placing different substituents on either C⁴ (carbon 4) or C⁵ (carbon 5) on the triazole ring, and analysis of the impact of each substituent relative to its position. Replacement of the hydroxyl group with acetate would assess the influence H₂O has on intramolecular hydrogen bonding and stabilization of conformer B and BD⁺.

Surprisingly, pathways that allowed for synthesis of disubstituted triazolyl dicarboxylate derivatives 16 also allowed for synthesis of and hexahydrobenzo-triazolo-oxazinone dicarboxylate derivatives 15 as discussed further. Compounds 15 provided a diaxial orientation of the protons geminal to the triazole and the lactone oxygen. They could be used for estimation of the ¹H NMR limiting parameters for conformer B and BD⁺.

Scheme 3.15. Library of Hexahydrobenzo-Triazolo-Oxazinone Dicarboxylate Derivatives.
Scheme 3.16. Library of Bis-Ethoxycarbonyl-trans-2-Triazolylicyclohexanol Derivatives.
Synthesis of trans-2-Triazolylcyclohexanol Dicarboxylate Derivatives

Scheme 3.17. Synthesis of trans-2-(1,4)Triazolylcyclohexanol/cyclohexylacetate Dicarboxylate Derivatives.

Compounds 11a, 11b, 12a and 12b (Scheme 3.17) were synthesized beginning with diethyl 4-cyclohexene-trans-1,2-dicarboxylate 1. Epoxidation of alken 1 was done with m-CBPA in DCM to give epoxide 2. The epoxide ring cleavage of compound 2 by azide anion was done with sodium azide and ammonium chloride in a 15:1 solution of DI H2O and ethanol to give diethyl-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate 10a.\textsuperscript{75,76} Azide 10a exposed to conditions of copper(I)-catalyzed “click reaction” (CuAAC) with CuSO\textsubscript{4}.5H\textsubscript{2}O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and H\textsubscript{2}O and gave triazoles 11a and 11b.
Azide 10a was acetylated using acyl chloride through refluxing in dry chloroform producing diethyl-5-azido-4-acetoxy-1,2-cyclohexanedicarboxylate 10b after purification.

Acetyl-azide 10b was treated with the same click reaction conditions as 10a and produced 12a and 12b.

Scheme 3.18. Synthesis of trans-2-(1,4 and 1,5)Triazolylcyclohexanol Dicarboxylates.

Azide 10a (Scheme 3.18) and 10b (Scheme 3.19) were also exposed to 1,3-dipolar cycloaddition reactions in different conditions: by refluxing in toluene with 1-octyne or phenylacetylene in separate reactions. Both azides produced triazole derivatives with a hexyl or phenyl substituents at C^4 or C^5, i.e. 11a, 11b and 12a, 12b with the substituents on the former and 11c, 11d and 12c, 12d with the substituents on the latter. Azide 10a and 10b also underwent
1,3-dipolar cycloaddition reactions in toluene with diphenylacetylene to produce triazole 13 and 14. (Scheme 3.20).


Compounds 15 and 16 were synthesized with azide 10a and a series of 2-alkynyl esters through 1,3-dipolar cycloaddition reactions in toluene. Tricyclic derivatives 15 (Scheme 3.21) went through triazole adduct 15* with ester at C5 and alkyl group at C4, and forms lactones due to esterification at high temperatures. The compounds 16 with esters at C4 and alkyl groups at C5 are stable (Scheme 3.21).

Conformational Study of trans-2-Triazolylcyclohexanol Dicarboxylate Derivatives

The fast equilibrium \([A + AH^+] \leftrightarrow [B + BH^+]\) (Scheme 3.22) was examined by \(^1\)H NMR spectroscopy (600 MHz). The vicinal coupling constants $^3J_{HH}$ between several protons attached to the cyclohexane moiety are strongly conformationally-dependent, which allows an assignment of a predominant conformation and an evaluation of the position of conformational equilibrium: large vicinal couplings, 9-12 Hz, are observed between the diaxial protons (as H1 and H2 in A, Scheme 3.22), and small values, 2-5 Hz, are measured for the axial-equatorial and equatorial-equatorial vicinal couplings protons (as H4 and H5 in A, Scheme 3.22).\(^{71}\) The observation of a single set of well-resolved multiplets with the averaged NMR parameters attests to high rates of both conformational and acid-base equilibria on the NMR time scale.

The conformer populations ($n_A$, $n_B$) in dilute solutions were estimated as described previously\(^{25–27,30,32,64,65,72}\) using Eliel’s equation\(^{10,13}\) applied to the averaged signal width $W = \Sigma J_{HH}$ (a sum of spin-spin couplings) of the protons geminal to the substituents: $W_{\text{observed}} = W_A \cdot n_A + W_B \cdot n_B$. The parameter $W$ was measured as a distance between terminal peaks of a multiplet. These signals were usually well resolved and had chemical shifts in a region apart from the signals of other protons (Scheme 3.22).
The limiting parameters $W_A$ and $W_B$ for individual conformers were estimated from the measurements for the conformational biased compounds $\text{19a, 19b and 38b}$ (Scheme 3.23). $W_B$ was assumed to equal 25.7 Hz for $H(O)$ geminal to OH and 27.0 Hz for $H(Tz)$ geminal to triazole from $\text{19a and 19b}$ (Table 10), and 10 Hz for $H(\text{COOEt})$ geminal to ethoxycarbonyl groups from previously studied similar structures. The limiting parameters due to conformational bias towards conformer $A$, $W_A$, were set as 9.0 Hz for $H(O)$ geminal to OH and 10.1 Hz for $H(Tz)$ geminal to triazole from $\text{38b}$, while $W_A$ for $H^1$ and $H^2$ was set as 27.0 Hz.
based on previous data from analogous compounds.\textsuperscript{25} Analogous data for other protons were used when possible to confirm the conformational assignment. Compounds 15 were initially considered for limiting parameters $W_B$ for the ethoxycarbonyls, but further inspection showed distortion of the cyclohexane rings of these compounds.

The $^1$H NMR data and the conformational parameters for compounds 11-14 and 16 are present in Table 10. Prior to acidification, the conformer B is already strongly predominant. Upon acidification, the predominance of conformer B (and the form BD$^{+}$) remains the same. The concentration of acid has no significant effect on the position of the equilibrium.

Table 10
$^1$H NMR Data and Conformational Parameters for 11-14 and 16.\textsuperscript{a})

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$ (O)</th>
<th>$H^1$ (Tz)</th>
<th>$H^2$</th>
<th>$H^2$</th>
<th>$\eta_B$ ($\eta_B$)</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
</tr>
</thead>
<tbody>
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<td>$\delta$ W, Hz</td>
<td>$\delta$ W, Hz</td>
<td>$\delta$ W, Hz</td>
<td>$\delta$ W, Hz</td>
<td>%</td>
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<td>+ CF$_3$COOD</td>
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<td>70</td>
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\textsuperscript{a}) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Poorly resolved signal; e) d-trifluoroacetic acid was added in large excess (x10$^{15}$) to CD$_3$OD solution.
(Table 10 Continued)

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<th>$H^1$ (Tz)</th>
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<th>$H^2$</th>
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<th>$\Delta G_{bs, b}^*$</th>
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<td>(~12)</td>
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<td>4.27</td>
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<td>23.3</td>
<td>4.83</td>
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<td>24.5</td>
<td>4.29</td>
<td>25.4</td>
<td>3.40</td>
<td>11.9</td>
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</table>

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Poorly resolved signal; e) d-trifluoroacetic acid was added in large excess ($10^{15}$) to CD$_2$OD solution.
<table>
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<th>solvent, acid</th>
<th>( H^1 ) (O)</th>
<th>( H^2 ) (O)</th>
<th>( H^3 ) (Tz)</th>
<th>( H^4 )</th>
<th>( n_B ) (mmol)</th>
<th>( \Delta G_{B-A} ) kJ/mol</th>
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<td>3.39</td>
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<td>11.7(^{ii})</td>
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</table>

16a- \( R' = \text{CH}_3, \ R'' = \text{CH}_2\text{CH}_3 \)

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<th>solvent, acid</th>
<th>( H^1 ) (O)</th>
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<th>( H^3 ) (Tz)</th>
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<th>( n_B ) (mmol)</th>
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<td>+ CF(_3)COOD (^c)</td>
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<td>13.7</td>
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16b- \( R' = (\text{CH}_2)_2\text{CH}_3, \ R'' = \text{CH}_3 \)

<table>
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<th>( H^1 ) (O)</th>
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<th>( n_B ) (mmol)</th>
<th>( \Delta G_{B-A} ) kJ/mol</th>
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<tr>
<td>+ CF(_3)COOD (^c)</td>
<td>4.08  22.7</td>
<td>5.39</td>
<td>23.3</td>
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16d- \( R' = (\text{CH}_2)_2\text{CH}_3, \ R'' = \text{CH}_3 \)

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<th>( n_B ) (mmol)</th>
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<td>3.39</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Poorly resolved signal; e) d-trifluoroacetic acid was added in large excess (x10\(^{15}\)) to CD\(_2\)OD solution.
Factors Affecting Conformational Equilibrium of *trans*-2-Triazolylcyclohexanol

Dicarboxylate Derivatives

**Effect of ethoxycarbonyl counterbalances.** All the studied compounds (11-14 and 16) showed conformational preference for conformer B (70-95%). This was unexpected due to the observed conformational preference for conformer A seen in analogous TACHs and *trans*-2-azaaryl sulfanylcylohexanols that had the same ethoxycarbonyl groups as counterbalances. From previously studied cyclohexane structures, we estimated the destabilizing effect of two axial ethoxycarbonyl groups as 7-8 kJ/mol in C₆D₆ and ~10 kJ/mol in (CD₃)₂CO. Adding the energy difference between conformer B and A (ΔGₜₐₜ-A) (Table 10), we can estimate the preference of the triazolyl group and hydroxyl groups for the diequatorial arrangement in B as 10-14 kJ/mol depending on the substituent on the triazole ring and the type of solvent. Such a strong preference was unexpected and very different from the properties of TACHs with 5 and even 6-membered cyclic amino-substituents.

**Effect of R-groups on triazole ring.** The existence of weak electron donating groups, hexyl for compounds 11 and phenyl for compounds 12, or moderate electron withdrawing groups, esters for compounds 16, on the triazole ring, has no effect on the conformational preference of these structures. This was unfortunate because analogous TACHs and *trans*-2-azaaryl sulfanylcylohexanols showed that adding substituents to the amino group or RS group (Table 4) would alter the basicity of the group and have an effect on the conformational equilibrium upon acidification. It is also noted that the existence of two bulky groups on C⁴ and C⁵ of the triazole ring (compound 13 with both R¹ and R² = phenyl) and derivatives with substituents at C⁵ only, significantly shifts the conformational equilibrium towards conformer B.
as compared to all other triazolyl derivatives. Apparently, this is due to the repulsion between the substituents at C⁵ and the atoms of the cyclohexane ring.

**Effect of solvent.** In solutions of nonpolar solvent CDCl₃ and polar solvent CD₃OD, all the studied compounds (11-14 and 16) showed conformational preference for conformer B. The derivatives with a substituent on C⁴ only showed slightly higher presence of conformer B because the non-polar solvents do not interfere with the intramolecular hydrogen bonding (OH...N(Tz)). The dissimilarity is seen in CD₃OD for the derivatives that have a substituent on C⁵ only and derivatives with a substituent on both C⁴ and C⁵. These compounds do not show different conformational preference in CD₃OD because the force due to the repulsion between the substituents at C⁵ and the cyclohexane ring is stronger than the intermolecular hydrogen bonding with the solvent.

**Effect of change in pH.** The unfortunate preexisting bias for conformer B means that these trans-2-triazolylcylohexanols are not efficient as conformational switches. This is exacerbated by the low pKₐ of the triazole which makes protonation of the group difficult, thus leading to relatively low stabilization of conformer BH⁺ from conformer B. With the addition of 10-15 fold excess d-TFA (pD ≈ 1.1), there was little to no effect on the conformer BH⁺’s population (Table 10).
Library of trans-2-Triazolyl-Cyclohexanol/-Cyclohexyl Acetate Derivatives


As seen from the results in Table 10, trans-2-triazolylcyclohexanol dicarboxylates already have a conformational bias towards conformer B where the hydroxyl and triazolyl groups are in equatorial positions and the trans-ethoxylcarbonyl groups are in axial positions.
This unexpected result led us to attempt to understand the interaction between the hydroxyl and triazolyl groups, and the importance of hydrogen bonding to this interaction. This was done using such counterbalances as methyl, phenyl and $t$-butyl groups, and altering the hydroxyl group with acetate while maintaining the triazolyl group. The varying conformational energy for each of these counterbalances to prefer the equatorial position, also known as A-Value, can be used to assess the energy needed to changes the orientation of the hydroxyl/acetate and triazolyl groups from diequatorial to diaxial positions. This is only possible if the counterbalances are cis to the hydroxyl/acetate and triazolyl groups. Compounds of this design were suggested for synthesis. (Scheme 3.23).

**Synthesis of trans-2-Triazolylcyclohexanol Derivatives**

Compounds 18 and 19 (Scheme 3.24 and 3.25) were synthesized beginning with commercially available cyclohexene oxide 4. The ensuing epoxide ring cleavage by azide anion was done with sodium azide and ammonium chloride in a 15:1 solution of H$_2$O and ethanol to produce azide 17a. Azide 17a was acetylated using acyl chloride through refluxing in dry chloroform to produce Acetyl-azide 17b. Both azides 17a and 17b were exposed to copper(I)-catalyzed “click reaction” (CuAAC) conditions with CuSO$_4$.5H$_2$O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and DI H$_2$O to give triazoles 18a,b and 19a,b respectively (Scheme 3.24). Azide 17a was also exposed to other “click reaction” conditions by refluxing in toluene with diphenylacetylene to give triazole 18c (Scheme 3.25).


Compounds 24-29 (Scheme 3.26) were synthesized beginning with commercially available 4-methyl/phenyl/t-butylcyclohexene. Each of these alkenes was epoxidized with m-CPBA in DCM to produce an inseparable mixture of as syn and anti epoxides (20a, 20b and 20c) with each counterbalance. Epoxide ring cleavage by azide anion was done with sodium azide and ammonium chloride in a 15:1 solution of H2O and ethanol to give azide mixtures as
Constitutional isomer pairs 21a, b, 22a, b and 23a, b. Compounds 21a, b, 22a, b and 23a, b were exposed to copper(I)-catalyzed “click reaction” (CuAAC) conditions with CuSO₄.5H₂O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and DI H₂O to give triazoles 24-29.


Constitutional isomer pairs 21a, b, 22a, b and 23a, b were acetylated using acyl chloride through refluxing in dry chloroform to produce Acetyl-azido constitutional isomer pairs 30a, b, 31a, b and 32a, b. Compounds 30a, b, 31a, b and 32a, b were exposed to copper(I)-catalyzed “click reaction” (CuAAC) conditions with CuSO₄.5H₂O, ascorbic acid and 1-octyne or
phenylacetylene in a 2:7 solution of dioxane and H₂O to give triazoles 33-38 whose isomers were separated when possible (Scheme 3.27).

Scheme 3.27. Synthesis of trans-2-Triazolyl-4/5-Methyl/Phenyl/t-Butyl-Cyclohexyl Acetates.

Conformational Study of trans-2-Triazolylcyclohexanol Derivatives with Counterbalances

A similar fast equilibrium in [A + AH⁺] ⇌ [B + BH⁺] (Scheme 3.22) was examined for trans-2-triazolylcyclohexanols with counterbalances (compounds 24-29 and 33-38) by ¹H NMR spectroscopy (600 MHz). The conformer populations (nₐ, nₐ) in dilute solutions were estimated using the same limiting parameters (Wₐ, W₉) and the signal width W for signals of interest.
Table 11
$^1H$ NMR Data and Conformational Parameters for trans-2-Triazolyl-5-Methyl/Phenyl/t-Butyl-Cyclohexanols

![Diagram](image)

<table>
<thead>
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<th>solvent, acid</th>
<th>$H^1(OR)$</th>
<th>$H^1(Tz)$</th>
<th>$n_B$</th>
<th>$\Delta G_{B-A}, \text{kJ/mol}$</th>
<th>$\Delta G_{B-A}, \text{kcal/mol}$</th>
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</thead>
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<td>$W, Hz$</td>
<td>$\delta$</td>
<td>$W, Hz$</td>
<td>%</td>
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<td></td>
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<td>95</td>
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<tr>
<td><strong>18b-</strong> $R = H$, $R^1 = \text{phenyl}$, $R^2 = H$</td>
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<td>96</td>
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<td>+ CF$_3$COOD $e)$</td>
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<td>24.8$^{b}$</td>
<td>4.32</td>
<td>26.5</td>
<td>96</td>
</tr>
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<td>+ CF$_3$COOD $e)$</td>
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<td>97</td>
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<td>4.60</td>
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<tr>
<td>+ CF$_3$COOD $e)$</td>
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<td>25.7$^{a}$</td>
<td>4.61</td>
<td>27.0$^{a}$</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) $d$-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal.
(Table 11 Continued)

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$ (OR) $\delta$ $W$, Hz</th>
<th>$H^2$ (Tz) $\delta$ $W$, Hz</th>
<th>$n_B(n_{BD})$</th>
<th>$\Delta G_B-A$, kJ/mol</th>
<th>$\Delta G_B-A$, kcal/mol</th>
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<th>$H^2$ (Tz) $\delta$ $W$, Hz</th>
<th>$n_B(n_{BD})$</th>
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<td>25.1</td>
<td>91 -5.5 -1.32</td>
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<th>$n_B(n_{BD})$</th>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_B$; e) d-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal.
(Table 11 Continued)

![Chemical Structures]

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<td>$\text{CD}_3\text{OD}$</td>
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<th>$38b$- $R = \text{Ac}$, $R^1 = \text{phenyl}$, $R^2 = \text{C(CH}_3)_3$</th>
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<td>$\text{CD}_3\text{OD}$</td>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_b$; e) $\text{d}$-trifluoroacetic acid was added in large excess ($x10^{-15}$) to $\text{CD}_3\text{OD}$ solution; f) Poorly resolved signal.
Table 12
$^1H$ NMR Data and Conformational Parameters for trans-2-Triazolyl-4-Methyl/Phenyl/t-Butyl-Cyclohexanols

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$ (OR) $\delta$, W, Hz</th>
<th>$H^1$ (Tz) $\delta$, W, Hz</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
<th>$\Delta G_{B-A}$, kcal/mol</th>
</tr>
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<tbody>
<tr>
<td>CDCl$_3$</td>
<td>3.98, 24.29</td>
<td>4.07, 25.4</td>
<td>91, -5.6</td>
<td>-1.34</td>
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<td>4.24, 25.7</td>
<td>91, -5.5</td>
<td>-1.32</td>
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<td>4.25, 25.8</td>
<td>91, -5.7</td>
<td>-1.36</td>
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<td>92, -6.0</td>
<td>-1.42</td>
</tr>
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<td>92, -5.9</td>
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* a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_A$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_2$OD solution; f) Poorly resolved signal; g) $J_{\text{HCOH}}$ was subtracted.
(Table 12 Continued)

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$(OR)</th>
<th>$H^2$(Tz)</th>
<th>$n_{BB}(n_{BD})$</th>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Unresolved signal (a width at 1/3 of its height is shown); d) Used as $W_A$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution; f) Poorly resolved signal; g) $J_{HCOH}$ was subtracted.
Factors Affecting Conformational Study of *trans*-2-Triazolylcyclohexanol Derivatives with Counterbalances

**Effect of counterbalances.** The conformational preference of the compounds studied varied depending on the strength of the counterbalances. With the A-value for the methyl, phenyl and *t*-butyl groups listed as 1.75 kcal/mol, 2.80 kcal/mol and 4.50 kcal/mol respectively, the variation in energy from each of these groups alters the conformation of the triazole and hydroxyl/acetate groups on the cyclohexane ring. The conversion of Gibbs free energy (ΔG) from kJ/mol to kcal/mol allows for direct comparison of the A-values and energy from the experimental data.

As expected, all the compounds without a counterbalance (18a,b,c and 19a,b) showed complete preference for conformer B in acid and non-acidic environments (Table 11). This is supported by the wide signal widths for the axial protons geminal to the triazole and hydroxyl/acetate groups that are in axial positions. This diequatorial orientation is also supported by the crystal structure of 18b (Figure 3.10). The signal widths in ¹H NMR from these models were used as limiting parameters, *W*₇, for the triazole and hydroxyl/acetate groups in the conformational equilibrium of all *trans*-2-triazolylcyclohexanols.
Figure 3.10. X-ray crystal structure of 18b.

With the methyl group as the counterbalance (compounds 24a,b, 25a,b, 33a,b and 34a,b) (Table 11 and 12), there is still a strong conformational preference for B in acid and non-acidic environments. This means that the conformational energy of the methyl group is not sufficient to alter the position of the triazole and hydroxyl/acetate groups and interruption the interaction between the groups.

With the phenyl group as the counterbalance (compounds 26a,b, 27a,b, 35a,b and 36a,b) (Table 11 and 12), the conformational preference for B varies. In CDCl$_3$, the preference for B is significantly higher compared to CD$_3$OD for compounds 26a,b and 35a,b that have triazole and hydroxyl substituents. Compounds with triazole and acetoxy substituents (27a,b and 36a,b) have a stronger preference for A in CDCl$_3$ as compared to CD$_3$OD apparently due to lack of intramolecular hydrogen bonding. Hence, conformational energy of the phenyl group is sufficient to partially alter the position of the triazole and hydroxyl/acetate groups and break the interaction between the groups in CD$_3$OD, i.e., the A-value of the phenyl and the strength based on the interaction and conformational energy of the triazole and hydroxyl/acetate substituents are relatively close. No change in conformational preference is seen in acid or non-acidic
environments of CD$_3$OD. The bulky $t$-butyl counterbalance in compounds $28a,b$, $29a,b$, $37a,b$ and $38a,b$ (Table 11 and 12) alters the conformational preference to conformer A regardless of solvent. This preference does not change in acid or non-acidic environments. It means that the conformational strength of the $t$-butyl group is sufficient to alter the position of the triazole and hydroxyl/acetate groups and break the interaction between the groups.

**Effect of solvent.** The variation in conformation is clearly seen in compounds $26a,b$, $27a,b$, $35a,b$ and $36a,b$ (Table 11 and 12). In nonpolar solvent CDCl$_3$, compounds $26a,b$, $27a,b$ have a high preference for conformer B. The hydroxyl group in these compounds is able to participate in intramolecular hydrogen bonding ($\text{OH...N(Tz)}$) with no interference from the solvent. For these same compounds, polar solvent CD$_3$OD disrupts the intramolecular hydrogen bonding by hydrogen bonding with the hydroxyl group intermolecularly and increases preference for conformer A. The same intermolecular interactions are present for compounds $35a,b$ and $36a,b$ in CD$_3$OD even though they have an acetate group. But in CDCl$_3$, the acetate group has no significant attraction with the triazolyl group and the phenyl counterbalance is able to force a preference for conformer A.

**Library of cis/trans-triazolycyclohexanes**

The results in Table 11-12 show that *trans*-2-triazolycyclohexanol derivatives have a conformational bias towards conformer B with the hydroxyl/acetoxy and triazolyl groups in equatorial positions. The results also showed that any counterbalance with an A-value of approximately 2.80 kcal/mol (phenyl) or more can start to affect the conformational bias and increase preference for conformer A. Furthermore, the conformational anchoring of the $t$-butyl group was sufficient to alter the positions of the hydroxyl/acetate and triazolyl groups from equatorial to axial, thus altering the bias from conformer B to A.
These results prompted us to estimate the so far unknown conformational energy of the triazolyl group independently. With no data reported on the A-value of the triazole and its growing synthetic use in the pharmaceutical and chemical industries, it is important to know the rating for the bulkiness of this group and its preference of position on a cyclohexane ring. This was done in a classical way by using the same counterbalances of methyl, phenyl and t-butyl groups, and placing them directly across the triazolyl group on a cyclohexane ring. The varying conformational energy of the counterbalances would cause “haggling” with the triazole for the equatorial position on the cyclohexane ring and the energetic preference for this position would go to the substituent with a higher A-value.

Synthesis of the compounds necessary to satisfy this approach meant availability of both 
\textit{cis} and \textit{trans} configurational isomers to show the limiting parameters for all counterbalances and the triazolyl group when monitoring their conformational dependence. Compounds of this nature were proposed for synthesis (Scheme 3.28).
Scheme 3.28. Library of cis/transTriazolylcyclohexanes.

Synthesis of Triazolylcyclohexanes

Scheme 3.29. Synthesis of Triazolylcyclohexanes.
Compounds 40a,b were synthesized beginning with commercially available bromocyclohexane (Scheme 3.29). A nucleophilic substitution (Sn2) was done with azide anion using sodium azide in DMSO by way of reflux to produce azidocylohexane 39. Azide 39 was exposed to copper(I)-catalyzed “click reaction” (CuAAC) conditions with CuSO4.5H2O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and DI H2O to give triazoles 40a and 40b respectively (Scheme 3.29).

Compounds 43-45 (Scheme 3.30) were synthesized beginning with commercially available 4-methyl/pheny/r-butylcyclohexanols. All alcohols were tosylated in chloroform with pyridine and p-toluenesulfonyl chloride to produce compounds 41a-c. A nucleophilic substitution (Sn2) was done with compounds 41a-c and azide anion using sodium azide in DMSO by way of reflux to produce azides 42a-c. Azides 42a-c were exposed to copper(I)-catalyzed “click reaction” (CuAAC) conditions with CuSO4.5H2O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and DI H2O to give triazoles 43a,b, 44a,b and 45a,b respectively (Scheme 3.30). When possible, the configurational isomers were separated by column chromatography and independently analyzed (Figure 3.11).
Scheme 3.30. Synthesis of *cis/trans*-Triazolyl-4Methyl/Phenyl/t-Butyl-Cyclohexanes.
Figure 3.11. $^1$H NMR confirming separation of configuration isomers of $43b$.

Conformational Study of cis/trans-Triazolylcyclohexanes


The fast equilibrium $[B] \rightleftharpoons [BH^+]$ (Scheme 3.31) was examined by $^1$H NMR spectroscopy (600 MHz) for the with trans configuration isomers. It is important to note that these isomers don’t have any preference for conformer A due to repulsion of both substituents with the cyclohexane ring. The conformation is biased towards conformer B in nonacidic media and towards BH$^+$ in acid media.
Scheme 3.32. Conformational Equilibrium in *cis*-Triazoleylcyclohexanes.

For the *cis* configuration isomer, the fast equilibrium \([A + AH^+] \rightleftharpoons [B + BH^+]\) (Scheme 3.32) was considered. With the variations of the counterbalance conformational energy, the preference for conformer \(A\) is an option in the case of a strong anchor like \(t\)-butyl. Both conformers \(A\) and \(B\) can be protonated to give \(AH^+\) and \(BH^+\), and both protonated conformers should be considered during conformational analysis.

The conformer populations \((n_A, n_B)\) in dilute solutions were estimated from the averaged signal width \(W = \Sigma J_{HH}\) (a sum of spin-spin couplings) of the protons geminal to the triazole:

\[
W_{\text{observed}} = W_A n_A + W_B n_B.
\]

The limiting parameters \(W_A\) and \(W_B\) for individual conformers were obtained from the measurements for compounds 45a and 45b (Scheme 3.28). \(W_B\) was assumed to equal 32.4 Hz for H(Tz) geminal to triazole from 45a and 45b (Table 13). The limiting parameters due to conformational bias towards conform \(A\), \(W_A\), was set 12 Hz for H(Tz) geminal to triazole based on analogous compounds.\(^{81}\)
Table 13
$^1H$ NMR Data and Conformational Parameters for trans-Triazolyl-4-Methyl/Phenyl/t-Butyl-Cyclohexanes

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<th>$W$, Hz</th>
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43a (trans)- R = n-C$_6$H$_{13}$, R$^1$ = CH$_3$

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44a (trans)- R = n-C$_6$H$_{13}$, R$^1$ = Phenyl

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<th>$\delta$</th>
<th>$W$, Hz</th>
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<th>$\Delta G_{B-A}$</th>
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<td>kcal/mol</td>
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45a (trans)- R = n-C$_6$H$_{13}$, R$^1$ = C(CH$_3$)$_3$

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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Poorly resolved signal; d) Used as $W_B$; e) d-trifluoroacetic acid was added in large excess ($x10^{-15}$) to CD$_3$OD solution.
(Table 13 Continued)

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<th>$n_B (n_{BD^+})$</th>
<th>$\Delta G_{B-A^+}$, kJ/mol</th>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Poorly resolved signal; d) Used as $W_B$; e) $d$-trifluoroacetic acid was added in large excess ($x10^{15}$) to CD$_3$OD solution.

Table 14
$^1$H NMR Data and Conformational Parameters for cis-2-Triazolyl-4-Methyl/Phenyl/t-Butyl-Cyclohexanols

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<th>$\Delta G_{B-A^+}$, kJ/mol</th>
<th>$\Delta G_{B-A^+}$, kcal/mol</th>
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a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Poorly resolved signal; d) $d$-trifluoroacetic acid was added in large excess ($x10^{15}$) to CD$_3$OD solution.
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<tr>
<td>44b (cis)- R = phenyl, R¹ = Phenyl</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CDCl₃</td>
<td>4.76</td>
<td>16.7</td>
<td>23</td>
<td>2.9</td>
<td>0.71</td>
</tr>
<tr>
<td>CD₃OD</td>
<td>4.83</td>
<td>16.2</td>
<td>21</td>
<td>3.3</td>
<td>0.79</td>
</tr>
<tr>
<td>+ CF₃COOD d)</td>
<td>4.85</td>
<td>16.3</td>
<td>21</td>
<td>3.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

<p>| | | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>45a (cis)- R = n-C₆H₁₃, R¹ = C(CH₃)₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDCl₃</td>
<td>4.57</td>
<td>13.3</td>
<td>6</td>
<td>6.6</td>
<td>1.57</td>
</tr>
<tr>
<td>CD₃OD</td>
<td>4.57</td>
<td>12.8</td>
<td>4</td>
<td>7.8</td>
<td>1.87</td>
</tr>
<tr>
<td>+ CF₃COOD d)</td>
<td>4.60</td>
<td>12.8</td>
<td>4</td>
<td>7.8</td>
<td>1.87</td>
</tr>
</tbody>
</table>

<p>| | | | | | |</p>
<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>45b (cis)- R = phenyl, R¹ = C(CH₃)₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDCl₃</td>
<td>4.67</td>
<td>13.2</td>
<td>6</td>
<td>6.8</td>
<td>1.62</td>
</tr>
<tr>
<td>CD₃OD</td>
<td>4.69</td>
<td>12.7</td>
<td>3</td>
<td>8.2</td>
<td>1.95</td>
</tr>
<tr>
<td>+ CF₃COOD d)</td>
<td>4.70</td>
<td>12.7</td>
<td>3</td>
<td>8.2</td>
<td>1.95</td>
</tr>
</tbody>
</table>

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) Partially or completely overlapped with other signals; c) Poorly resolved signal; d) d-trifluoroacetic acid was added in large excess (x10⁻³) to CD₃OD solution.
Factors Affecting Conformational Equilibrium of \textit{trans}-2-Triazolylcyclohexanes

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3_12.png}
\caption{\textsuperscript{1}H NMR signal \((\text{H}^1)\) for 44b.}
\end{figure}

**Effect of counterbalances.** The compounds 40a and 40b (Table 13), that have no counterbalance, showed an expected preference for the diequatorial conformer B. Acidic media had no effect on the conformational equilibrium. All the \textit{trans} isomers showed total preference for conformer B regardless of the counterbalance and acidity of the environment. This arrangement was used to determine the limiting parameter, \(W_B\), for these triazolylcyclohexanes.

The variation in conformer population for the \textit{cis} isomers was used to estimate the conformational energy of the triazolyl group. As the A-value increases for the counterbalances on the cyclohexane ring, the preference for conformer A increases. The equilibrium Gibbs free energy, \(\Delta G_{B-A}\), and the A-value for the counterbalance can be used to estimate the conformational energy of the triazolyl group.
Table 15
$^1{H}$ NMR Data and Conformational Parameters for cis-Triazolyl-4-Methyloacyclohexanols 43a and 43b $^{a)}$

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H'$ (Tz)</th>
<th>$\delta$</th>
<th>W, Hz</th>
<th>$n_B(n_{BD^+})$</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
<th>$\Delta G_{B-A}$, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCl$_3$</td>
<td>4.43</td>
<td>24.7</td>
<td>62</td>
<td>-1.2</td>
<td>-0.29</td>
<td></td>
</tr>
<tr>
<td>CD$_3$OD</td>
<td>4.49</td>
<td>24.2</td>
<td>60</td>
<td>-1.0</td>
<td>-0.23</td>
<td></td>
</tr>
<tr>
<td>CD$_3$OD + CF$_3$COOD $^{d)}$</td>
<td>4.51</td>
<td>24.3</td>
<td>60</td>
<td>-1.0</td>
<td>-0.24</td>
<td></td>
</tr>
</tbody>
</table>

43b (cis) $^{b)}$  R = phenyl

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H'$ (Tz)</th>
<th>$\delta$</th>
<th>W, Hz</th>
<th>$n_B(n_{BD^+})$</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
<th>$\Delta G_{B-A}$, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCl$_3$</td>
<td>4.55</td>
<td>24.5</td>
<td>61</td>
<td>-1.1</td>
<td>-0.27</td>
<td></td>
</tr>
<tr>
<td>CD$_3$OD</td>
<td>4.59</td>
<td>24.3</td>
<td>60</td>
<td>-1.0</td>
<td>-0.24</td>
<td></td>
</tr>
<tr>
<td>CD$_3$OD + CF$_3$COOD $^{d)}$</td>
<td>4.62</td>
<td>24.3$^{(b)j}$</td>
<td>60</td>
<td>-1.0</td>
<td>-0.24</td>
<td></td>
</tr>
</tbody>
</table>

$^{a)}$ 600 MHz; 0.02-0.03 M solutions at 294K; $^{b)}$ Partially or completely overlapped with other signals; $^{c)}$ Poorly resolved signal; $^{d)}$ d-trifluoroacetic acid was added in large excess ($x10^{15})$ to CD$_3$OD solution.

\[
\Delta G^o_{B-A} = -RT\ln \frac{[B]}{[A]} = -RT\ln \frac{[60]}{[40]} \approx -0.24 \text{ kcal/mol}
\]

\[
\Delta G^o_{TZ} = \Delta G^o_{B-A} + \Delta G^o_{CH_3} = -0.24 - 1.74 = -1.98 \approx 2.0 \text{ kcal/mol}
\]

With the methyl group as the counterbalance, the 1.74 kcal/mol A-value is able to change the conformational preference towards conformer A while still keeping conformer B as the major conformer in the equilibrium. Addition of excess d-TFA has no effect on the population of either conformer. The conformational energy was determined in CD$_3$OD because the values from $\Delta G_{B-A}$ were consistent as compared to CDCl$_3$. With the use of the A-value and -0.24 kcal/mol for $\Delta G_{B-A}$ (Table 13 and 14), the conformational energy of the triazolyl group was estimated as approximately 2.0 kcal/mol. This is a higher conformational energy than for the methyl group.
Table 16
$^1H$ NMR Data and Conformational Parameters for cis-Triazolyl-4-Phenylcyclohexanols 44a and 44b $^a$)

<table>
<thead>
<tr>
<th>solvent, acid</th>
<th>$H^1$(Tz)</th>
<th>$\delta$</th>
<th>$W$, Hz</th>
<th>$n_B(n_B^*)$</th>
<th>$\Delta G_{B-A}$, kJ/mol</th>
<th>$\Delta G_{B-A}$, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCl$_3$</td>
<td></td>
<td>4.64</td>
<td>17.1</td>
<td>25</td>
<td>2.7</td>
<td>0.64</td>
</tr>
<tr>
<td>CD$_3$OD</td>
<td></td>
<td>4.84</td>
<td>16.2</td>
<td>21</td>
<td>3.3</td>
<td>0.79</td>
</tr>
<tr>
<td>+ CF$_3$COOD $^b$</td>
<td></td>
<td>4.87</td>
<td>16.2</td>
<td>21</td>
<td>3.3</td>
<td>0.79</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td></td>
<td>4.76</td>
<td>16.7</td>
<td>23</td>
<td>2.9</td>
<td>0.71</td>
</tr>
<tr>
<td>CD$_3$OD</td>
<td></td>
<td>4.83</td>
<td>16.2</td>
<td>21</td>
<td>3.3</td>
<td>0.79</td>
</tr>
<tr>
<td>+ CF$_3$COOD $^b$</td>
<td></td>
<td>4.85</td>
<td>16.3</td>
<td>21</td>
<td>3.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) d-trifluoroacetic acid was added in large excess (x10$^{-15}$) to CD$_3$OD solution.

$$
\Delta G^o_{B-A} = -RT \ln \left[ \frac{[B]}{[A]} \right] = -RT \ln \left[ \frac{[B]}{[A]} \right] \approx 0.79 \ \text{kCal/mol} \quad \Delta G^o_{Ph} = -2.80 \ \text{kCal/mol}
$$

$$
\Delta G^o_{TZ} = \Delta G^o_{B-A} + \Delta G^o_{Ph} = 0.79 - 2.80 = -2.01 \approx -2.0 \ \text{kCal/mol}
$$

The phenyl group alters the conformational equilibrium to give preference to A while keeping B as the minor population. Addition of excess d-TFA has no effect on the population of either conformer. With the use of the A-value for phenyl (2.80 kcal/mol) and 0.79 kcal/mol $\Delta G_{B-A}$ (Table 15 and 16), conformational energy of the triazolyl group was estimated again to be approximately 2.0 kcal/mol. This corresponds to the results from the equilibrium that show a
significant preference for conformer A with the triazole preferring the axial position due to the higher conformational energy of the phenyl group.

The conformational results from cis-triazolyl-4-methylcyclohexanes (43a and 43b) and cis-triazolyl-4-phenylcyclohexanes (44a and 44b) show that the conformational energy of the triazolyl group is between 1.74 and 2.80 kcal/mol because of the preference for B in the former and the preference for A in the latter. The compounds 45a and 45b (Table 14), with the t-butyl counterbalance, showed total preference for conformer A. This is expected because of the conformational energy of the t-butyl ‘anchor” (4.50 kcal/mol) is large and firmly holds the triazolyl group in the axial position. This result shows that the A-value of the triazole is significantly lower than that of t-butyl.

**Calculations for the Conformational Energy of the Triazolyl Group**

In order to support the results in Tables 13, 14 and 15, calculations were done on model compounds to determine the conformational energy of the triazolyl group on a cyclohexane ring. Initial training calculations were done on simple cyclohexane models with methyl (A<sup>eq</sup> and A<sup>ax</sup>) and phenyl(B<sup>eq</sup> and B<sup>ax</sup>) (Figure 3.13) substituents in reference to previously obtained conformational energies in gas phase and in methanol.<sup>82,83</sup>

All the calculations were done using Gaussian 09 program package and carried out by the group of Dr. Hyun Joo. Initially the models were optimized to obtain geometry with the lowest potential energy. This optimization included rotation of the substituents along a particular bond while allowing the rest of the molecule to accommodate the changes. This would ensure that the lowest energy structure was obtained with the consideration of all rotamers of each model. The geometry optimizations were performed at MP2 level with 6-311+G(d,p) basis set.<sup>84</sup>
To confirm that the geometry of each optimized structure was at the true minimum, vibration frequency calculations were carried out. From these calculations, thermodynamic correction terms including zero point vibration energy, thermal correction ($C_p$) to enthalpy ($\Delta H^o$), and entropy ($\Delta S^o$) were attained. For more accurate description of thermodynamics of the axial and equatorial conformers, coupled cluster CCSD(T) method was used for single point energy calculation based on the MP2 optimized geometries of each structure. This was done to find the lowest potential energy for the already optimized structures while accounting for all excitations, i.e. up to triple excitations (T). These excitations included interactions of the molecules in gas phase and in methanol which was the experimental environment.

Figure 3.13. Optimized structures of substituted model cyclohexanes.
Figure 3.14. Optimized structures of triazolycyclohexanes.
The results from the simple models agreed with the previous studies of calculated $\Delta G^o$ in the gas phase for the methyl and phenyl groups as 1.99 kcal/mol and 3.06 kcal/mol respectively (Table 16). In methanol the calculated $\Delta G^o_{sol}$ for the methyl and phenyl groups, 1.96 kcal/mol and 3.20 kcal/mol respectively, agree with the gas phase results. The same calculations were done for the triazolylcycohexanes with these same substituents to estimate the A-value of the triazolyl group.

Table 17
*Calculated Conformational Enthalpy ($\Delta H^o$), Free Energy ($\Delta G^o$) and Free Energy of Solvation in Methanol ($\Delta G^o_{sol}$) for Substituted Cyclohexanes at 298K*

<table>
<thead>
<tr>
<th></th>
<th>$\Delta H^o$</th>
<th>$\Delta G^o$</th>
<th>$\Delta G^o_{sol}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MP2/SBS</td>
<td>MP2/LBS</td>
<td>CCSD(T)/SB S</td>
</tr>
<tr>
<td>($A^{ax} - A^{eq}$)</td>
<td>1.90</td>
<td>1.84</td>
<td>1.94</td>
</tr>
<tr>
<td>($B^{ax} - B^{eq}$)</td>
<td>3.02</td>
<td>2.40</td>
<td>3.32</td>
</tr>
<tr>
<td>($40^{Tz-ax} - 40^{Tz-eq}$)</td>
<td>1.32</td>
<td>1.44</td>
<td>1.57</td>
</tr>
<tr>
<td>($43^{Tz-ax} - 43^{Tz-eq}$)</td>
<td>-0.47</td>
<td>-0.59</td>
<td>-0.23</td>
</tr>
<tr>
<td>($44^{Tz-ax} - 44^{Tz-eq}$)</td>
<td>-2.03</td>
<td>-1.39</td>
<td>-1.99</td>
</tr>
<tr>
<td></td>
<td>MP2/SBS</td>
<td>MP2/LBS</td>
<td>CCSD(T)/SB S</td>
</tr>
<tr>
<td>($A^{ax} - A^{eq}$)</td>
<td>2.01</td>
<td>1.95</td>
<td>2.05</td>
</tr>
<tr>
<td>($B^{ax} - B^{eq}$)</td>
<td>3.38</td>
<td>2.76</td>
<td>3.68</td>
</tr>
<tr>
<td>($40^{Tz-ax} - 40^{Tz-eq}$)</td>
<td>1.49</td>
<td>1.41</td>
<td>1.85</td>
</tr>
<tr>
<td>($43^{Tz-ax} - 43^{Tz-eq}$)</td>
<td>-0.41</td>
<td>-0.54</td>
<td>-0.17</td>
</tr>
<tr>
<td>($44^{Tz-ax} - 44^{Tz-eq}$)</td>
<td>-1.87</td>
<td>-1.24</td>
<td>-1.84</td>
</tr>
<tr>
<td></td>
<td>MP2/SBS</td>
<td>MP2/LBS</td>
<td>CCSD(T)/SB S</td>
</tr>
<tr>
<td>($A^{ax} - A^{eq}$)</td>
<td>1.98</td>
<td>1.92</td>
<td>2.02</td>
</tr>
<tr>
<td>($B^{ax} - B^{eq}$)</td>
<td>3.52</td>
<td>2.90</td>
<td>3.82</td>
</tr>
<tr>
<td>($40^{Tz-ax} - 40^{Tz-eq}$)</td>
<td>2.14</td>
<td>2.06</td>
<td>2.50</td>
</tr>
<tr>
<td>($43^{Tz-ax} - 43^{Tz-eq}$)</td>
<td>0.18</td>
<td>0.09</td>
<td>0.50</td>
</tr>
<tr>
<td>($44^{Tz-ax} - 44^{Tz-eq}$)</td>
<td>-1.04</td>
<td>-0.70</td>
<td>-1.01</td>
</tr>
</tbody>
</table>
The results from the triazolyl models (Table 16 and Figure 3.14) show agreement with the $^1$H NMR conformational studies with these same counterbalances (Tables 15 and 16). In methanol specifically, the calculated $\Delta G^\circ_{sol}$ for the triazolyl group (2.41 kcal/mol) is between that of the methyl and phenyl groups. This would mean that for the cis-triazolyl-4-methylcyclohexane models, the conformer with the triazolyl group in the equatorial position and methyl group in the axial position ($43^{Tz\text{-eq}}$) is more stable than the conformer with the triazolyl group in the axial position and methyl group in the equatorial position ($43^{Tz\text{-ax}}$) by 0.42 kcal/mol. This energy difference was seen experimentally in the conformer population distribution of ~60% for conformer B ($43^{Tz\text{-eq}}$) and ~40% for conformer A ($43^{Tz\text{-ax}}$) as 0.24 kcal/mole from cis derivative 43.

The results from the cis-triazolyl-4-phenylcyclohexane models also comply with the $^1$H NMR conformational studies. The conformer with the triazolyl group in the equatorial position and phenyl group in the axil position ($44^{Tz\text{-eq}}$) is less stable than the conformer with the triazolyl group in the axial position and phenyl group in the equatorial position ($44^{Tz\text{-ax}}$) by 0.68 kcal/mol. This significant energy difference was also seen in the conformer population distribution of ~21% for conformer B ($44^{Tz\text{-eq}}$) and ~71% for conformer A ($44^{Tz\text{-ax}}$) as 0.79 kcal/mole from cis derivative 44. Thus, the experimental data from $^1$H NMR conformational studies and the calculations approximate the conformational energy of the triazolyl group in methanol to ~2.0 kcal/mol.

**Glycosidase Inhibitors and Activators**

The effect of small molecules on glycosidases can result in inhibition, activation or have no effect on the enzymes activity. As mentioned before, these small molecules need to be structurally similar to the substrate or transition state especially if they are to have any inhibitory
effect on an enzyme.\textsuperscript{56,57} Polar groups, like hydroxyl, amino, amide, carboxylic or carboxylate groups, around a molecule analogous to a carbohydrate usually produced significant inhibition to glycosidases.\textsuperscript{57} Recently our group demonstrated the effect of 4-hydroxy-5-alkoxy-1,2-cyclohexanedicarboxylic acids on activity of β-D-glucosidases and β-D-galactosidases isolated from fungi \textit{Aspergillus} and \textit{Penicillium} sp.\textsuperscript{85,86} The results showed that the presence of two carboxylic groups and one hydroxyl group is important for efficient inhibition. The magnitude of inhibition depends on the configuration of the substituents, with preference for configuration in B (Scheme 3.33). The length of the alkoxy group OR was important for inhibition of β-D-glucosidases for both \textit{Aspergillus oryzae} and \textit{Penicillium canescens}.\textsuperscript{85,86}

\begin{center}
\includegraphics[width=\textwidth]{Scheme33}
\end{center}

\textit{Scheme 3.33.} 4-Hydroxy-5alkoxy-1,2-Cyclohexanedicarboxylic Acids-Glycosidase Inhibitors. \textsuperscript{85,86}

With the increased use of the triazole moiety in drug synthesis, \textsuperscript{87,88} specifically as glycosidase inhibitors,\textsuperscript{62,88–90} combined with the glycosidase activity seen in 4-hydroxy-5-alkoxy-1,2-cyclohexanedicarboxylic acid derivatives, new triazolyl-1,2-cyclohexanedicarboxylic acids (Scheme 3.34), triazolyl-cyclohexanol and hexahydrobenzo-triazolo-ozazinone derivatives (Scheme 3.37) are of interest and they were synthesized for the first time through click chemistry\textsuperscript{91} and checked for glycosidase activity.
Library of 2-Triazolylcyclohexanol Dicarboxylic acids

Scheme 3.34. Library of trans-5-Triazolyl-4-Cylohexanol-trans/cis1-2-Dicarboxylic Acids.

A library of trans-5-triazolyl-4-cyclohexanol-trans-1-2-dicarboxylic acid derivatives 47a and 47b and trans-5-triazolyl-4-cyclohexanol-cis-1-2-dicarboxylic acid derivatives 55a, 55b, 56a and 56b were proposed for synthesis and studied as potential glycosidase activity. Compounds 55 and 56 were designed with cis carboxylic groups and trans hydroxyl and triazolyl groups. This is analogous to the 4-hydroxy-5-alkoxy-1,2-cyclohexanedicarboxylic acid derivatives that showed the most glycosidase inhibition in the previous study (Scheme 3.33).85,86 Synthesis of all dicarboxylic acids derivatives was proposed with hexyl and phenyl groups on the carbon 4 (C4) of the triazole. The hexyl long chain was proposed due to structural similarity to alkoxy groups in the previous study. In contrast to the long chain long chain alkoxy groups, a phenyl that is bulky would provide insight on bulky groups in the same position.
Synthesis of trans/cis-2-Triazolylcyclohexanol Dicarboxylic acid


Compounds 47a and 47b (Scheme 3.35) were synthesized beginning with diethyl 4-cyclohexene-trans-1,2-dicarboxylate 1. Diethyl 4-cyclohexene-trans-1,2-dicarboxylate 1 was previously synthesized\textsuperscript{19,29,30} through Diels-Alder reaction between butadiene sulfone and diethyl fumarate. The product had a \textit{trans} orientation of the ethoxylcarbonyl groups. The ensuing epoxidation of alkene 1 was done with \textit{m}-CBPA in DCM to give epoxide 2. The subsequent epoxide ring cleavage by azide ion was done with sodium azide and ammonium chloride in a 15:1 solution of H\textsubscript{2}O and ethanol. Diethyl-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate 10a was obtained as a yellow oil without purification. Azide 10a was used in a copper(I)-catalyzed “click reaction” with CuSO\textsubscript{4}.5H\textsubscript{2}O, ascorbic acid and 1-octyne or phenylacetylene in a 2:7 solution of dioxane and H\textsubscript{2}O to give 1,2,3-triazolyl derivatives 11a and 11b respectively.
Compounds \textbf{11a} and \textbf{11b} were hydrolyzed with potassium hydroxide to yield diacids \textbf{47a} and \textbf{47b}.

\textit{Cis} dicarboxylic acids \textbf{55a}, \textbf{55b}, \textbf{56a} and \textbf{56b} (Scheme 3.36) were synthesized beginning with dimethyl-4-cyclohexene-\textit{cis}-1,2-dicarboxylate \textbf{50}. Compound \textbf{50} was synthesized through the alcoholysis of \textit{cis}-1,2,3,6-tetrahydrophthalic anhydride in methanol with sulfuric acid.\textsuperscript{85} This was followed by epoxidation with \textit{m}-CBPA in DCM to give dimethyl 7-oxabicyclo[4.1.0]heptane-\textit{cis}-3,4-dicarboxylates (\textbf{50-syn}), yellow oil, and (\textbf{50-anti}), white crystals, that were separated by column chromatography. The ensuing azido-epoxide ring cleavage was done with sodium azide and ammonium chloride in the same conditions as azide \textbf{10} for both epoxides \textbf{50-syn} and \textbf{50-anti}. This dimethyl (1R*, 2S*, 4R*, 5R*)-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate \textbf{51} and dimethyl (1R*, 2S*, 4S*, 5S*)-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate \textbf{52} respectively. Azides \textbf{51} and \textbf{52} were treated with “click reactions” conditions, similar to azide \textbf{10a}, and produced dimethyl (1S*, 2R*, 4S*, 5S*)-5-(4-hexyl/phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate \textbf{53a} and \textbf{53b}, and dimethyl (1S*, 2R*, 4R*, 5R*)-5-(4-hexyl/phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate \textbf{54a} and \textbf{54b} respectively. Compounds \textbf{53} and \textbf{54} were hydrolyzed with potassium hydroxide to yield diacids \textbf{55} and \textbf{56}. 
NMR Analysis of *trans*-5-Triazolyl-4-Cyclohexanol-*trans*-1-2-Dicarboxylic Acids and *trans*-5-Triazolyl-4-Cyclohexanol-*cis*-1-2-Dicarboxylic Acids

The configuration of the structures and their predominant conformations were determined using $^1$H NMR, $^{13}$C NMR, and 2D NMR techniques that include COSY, HMQC and HMBC. $^1$H NMR helped to elucidate the equatorial and/or axial orientations of the vicinal protons, for all substituents on each compound.

![Chemical structure](image)

**Figure 3.15.** $^1$H NMR signals of *trans*-5-triazolyl-4-cyclohexanol-*trans*-1-2-dicarboxylic acid 47a (in (CD$_3$)$_2$CO).

The structural assignment of the *trans*-1-2-dicarboxylic acid derivatives, like 47a (Figure 3.15), was relatively straightforward. The large spin-spin coupling constants support the *trans*-diaxial orientation of protons $H^4$ and $H^5$, i.e., implying a diequatorial orientation for the hydroxyl and triazolyl groups. The small spin-spin coupling constants support the *trans*-diequatorial orientation of protons $H^1$ and $H^2$ in which both carboxylic groups are in a diaxial orientation.
The structural assignment of the cis-1-2-dicarboxylic acid derivatives, like 55a (Figure 3.16), differs from that of trans-1-2-dicarboxylic acid derivatives due the axial-equatorial orientation of the carboxylic groups. Two small spin-spin coupling constants of H^2 to H^1 and H^3e, and one large spin-spin coupling constant of H^2 to H^3a support the orientation of the carboxylic groups.

\[
\begin{align*}
J_{2,1} &= 4.04 \text{ Hz} \\
J_{2,3e} &= 4.04 \text{ Hz} \\
J_{2,3a} &= 12.91 \text{ Hz}
\end{align*}
\]

Figure 3.16. $^1$H NMR signals of trans-5-triazolyl-4-cyclohexanol-trans-1-2-dicarboxylic acid 55a (in CDCl$_3$).

Library of trans-2-Triazolylcyclohexanol and Hexahydrobenzo-Triazolo-Oxazinone Derivatives for Glycosidase Assays

With interest in the design of previously studied 4-hydroxy-5-alkoxy-1,2-cyclohexanedicarboxylic acid, it was evident that the carboxylic groups, hydroxyl group and alkoxy chain were of importance in the inhibition of glycosidases. With the design of a library of cis and trans dicarboxylic acid derivatives in Scheme 3.34, trans-2-triazolylcyclohexanol derivatives (Scheme 3.37) were proposed because they would help show whether glycosidase activity is affected by the absence of the carboxylic groups. While synthesizing these trans-2-
triazolylcyclohexanols, hexahydrobenzo-triazolo-oxazinone derivatives \(57\) were produced and included in the study as well.

*Scheme 3.37.* Library of \textit{trans}-2-triazolylcyclohexanols and hexahydrobenzo-triazolo-oxazinones.
Synthesis of *trans*-2-Triazolylcyclohexanol and Hexahydrobenzo-Triazolo-Oxazinone Derivatives

Lactones 57 and *trans*-2-triazolylcyclohexanols 58 were synthesized beginning with commercially available cyclohexene oxide 4. Epoxide ring cleavage of compound 4 was done in similar condition for epoxide 2 and produced 2-azidocyclohexanol 24a. Azide 24 was obtained as a yellow oil without purification. Azide 24 was exposed to “click” 1,3-dipolar cycloaddition reactions by refluxing in toluene with a series of 2-alkynyl esters. Tricyclic derivatives 57 (Scheme 3.38) goes through triazole adduct 57* 77,78 with ester at C5 and hydrocarbon at C4, which are unstable at high temperatures and further reacts through esterification to form lactones. The triazole adducts with ester at C4 and hydrocarbon at C5 is stable and affords compounds 58.
(54-70% yield). (Scheme 3.38). Similar to the synthesis of derivatives 57a-d (Scheme 3.38), azide 24a was treated with dimethyl/ethyl acetylenedicarboxylate by refluxing in toluene. These click reaction conditions resulted into lactones 57e and 57f (Scheme 3.39).

![Scheme 3.39. Synthesis of Hexahydrobenzo-Triazolo-Oxazinone-4-Carboxylate Derivatives.](image)

Azide 24a was also used in ‘click reaction” conditions with CuSO₄·5H₂O, ascorbic acid and 2-alkynyl esters in a 2:7 solution of dioxane and H₂O. These conditions facilitated the decarboxylation of the alkyne, which is also catalyzed by Cu⁺,⁹²⁻⁹⁶ leaving a terminal alkyne to react with 24a and give trans-2-triazolycyclohexanol derivative 59a-c (Scheme 3.40).
NMR Analysis of trans-2-Triazolycyclohexanols

The diequatorial orientation of the hydroxyl and triazolyl groups has already been confirmed by $^1$H NMR for trans-2-triazolylycyclohexanols (compounds 18 and 19: Table 11). The signal widths (~23-26Hz) and shape of the signals (ddd or td) for the axial protons geminal to either functional group accounts for two large couplings and one small coupling for each of the signals. But to confirm the substituents on 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles, Nuclear Overhauser Effect Spectroscopy (NOESY) NMR experiment was used.

NOESY is useful in identifying which protons are close to each other in space irrespective of bonding connectivity. This is done by irradiating the signal for the proton/s of interest on the $^1$H NMR spectrum and a response will be seen by the signals present within a given spatial environment.

Figure 3.17. NOE experiment for 58b in CDCl$_3$.

In order to solve the structural connectivity problem of 1,4-disubstituted and 1,4&5-trisubstituted 1,2,3-triazoles with NOE, 1,4-disubstituted triazole 59c (Figure 3.17) and 1,4&5-
trisubstituted triazole 58b (Figure 3.18) were explored. By irradiating the protons on the α-carbon (\(-\text{CH}_2\)), a response is expected from signals on the hydrocarbon chain and any other protons within the vicinity.

For the NOE of 58b (\(-\text{CH}_2\) at 2.95 ppm, Figure 3.17), a response was seen from the protons on the hydrocarbon chain as expected. The notable response from proton geminal to the triazole on the cyclohexane ring supports the proposed structure. The absence of response from the methoxy protons attached to C⁵ on the triazole ring also supports the proposed structure. For the NOE of 59c (\(-\text{CH}_2\) at 2.68 ppm, Figure 3.18), besides the expected response from the protons on the hydrocarbon chain, there was only a response from the proton on C⁴ of the triazole ring. The absence of response from any protons on the cyclohexane ring supports the proposed structure.

*Figure 3.18.* NOE experiment for 59c in CDCl₃.
The structures of the lactones 57 are different from the other synthesized compounds because of the lactone locks the structure into a tricyclic ring. With the carbonyl attached at C4 and a hydrocarbon chain or ester group at C5 on the triazole ring, there is separation of the protons on the triazole and cyclohexane rings. To confirm the structure of these tricyclic compounds, an NOE experiment was done for 57f (Figure 3.19). By irradiating the protons on the α-carbon on the ethoxy group (-CH2), a response was seen from signals on the β-carbon (-CH3). This coupled with the absence of a response from any protons on the cyclohexane ring supports the proposed structure.

The orientation of the substituents on hexahydrobenzo-triazolo-oxazinone derivatives can also be seen in the X-ray crystal structure of 57e (Figure 3.20). The fused planer lactone and triazole rings separate the cyclohexane ring from ester further confirming the results from the NOE experiment of 57f that has the same structure. The x-ray structure also shows the planar
nature of the methoxycarbonyl and triazole ring that a fused to the heterocyclic ring of the lactone in a half-chair conformation.

Figure 3.20. X-ray crystal structure for 57e.

Inhibition Assay for trans/cis-2-Triazolycyclohexanol Dicarboxylic Acid, trans-2-Triazolycyclohexanol and Hexahydrobenzo-Triazolo-Oxazinone Derivatives

The synthesized compounds 47, 55, 56, 57, 58 and 59 were assayed for glycosidase activity against glycosidases in multi-enzyme complexes isolated from Penicillium Canescens and Aspergillus Oryzae. The complex from P.canescens contained α-D galactosidase, β-D-galactosidase and β-D-glucosidase. The complex from A.oryzae contained α-D galactosidase, β-D-galactosidase, α-D-glucosidase and β-D-glucosidase. These assays were performed under direct supervision of Dr. Natalia Samoshina.

The experiments were performed in a standard way by monitoring the release of p-nitrophenol from its related p-nitrophenyl glycosides. The released p-nitrophenol’s concentration was analyzed spectrophotometrically at 400nm (Scheme 3.41). The combination
of enzymes and substrate combinations were chosen so that the degree of hydrolysis was between 10% and 20% over the course of the assay. The assumption for these conditions is that the amount of substrate is high enough to give a linear relationship within a given amount of time for the first stage of the reaction. After a fixed period of time, the reaction was stopped by adding 0.5M Na₂CO₃ which makes the solution basic leading to inactivation of the enzymes and the deprotonation of p-nitrophenol, hence producing a yellow color. The color intensity correlates with the amount of p-nitrophenol produced when the enzyme acts on the substrate. All synthesized compounds underwent a preliminary screening and the results are reported in Figures 3.21, 3.22 and 3.23.

Scheme 3.41. Glycosidase Activity Assay.
Figure 3.21. Effect of trans-5-triazolo[1,5-a]pyridine-1-2-dicarboxylic acids \(47a, b\), \(55a, b\) and \(56a, b\) (1mM) on the activity of glycosidases from *Aspergillus Oryzae* (A) and *Penicillium Canescens* (B).

*Trans*-dicarboxylic acid derivatives \(47\) were assayed against the enzymes from *A. oryzae* and *P. canescens* in Figure 3.21 A and B respectively. Compounds \(47a\) and \(47b\) showed no inhibition of any of the enzymes in *A. oryzae* or *P. canescens*. But, both \(47a\) and \(47b\) unexpectedly showed the highest activation for \(\beta\)-D-galactosidase from *A. oryzae*. This rare activation for \(\beta\)-D-galactosidase is important because of the recent searcher for activators of \(\beta\)-D-
galactosidase for the treatment of gangliosidosis (CDC 2019). Both compounds also showed weak activation for \( \beta \)-D-glucosidase from \( A.oryzae \).

Cis-Dicarboxylic acid derivatives 55 were assayed against the same enzymes and their results were specific for each of the enzymes. The results found in \( \alpha \)-D-galactosidase, \( \beta \)-D-galactosidase, \( \alpha \)-D-glucosidase and \( \beta \)-D-glucosidase from \( A.oryzae \) showed weak inhibition in most enzyme, but strong inhibition specifically for 55a in \( \alpha \)-D galactosidase (Figure 3.21A). Compound 55b only showed weak inhibition for all the same enzymes. In \( P.canescens \), both 55a and 55b showed strong inhibition in \( \alpha \)-D galactosidase and \( \beta \)-D-glucosidase respectively (Figure 3.21B). Weak activation was noticed for 55b in \( \beta \)-D-galactosidase.

Cis-Dicarboxylic acid derivatives 56 underwent similar assays to their diastereomers 55 and their results were not as significant. In \( \beta \)-D-galactosidase from \( A.oryzae \), 56a showed weak activation while 56b showed strong activation (Figure 3.21A). 56b also showed weak inhibition in \( \alpha \)-D-galactosidase from \( A.oryzae \). Apart from the weak activation by 56b in \( \beta \)-D-glucosidase, all the other results from the enzymes from \( P.canescens \) were insignificant.
Figure 3.22. Effect of hexahydrobenzo-triazolo-oxazinones 57a-f (1mM) on the activity of glycosidases from *Aspergillus Oryzae* (A) and *Penicillium Canescens* (B).

Lactones 57a-f underwent similar assays to compounds 47, 55 and 56 (Figure 3.21).

Consistent trends were seen in the results of these compounds. In the enzymes from *A. oryzae*, all derivatives showed weak inhibition for α-D-glucosidase and α-D galactosidase while the results for β-D-glucosidase and β-D galactosidase were insignificant (Figure 3.22A). In the enzymes from *P. canescens*, all derivatives weak to strong activation for β-D-glucosidase and β-D galactosidase while the results for β-D galactosidase were insignificant (Figure 3.22B).
Figure 3.23. Effect of trans-2-triazolylcyclohexanols 58a-d and 59a-c (1mM) on the activity of glycosidases from *Aspergillus Oryzae* (A) and *Penicillium Canescens* (B).

*Trans*-2-Triazolylcyclohexanol derivatives 58a-d and 59a-c underwent similar assays to compounds 47, 55 and 56 (Figure 3.21) and lactones 57 (Figure 3.22). Consistent trends were seen in the results of these compounds. In the enzymes from *A. oryzae*, all derivatives showed weak inhibition for α-D-glucosidase and α-D galactosidase (Figure 3.23A). Interestingly, increased activation was noticed with the lengthening of the hydrocarbon chain at C₅ on the triazole ring for compounds 58a-d when assayed against β-D-glucosidase and β-D galactosidase.
Furthermore, the reverse effect was seen the lengthening of the hydrocarbon chain at C4 on the triazole ring for compounds 59a-c for the same enzymes. In the enzymes from *P. canescens*, all derivatives weak to strong activation for β-D-glucosidase and β-D galactosidase while the results for β-D galactosidase were insignificant (Figure 3.23B).
Trans-2-(azaaryl)sulfanyl-cyclohexanols, analogous to trans-2-aminocyclohexanols (TACHs), underwent pH-induced conformational switches in acidic media. The range of switching varied based on the basicity of the azaaryl groups and the intramolecular interactions of these groups with the hydroxyl group.

Trans-2-triazolylcyclohexanols, also analogous to trans-2-aminocyclohexanols (TACHs), showed initial conformational bias that decreased the efficiency of these compounds as potential conformational switches. The interactions between the triazolyl and hydroxyl groups were studied to quantify their effects on the bias. The unknown conformational energy of the triazolyl group was estimated.

The glycosidase studies showed some activity of carbohydrate hydrolytic enzymes (β-D-glucosidase and β-D-galactosidase) in both A. oryzae and P. canescens for trans-5-triazolylcyclohexanol-1-2-dicarboxylic acid derivatives, triazolyl-lactones and trans-2-triazolylcyclohexanols. Selective inhibition for β-D-glucosidase and α-D-galactosidase in both P. canescens and A. oryzae was seen certain cis-5-triazolylcyclohexanol-1-2-dicarboxylic acid derivatives.

The results of our research have been partially published in journals and presented at National Meetings of the American Chemical Society.
JOURNAL ARTICLES

- **Ruyonga RM**, Mendoza O, Samoshin VV. *Trans-2-(Azaaryl sulfanyl)-cyclohexanol derivatives as potential pH-triggered conformational switches*. Mendeleev Communications 2018; **Accepted for publication**.

POSTERS AND PRESENTATIONS


- **Ruyonga RM**, Samoshin VV. Exploration of *trans-2-(1,2,3-triazolyl)-cyclohexanols* as potential conformational switches. Abstracts of Papers, 253th ACS National Meeting & Exposition; American Chemical Society: San Francisco, CA, United States, August 2-6, 2017; pp. ORGN-565 (**Poster**).

- **Ruyonga RM**, Melina H, Bianca N, Samoshin VV. Exploration of *trans-2-(1,2,3-triazolyl)-cyclohexanols* as potential inhibitors for fungal glycosidases. Abstracts of Papers, 253th ACS National Meeting & Exposition; American Chemical Society: San Francisco, CA, United States, August 2-6, 2017; pp. CHED-1180 (**Poster**).
Synthesis

General procedure for epoxidation of alkynes ([Diethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (2)]).

\[
\text{m-CPBA (5.7 g, 33 mmol) was dissolved in 150 mL of dry CH}_2\text{Cl}_2 \text{ at } 0^\circ\text{C. Diethyl 4-cyclohexene-trans-1,2-dicarboxylate (22 mmol) was added in small portions at } 0^\circ\text{C while stirring. The stirring continued at } 0^\circ\text{C for 13 h. After consumption of the starting material (TLC, hexane/EtOAc 7:3), 50 mL of CHCl}_3. \text{Reaction mixture was washed 2 x 25 mL of 0.4 M sodium sulfite solution, 2 x 25 mL of saturated Na}_2\text{CO}_3 \text{ and 2 x 25 mL of brine by. The organic phase was separated dried for 12 h over anhyd Na}_2\text{SO}_4, \text{and all solvent was removed on rotary evaporator to yield a crude product. Initial ratio adjustments were made for other epoxidations.} \\
\text{Diethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (2)}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

A yellow oil of the crude product initially of 3.8 g was obtained. Product was purified by column chromatography (hexane/EtOAc 3:1) to give 3.4 g (60%) of a colorless oil of pure epoxide. Rf: 0.56 (Hexane: EtOAc, 10:1). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 1.23 (t, \(J = 7.1 \text{ Hz, } 3\text{H; CH}_3\)), 1.24 (t, \(J = 7.1 \text{ Hz, } 3\text{H; CH}_3\)), 1.89 (ddd, \(J = 14.9, 10.7, 2.1 \text{ Hz, } 1\text{H; H5a}\)), 2.05 (dd, \(J = 15.3, 10.9 \text{ Hz, } 1\text{H; H2a}\)), 2.31 (ddd, \(J = 15.5, 6.7, 4.7 \text{ Hz, } 1\text{H; H2e}\)), 2.46 (ddd, \(J = 14.8, 4.8, 1.9 \text{ Hz, H5e}\)), 2.59 (dt, \(J = 10.8, 6.6 \text{ Hz, } 1\text{H; H3}\)), 2.82 (dt, \(J = 10.7, 4.8 \text{ Hz, H4}\)), 3.18 (t, \(J = 4.4 \text{ Hz, H1}\)), 3.25 (m, H6), 4.13 (m, 4H, OCH\(_2\)). \(^13\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 14.15 (2CH\(_3\), Et),
26.40 (C2), 27.30 (C5), 37.80 (C3), 40.11 (C4), 50.34 (C1), 51.94 (C6), 60.74 (2C, OCH₂), 173.79, 174.71 (C=O). HMRS: C₁₂H₁₉O₅⁺ [M+H]_{cal} m/z 243.1227; [M+H]_{exp} m/z 243.1231.

**Dimethyl 7-oxabicyclo[4.1.0]heptane-cis-3,4-dicarboxylates (49-syn) and (49-anti)**

Epoxides 49-syn and 49-anti were prepared from dimethyl 4-cyclohexene-cis-1,2-dicarboxylate 7 (12.6 g , 63 mmol) as described in the epoxidation procedure and separated by column chromatography (Hex:EtOAc/1:1).

(1R,3S,4R,6S)-dimethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (49-syn)

![Diagram of (1R,3S,4R,6S)-dimethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (49-syn)](image)

Yielded a yellow oil of 4.4 g (37%). ¹H NMR (600 MHz, CDCl₃): δ 2.12 (dd, J=15.2, 4.7 Hz, 2H; H₂eq, H₅eq), 2.67 (dd, J=15.5, 6.7 Hz, 2H; H₂ax, H₅ax), 2.74 (m, 2H; H₃, H₄), 3.16 (m, 2H, H₁, H₆), 3.67 (s, 6H, OCH₃). ¹³C NMR (150 MHz, CDCl₃): δ 24.84 (C₂, C₅), 37.59 (C₃, C₄), 51.02 (C₁, C₆), 51.95 (OCH₃), 173.08 (C=O). C₁₀H₁₅O₅ [M+H]_{cal} m/z 215.0914; [M+H]_{exp} m/z 215.0922.

(1R,3R,4S,6S)-dimethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (49-anti)

![Diagram of (1R,3R,4S,6S)-dimethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (49-anti)](image)

Yielded a colorless oil of 6.0 g (48%). ¹H NMR (600 MHz, CDCl₃): δ 2.24 (m, 4H; H₂ax, H₂eq, H₅ax, H₅eq), 2.91 (m, 2H; H₃, H₄), 3.23 (m, 2H; H₁, H₆), 3.68 (s, 6H, OCH₃).
$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 24.82 (C2, C5), 37.70 (C3, C4), 51.62 (C1, C6), 52.11 (OCH$_3$), 173.57 (C=O). C$_{10}$H$_{15}$O$_5$ [M+H]$^+$ cal m/z 215.0914; [M+H]$^+$ exp m/z 215.0942

3-(methyl)-7-oxabicyclo[4.1.0]heptane (20a)

The product was isolated as a colorless oil by column chromatography (silica gel; Hex: EtOAc, 40:1): yield 925mg (84%). Rf: 0.49 (Hex: EtOAc, 10:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.84 (d, $J$ = 7.0 Hz, 3H; CH$_3$), 0.87 (m, 1H; H4), 1.22-1.33 (m, 1H; H3), 1.38 (m, 1H; H4), 1.70 (dddd, $J$ = 14.8, 12.5, 5.2, 1.5 Hz, H2ax), 1.81 (ddd, $J$ = 15.6, 11.4, 6.6 Hz, H5ax), 1.96 (m, H5eq), 2.10 (ddd, $J$ = 14.9, 4.2, 2.0 Hz, H2eq), 3.10 (m, 2H; H1, H6), $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 21.71 (CH$_3$), 23.47 (C5), 25.26 (C4), 29.04 (C3), 33.62 (C2), 51.56 (C1), 53.23 (C6).HRMS: C$_7$H$_{12}$O requires [2M+H]+$^+$ m/z 225.1855, [M+H]+$^+$ m/z 113.0966; observed m/z 225.1858, 113.0970.

3-(phenyl)-7-oxabicyclo[4.1.0]heptane (20b)

The product was isolated as a colorless oil by column chromatography (silica gel; Hexane: EtOAc, 7:3): yield 853 mg (78%). Rf: 0.25 (Hex: EtOAc, 7:3).$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.47 (m, 1H, H4), 1.52 (m, H4eq), 1.69 (m, 2H, H5eq, H5ax), 1.88 (m, 1H; H2ax), 2.11 (ddd, $J$ = 14.9, 4.1, 2.1 Hz, 1H; H2eq), 3.21 (t, $J$ = 4.4 Hz, H6), 3.32 (m, H1), 7.29 (m, 2H; Ph), 7.34 (m, 2H; Ph), 7.37 (m, 1H; Ph). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 24.13 (C4), 25.86 (C5), 28.30 (C2), 39.59 (C3), 51.99 (C1), 53.73 (C6) 124.24, 124.36, 124.94, 125.04,
125.17 (CH; Ph), 145.51 (C; Ph). HRMS: C₈H₁₂O₃ [M+H]+ m/z 157.0865; observed m/z 157.0512.

3-(tert-butyl)-7-oxabicyclo[4.1.0]heptane (20c)

![Chemical structure](image)

The product was isolated as a colorless oil by column chromatography (silica gel; Hexane: EtOAc, 40:1): yield 0.52 g (84%). Rf: 0.25 (Hex: EtOAc, 40:1). ¹H NMR (600 MHz, CDCl₃): δ 0.81 (s, 9H, CH₃), 1.07 (ddd, J = 4.1, 12.5, 25.1 Hz, 1H, H₄ax), 1.22 (m, 1H, H₃), 1.37 (m, 1H, H₄eq), 1.50 (m, 1H, H₂ax), 1.75 (ddd, J = 15.4, 12.9, 6.3 Hz, H₅ax), 2.04 (dtd, J = 15.5, 5.9, 1.7 Hz, H₅eq), 2.16 (m, 1H; H₂), 3.11 (m, 1H; H₆), 3.21 (m, 1H; H₁). ¹³C NMR (150 MHz, CDCl₃): δ 19.1 ((CH₃)₃), 25.4 (C₅), 26.7 (C₃), 27.3 (C₆), 43.1 (C(CH₃)₃), 52.6 (C₂), 54.5 (C₁). HMRS: C₁₀H₁₉O⁺ [M+H] cal m/z 155.1430; [M+H] exp m/z 155.1445.

General procedure for epoxide cleavage with azaaryl groups

Epoxide (1.11 mmol) and sodium tetraborate (1.30 mmol) were dissolved in 10 mL of THF and/or H₂O solution at r.t. Under Ar, azaaryl (1.70 mmol) was added while stirring at r.t. Reaction was monitored (TLC) until the consumption of epoxide. Reaction was diluted with 7 mL of H₂O and washed with 3 X 15 mL CH₂Cl₂. The combined organic layer was dried for 12 h over anhy Na₂SO₄, the solvent removed by rotary evaporator and the product isolated by column chromatography.
Diethyl cis-4-hydroxy-trans-5-(phenylthio)cyclohexane-trans-1,2-dicarboxylate (3a)

Reaction occurred in 10 mL of H$_2$O:THF (1:1). The residue was isolated as colorless oil by column chromatography (silica gel; DCM:EtOAc, 9:1) to give a yield 296 mg (79%). $R_f$; 0.50 (DCM:EtOAc, 9:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.20 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.21 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.83 (m, 1H; H3eq), 1.88 (m, 1H; H6eq), 2.27 (ddd, $J = 13.9$, 8.5, 3.1 Hz, 1H; H3ax), 2.35 (ddd, $J = 14.0$, 8.4, 4.1 Hz, 1H; H6ax), 2.42 (s, 1H; OH), 3.11 (td, $J = 8.1$, 4.2 Hz, 1H; H1), 3.16 (td, $J = 8.2$, 4.4 Hz, 1H; H2), 3.24 (m, 1H; H5), 3.81 (m, 4H; OCH$_2$), 7.24 (m, 1H; Ph), 7.29 (m, 2H; Ph), 7.42 (m, 2H; Ph). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 14.21 (2CH$_3$, Et), 29.02 (C6), 31.24 (C3), 39.93 (C2), 40.52 (C1), 50.33 (C5), 60.94, 60.96 (OCH$_2$), 68.12 (C4), 99.98 (C, Ph), 127.54 (CH, Ph), 129.18 (2CH, Ph), 132.31 (2CH, Ph), 173.87, 174.03 (C=O). HMRS: C$_{18}$H$_{25}$O$_5$S$^+ [M+H]$ cal m/z 353.1417; [M+H]$^+$ exp m/z 353.1432.

Diethyl cis-4-hydroxy-trans-5-(-p-tolylthio)cyclohexane-trans-1,2-dicarboxylate (3b)

Reaction occurred in 10 mL of H$_2$O:THF (1:1). The residue was isolated as colorless oil by column chromatography (silica gel; DCM:EtOAc, 9:1) to give a of yield 293 mg (81%). $R_f$; 0.54 (DCM:EtOAc, 9:1). $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 1.14 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.15 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.83 (m, 3H; H3ax, H3eq, H6eq), 2.11 (ddd, $J = 13.4$, 12.9, 4.1 Hz, 1H;
H6ax), 2.81 (ddd, \( J = 12.2, 11.1, 3.7 \text{ Hz}, \text{ H1} \)), 2.90 (td, \( J = 11.3, 4.4 \text{ Hz}, \text{ H2} \)), 3.34 (s, 3H; CH3, tolyl), 3.39 (q, \( J = 3.3 \text{ Hz}, \text{ H5} \)), 3.79 (quin, \( J = 3.2 \text{ Hz}, \text{ H4} \)), 4.04 (m, 4H; OCH2), 5.30 (d, \( J = 3.5 \text{ Hz}, \text{ H1}; \text{ OH} \)), 7.17 (m, 2H; tolyl), 7.32 (m, 2H; tolyl). \(^{13}\)C NMR (150 MHz, DMSO-d6): \( \delta \) 14.52, 14.54 (2CH3; Et), 21.11 (CH3; tolyl), 28.00 (C6), 30.92 (C3), 39.16 (C2), 39.89 (C1), 48.69 (C5), 60.64, 60.71 (OCH2), 66.25 (C4), 130.46 (2CH; tolyl), 131.02 (C, tolyl), 131.75 (2CH; tolyl), 137.28 (C, tolyl), 174.27, 174.77 (C=O). HMRS: C19H27O5S+ [M+H]cal m/z 367.1574; [M+H]exp m/z 367.1398.

Diethyl cis-4-hydroxy-trans-5-(pyridine-2-yl-thio)cyclohexane-trans-1,2-dicarboxylate (3c)

Reaction occurred in 10 mL of H2O. The residue was isolated as colorless oil by column chromatography (silica gel; Hex:EtOAc, 7:3) to give a yield of 293 mg (65%). \( R_f \); 0.20 (hexane:EtOAc, 7:3). \(^1\)H NMR (600 MHz, CD3OD): \( \delta \) 1.23 (t, \( J = 7.0 \text{ Hz}, \text{ 3H}; \text{ CH3} \)), 1.25 (t, \( J = 7.1 \text{ Hz}, \text{ 3H}; \text{ CH3} \)), 1.92 (m, 1H; H2ax), 2.02 (m, 2H; H2eq, H6eq), 2.35 (ddd, \( J = 13.8, 12.4, 4.1 \text{ Hz}, \text{ 1H}; \text{ H6ax} \)), 2.90 (ddd, \( J = 12.0, 10.9, 3.8 \text{ Hz}, \text{ 1H}; \text{ H1} \)), 3.07 (ddd, \( J = 12.0, 10.8, 4.1 \text{ Hz}, \text{ 1H}; \text{ H2} \)), 4.03 (q, \( J = 3.5 \text{ Hz}, \text{ H4} \)), 4.13 (m, 4H; OCH2), 4.19 (q, \( J = 3.5 \text{ Hz}, \text{ 1H}; \text{ H5} \)), 7.11 (m , 1H; pyridinyl), 7.30 (m , 1H; pyridinyl), 7.62 (td , \( J = 8.0, 2.0 \text{ Hz}, \text{ 1H}; \text{ pyridinyl} \)), 8.41 (m , 1H; pyridinyl). \(^{13}\)C NMR (150 MHz, CD3OD): \( \delta \) 13.12 (2CH3, Et), 28.11 (C6), 31.15 (C3), 39.09 (C2), 40.84 (C1), 44.14 (C5), 60.50, 6055 (OCH2), 67.42 (C4), 120.06, 122.76, 136.64, 146.27 (CH, pyridinyl), 157.45 (C, pyridinyl), 174.41, 174.52 (C=O). HMRS: C17H24NO5S+ [M+H]cal m/z 354.1370; [M+H]exp m/z 354.1371.
**Diethyl cis-4-hydroxy-trans-5-(pyridine-4-yl-thio)cyclohexane-trans-1,2-dicarboxylate (3d)**

Reaction occurred in 10 mL of H$_2$O. The residue was isolated as yellow oil by column chromatography (silica gel; EtOAc) to give a yield of 280 mg (72%). \(R_f; \ 0.34\) (EtOAc). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.24 (t, $J = 7.0$ Hz, 3H; CH$_3$), 1.25 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.99 (m, 3H; H3ax, H3eq, H6eq), 2.41 (ddd, $J = 14.2$, 11.4, 4.1 Hz, 1H; H6ax), 2.94 (ddd, $J = 11.2$, 10.1, 3.8 Hz, 1H; H1), 3.10 (td, $J = 10.2$, 4.4 Hz, 1H; H2), 3.76 (q, $J = 4.1$ Hz, H5), 3.97 (q, $J = 3.9$ Hz, H4), 4.14 (m, 4H; OCH$_2$), 7.37 (m, 2H; pyridinyl), 8.34 (m, 2H; pyridinyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 13.13 (2CH$_3$, Et), 27.81 (C6), 30.99 (C3), 39.30 (C2), 40.41 (C1), 44.97 (C5), 60.60, 60.72 (OCH$_2$), 66.71 (C4), 121.62 (2CH; pyridinyl), 148.48 (2CH; pyridinyl), 174.14, 174.66 (C=O). HMRS: C$_{17}$H$_{24}$NO$_5$S$^+$ [M+H]$^+$ $m/\ell$ 354.1370; [M+H]$^+$ $m/\ell$ 354.1382.

**Diethyl cis-4-hydroxy-trans-5-(pyrimidin-2-yl-thio)cyclohexane-trans-1,2-dicarboxylate (3e)**

Reaction occurred in 10 mL of H$_2$O:THF (1:1). The residue was isolated as yellow oil by column chromatography (silica gel; Hex:EtOAc, 7:3) to give a yield of 0.184 mg (47%). \(R_f; \ 0.13\) (hexane:EtOAc, 7:3). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.23 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.25 (t, $J = 7.0$ Hz, 3H; CH$_3$), 1.88 (m, 1H; H2ax), 2.04 (dtd, $J = 14.1$, 4.0, 1.5 Hz, 1H; H3eq), 2.10 (dt, $J = 13.9$, 3.5 Hz, H6eq), 2.37 (ddd, $J = 13.6$, 12.8, 4.2 Hz, 1H; H6ax), 2.86 (ddd, $J = 12.3$, 12.8, 4.2 Hz, 1H; H6ax).
11.0, 3.8 Hz, 1H; H1), 3.08 (ddd, J = 12.1, 11.1, 4.0 Hz, 1H; H2), 4.10 (q, J = 3.7 Hz, 1H; H4), 4.13 (m, 4H; OCH2), 4.22 (q, J = 3.6 Hz, 1H; H5), 7.16 (t, J = 4.9 Hz, 1H; pyrimidinyl), 8.58 (d, J = 4.9 Hz, 2H; pyrimidinyl). $^{13}$C NMR (150 MHz, CD3OD): δ 13.10 (2CH3, Et), 27.89 (C6), 31.23 (C3), 39.03 (C1), 40.96 (C2), 44.60 (C5), 60.50, 60.58 (OCH2), 67.07 (C4), 117.13 (CH; pyrimidinyl), 157.65 (2C, CH; pyrimidinyl), 170.61 (C; primidinyl) 174.53 (C=O), 175.09 (C=O). HRMS: C16H23N2O5S+ [M+H]cal m/z 355.1322 ; [M+H]exp m/z 355.1334.

Diethyl cis-4-hydroxy-trans-5-((1H-imidazol-2-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3f)

![Chemical structure](image)

Reaction occurred in 10 mL of H2O. The residue was isolated as yellow oil by column chromatography (silica gel; DCM:MeOH, 9:1) to give a yield of 0.305 mg (80%). Rf; 0.13 (DCM:MeOH, 9:1). $^1$H NMR (600 MHz, CD3OD): δ 1.23 (t, J = 7.1 Hz, 3H; CH3), 1.25 (t, J = 7.1 Hz, 3H; CH3), 1.90 (m, 2H; H3eq, H6eq), 2.08 (m, 1H; H3ax), 2.22 (ddd, J = 13.1, 11.5, 4.1 Hz, 1H; H6ax), 2.96 (ddd, J = 11.4, 10.2, 3.8 Hz, 1H; H1), 3.04 (ddd, J = 11.0, 10.5, 4.0 Hz, 1H; H2), 3.46 (q, J = 3.8 Hz, H5), 3.85 (q, J = 3.7 Hz, H4), 4.12 (m, 4H; OCH2), 4.88 (s, OH), 7.12 (s, 2H; imidazolyl). $^{13}$C NMR (150MHz, CD3OD): δ 13.14, 13.17 (2CH3, Et), 27.94 (C6), 30.37 (C3), 39.30 (C2), 39.97 (C1), 49.74 (C5), 60.53, 60.61 (OCH2), 66.96 (C4), 124.12 (C, imidazolyl), 137.37 (2CH, imidazolyl), 174.33, 174.84 (C=O). HRMS: C15H20N2O5S+ [M+H]cal m/z 343.1322; [M+H]exp m/z 343.1341.
Diethyl-4-hydroxy-t-5-((1-methyl-1H-imidazol-2-yl)thio)-cyclohexane-r-1,t-2-dicarboxylate (3g)

Reaction occurred in 10 mL of H₂O. The residue was isolated as colorless oil by column chromatography (silica gel; Hex:EtOAc, 1:4) to give a yield of 481 mg (79%). Rf; 0.23
(hexane:EtOAc, 1:4). ¹H NMR (600 MHz, CD₃OD): δ 1.23 (t, J = 7.1 Hz, 3H; CH₃), 1.25 (t, J = 7.0 Hz, 3H; CH₃), 1.88 (dt, J = 14.1, 3.9 Hz, 1H; H6eq), 1.94 (dt, J = 14.0, 4.0 Hz, 1H; H3eq), 2.06 (m, 1H; H3ax), 2.22 (ddd, J = 14.1, 11.3, 4.0 Hz, 1H; H6ax), 2.99 (ddd, J = 11.1, 10.1, 3.8 Hz, 1H; H2), 3.05 (td, J = 11.1, 4.0 Hz, 1H; H1), 3.45 (q, J = 4.0 Hz, 1H; H5), 3.77 (s, 3H; CH₃-imidazolyl), 3.88 (q, J = 3.8 Hz, 1H; H4), 4.13 (m, 4H; OCH₂), 7.04 (d, J = 1.4 Hz, 1H; H; imidazolyl), 7.24 (d, J = 1.4 Hz, 1H; H; imidazolyl). ¹³C NMR (150 MHz, CD₃OD): δ 13.11, 13.12 (2CH₃, Et), 28.02 (C6), 30.64 (C3), 32.90 (CH₃; imidazolyl) 39.30 (C2), 40.12 (C1), 49.99 (C5), 60.55, 60.61 (OCH₂), 66.98 (C4), 123.76, 128.56 (2C, CH; imidazolyl), 139.08 (C; imidazolyl) 174.19, 174.77 (C=O). HRMS: C₁₆H₂₅N₂O₂S⁺ [M+H]calc m/z 357.1479 ; [M+H]exp m/z 357.1483.
Diethyl cis-4-hydroxy-trans-5-((1H-1,2,4-triazol-3-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3h)

Reaction occurred in 10 mL of H₂O. The residue was isolated as colorless oil by column chromatography (silica gel; Hex:EtOAc, 1:4) to give a yield of 251 mg (69%). Rₛ; 0.46
(hexane:EtOAc, 1:4). $^1$H NMR (600 MHz, CD₃OD): δ 1.23 (t, $J = 7.1$ Hz, 3H; CH₃), 1.24 (t, $J = 7.1$ Hz, 3H; CH₃), 1.97 (m, 2H; H3ax, H3eq), 2.05 (dt, $J = 14.0$, 3.6 Hz, 1H; H6eq), 2.31 (ddd, $J = 14.0$, 12.2, 4.0 Hz, 1H; H6ax), 2.91 (ddd, $J = 12.0$, 10.7, 3.8 Hz, 1H; H1), 3.06 (td, $J = 10.6$, 5.4 Hz, 1H; H2), 3.86 (q, $J = 3.6$ Hz, H5), 4.02 (q, $J = 3.3$ Hz, H4), 4.13 (m, 4H; OCH₂), 8.36 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD₃OD): δ 13.12 (2CH₃, Et), 27.98 (C6), 30.56 (C3), 39.13 (C2), 40.22 (C1), 47.36 (C5), 60.52, 60.60 (OCH₂), 67.02 (C4), 146.43 (CH, triazolyl), 157.62 (C, triazolyl), 174.38, 174.92 (C=O). HMRS: C₁₄H₁₁N₃O₅S⁺ [M+H]cal m/z 344.1275; [M+H]exp m/z 344.1283.

Diethyl cis-4-hydroxy-trans-5-((3-amino-1H-1,2,4-triazol-5-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3i)

Reaction occurred in 10 mL of H₂O. The residue was isolated as light yellow oil by column chromatography (silica gel; Hex:EtOAc, 1:4) to give a yield of 141 mg (43%). Rₛ; 0.1 (hexane:EtOAc, 1:4). $^1$H NMR (600 MHz, CD₃OD): δ 1.23 (t, $J = 7.1$ Hz, 3H; CH₃), 1.24 (t, $J =
7.1 Hz, 3H; CH₃), 1.95 (m, 2H; H3ax, H3eq), 2.04 (dt, J = 14.0, 3.6 Hz, 1H; H6eq), 2.26 (ddd, J = 13.9, 12.3, 4.1 Hz, 1H; H6ax), 2.89 (ddd, J = 12.0, 10.9, 3.8 Hz, 1H; H1), 3.03 (m, 1H; H2), 3.73 (q, J = 3.6 Hz, H5), 4.00 (q, J = 3.3 Hz, H5), 4.12 (m, 4H; OCH₂).

13C NMR (150 MHz, CD₃OD): δ 13.10 (2CH₃, Et), 27.94 (C6), 30.46 (C3), 39.12 (C2), 40.18 (C1), 47.24 (C5), 60.48, 60.54 (OCH₂), 67.10 (C4), 155.54, 158.87 (C, triazolyl), 174.52, 174.99 (C=O).

HMRS: C₁₄H₂₃N₄O₅S⁺ [M+H]_{cal} m/z 359.1384; [M+H]_{exp} m/z 359.1379.

Diethyl cis-4-hydroxy-trans-5-((5-(pyridin-3-yl)-4H-1,2,4-triazol-3-ylthio)cyclohexane-trans-1,2-dicarboxylate (3j)

Reaction occurred in H₂O:THF (1:1). The residue was isolated as white crystals by column chromatography (silica gel; DCM:MeOH, 19:1) to give a yield of 281 mg (63%). Rf; 0.45 (DCM:MeOH, 19:1). ¹H NMR (600 MHz, CD₃OD): δ 1.23 (t, J = 7.1 Hz, 3H; CH₃), 1.24 (t, J = 7.1 Hz, 3H; CH₃), 2.00 (m, 2H; H3ax, H3eq), 2.11 (dt, J = 14.1, 3.9 Hz, 1H; H6eq), 2.37 (ddd, J = 14.0, 11.8, 4.1 Hz, 1H; H6ax), 2.95 (ddd, J = 11.6, 10.3, 3.8 Hz, 1H; H1), 3.09 (m, 1H; H2), 3.96 (q, J = 3.8 Hz, H5), 4.08 (q, J = 3.7 Hz, H5), 4.13 (m, 4H; OCH₂) 7.56 (m, 1H; pyridinyl), 8.41 (m, 1H; pyridinyl), 8.61 (m, 1H; pyridinyl), 9.17 (m, 1H; pyridinyl). ¹³C NMR (150 MHz, CD₃OD): δ 13.11, 13.12 (2CH₃, Et), 28.11 (C6), 30.72 (C3), 39.22 (C2), 40.32 (C1), 47.88 (C5), 60.56, 60.66 (OCH₂), 67.08 (C4), 124.13 (CH, pyridinyl), 125.97 (C, pyridinyl), 134.25, 146.60, 149.68 (CH, pyridinyl), 149.71, 160.11 (C, triazolyl), 174.21, 174.83 (C=O).

HMRS: C₁₉H₂₅N₄O₅S⁺ [M+H]_{cal} m/z 421.1540; [M+H]_{exp} m/z 421.1561.
Diethyl cis-4-hydroxy-trans-5-((1H-benzoimidazol-2-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3k)

Reaction occurred in 10 mL of H$_2$O. The residue was isolated as white crystals by column chromatography (silica gel; Hex:EtOAc, 1:1) to give a yield 361 mg (61%). $R_f$: 0.37 (hexane:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.22 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.24 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.90 (m, 1H; H3ax), 1.98 (m, 1H; H6ax), 2.32 (m, 1H; H3eq), 2.52 (m, 1H; H6eq), 3.10 (m, 1H; H1), 3.27 (m, 1H; H2), 3.86 (m, 1H; H5), 4.00 (dt, $J$ = 7.5, 3.3 Hz, 1H; H4), 4.15 (m, 4H; OCH$_2$), 7.18 (m, 2H; Ph), 7.47 (s, 2H; Ph). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 14.23 (2CH$_3$, Et), 29.12 (C6), 32.52 (C3), 40.19 (C2), 41.01 (C1), 49.12 (C5), 61.21, 61.30 (OCH$_2$), 70.31 (C4), 121.63 (4CH, Ph), 149.57 (C, Ph), 163.55 (C, imidazolyl), 173.48, 174.15 (C=O). HMRS: C$_{19}$H$_{25}$NO$_5$S$^+$ [M+H]$_{\text{cal}}$ m/z 393.1479; [M+H]$_{\text{exp}}$ m/z 393.1483.

Diethyl cis-4-hydroxy-trans-5-((benzothiazol-2-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3l)

Reaction occurred in 10 mL of H$_2$O. The residue was isolated as colorless oil by column chromatography (silica gel; Hex:EtOAc, 1:1) to give a yield of 309 mg (68%). $R_f$: 0.54 (hexane:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.25 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.24 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.95 (m, 1H; H3ax), 2.11 (m, 1H; H6ax), 2.27 (m, 1H; H3eq), 2.54 (m, 1H; H6eq), 3.06 (m, 1H; H1), 3.24 (dt, $J$ = 7.6, 4.4 Hz, 1H; H2), 3.66 (br. s, 1H; OH), 4.08 (m, 1H; OH).
H4), 4.12 (m, 1H; H5), 4.17 (m, 4H; OCH2), 7.31 (m, 1H; Ph), 7.41 (m, 1H; Ph), 7.75 (m, 1H; Ph), 7.84 (m, 1H; Ph). 13C NMR (150 MHz, CDCl3): δ 14.25 (2CH3, Et), 28.80 (C6), 32.21 (C3), 39.84 (C2), 40.98 (C1), 49.79 (C5), 61.06, 61.15 (OCH2), 69.56 (C4), 121.15, 121.64, 124.76, 126.31 (CH, Ph), 134.49, 152.76 (C, Ph), 165.90 (C, thiazolyl), 173.41, 173.91 (C=O).

HMRS: C19H24NO6S2+ [M+H]cal m/z 410.1090; [M+H]exp m/z 410.1105.

Diethyl cis-4-hydroxy-trans-5-((benzoxazol-2-yl)thio)cyclohexane-trans-1,2-dicarboxylate (3m)

Reaction occurred in 10 mL of H2O. The residue was isolated as colorless oil by column chromatography (silica gel; Hex:EtOAc, 1:1) to give a yield of 265 mg (56%). Rf; 0.45 (hexane:EtOAc, 1:1). 1H NMR (600 MHz, CDCl3): δ 1.25 (t, J = 7.0 Hz, 3H; CH3), 1.26 (t, J = 7.1 Hz, 3H; CH3), 1.95 (m, 1H; H3eq), 2.12 (m, 1H; H6eq), 2.26 (m, 1H; H3ax), 2.55 (m, 1H; H6ax), 3.06 (dt, J = 7.7, 4.3 Hz, 1H; H1), 3.24 (dt, J = 7.6, 4.4 Hz, 1H; H2), 3.67 (s, 1H; OH), 4.07 (m, 1H; H4), 4.12 (m, 1H; H5), 4.17 (m, 4H; OCH2), 7.31 (m, 1H; Ph), 7.41 (m, 1H; Ph), 7.75 (m, 1H; Ph), 7.84 (m, 1H; Ph). 13C NMR (150 MHz, CDCl3): δ 14.26 (2CH3, Et), 28.80 (C6), 32.20 (C3), 39.84 (C2), 40.98 (C1), 49.79 (C5), 61.05, 61.14 (OCH2), 69.53 (C4), 121.15, 121.64, 124.76, 126.32 (CH, Ph), 135.49, 152.76 (C, Ph), 165.89 (C, oxazolyl) 173.44, 173.41 (C=O). HMRS: C19H24NO6S2+ [M+H]cal m/z 394.1319; [M+H]exp m/z 394.1325.
Trans-2-(phenylthio)cyclohexanol (5a)

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\text{\includegraphics[width=0.2\textwidth]{trans2phenylthiocyclohexanol.png}}
\]

Reaction occurred in 10 mL of H\textsubscript{2}O:THF (1:1). The residue was isolated as colorless oil by column chromatography (silica gel; DCM:Hex, 4:1) to give a yield of 199 mg (87\%). R\text{f}; 0.52 (DCM:hexane, 4:1). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ 1.28 (m, 4H; H4eq, H4ax, H5eq, H5ax), 1.70 (m, 2H; H3eq, H3ax), 2.11 (m, 2H; H6eq, H6ax), 2.78 (ddd, J = 12.8, 8.9, 3.0 Hz, 1H; H2), 3.33 (ddd, J = 15.0, 7.3, 2.5 Hz, 1H, H1), 7.30 (m, 3H; Ph), 7.48 (m, 2H; Ph). \textsuperscript{13}C NMR (150MHz, CDCl\textsubscript{3}): δ 24.23 (C4), 26.18 (C5), 32.86 (C3), 33.94 (C6), 56.74 (C2), 72.15 (C1), 99.68 (C, Ph), 127.74 (CH; Ph), 129.02 (2CH; Ph), 133.91 (2CH; Ph). HMRS: C\textsubscript{12}H\textsubscript{17}NOS\textsuperscript{+} [M+H]\text{cal m/z} 209.0995; [M+H]\text{exp m/z} 209.0962.

Trans-2-(p-tolylthio)cyclohexanol (5b)

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\text{\includegraphics[width=0.2\textwidth]{trans2pтолylthiocyclohexanol.png}}
\]

Reaction occurred in 10 mL of H\textsubscript{2}O:THF (1:1). The residue was isolated as colorless oil by column chromatography (silica gel; DCM:Hex, 9:1) to give a yield of 182 mg (85\%). R\text{f}; 0.50 (DCM:hexane, 9:1). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ 1.26 (m, 4H; H4eq, H4ax, H5eq, H5ax), 1.76 (m, 2H; H3eq, H3ax), 2.07 (m, 2H; H6eq, H6ax), 2.35 (s, 3H; CH\textsubscript{3}), 2.12 (m, 1H; H2), 3.29 (dt, J = 10.3, 4.4 Hz, 1H, H1), 7.12 (m, 2H; toyl), 7.37 (m, 2H; toyl). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ 21.34 (CH\textsubscript{3}), 23.53 (C4), 26.19 (C5), 31.42 (C3), 33.27 (C6), 57.24 (C2), 72.82 (C1), 98.24 (C; toyl), 129.86 (2C; toyl), 134.19 (2C; toyl) 138.25 (C; toyl). HMRS: C\textsubscript{13}H\textsubscript{19}NOS\textsuperscript{+} [M+H]\text{cal m/z} 223.1151; [M+H]\text{exp m/z} 223.1129.
Trans-2-(pyridin-2-ylthio)cyclohexanol (5c)

Reaction occurred in 10 mL of H$_2$O. The residue was isolated as a yellow oil by column chromatography (silica gel; DCM:EtOAc, 9:1) to give a yield of 180 mg (78%). $R_f$; 0.27 (DCM:EtOAc, 9:1). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.33 (m, 3H; H3, H4, H5), 1.49 (m, 1H; H6ax), 1.77 (m, 2H; H4, H5), 2.14 (m, 1H; H6eq), 2.22 (m, 1H; H3eq), 3.42 (ddd, $J$ = 12.8, 9.9, 4.0 Hz, 1H; H1), 3.51 (td, $J$ = 10.1, 4.3 Hz, 1H; H2), 6.13 (s, 1H; OH), 7.03 (ddd, $J$ = 7.3, 5.1, 1.1 Hz, 1H; H; pyridinyl), 7.29 (dt, $J$ = 8.1, 1.0 Hz, 1H; H; pyridinyl), 7.51 (ddd, $J$ = 7.9, 7.5, 1.9 Hz, 1H; H; pyridinyl), 8.35 (m, 1H; H; pyridinyl). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 24.26 (C5), 26.38 (C4), 32.50 (C6), 36.28 (C3), 52.41 (C2), 76.09 (C1), 120.16, 123.44, 136.66, 148.76 (CH; pyridinyl), 159.62 (C; pyridinyl). HRMS: C$_{11}$H$_{16}$NOS $^+ \ [M+H]_{Cal}$ m/z 210.0947; $[M+H]_{exp}$ m/z 210.0954.

Trans-2-(pyridin-4-ylthio)cyclohexanol (5d)

Reaction occurred in 10 mL of H$_2$O. The residue was isolated as white crystals by column chromatography (silica gel; EtOAc:MeOH, 9:1) to give a yield of 209 mg (83%). $R_f$; 0.38 (EtOAc:MeOH, 9:1). $^1$H NMR (150 MHz, CDCl$_3$): δ 1.39 (m, 4H; H4eq, H4ax, H5eq, H5ax), 1.77 (m, 2H; H3ax, H3eq), 2.17 (m, 2H; H6eq, H6ax), 2.14 (m, 1H; H6eq), 2.22 (m, 1H; H3eq), 3.16 (ddd, $J$ = 12.8, 8.8, 3.2 Hz, 1H; H2), 3.49 (td, $J$ = 10.0, 4.3 Hz, 1H; H1), 7.24 (m, 2H; pyridinyl), 8.39 (m, 2H; pyridinyl). $^{13}$C NMR (600 MHz, CDCl$_3$): δ 24.07 (C5), 26.08 (C5),
32.54 (C3), 34.28 (C6), 53.68 (C2), 73.15 (C1), 122.69 (C; pyridinyl), 147.66, 149.84 (CH;
pyridinyl). HRMS: C_{11}H_{16}NO_{5}^{+} [M+H]_{\text{Cal}} m/z 210.0947 ; [M+H]_{\text{exp}} m/z 210.0931.

*Trans*-2-(*pyrimidin-2-yl*thio)cyclohexanol (*5e*)

[Diagram of the compound]

Reaction occurred in 10 mL of H_{2}O. The residue was purified as colorless oil by column
cchromatography (silica gel; Hex:EtOAc, 1:1) to give a yield of 0.162 mg (70%). R_{f}; 0.21
(hexane:EtOAc, 1:1). \textsuperscript{1}{H} NMR (150 MHz, CD_{3}OD): \(\delta\) 1.47 (m, 4H; H3, H4, H5, H6), 1.68 (m, 
1H; H4ax), 1.78 (m, 1H; H5ax), 2.08 (m, 1H; H6ax), 2.27 (m, 1H; H3ax), 3.57 (td, \(J = 9.4, 4.0\)
Hz, 1H; H1), 3.77 (ddd, \(J = 10.6, 9.5, 4.1\) Hz, 1H; H2), 7.11 (t, \(J = 4.9\) Hz, 1H; H; pyrimidinyl), 
8.54 (d, \(J = 4.9\) Hz, 2H, H; pyrimidinyl). \textsuperscript{13}{C} NMR (600 MHz, CD_{3}OD): \(\delta\) 23.64 (C5), 25.17 
(C4), 31.72 (C3), 34.64 (C6), 50.51 (C2) 71.58 (C1), 116.63 (CH; pyrimidinly), 157.31 (2C, CH; 
pyrimidinly), 172.36 (C; pyrimidinly). HRMS: C_{10}H_{15}N_{2}O_{5}^{+} [M+H]_{\text{Cal}} m/z 211.0900 ; 
[M+H]_{\text{exp}} m/z 211.0915.

*Trans*-2-(*1-H-imidazol-2-yl*thio)cyclohexanol (*5f*)

[Diagram of the compound]

Reaction occurred in 10 mL of H_{2}O:THF (1:1). The residue was isolated as white

(crystals after recrystallization in EtOH to give a of yield 312 mg (69%). R_{f}; 0.28 (EtOAc). \textsuperscript{1}{H}
NMR (150 MHz, CD_{3}OD): \(\delta\) 1.39 (m, 4H; H3, H4, H5, H6), 1.68 (m, 2H; H4, H5), 1.99 (m, 2H; 
H3, H6), 2.87 (m, 1H; H2), 3.35 (td, \(J = 9.8, 4.3\) Hz, 1H; H1), 7.10 (s, 2H; imidazolyl). \textsuperscript{13}{C}
NMR (600 MHz, CD_{3}OD): \(\delta\) 23.92 (C5), 25.35 (C4), 32.11 (C3), 34.57 (C6), 54.91 (C2), 72.52
(C1), 123.92 (2CH; imidazolyl), 137.85 (C; imidazolyl). HRMS: C9H15N2OS+ [M+H]_{cal} m/z 199.0900; [M+H]_{exp} m/z 199.0853.

**Trans-2-((1-methyl-1-H-imidazol-2-yl)thio)cyclohexanol 5g**

![Chemical Structure](image)

Reaction occurred in 10 mL of H2O. The residue was isolated as colorless oil by column chromatography (silica gel; EtOAc) to give a yield of 168 mg (27%). Rf; 0.34 (EtOAc). ¹H NMR (600 MHz, CD3OD): δ 1.30 (m, 4H; H3, H4, H5, H6), 1.64 (m, 1H; H4), 1.72 (m, 1H; H5), 1.94 (m, 1H; H3), 2.02 (m, 1H; H6), 2.94 (ddd, J = 11.1, 9.5, 4.0 Hz, 1H; H2), 3.39 (td, J = 9.7, 4.2 Hz, 1H; H1), 3.75 (s, 3H; CH3-imidazolyl), 7.02 (d, J = 1.3 Hz, 1H; H; imidazolyl), 7.21 (d, J = 1.3 Hz, 1H; H; imidazolyl). ¹³C NMR (150 MHz, CD3OD): δ 23.90 (C5), 25.30 (C4), 32.26 (C3), 33.02 (C1), 34.82 (C6), 55.41 (C2), 72.78 (C1), 123.46, 128.13 (CH; imidazolyl), 139.72 (C; imidazolyl). HRMS: C10H17N2OS+ [M+H]_{cal} m/z 213.1063; [M+H]_{exp} m/z 213.1056.

**Trans-2-((1-H-1,2,4-triazol-3-yl)thio)cyclohexanol (5h)**

![Chemical Structure](image)

Reaction occurred in 10 mL of H2O. The residue was isolated as light yellow oil by column chromatography (silica gel; Hex:EtOAc, 1:9) to give a yield of 169 mg (34%). Rf; 0.27 (Hex:EtOAc, 1:9). ¹H NMR (600 MHz, CDCl3): δ 133 (m, 4H; H3, H4, H5, H6), 1.75 (m, 2H; H4, H5), 2.16 (m, 2H; H3, H6), 3.15 (ddd, J = 13.1, 9.2, 3.5 Hz, 1H; H2), 3.59 (td, J = 10.2, 4.4 Hz, 1H; H1), 8.07 (s, 1H; H; triazolyl). ¹³C NMR (150 MHz, CDCl3): δ 24.26 (C4), 26.13 (C5),
32.82 (C3), 35.26 (C6), 54.60 (C2), 75.12 (C1), 126.81 (CH; triazolyl), 137.14 (C; triazolyl).

HRMS: C₈H₁₄N₃O₃⁺ [M+H]_{cal} m/z 200.0852 ; [M+H]_{exp} m/z 200.0942.

*Trans-2-((3-amino-1H-1,2,4-triazol-5-yl)thio)cyclohexanol (5i)*

Reaction occurred in 10 mL of H₂O. The residue was isolated as white crystals by column chromatography (silica gel; EtOAc) to give a yield of 269 mg (63%). Rf; 0.32 (EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 131 (m, 4H; H₃, H₄, H₅, H₆), 1.76 (m, 2H; H₄, H₅), 2.13 (m, 2H; H₃, H₆), 3.20 (ddd, J = 13.0, 8.8, 3.9 Hz, 1H; H₂), 3.62 (td, J = 10.5, 4.0 Hz, 1H; H₁), 7.92 (s, 1H; H; triazolyl), 8.14 (br.s, 2H; H, triazolyl). ¹³C NMR (150 MHz, CDCl₃): δ 23.54 (C₄), 27.28 (C₅), 33.04 (C₃), 34.97 (C₆), 56.87 (C₂), 77.26 (C₁), 131.28 (CH; triazolyl), 138.27 (C; triazolyl). HRMS: C₈H₁₅N₄O₃⁺ [M+H]_{cal} m/z 215.0961 ; [M+H]_{exp} m/z 215.1123.

*Trans-2-((5(pyridine-4-yl)-4H-1,2,4-triazol-3-yl)thio)cyclohexanol (5j)*

Reaction occurred in 10 mL of H₂O. The residue was isolated as light yellow oil by column chromatography (silica gel; DCM:MeOH, 9:1) to give a yield of 169 mg (51%). Rf; 0.36 (DCM:MeOH, 9:1). ¹H NMR (600 MHz, CD₃OD): δ 1.40 (m, 4H; H₃, H₄, H₅, H₆), 1.68 (m, 1H; H₄), 1.75 (m, 1H; H₅), 2.08 (m, 1H; H₃ax), 2.17 (m, 1H; H₆ax), 3.39 (ddd, J = 12.4, 8.4, 2.9 Hz, 1H; H2), 3.55 (td, J = 9.7, 4.2 Hz, 1H; H1), 7.55 (m, 1H; H; pyridinyl), 8.40 (dt, J = 8.0, 1.9 Hz, 1H; H; pyridinyl), 8.60 (m, 1H; H; pyridinyl), 9.16 (m, 1H; H; pyridinyl). ¹³C NMR (150 MHz, CD₃OD): δ 23.78 (C₅), 25.20 (C₄), 32.24 (C₃), 34.81 (C₆), 54.02 (C₂), 72.87 (C₁),
124.14, 125.08, 126.62, 128.59 (CH; pyridinyl) 134.50, 146.72 (C; triazolyl), 149.81 (C; triazolyl). HRMS: C_{13}H_{17}N_{4}OS\textsuperscript{+} [M+H]\textsubscript{cal} m/z 277.1118; [M+H]\textsubscript{exp} m/z 277.1159.

Trans-2-(benzoimidazol-2-ylthio)cyclohexanol (5k)

Reaction occurred in 10 mL of H\textsubscript{2}O. The residue was isolated as light yellow oil by column chromatography (silica gel; Hex:EtOAc, 4:1) to give a yield of 169 mg (34\%). R\textsubscript{f}; 0.51 (Hex:EtOAc, 4:1). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ 1.30 (m, 3H; H3, H4, H5), 1.45 (m, 1H; H6ax), 1.76 (m, 2H; H4, H5), 2.19 (m, 2H; H6eq, H3eq), 3.36 (m, 1H; H1), 3.65 (td, J = 10.4, 4.4 Hz, 1H; H2), 7.19 (m, 2H; H; Ph), 7.49 (m, 2H; H; Ph). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ 24.17 (C5), 26.14 (C4), 32.72 (C6), 35.86 (C3), 52.62 (C2), 76.18 (C1), 114.31, 122.63 (4CH; Ph), 150.71 (2C; Ph), 159.62 (C; imidazolyl). HRMS: C_{13}H_{17}N_{2}OS\textsuperscript{+} [M+H]\textsubscript{cal} m/z 249.1056; [M+H]\textsubscript{exp} m/z 249.1101.

Trans-2-(benzothiazol-2-ylthio)cyclohexanol (5l)

Reaction occurred in 10 mL of H\textsubscript{2}O. The residue was isolated as light yellow oil by column chromatography (silica gel; Hex:EtOAc, 4:1) to give a yield of 329 mg (62\%). R\textsubscript{f}; 0.31 (Hex:EtOAc, 4:1). \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}OD): δ 1.41 (m, 3H; H3, H4, H5), 1.59 (m, 1H; H6eq), 1.70 (m, 1H; H4eq), 1.78 (m, 1H; H5eq), 2.08 (m, 1H; H6ax), 2.34 (m, 1H; H3ax), 3.59 (td, J = 9.5, 4.2 Hz, 1H; H1), 3.72 (ddd, J = 12.3, 8.2, 2.8 Hz, 1H; H1), 7.31 (m,1H; H; Ph), 7.43 (m, 1H; H; Ph), 7.82 (m,2H; H; Ph). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ 23.55 (C5), 25.29 (C4),
32.12 (C6), 34.80 (C3), 54.76 (C2), 71.99 (C1), 120.59, 121.03, 124.26, 126.04 (4CH; Ph),
135.27 (C; thiazolyl), 152.91, 167.74 (2C; Ph). HRMS: C\textsubscript{13}H\textsubscript{16}NOS\textsubscript{2}\textsuperscript{+} [M+H]\textsubscript{Cal} m/z 266.0668 ; [M+H]\textsubscript{exp} m/z 266.0712.

*Trans*-2-(benzoxazol-2-ylthio)cyclohexanol (5m)

![Chemical Structure](image)

Reaction occurred in 10 mL of H\textsubscript{2}O. The residue was isolated as brown crystals by
column chromatography (silica gel; Hex:EtOAc, 1:2) to give a yield of 144 mg (29%). R\textsubscript{f}; 0.48
(Hex:EtOAc, 1:2). \textsuperscript{1}H NMR (600 MHz, DMSO-d6): δ 1.39 (m, 3H; H3, H4, H5, H6), 1.64 (m,
2H; H4, H5), 2.06 (m, 1H; H3eq), 2.13 (m, 1H; H6eq), 2.31 (br.s, 1H; OH), 3.50 (td, J = 9.3, 4.0
Hz, 1H; H1), 3.64 (td, J = 10.1, 3.6 Hz, 1H; H2), 7.07 (m,2H; Ph), 7.13 (m, 1H; H; Ph), 7.30
(m,2H; H; Ph). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): δ 19.54 (C5), 24.44 (C4), 25.56 (C6), 32.21 (C3),
54.15 (C2), 70.93 (C1), 119.00, 121.85, 131.02, 141.79 (4CH; Ph), 151.30, 155.13 (C; Ph),
164.74 (C; oxazolyl). HRMS: C\textsubscript{13}H\textsubscript{16}NO\textsubscript{2}S\textsuperscript{+} [M+H]\textsubscript{Cal} m/z 250.0896 ; [M+H]\textsubscript{exp} m/z 250.0621.
Compounds 8a and 9a were prepared in the same reaction. Reaction occurred in 10 mL of H$_2$O. Products were separated by column chromatography (silica gel; DCM:EtOAc, 9:1) to give a colorless oil for 8a and white crystals for 9a.

(1R,2R,5S)-4-(tert-butyl)-2-(pyridin-2-ylthio)cyclohexanol (8a)

Reaction yielded 103 mg (44%) of 8a. Rf: 0.48 (DCM:EtOAc, 9:1). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.88 (s, 9H; C(CH$_3$)$_3$), 1.30 (m, 2H; H5eq, H5ax), 1.53 (m, 1H; H3ax), 1.64 (m, 2H; H3eq, H6ax), 1.84 (m, 1H; H6eq), 2.26 (tt, $J$ = 13.8, 4.0 Hz, 1H; H4), 4.05 (m, 1H; H2), 4.07 (q, $J$ = 3.1 Hz, 1H; H1), 7.08 (m, 1H; H; pyridinyl), 7.26 (m, 1H; H; pyridinyl), 7.61 (m, 1H; H; pyridinyl), 8.38 (m, 1H; pyridinyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 22.18 (C5), 25.41 (3C, C(CH$_3$)$_3$), 26.49(C3), 27.42 (C, t-butyl), 32.26 (C6), 40.38 (C4), 44.80 (C2), 69.44 (C1), 119.81, 122.63, 136.37, 149.43 (CH; pyridinyl), 158.57 (C; pyridinyl). HRMS: C$_{16}$H$_{26}$NOS$^+ \ [M+H]_{cal}$ m/z 280.1730 ; [M+H]$_{exp}$ m/z 280.1762.

(1S,2S,5R)-5-(tert-butyl)-2-(pyridin-2-ylthio)cyclohexanol (9a)

Reaction yielded 118 mg (47%) of 9a. Rf: 0.46 (DCM:EtOAc, 9:1). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.85 (s, 9H; C(CH$_3$)$_3$), 1.26 (m, 2H; H4eq, H4ax), 1.62 (m, 2H; H3eq, H3ax), 1.94 (m, 2H; H6eq, H6ax), 2.26 (m, 1H; H4), 3.93 (q, $J$ = 3.0 Hz, 1H; H1), 4.16 (m, 1H, H2), 7.01 (m, 1H; H; pyridinyl), 7.24 (m, 1H; H; pyridinyl), 7.72 (m, 1H; H; pyridinyl), 8.27 (m, 1H;
H; pyridinyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 23.57 (C5), 25.32 (3C, C(CH$_3$)$_3$), 25.87 (C3), 28.13 (C; t-butyl) 32.20 (C6), 40.12 (C4), 45.27 (C2), 69.19 (C1), 118.54, 121.98, 134.21, 150.28 (CH; pyridinyl), 156.94 (C; pyridinyl). HRMS: C$_{16}$H$_{26}$NOS$^+$ [M+H]$_{cal}$ m/z 280.1730; [M+H]$_{exp}$ m/z 280.1755.

Compounds 8b and 9b were prepared in the same reaction. Reaction occurred in 10 mL of H$_2$O. Products were separated by column chromatography (silica gel; EtOAc) to give white crystals for both products.

$^{(1R,2R,4S)}$-2-((imidazol-2-yl)thio)-4-(t-butyl)cyclohexanol (8b)

![Chemical structure of 8b](image)

Reaction yielded 95 mg (28%) of 8b. Rf: 0.27 (EtOAc). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.85 (s, 9H; C(CH$_3$)$_3$), 1.38 (m, 2H; H5eq, H5ax), 1.55 (m, 2H; H3eq, H3ax), 1.70 (m, 2H; H6eq, H6ax), 2.11 (m, 1H; H4), 3.44 (m, 1H; H2), 3.94 (m, 1H; H1), 7.92 (m, 2H; H; imidazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 20.34 (C4), 26.23 (3C, C(CH$_3$)$_3$), 26.30 (C3), 27.66 (C; t-butyl), 3.150 (C5), 41.92 (C2), 51.65 (C1), 115.62, 116.11 (CH, imidazolyl), 139.24(C, imidazolyl). HRMS: C$_{13}$H$_{23}$N$_2$OS$^+$ [M+H]$_{cal}$ m/z 255.1526; [M+H]$_{exp}$ m/z 255.1546.

$^{(1S,2S,5R)}$-2-((imidazol-2-yl)thio)-5-(tert-butyl)cyclohexanol (9b)

![Chemical structure of 9b](image)

Reaction yielded 111 mg (42%) of 9b. Rf: 0.31 (EtOAc). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.85 (s, 9H; C(CH$_3$)$_3$), 1.40 (m, 2H; H4eq, H4ax), 1.53 (m, 1H; H3ax), 1.72 (m, 2H; H3eq, H6ax), 1.88 (m, 1H; H6eq), 2.04 (m, 1H; H5), 3.58 (sextet, J = 2.3 Hz, 1H; H2), 3.87 (q, J = 2.8
Hz, 1H; H1), 7.08 (m, 2H; H; imidazolyl). 13C NMR (150 MHz, CD3OD): δ 20.34 (C4), 26.18 (3C, C(CH3)3), 26.30 (C3), 27.66 (C, t-butyl), 3.150 (C5), 41.92 (C2), 51.65 (C1), 115.77, 116.28 (CH, imdazolyl), 139.24(C, imidazolyl). HRMS: C13H23N2OS+ [M+H]_cal m/z 255.1526 ; [M+H]_exp m/z 255.1534.

Compounds 8c and 9c were prepared in the same reaction. Reaction occurred in 10 mL of H2O. Products could not be separated by column chromatography (silica gel; Hexane: EtOAc, 9:1). Yield for both was 192 mg (52%) after attempted separation. Rf: 0.58 (Hexane: EtOAc, 9:1).

**1R,2R,4S)-2-((benzoimidazol-2-ylthio)-4-(t-butyl)cyclohexanol (8c)**

Product appeared as white crystals. 1H NMR (600 MHz, CD3OD): δ 0.85 (s, 9H; C(CH3)3), 1.23 (m, 2H; H5eq, H5ax), 1.59 (m, 2H; H3eq, H3ax), 1.68 (m, 1H; H6), 2.08 (m, 1H; H6), 2.31 (tt, J = 13.6, 4.1 Hz, 1H; H4), 3.95 (m 1H; H1), 4.08 (m, 1H, H2). 7.20 (m, 4H; Ph).

13C NMR (150 MHz, CD3OD): δ 23.57 (C4), 25.32 (3C, C(CH3)3), 25.87(C5), 32.14 (C; t-butyl) 32.20 (C6), 40.12(C3), 49.28 (C2), 60.25 (C1), 112.38, 116.28, 125.36, 135.47 (CH; Ph), 159.25, 161.59 (C; imidazolyl). HRMS: C17H25N2OS+ [M+H]_cal m/z 305.1682 ; [M+H]_exp m/z 305.1665 (8c and 9c).
(1S,2S,5R)-2-((benzimidazol-2-yl)thio)-5-(tert-butyl)cyclohexanol (9c)

Product appeared as white crystals. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.87 (s, 9H; C(CH$_3$)$_3$), 1.24 (m, 2H; H4eq, H4ax), 1.59 (m, 2H; H3eq, H3ax), 1.80 (m, 2H; H6eq, H6ax), 2.09 (m, 1H; H5), 3.93 (m 1H; H2), 4.08 (m, 1H, H1). 7.49 (m, 4H; Ph). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 23.57 (C4), 25.32 (3C, C(CH$_3$)$_3$), 25.87(C5), 32.14 (C; t-butyl) 32.20 (C6), 40.12(C3), 49.28 (C2), 60.25 (C1), 112.38, 116.28, 125.36, 135.47 (CH; Ph), 159.25, 161.59 (C; imidazolyl). HRMS: C$_{17}$H$_{25}$N$_2$OS$^+$ [M+H]$^\text{cal}$ m/z 305.1682 ; [M+H]$^\text{exp}$ m/z 305.1665 (8c and 9c).
General procedure for acetylation of trans-2-(azaarylsulfanyl)-cyclohexanols

Compound 3k (0.4 g, 1.0 mmol) was dissolved 20 ml of dried CHCl₃. Excess acetyl chloride (2 ml) was added to the solution and allowed to reflux. Upon consumption of the 3k, reaction was diluted with 20 ml of CHCl₃ and neutralized with Na₂CO₃ crystals. Na₂CO₃ was filtered off and organic solution was dried for 12 h over anhyd Na₂SO₄. Organic solution was filtered and removed by rotary evaporator to give the crude product that was purified by column chromatography (silica gel; Hex:EtOAc, 4:1) to give a yield 239 mg (60%) as a yellow oil 3x.

**Diethyl-4-((1H-benzoimidazol-2-ylthio)-5-acetoxycyclohexane-1,2-dicarboxylate (3x)**

![Chemical structure of Diethyl-4-((1H-benzoimidazol-2-ylthio)-5-acetoxycyclohexane-1,2-dicarboxylate (3x)](image)

$^1$H NMR (600 MHz, CDCl₃): δ 1.24 (t, $J$ = 7.1 Hz, 3H; CH₃), 1.25 (t, $J$ = 7.1 Hz, 3H; CH₃), 2.23 (m, 2H; H3eq, H3ax), 2.36 (m, 2H; H6eq, H6ax), 3.02 (m, 2H; H1, H2), 4.15 (m, 4H; OCH₂), 4.55 (m, 1H; H4), 5.35 (q, $J$ = 3.0 Hz, 1H; H4), 7.31 (m, 2H; Ph), 7.63 (m, 2H; Ph). $^{13}$C NMR (150 MHz, CDCl₃): δ 14.15 (2CH₃, Et), 28.54 (C6), 31.69 (C3), 39.57 (C2), 41.28 (C1), 49.23 (C5), 61.37, 61.54 (OCH₂), 71.39 (C4), 122.34, 122.84, 123.50, 123.71 (4CH, Ph), 149.95, 150.28 (C, Ph), 162.15 (C, imidazolyl), 168.25, 172.18, 174.73 (C=O). HMRS: C$_{21}$H$_{27}$N$_2$O$_6$S$^+$ [M+H]$^+$cal m/z 434.5059; [M+H]$^+$exp m/z 434.5059.

General procedure for tosylation of alcohols

Alcohol (20 mmol) was dissolved in pyridine (25 mL) and cooled in an ice bath (0-5 °C). Methanesulfonyl chloride or 4-Toluenesulfonyl chloride (24 mmol) was then added in small portions with constant stirring. The reaction was completed in 3 h (monitored by TLC). Ether (30 mL) and water (7 mL) were added and the organic layer was washed successively with 2 N HCl, 5% NaHCO₃, and water and dried for 12 h over anhyd Na₂SO₄. Organic solution was filtered and solvent removed by rotary evaporator to give the crude product.

4-methylcyclohexyl methanesulfonate (41a)

\[
\text{cis-41a:} \quad \text{H NMR (600 MHz, CDCl₃): } \delta 0.88 (s, 3H; CH₃), 1.01 (m, 2H; H3, H5), 1.24 (m, 1H; H4), 1.27 (m, 2H; H3, H5), 1.75 (m, 2H; H2eq, H6eq), 2.00 (m, 2H; H2ax, H6ax), 2.98 (m, 3H; CH₃), 4.92 (m, 1H; H1).
\]

13C NMR (150 MHz, CDCl₃): \[\delta 20.21 (CH₃), 26.34 (C2), 26.78 (C6), 28.64 (C3), 28.78 (C5), 32.64 (C4), 35.13 (CH₃). \]

HRMS: C₈H₁₇O₃S⁺ [M+H]_{cal} m/z 193.0893; [M+H]_{exp} m/z 193.0881.

\[
\text{trans-41a:} \quad \text{H NMR (600 MHz, CDCl₃): } \delta 0.86 (s, 3H; CH₃), 1.01 (m, 2H; H3, H5), 1.24 (m, 1H; H4), 1.27 (m, 2H; H3, H5), 1.77 (m, 2H; H2eq, H6eq), 2.09 (m, 2H; H2ax, H6ax), 2.97 (m, 3H; CH₃), 4.55 (m, 1H; H1).
\]

13C NMR (150 MHz, CDCl₃): \[\delta 20.21 (CH₃), 26.68 (C2), 25.87 (C6), 28.64 (C3), 28.78 (C5), 32.64 (C4), 35.06 (CH₃). \]

The reaction gave 2.89 g (75%) of the crude product 41a as a colorless oil containing both cis and trans isomers that could not be separated by column chromatography (cis:trans: = 1:3): Rf: 0.39 (Hex:EtOAc, 10:1); trans-41a: 1H NMR (600 MHz, CDCl₃): \[\delta 0.86 (s, 3H; CH₃), 1.01 (m, 2H; H3, H5), 1.24 (m, 1H; H4), 1.27 (m, 2H; H3, H5), 1.77 (m, 2H; H2eq, H6eq), 2.09 (m, 2H; H2ax, H6ax), 2.97 (m, 3H; CH₃), 4.55 (m, 1H; H1). \]

13C NMR (150 MHz, CDCl₃): \[\delta 20.21 (CH₃), 26.34 (C2), 26.78 (C6), 28.64 (C3), 28.78 (C5), 32.64 (C4), 35.06 (CH₃). \]
The reaction gave 3.02 g (88%) of the crude product 41b as a colorless oil containing both cis and trans isomers that could not be separated by column chromatography (cis:trans: = 1:4): Rf: 0.39 (Hex:EtOAc, 10:1); trans-41b: $^1$H NMR (600 MHz, CDCl$_3$): δ 1.49 (m, 2H; H2eq, H6eq), 1.62 (m, 2H; H3eq, H5eq), 1.90 (m, 2H; H2ax, H6ax), 2.08 (m, 2H; H3ax, H5ax), 2.44 (m, 3H; CH$_3$), 2.47 (m, 1H; H4), 4.49 (m, 1H; H1), 7.27 (m, 1H; Ph), 7.29 (m, 2H; Ph), 7.32 (m, 2H; Ph), 7.84 (m, 2H; p-tol), 7.92 (m, 2H; p-tol). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 21.72 (CH$_3$), 27.10 (C3), 27.19 (C5), 29.98 (C2), 30.08 (C6), 40.19 (C4), 74.48 (C1), 124.35, 124.97, 125.84 (CH; pH), 127.51, 127.43 (CH; p-tol), 128.48, 129.02 (CH; pH), 129.87, 129.99 (CH; p-tol), 140.06, 144.47 (C; p-tol), 149.44 (C; pH). cis-41a δ 1.49 (m, 2H; H2eq, H6eq), 1.62 (m, 2H; H3eq, H5eq), 1.90 (m, 2H; H2ax, H6ax), 2.08 (m, 2H; H3ax, H5ax), 2.42 (m, 1H; H4), 2.44 (m, 3H; CH$_3$), 4.87 (m, 1H; H1), 7.27 (m, 1H; Ph), 7.29 (m, 2H; Ph), 7.32 (m, 2H; Ph), 7.84 (m, 2H; p-tol), 7.92 (m, 2H; p-tol). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 21.84 (CH$_3$), 27.19 (C3), 27.42 (C5), 29.98 (C2), 30.08 (C6), 40.19 (C4), 74.48 (C1), 124.35, 124.97, 125.84 (CH; pH), 127.51, 127.43 (CH; p-tol), 128.44, 129.37 (CH; pH), 129.71, 129.99 (CH; p-tol), 140.06, 144.17 (C; p-tol), 144.34 (C; pH). HRMS: C$_{19}$H$_{23}$O$_3$S$^+ [M+H]_{cal} m/z$ 331.1362; [M+H]$_{exp}$ m/z 331.1354.

4-phenylcyclohexyl p-toluenesulfonate (41b)
The reaction gave 4.37 g (73%) of the crude product 41c as a colorless oil containing both cis and trans isomers that could not be separated by column chromatography (cis:trans = 1:3): Rf: 0.34 (Hex:CHCl₃, 3:2); trans-41c: ¹H NMR (600 MHz, CDCl₃): δ 0.80 (s, 9H; CH₃), 1.21 (m, 2H; H3, H5), 1.29 (m, 1H; H4), 1.34 (m, 2H; H3, H5), 1.72 (m, 2H; H2eq, H6eq), 1.84 (m, 2H; H2ax, H6ax), 2.48 (m, 3H; CH₃), 4.72 (m, 1H; H1), 7.31 (m, 2H; p-tol), 7.94 (m, 2H; p-tol). ¹³C NMR (150 MHz, CDCl₃): δ 21.34 (CH₃), 24.64 (C3), 24.79 (C5), 26.45 ((CH₃)₃), 28.78 (C6), 32.01 (C2), 33.94 (C(CH₃)₃), 38.01 (C4), 87.84 (C1), 120.17, 120.87, 121.49, 121.67 (CH: p-tol), 141.32, 143.25 (C: p-tol). cis-41c: ¹H NMR (600 MHz, CDCl₃): δ 0.82 (s, 9H; CH₃), 1.23 (m, 2H; H3, H5), 1.27 (m, 2H; H3, H5), 1.30 (m, 1H; H4), 1.81 (m, 2H; H2eq, H6eq), 1.83 (m, 2H; H2ax, H6ax), 2.43 (m, 3H; CH₃), 4.33 (m, 1H; H1), 7.43 (m, 2H; p-tol), 7.77 (m, 2H; p-tol). ¹³C NMR (150 MHz, CDCl₃): δ 21.34 (CH₃), 24.64 (C3), 24.79 (C5), 26.45 (CH₃)₃, 28.78 (C6), 32.01 (C2), 33.94 (C(CH₃)₃), 38.01 (C4), 87.84 (C1), 120.17, 120.87, 121.49, 121.67 (CH: ph), 141.32, 143.25 (C: ph). HRMS: C₁₇H₂₇O₃S⁺ [M+H]cal m/z 311.1675; [M+H]exp m/z 311.1800.

General procedure for azido epoxide cleavage

Epoxide (0.3 g, 2 mmol) was dissolved in 32 mL mixture of EtOH/H₂O (15:1), NH₄Cl (0.2 g, 3 mmol) was added while stirring. NaN₃ (0.2 g, 3 mmol) was dissolved in the reaction mixture and reaction mixture was heat to reflux for 24 h while monitoring the consumption of epoxide (TLC, Hex:EtoAc/ 7:3). All solvent was removed on rotary evaporator. The crude
product was dissolved in 25 mL of EtoAc and washed with x3 10 mL of DI H$_2$O. The organic solution was separated and dried for 12 h over anhyd Na$_2$SO$_4$. Organic solution was filtered and removed by rotary evaporator to give the crude product.

*Diethyl-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate (10a)*

Azide 10a was synthesized from epoxide 2. Reaction yielded a yellow oil of 399 mg (84%) with no purification needed. Rf: 0.46 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.24 (t, $J$ =7.0 Hz, 3H; CH$_3$), 1.25 (t, $J$ =7.1 Hz, 3H; CH$_3$), 1.80 (ddd, $J$ =13.9, 7.0, 4.3 Hz, 1H; H3ax), 1.84 (ddd, $J$ =13.8, 7.1, 4.4 Hz, 1H; H6ax), 2.07 (m, 2H; 1H, H3eq), 2.19 (ddd, $J$ =13.6, 8.6, 3.8 Hz, 1H; H6eq), 2.25 (br.s, OH), 3.03 (dt, $J$ =4.4, 7.9 Hz, 1H; H1), 3.11 (dt, $J$ =4.4, 7.9 Hz, 1H; H2), 3.60 (dt, $J$ =6.6, 3.7 Hz, 1H; H5), 3.77 (m, 1H; H4), 4.14 (m, 4H; OCH$_2$). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 14.22 (CH$_3$), 14.23 (CH$_3$), 27.42 (C3), 30.74 (C6), 39.41 (C2), 39.66 (C1), 60.10, 61.04 (OCH$_2$), 61.59(C5), 68.22 (C4), 173.44, 173.66 (C=O). HRMS: C$_{12}$H$_{19}$N$_3$O$_5$ [M+H]$^+$ cal m/z 286.1397; [M+H]$^+$ exp m/z 286.1404.

*Trans-2-Azidocyclohexanol (17a)*

Azide 17a was synthesized from epoxide 4. Reaction yielded a light-yellow oil of 1.24 g (81%) with no purification needed. Rf: 0.33 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.28 (m, 4H; H3ax, H4ax, H5ax, H6ax), 1.74 (m, 2H; H4eq, H5eq), 2.02 (m, 2H; H3ax, H6ax), 2.46 (s, 1H, OH), 3.16 (ddd, $J$ = 12.4, 8.0, 3.2 Hz, 1H; H2), 3.38 (m, 1H; H1). $^{13}$C NMR (150
Compounds 21a and 21b were prepared in the same reaction. Reaction occurred in a reflux of epoxide 20a and NaN₃. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 21a and 21b with a yield of 0.82 g (88.0%). Rf: 0.45 (Hex:EtOAc, 7:3). Products 21a and 21b exist in a 1:1 ratio in the reaction mixture.

**(1R,2R,4S)-2-azido-4-methylcyclohexanol (21a)**

\[
\begin{align*}
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{N}_3
\end{align*}
\]

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 0.83 (m, 3H; CH₃), 1.17 (m, 2H; H3eq, H5eq), 1.40 (m, 1H; H6eq), 1.51 (m, 1H; H5ax), 1.53 (m, 1H; H3ax), 1.63 (m, 1H; H4), 1.79 (m, H6ax), 2.72 (s, 1H, OH), 3.09 (dd, $J = 12.2, 7.8, 3.5$ Hz, 1H; H2), 3.63 (m, 1H; H1).

$^{13}$C NMR (150 MHz, CDCl₃): $\delta$ 18.83 (CH₃), 25.72 (C4), 27.74 (C6), 28.44 (C5), 33.42 (C3), 66.47 (C2), 74.69 (C1).

HRMS: C₇H₁₄N₃O⁺ [M+H]$_{cal}$ m/z 156.1131; [M+H]$_{exp}$ m/z 156.1152.

**(1R,2R,5S)-2-azido-5-methylcyclohexanol (21b)**

\[
\begin{align*}
\text{H}_3\text{C} & \text{OH} \\
\text{H}_3\text{C} & \text{N}_3
\end{align*}
\]

$^1$H NMR (600 MHz, CDCl₃): $\delta$ 0.87 (m, 3H; CH₃), 1.16 (m, 1H; H4eq), 1.19 (m, 1H; H6eq), 1.34 (m, 1H; H4ax), 1.40 (m, 1H; H3ax), 1.59 (m, 2H; H3eq, H6ax), 1.69 (m, 1H; H5), 2.99 (s, 1H, OH), 3.01 (dd, $J = 12.3, 7.7, 3.5$ Hz, 1H; H2), 3.82 (m, 1H; H1).

$^{13}$C NMR (150 MHz, CDCl₃): $\delta$ 18.69 (CH₃), 25.78 (C5), 26.47 (C4), 28.44 (C6), 36.87 (C3), 67.89 (C2), 78.61 (C1).

HRMS: C₇H₁₄N₃O⁺ [M+H]$_{cal}$ m/z 156.1131; [M+H]$_{exp}$ m/z 156.1152.
Compounds 22a and 22b were prepared in the same reaction. Reaction occurred in a reflux of epoxide 20b and NaN₃. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 22a and 22b with a yield of 0.71 g (80.3%). Rf: 0.64 (Hex:EtOAc, 7:3). Products 22a and 22b exist in a 1:1 ratio in the reaction mixture.

**(1R,2R,4S)-2-azido-4-phenylcyclohexanol (22a)**

![Diagram of (1R,2R,4S)-2-azido-4-phenylcyclohexanol (22a)]

**¹H NMR (600 MHz, CDCl₃): δ 1.70 (m, 2H; H3eq, H5eq), 1.86 (m, 1H; H6eq), 1.92 (m, 1H; H5ax), 2.09 (m, 1H; H6ax), 2.20 (m, 1H, H3ax), 3.04 (m, 1H; H4), 3.86 (m, 1H, H2), 3.95 (q, J = 2.6 Hz, 1H; H1), 7.21 (m, 1H; Ph), 7.26 (m, 2H; Ph), 7.30 (m, 2H; Ph). **¹³C NMR (150 MHz, CDCl₃): δ 23.64 (C5), 27.65 (C6), 30.54 (C3), 41.01 (C4), 62.84 (C2), 69.34 (C1), 123.45, 123.97, 124.09, 125.11, 125.67 (CH; Ph), 134.02 (C; Ph). HRMS: C₁₂H₁₆N₃O⁺ [M+H]_{cal} m/z 218.1288; [M+H]_{exp} m/z 218.1302.

**(1R,2R,5S)-2-azido-5-phenylcyclohexanol (22b)**

![Diagram of (1R,2R,5S)-2-azido-5-phenylcyclohexanol (22b)]

**¹H NMR (600 MHz, CDCl₃): δ 1.70 (m, 1H; H4eq), 1.80 (m, 1H; H3eq), 1.83 (m, 2H; H6ax, H6eq), 1.92 (m, 1H; H4ax), 2.09 (m, 1H, H3ax), 2.94 (m, 1H; H5), 3.69 (m, 1H, H2), 3.76 (q, J = 2.7 Hz, 1H; H1), 7.21 (m, 1H; Ph), 7.26 (m, 2H; Ph), 7.30 (m, 2H; Ph). **¹³C NMR (150 MHz, CDCl₃): δ 22.36 (C3), 26.45 (C4), 28.46 (C6), 40.54 (C5), 61.64 (C2), 70.34 (C1), 122.34,
Compounds 23a and 23b were prepared in the same reaction. Reaction occurred in a reflux of epoxide 20c and NaN₃. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 23a and 23b with a yield of 1.17 g (82.0%). Rf: 0.60 (Hex:EtOAc, 7:3). Products 23a and 23b exist in a 1:1 ratio in the reaction mixture.

(1R,2R,4S)-2-azido-4-(tert-butyl)-cyclohexanol (23a)

\[
\begin{align*}
\text{H NMR (600 MHz, CDCl}_3\text{): } & \delta 0.86 (m, 9H; CH}_3\text{), 1.27 (m, 1H; H5eq), 1.32 (m, 1H; H3eq), 1.47 (m, 1H; H6eq), 1.56 (m, 2H; H3ax, H5ax), 1.79 (m, 1H, H4), 1.83 (m, 1H; H6ax), 2.03 (s, 1H, OH), 3.67 (q, J = 2.8 Hz, 1H; H2), 3.80 (m, 1H; H1).} \\
\text{13C NMR (150 MHz, CDCl}_3\text{): } & \delta 20.19 (C5), 24.90 (C6), 27.40 ((CH}_3\text{)_3}, 32.24 (\text{C(CH}_3\text{)_3}), 40.23 (C4), 60.72 (C2), 68.71 (C1).}
\end{align*}
\]

HRMS: C₁₀H₂₀N₃O⁺ [M+H]₁cal m/z 198.1601; [M+H]₁exp m/z 198.1616.

(1R,2R,5S)-2-azido-5-(tert-butyl)-cyclohexanol (23b)

\[
\begin{align*}
\text{H NMR (600 MHz, CDCl}_3\text{): } & \delta 0.89 (m, 9H; CH}_3\text{), 1.27 (m, 2H; H4ax, H4eq), 1.49 (m, 1H; H6eq), 1.60 (m, 2H; H3eq, H6ax), 1.88 (tt, J = 3.7, 13.8 Hz, 1H; H5), 1.91 (m, 1H; H3ax), 2.05 (s, 1H, OH), 3.80 (m, 1H; H2), 3.94 (q, J = 2.9 Hz, 1H; H1).} \\
\text{13C NMR (150 MHz, CDCl}_3\text{): }
\end{align*}
\]

HRMS: C₁₀H₂₀N₃O⁺ [M+H]₁cal m/z 198.1601; [M+H]₁exp m/z 198.1616.
δ 20.19 (C4), 24.90 (C3), 27.40 ((CH₃)₃), 29.29 (C6), 32.28 (C(CH₃)₃), 41.39 (C5), 61.86 (C2), 67.25 (C1). HRMS: C₁₀H₂₀N₃O⁺ [M+H]cal m/z 198.1601; [M+H]exp m/z 198.1616.

*Dimethyl(1R*, 2S*, 4S*, 5S*)-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate (51)*

![Structure of 51](image)

51 was synthesized from epoxide 50-anti. Reaction yielded a light-yellow oil 234 mg (77%) with no purification needed. ¹H NMR (600 MHz, CD₃OD): δ 1.62 (ddd, J =13.6, 11.7, 5.0 Hz, 1H; H₆ax), 1.87 (quintet, J = 12.2 Hz, 1H; H₃ax), 2.22 (dt, J = 13.5, 4.2 Hz: 1H, H₃eq), 2.33 (dt, J =13.8, 4.1 Hz, 1H; H₆eq), 2.75 (dt, J =11.9, 4.2 Hz, 1H; H₂), 3.22 (q, J = 3.8 Hz, 1H; H₁), 3.29 (m, 1H; H₅), 3.48 (ddd, J =10.6, 9.2, 4.2 Hz, 1H; H₄), 3.66 (s,3H; CH₃), 3.69 (s, 3H; CH₃). ¹³C NMR (600 MHz, CD₃OD): δ 30.29 (C6), 31.56 (C3), 40.43 (C1), 41.08 (C2), 51.03, 51.14 (OCH₃), 63.71 (C5), 72.22 (C4), 173.22, 173.39(C=O). HRMS: C₁₀H₁₆N₃O₅ [M+H]Cal m/z 258.1084; [M+H]exp m/z 258.1062.

*Dimethyl(1R*, 2S*, 4R*, 5R*)-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate (52)*

![Structure of 52](image)

51 was synthesized from epoxide 50-syn. Reaction yielded a yellow oil of 0.4 g (78%) with no purification needed. ¹H NMR (600 MHz, CDCl₃): δ 1.70 (ddd, J = 13.7, 10.9, 5.0 Hz, H₆ax), 1.83 (quintet, J = 12.3 Hz, H₃ax), 2.26 (dt, J = 13.7, 4.2 Hz: H₃eq), 2.32 (dt, J = 13.7, 4.1 Hz: H₆eq), 2.80 (dt, J =11.7, 4.1 Hz: H₂), 3.25 (q, J =4.2 Hz, H₁), 3.30 (m, 1H, H₅), 3.45 (ddd,
\( J = 9.8, 9.5, 4.3 \text{ Hz, H4}, 3.66 \text{ (s, 3H; CH}_3), 3.69 \text{ (s, 3H; CH}_3) \). \(^{13}\text{C NMR (150 MHz, CD}_3\text{OD):} \delta \)

28.15 (C6), 33.26 (C3), 40.55 (C1), 40.95 (C2), 51.06, 51.10 (OCH\(_3\)), 64.87 (C5), 69.66 (C4), 173.25, 173.49(C=O). HRMS: C\(_{10}\)H\(_{16}\)N\(_3\)O\(_5\) [M+H]\(_{\text{cal}}\) \( m/\zeta \) 258.1084; [M+H]\(_{\text{exp}}\) \( m/\zeta \) 258.1192.

**General procedure for acetylation of azidocyclohexanols**

Alcohol (2.0 mmol) was dissolved 20 ml of dried CHCl\(_3\). Excess acetyl chloride (2 ml) was added to the solution and allowed to reflux. Upon consumption of the alcohol, reaction was diluted with 20 ml of CHCl\(_3\) and neutralized with Na\(_2\)CO\(_3\) crystals. Na\(_2\)CO\(_3\) was filtered off and organic solution was dried for 12 h over anhyd Na\(_2\)SO\(_4\). Organic solution was filtered and removed by rotary evaporator to give the crude product.

**Diethyl-5-azido-4-acetoxy-1,2-cyclohexanedicarboxylate (10b)**

\[
\begin{align*}
\text{N}_3 \\
\text{O} & \quad \text{O} & \quad \text{O} \\
& \quad \text{O} & \quad \text{O} & \quad \text{O} \\
& \quad \text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

10b was synthesized from alcohol 10a. Reaction yielded a yellow oil of 530 mg (81%) with no purification needed. Rf: 0.77 (Hex:EtOAc, 7:3). \(^1\text{H NMR (600 MHz, CDCl}_3\):} \delta 1.24 (t, \( J = 7.1 \text{ Hz, 3H; CH}_3\)), 1.25 (t, \( J = 7.1 \text{ Hz, 3H; CH}_3\)), 1.98 (m, 4H; H3eq, H3ax, H6eq, H6ax), 2.08 (s, 3H; CH\(_3\)-Acetyl), 2.94 (dt, \( J = 9.8, 4.7 \text{ Hz, 1H; H2}\)), 2.98 (dt, \( J = 9.2, 5.7 \text{ Hz, 1H; H1}\)), 3.79 (q, \( J = 4.4 \text{ Hz, 1H; H5}\)), 4.15 (m, 4H; OCH\(_2\)), 4.91 (q, \( J = 4.3 \text{ Hz, 1H; H4}\)). \(^{13}\text{C NMR (600 MHz, CDCl}_3\):} \delta 14.10 (CH\(_3\)), 14.12 (CH\(_3\)), 21.08 (CH\(_3\)-Acetyl), 27.79 (C3), 27.93 (C6), 39.01 (C2), 39.50 (C1), 57.81(C5), 61.00 (2C, OCH\(_2\)), 69.07 (C4), 169.72, 173.43, 173.71 (C=O). HRMS: C\(_{14}\)H\(_{21}\)N\(_3\)O\(_6\) [M+H]\(_{\text{cal}}\) \( m/\zeta \) 328.1509; [M+H]\(_{\text{exp}}\) \( m/\zeta \) 328.1504.
Diethyl-5-azido-4-acetoxy-1,2-cyclohexanedicarboxylate (20b)

20b was synthesized from alcohol 20a. Reaction yielded a light-yellow oil of 133 mg (79%) with no purification needed. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.27 (m, 4H; H3, H4, H5, H6), 1.71 (m, 2H; H4, H5), 2.02 (m, 2H; H3, H6), 2.08 (s, 3H; CH$_3$), 3.36 (dt, $J = 10.4, 4.5$ Hz, 1H; H2), 4.65 (dt, $J = 9.9, 4.6$ Hz, 1H; H1). $^{13}$C NMR (600 MHz, CDCl$_3$): $\delta$ 21.20 (CH$_3$), 23.46 (C4), 23.82 (C5), 30.37 (C3), 30.63 (C6), 63.17 (C2), 75.54 (C1), 170.48 (C=O). HRMS: C$_8$H$_{13}$N$_3$O$_2$ [M+H]$_{\text{cal}}$ m/z 184.1086; [M+H]$_{\text{exp}}$ m/z 184.1098.

Compounds 30a and 30b were prepared in the same reaction. Reaction occurred in a reflux of azides 21a and 21b with acetyl chloride. Products remained a mixture and were NOT separated by column chromatography to give a yellow oil of both 30a and 30b with a yield of 0.342 g (91.2%). Rf: 0.79 (Hex:EtOAc, 7:3). Products 30a and 30b exist in a 1:1 ratio in the reaction mixture.

$^{1R,2R,4S}$-2-azido-4-methylcyclohexyl acetate (30a)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.91 (s, 3H; CH$_3$), 1.13 (m, 1H; H5eq), 1.27 (m, 2H; H3ax, H5ax), 1.47 (m, 1H; H6eq), 1.54 (m, 1H; H3eq), 1.65 (m, 1H, H4), 1.83 (m, 1H; H6ax), 2.06 (s, 3H; CH$_3$), 3.58 (m, 1H; H2), 4.74 (m, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 20.13,
21.74 (CH₃), 24.47 (C6), 26.53 (C4), 27.49 (C5), 32.43 (C3), 61.55 (C2), 76.14 (C1), 170.31 (C=O). HRMS: C₉H₁₆N₃O₂⁺ [M+H]_{cal} m/z 198.1237; [M+H]_{exp} m/z 198.1245.

(1R,2R,5S)-2-azido-5-methylcyclohexyl acetate (30b)

\[ \begin{array}{c}
\text{H}_3\text{C} \\
\text{NO}_2 \\
\text{N}_3 \\
\text{H}_2\text{C}
\end{array} \]

¹H NMR (600 MHz, CDCl₃): δ 0.97 (s, 3H; CH₃), 1.134 (m, 1H; H4eq), 1.22 (m, 2H; H4ax, H6eq), 1.59 (m, 1H; H5), 1.67 (m, 1H; H6ax), 1.69 (m, 1H; H3eq), 1.94 (m, 1H; H3ax), 2.08 (s, 3H; CH₃), 3.69 (m, 1H; H2), 4.89 (m, 1H; H1). ¹³C NMR (150 MHz, CDCl₃): δ 20.74, 21.87 (CH₃), 22.97 (C3), 27.24 (C4), 30.21 (C5), 34.24 (C6), 62.04 (C2), 76.81 (C1), 170.54 (C=O). HRMS: C₉H₁₆N₃O₂⁺ [M+H]_{cal} m/z 198.1237; [M+H]_{exp} m/z 198.1245.

Compounds 31a and 31b were prepared in the same reaction. Reaction occurred in a reflux of azides 22a and 22b with acetyl chloride. Products remained a mixture and were NOT separated by column chromatography to give a yellow oil of both 31a and 31b with a yield of 0.609 g (81.0%). Rf: 0.78 (Hex:EtOAc, 7:3). Products 31a and 31b exist in a 1:1 ratio in the reaction mixture.

(1R,2R,4S)-2-azido-4-phenylcyclohexyl acetate (31a)

\[ \begin{array}{c}
\text{O} \\
\text{N}_3 \\
\text{H}_2\text{C}
\end{array} \]

¹H NMR (600 MHz, CDCl₃): δ 1.75 (m, 1H; H5eq), 1.83 (m, 1H; H6ax), 1.94 (m, 1H; H3eq), 2.02 (m, 1H; H6eq), 2.06 (m, 1H; H5ax), 2.11 (s, 3H; CH₃), 2.91 (m, 1H; H4), 3.89 (m,
1H; H2), 5.01 (q, J = 3.4 Hz, 1H; H1), 7.21 (m, 1H; Ph), 7.31 (m, 2H; Ph), 7.38 (m, 2H; Ph). 13C NMR (150 MHz, CDCl3): δ 20.96 (CH3), 23.84 (C6), 25.69 (C5), 29.73 (C3), 34.90 (C4), 63.47 (C2), 77.43 (C1), 124.35, 124.47 (CH; Ph), 125.46, 125.49 (CH; Ph), 128.08 (CH; Ph), 147.01 (C; Ph), 170.14 (C=O). HRMS: C14H18N3O2+ [M+H]cal m/z 260.1394; [M+H]exp m/z 260.1388.

(1R,2R,5S)-2-azido-5-phenylcyclohexyl acetate (31b)

1H NMR (600 MHz, CDCl3): δ 1.75 (m, 1H; H4eq), 1.79 (m, 1H; H3ax), 1.82 (m, 1H; H6ax), 1.92 (m, 2H; H3eq, H4ax), 2.04 (m, 1H, H6eq), 2.12 (s, 3H; CH3), 2.91 (m, 1H; H5), 3.81 (m, 1H; H2), 4.92 (q, J = 3.6 Hz, 1H; H1), 7.23 (m, 1H; Ph), 7.34 (m, 2H; Ph), 7.39 (m, 2H; Ph). 13C NMR (150 MHz, CDCl3): δ 21.04 (CH3), 22.34 (C3), 26.04 (C4), 29.84 (C6), 37.87 (C5), 65.00 (C2), 78.94 (C1), 124.35, 124.47 (CH; Ph), 125.47, 125.48 (CH; Ph), 128.14 (CH; Ph), 147.47 (C; Ph), 171.47 (C=O). HRMS: C14H18N3O2+ [M+H]cal m/z 260.1394; [M+H]exp m/z 260.1388.

Compounds 32a and 32b were prepared in the same reaction. Reaction occurred in a reflux of azides 23a and 23b with acetyl chloride. Products remained a mixture and were NOT separated by column chromatography to give a yellow oil of both 31a and 31b with a yield of 0.9907 g (83.8%). Rf: 0.77 (Hex:EtOAc, 7:3). Products 31a and 31b exist in a 1:1 ratio in the reaction mixture.
(1R,2R,4S)-2-azido-4-(tert-butyl)cyclohexyl acetate (32a)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.86 (m, 9H; CH$_3$), 1.24 (m, 1H; H5ax), 1.32 (m, 1H; H3ax), 1.46 (m, 1H; H5eq), 1.49 (m, 1H; H3eq), 1.56 (m, 1H, H4), 1.76 (m, 2H; H6ax, H6eq), 2.06 (s, 3H; CH$_3$), 3.72 (q, $J = 3.0$ Hz, 1H; H2), 4.93 (m, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 19.47 (CH$_3$), 22.92 (C5), 24.70 ((CH$_3$)$_3$), 26.48 (C6), 29.55 (C3), 33.82 (C(CH$_3$)$_3$), 45.09 (C4), 62.17 (C2), 77.83 (C1), 178.14 (C=O). HRMS: C$_{12}$H$_{22}$N$_3$O$_2$ $^+$ [M+H]cal m/z 240.1707; [M+H]exp m/z 240.1733.

(1R,2R,5S)-2-azido-5-(tert-butyl)cyclohexyl acetate (32b)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.83 (m, 9H; CH$_3$), 1.30 (m, 2H; H4ax, H4eq), 1.34 (m, 1H; H6ax), 1.46 (m, 1H; H3ax), 1.50 (m, 1H, H6eq), 1.52 (m, 1H; H3eq), 1.56 (m, 1H; H5), 1.73 (m, 1H; H6eq), 1.82 (m, 1H; H6ax), 2.06 (s, 3H; CH3), 3.85 (m, 1H; H2), 4.80 (q, $J = 2.9$ Hz, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 19.32 (CH$_3$), 22.18 (C4), 23.94 (C3), 24.70 ((CH$_3$)$_3$), 26.98 (C6), 33.82 (C(CH$_3$)$_3$), 43.82 (C5), 64.57 (C2), 78.39 (C1), 176.10 (C=O). HRMS: C$_{12}$H$_{22}$N$_3$O$_2$ $^+$ [M+H]cal m/z 240.1707; [M+H]exp m/z 240.1733.
**General procedure for azido-tosylate/alkyl halide substitution (Sn2)**

Tosylate (2 mmol) or alkyl halide (2 mmol) was dissolved in 20 mL mixture of DMSO. NaN₃ (3 mmol) was dissolved in the reaction mixture and reaction mixture was heat to reflux for 48 h while monitoring the consumption of tosylate by TLC. All solvent was removed on rotary evaporator. The crude product was dissolved in 25 mL of EtOAc and washed with x3 10 mL of DI H₂O. The organic solution was separated and dried for 12 h over anhyd Na₂SO₄. Organic solution was filtered and removed by rotary evaporator to give the crude product.

**Azidocyclohexane (39)**

![Azidocyclohexane](image)

Compound 39 yielded yellow oil of 0.182 g (72%) without purification. Rf: 0.29 (Hex:EtOAc, 10:1). ¹H NMR (600 MHz, CDCl₃): δ 1.34 (m, 6H; H3eq, H3ax, H4eq, H4ax, H5eq, H5ax), 1.77 (m, 2H; H2ax, H6ax), 1.90 (m, 2H; H2eq, H6eq), 3.31 (m, 1H; H1). ¹³C NMR (150 MHz, CDCl₃): δ 24.32 (C3, C5), 25.35 (C4), 31.69 (C2, C6), 60.00 (C1). HRMS: C₁₆H₁₂N₃⁺[M+H]_{cal} m/z 126.1015; [M+H]_{exp} m/z 126.1031.

**1-azido-4-methylcyclohexane(42a)**

![1-azido-4-methylcyclohexane](image)

Compound 42a yielded yellow oil without purification. Rf: 0.31 (Hex:EtOAc, 19:1).

*trans*-42a: ¹H NMR (600 MHz, CDCl₃): δ 0.71 (s, 3H; CH₃), 0.93 (m,1H, H4), 1.32 (m, 4H; H3, H3, H5, H5), 1.56 (m, 2H; H2ax, H6ax), 1.91 (m, 2H; H2eq, H6eq), 3.84 (m, 1H; H1). ¹³C NMR (150 MHz, CDCl₃): δ 26.38 (C3), 26.42 (C5), 26.49 (CH₃), 30.18 (C2, C6), 42.17 (C4), 57.02 (C1). *cis*-42a: ¹H NMR (600 MHz, CDCl₃): δ 0.77 (s, 3H; CH₃), 0.96 (m,1H, H4), 1.14 (m, 2H;
H3, H5), 1.32 (m, 2H; H3, H5), 1.53 (m, 2H; H2ax, H6ax), 1.91 (m, 2H; H2eq, H6eq), 3.99 (m, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 26.33 (C3), 26.42 (C5), 26.49 (CH$_3$), 30.24 (C2), 30.54 (C6), 42.05 (C4), 57.57 (C1). HRMS: C$_7$H$_{14}$N$_3$ $^{+}$[M+H]$_{cal}$ m/z 140.1171; [M+H]$_{exp}$ m/z 140.1199.

1-azido-4-phenylcyclohexane(42b)

![Diagram of 1-azido-4-phenylcyclohexane]

Compound 42b yielded yellow oil without purification. Rf: 0.52 (Hex:EtOAc, 3:2).

trans-42b $^1$H NMR (600 MHz, CDCl$_3$): δ 1.70 (m, 4H; H3eq, H3ax, H5eq, H5ax), 1.80 (m, 2H; H2ax, H6ax), 1.99 (m, 2H; H2eq, H6eq), 2.51 (m, 1H; H4), 3.82 (m, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 28.40 (C3, C5), 30.11 (C2, C6), 43.45 (C4), 57.33 (C1), 100.31, 126.23, 126.91, 128.51, 128.53 (5CH; phenyl), 148.47 (C; phenyl).

cis-42b $^1$H NMR (600 MHz, CDCl$_3$): δ 1.70 (m, 4H; H3eq, H3ax, H5eq, H5ax), 1.80 (m, 2H; H2ax, H6ax), 1.99 (m, 2H; H2eq, H6eq), 2.54 (tt, J = 11.7, 3.6 Hz, 1H; H4), 3.97 (quintet, J = 3.1 Hz, 1H; H1). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 28.40 (C3, C5), 30.11 (C2, C6), 43.45 (C4), 57.33 (C1), 100.31, 126.23, 126.91, 128.51, 128.53 (5CH; phenyl), 148.47 (C; phenyl). HRMS: C$_{12}$H$_{14}$N$_3$ $^{+}$[M+H]$_{cal}$ m/z 200.1182; [M+H]$_{exp}$ m/z 200.1163.
Compound 42c yielded yellow oil of 0.477 mg (79%) with no purification needed. Rf: 0.42 (Hex:EtOAc, 5:2). trans-42c $^1$H NMR (600 MHz, CDCl$_3$): δ 0.851 (s, 9H, C(CH$_3$)$_3$), 1.10 (m, 1H; H4), 1.29 (m, 4H; H3ax, H3eq, H5ax, H5eq), 1.62 (m, 2H; H2, H6), 1.92 (m, 1H; H2), 2.03 (m, 1H; H6), 3.87 (m, 1H, H1). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 21.73 (C3), 26.03 (C5), 27.55 (3C(CH$_3$)$_3$), 30.45 (C(CH$_3$)$_3$), 32.31 (C6), 32.40 (C2), 47.76 (C4), 60.55 (C1). cis-42c $^1$H NMR (600 MHz, CDCl$_3$): δ 0.851 (s, 9H, C(CH$_3$)$_3$), 1.24 (m, 1H; H4), 1.29 (m, 4H; H3ax, H3eq, H5ax, H5eq), 1.62 (m, 2H; H2, H6), 1.92 (m, 1H; H2), 2.07 (m, 1H; H6), 3.87 (m, 1H, H1). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 21.73 (C3), 26.03 (C5), 27.55 (3C(CH$_3$)$_3$), 30.45 (C(CH$_3$)$_3$), 32.31 (C6), 32.40 (C2), 47.76 (C4), 60.55 (C1).

**General procedure for synthesis of triazoles through copper catalyzed click reactions.**

CuSO$_4$.5H$_2$O (10 mmol) was dissolved in 7 mL of H$_2$O. Azide (2 mmol), alkyne (2 mmol) and ascorbic acid (3 mmol) were dissolved in a mixture of 3 mL of H$_2$O and 2 mL of 1,4-dioxane. CuSO$_4$ solution was added to mixture and stirred for 8 hours while checking for completion with TLC. After completion mixture was washed with 2 x 20 ml CHCl$_3$, dried with anhydrous Na$_2$SO$_4$ crystals for 12 hours. Na$_2$SO$_4$ crystals were filtered off and rotary evaporator condensed crude product.
2-(4-hexyl-1H-1,2,3-triazol-1-yl)cyclohexanol (18a)

Compound 18a was isolated as colorless oil with a yield of 587 mg (81%). Rf: 0.36 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.87 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.26 (m, 2H; CH$_2$), 1.44 (m, 5H; CH$_2$, H6ax, H5ax, H5eq), 1.54 (m, 1H; H4ax), 1.69 (m, 2H; CH$_2$), 1.94 (m, 4H; H4eq, H3ax, CH$_2$), 2.19 (m, 2H; H3eq, H6eq), 2.79 (dd, $J$ = 8.8, 6.8 Hz, 2H; CH$_2$), 3.88 (dt, $J$ = 14.9, 5.4 Hz, 1H; H1), 4.32 (m, 1H; H2), 7.71 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 14.17 (CH$_3$), 22.65 (CH$_2$), 24.09 (C5), 24.81, 25.79, 29.48 (CH$_2$), 31.66 (C3), 31.71 (C4), 33.57 (CH$_2$), 62.27 (C6), 70.14 (C2), 72.71 (C1), 120.19(CH; triazolyl), 148.16 (C; triazolyl). HRMS: C$_{14}$H$_{26}$N$_3$O$^+$ [M+H]$_{Cal}$ m/z 252.2070; [M+H]$_{exp}$ m/z 252.2079.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)cyclohexyl acetate (19a)

Compound 19a was isolated as colorless oil with a yield of 168 mg (73%). Rf: 0.71 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.86 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.31 (m, 6H; 2CH$_2$, H6ax, H5ax), 1.63 (m, 3H; CH$_2$, H5eq), 1.84 (s, 1H; CH$_3$), 1.85 (m, 2H; CH$_2$), 1.93 (m, 2H; H4eq, H4ax), 2.21 (m, 2H; H3ax, H6eq), 2.68 (t, $J$ = 7.7 Hz, 2H; CH$_2$), 3.70 (m, 1H; H3eq), 4.48 (m, 1H; H2), 5.05 (td, $J$ = 10.4, 4.8 Hz, 1H; H1), 7.27 (s, 1H; triazolyl). $^{13}$C NMR
(150MHz, CDCl$_3$): δ 14.15 (CH$_3$), 20.84 (COCH$_3$), 22.64 (CH$_2$), 23.87 (C5), 24.81, 25.79, 29.48 (CH$_2$), 31.66 (C4), 31.63 (C6), 32.24 (C3), 63.12 (CH$_2$), 67.16 (C2), 74.02 (C1), 119.08 (CH; triazolyl), 143.20 (C; triazolyl), 170.04 (C=O). HRMS: C$_{16}$H$_{28}$N$_3$O$_2$ $^\text{[M+H]}$ $\text{Cal m/z 294.2176}$; $^\text{[M+H]}$ $\text{exp m/z 294.2182}$.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexanol (18b)

Compound 18b was isolated as white crystals with a yield of 524 mg (76%). Rf: 0.34 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.45 (m, 3H; H4ax, H5ax, H6eq), 1.89 (m, 2H; H4eq, H5eq), 1.95 (m, 1H; H3ax), 2.22 (m, 2H; H3eq, H6ax), 3.48 (br.s, 1H; OH), 4.06 (dt, J = 10.5, 4.4 Hz, 1H; H1), 4.15 (ddd, J = 12.5, 9.3, 4.1 Hz, 1H; H2), 7.29 (m, 1H; Ph), 7.35 (m, 2H; Ph), 7.67 (m, 2H; Ph), 7.75 (s, 1H; triazolyl). $^1$C NMR (150MHz, CDCl$_3$): δ 23.94 (C5), 24.76 (C4), 31.56 (C3), 33.66 (C6), 67.05 (C2), 72.64 (C1), 119.62 (CH; triazolyl), 125.46 (2C; Ph), 128.09 (C; Ph), 129.01 (2C; Ph), 131.32 (C; Ph), 148.21 (C; triazolyl). HRMS: C$_{14}$H$_{18}$N$_3$O$^+$ $^\text{[M+H]}$ $\text{Cal m/z 244.1444}$; $^\text{[M+H]}$ $\text{exp m/z 244.1452}$.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexyl acetate (19b)

Compound 19b was isolated as white crystals with a yield of 139 mg (85%). Rf: 0.37 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.47 (m, 3H; H4ax, H5ax, H6eq), 1.86 (s,
3H; CH₃), 1.97 (m, 3H; H3eq, H4eq, H5eq), 2.21 (m, 1H; H6ax), 2.28 (m, 1H; H3ax), 4.58 (ddd, J = 13.4, 9.3, 3.1 Hz, 1H; H2), 5.15 (dt, J = 10.5, 4.7 Hz, 1H; H1), 7.33 (m, 1H; Ph), 7.42 (m, 2H; Ph), 7.77 (s, 1H; triazolyl), 7.83 (m, 2H; Ph). ¹³C NMR (150MHz, CDCl₃): δ 20.80 (COCH₃), 23.76 (C5), 24.58 (C4), 32.36 (C3), 33.66 (C6), 63.26 (C2), 73.86 (C1), 118.00 (CH; triazolyl), 125.34 (2CH; Ph), 128.12 (CH; Ph), 128.99 (2CH; Ph), 130.21 (C; Ph), 149.94 (C; triazolyl), 171.37 (C=O). HRMS: C₁₆H₂₀N₃O₂⁺ [M+H]_{cal} m/z 286.1550; [M+H]_{exp} m/z 286.1557.

2-(4,5-diphenyl-1H-1,2,3-triazol-1-yl)cyclohexanol (18c)

Compound 18c was isolated as white crystals with a yield of 124 mg (83%). Rf: 0.31 (Hex:EtOAc, 7:3). ¹H NMR (600 MHz, CDCl₃): δ 1.15 (m, 1H; H5ax), 1.43 (m, 2H; H4ax, H5eq), 1.77 (m, 3H; H3eq, H3ax, H4eq), 2.09 (m, 1H; H6ax), 2.26 (m, 1H; H6eq), 3.85 (m, 1H; H2), 4.48 (ddd, J = 12.4, 8.1, 2.8 Hz, 1H; H1), 7.16 (m, 7H; Ph), 7.33 (m, 2H; Ph), 7.40 (m, 1H; Ph). ¹³C NMR (150MHz, CDCl₃): δ 24.30 (C5), 24.99 (C4), 32.42 (C3), 34.09 (C6), 64.92 (C2), 72.32 (C1), 127.19 (2CH; Ph), 127.83 (CH; Ph), 128.39 (2CH; Ph), 129.02 (2CH; Ph), 129.52, 129.83 (C; triazolyl), 130.71 (2C; Ph). HRMS: C₂₀H₂₂N₃O⁺ [M+H]_{cal} m/z 320.1752; [M+H]_{exp} m/z 320.1760.

Compounds 24a and 25a were prepared in the same reaction. Reaction occurred in a mixture of azides 21a and 21b with 1-octyne. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 24a and 25a with a yield of
226 mg (85%). Rf: 0.29 (Hex:EtOAc, 3:2). Products 24a and 25a exist in a 1:1 ratio in the reaction mixture.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-methylcyclohexanol (24a)

\[ \text{1H NMR (600 MHz, CDCl}_3\text{): } \delta 0.86 (t, J = 6.8 \text{ Hz, } 3\text{H; CH}_3), 1.08 (t, J = 6.9 \text{ Hz, } 3\text{H; CH}_3), 1.27 (m, 6\text{H; CH}_2), 1.31 (m, 1\text{H; H4}), 1.64 (m, 6\text{H; H5ax, H5eq, CH}_2), 1.97 (m, 2\text{H; H3ax, H3eq}), 2.19 (m, 2\text{H; H6ax, H6eq}), 2.63 (q, J = 7.8 \text{ Hz, } 2\text{H; CH}_2), 3.59 (br.s, 1\text{H; OH}), 3.98 (m, 1\text{H; H1}), 4.07 (m, 1\text{H; H2}), 7.28 (s, 1\text{H; triazolyl}). \]

\[ \text{13C NMR (150MHz, CDCl}_3\text{): } \delta 13.62, 20.44 (\text{CH}_3), 21.98, 26.37, 28.09 (\text{CH}_2), 28.92 (\text{C6}), 29.12 (\text{C3}), 30.11 (\text{C5}), 30.59 (\text{CH}_2), 30.68 (\text{C4}), 31.72 (\text{CH}_2), 63.81 (\text{C2}), 69.48 (\text{C1}), 127.02 (\text{CH; triazolyl}), 138.72 (\text{C; triazolyl}). \]

HRMS: C_{15}H_{27}N_{3}O^+ [M+H]_{\text{Cal}} m/z 265.2154; [M+H]_{\text{Exp}} m/z 265.2160.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-methylcyclohexanol (25a)

\[ \text{1H NMR (600 MHz, CD}_3\text{OD): } \delta 0.86 (t, J = 6.8 \text{ Hz, } 3\text{H; CH}_3), 1.08 (t, J = 6.9 \text{ Hz, } 3\text{H; CH}_3), 1.27 (m, 4\text{H; CH}_2), 1.31 (m, 2\text{H; H4ax, H4eq}), 1.44 (m, 3\text{H; H5, CH}_2), 1.97 (m, 2\text{H; H6ax, H6eq}), 2.09 (m, 2\text{H; H3ax, H3eq}), 2.19 (m, 2\text{H; CH}_2), 2.63 (q, J = 7.8 \text{ Hz, } 2\text{H; CH}_2), 3.48 (br.s, 1\text{H; OH}), 4.03 (ddd, J = 12.7, 8.4, 3.5 \text{ Hz, } 1\text{H; H1}), 4.42 (m, 1\text{H; H2}), 7.31 (s, 1\text{H; triazolyl}). \]

\[ \text{13C NMR (150MHz, CD}_3\text{OD): } \delta 13.03, 21.42 (\text{CH}_3), 22.73 (\text{C4}), 22.91, 25.27, 26.91 (\text{CH}_2), \]
Compounds 33a and 34a were prepared in the same reaction. Reaction occurred in a mixture of azides 30a and 30b with 1-octyne. Products remained a mixture and were NOT separated by column chromatography to give a yellow oil of both 33a and 34a with a yield of 184 mg (84%). Rf: 0.49 (Hex:EtOAc, 3:2). Products 33a and 34a exist in a 1:1 ratio in the reaction mixture.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-methylcyclohexyl acetate (33a)

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{O} & \\
\text{H}_2\text{C} & \\
\text{H}_3\text{C} & \\
\text{N} & \\
\text{C} & \\
\text{C} & \\
\text{C} & \\
\end{align*}
\]

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.86 ($t, J = 6.9$ Hz, 3H; CH$_3$), 1.10 ($t, J = 6.9$ Hz, 3H; CH$_3$), 1.29 (m, 5H; CH$_2$, H5eq), 1.71 (m, 6H; H5ax, H6eq, CH$_2$), 1.89 (s, 3H; CH$_3$), 1.97 (m, 1H; H4), 2.11 (m, 3H; H3ax, H3eq, H6ax), 2.68 (m, 2H; CH$_2$), 3.71 (br.s, 1H; OH), 4.70 (m, 1H; H2), 5.07 ($td, J = 9.3, 4.5$ Hz, 1H; H1), 7.31 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 12.13, 19.87 (CH$_3$), 20.83 (COCH$_3$), 22.70 (CH$_2$), 25.93 (C6), 26.44, 28.71 (CH$_2$), 29.03 (C3), 29.57 (C3), 30.85 (C5), 32.47 (CH$_2$), 62.59 (C2), 73.41 (C1), 119.92 (CH; triazolyl), 137.33 (C; triazolyl), 172.12 (C=O). HRMS: C$_{17}$H$_{30}$N$_3$O$_2^+$ [M+H]$_{\text{cal}}$ m/z 308.2333; [M+H]$_{\text{exp}}$ m/z 308.2342.
2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-methylcyclohexyl acetate (34a)

![Chemical structure of 2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-methylcyclohexyl acetate (34a)](image)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.87 ($t$, $J = 6.9$ Hz, 3H; CH$_3$), 1.09 ($t$, $J = 6.9$ Hz, 3H; CH$_3$), 1.34 (m, 6H; CH$_2$, H$_4$ax, H$_4$eq), 1.71 (m, 6H; H$_6$ax, H$_6$eq, CH$_2$), 1.89 (s, 3H; CH$_3$), 2.02 (m, 1H; H$_5$), 2.11 (m, 2H; H$_3$ax, H$_3$eq), 2.68 (m, 2H; CH$_2$), 3.76 (br.s, 1H; OH), 4.45 ($td$, $J = 9.7$, 4.1 Hz, 1H; H$_2$), 5.32 ($td$, $J = 9.4$, 4.3 Hz, 1H; H$_1$), 7.31 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 12.15, 19.87 (CH$_3$), 20.88 (COCH$_3$), 22.70 (CH$_2$), 24.40 (C3), 27.44, 27.79, 28.05 (CH$_2$), 28.89 (C4), 31.11 (C5), 32.47 (CH$_2$), 36.00 (C6), 63.92 (C2), 70.34 (C1), 121.45 (CH; triazolyl), 134.68 (C; triazolyl), 171.96 (C=O). HRMS: C$_{17}$H$_{30}$N$_3$O$_2$ $^+ [M+H]_{cat}$ m/z 308.2333; [$M+H]_{exp}$ m/z 308.2342.

Compounds 24b and 25b were prepared in the same reaction. Reaction occurred in a mixture of azides 21a and 21b with phenylacetylene. Products remained a mixture and were NOT separated by column chromatography to give white crystals of both 24b and 25b with a yield of 209 mg (84.3%). Rf: 0.41 (Hex:EtOAc, 3:2). Products 24b and 25b exist in a 1:1 ratio in the reaction mixture.
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-methylcyclohexanol (24b)

\[
\begin{align*}
&\text{1H NMR (600 MHz, CDCl}_3\text{): } \delta 1.12 (d, J = 7.2 \text{ Hz}, 3 \text{H; CH}_3), 1.65 (\text{m, 1H; H4}), 1.74 \text{ (m, 2H; H5ax, H5eq)}, 2.02 \text{ (m, 2H; H3eq, H6eq)}, 2.23 \text{ (m, 2H; H3ax, H6ax)}, 3.25 \text{ (br.s, 1H; OH)}, \\
&4.08 \text{ (m, 1H; H1)}, 4.44 (\text{ddd, } J = 12.6, 8.5, 3.6 \text{ Hz, 1H; H2}), 7.32 \text{ (m, 1H; Ph)}, 7.38 \text{ (m, 2H; Ph)}, 7.73 \text{ (m, 2H; Ph)}, 7.28 \text{ (s, 1H; triazolyl).} \\
&\text{13C NMR (150MHz, CDCl}_3\text{): } \delta 20.68 \text{ (CH}_3\text{)}, 25.53 \text{ (C3)}, 25.96 \text{ (C6)}, 28.06 \text{ (C5)}, 30.01 \text{ (C4)}, 64.23 \text{ (C2)}, 70.92 \text{ (C1)}, 126.02, 126.34, 126.92 \text{ (CH; Ph)}, 127.02 \text{ (CH; triazolyl)}, 131.28, 131.88 \text{ (CH; Ph)}, 133.69 \text{ (C; Ph)}, 149.31 \text{ (C; triazolyl).} \\
&\text{HRMS: } \text{C}_{15}\text{H}_{20}\text{N}_3\text{O}^+ \text{[M+H]}_{\text{cal}} m/z 258.1601; \text{[M+H]}_{\text{exp}} m/z 258.1609.
\end{align*}
\]

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-methylcyclohexanol (25b)

\[
\begin{align*}
&\text{1H NMR (600 MHz, CDCl}_3\text{): } \delta 1.24 (s, 3 \text{H; CH}_3), 1.65 \text{ (m, 1H; H5)}, 1.72 \text{ (m, 2H; H4ax, H4eq)}, 2.02 \text{ (m, 2H; H6ax, H6eq)}, 2.23 \text{ (m, 2H; H3ax, H3eq)}, 3.25 \text{ (br.s, 1H; OH)}, 4.12 \text{ (m, 1H; H1)}, 4.39 (\text{ddd, } J = 12.7, 8.4, 3.3 \text{ Hz, 1H; H2}), 7.33 \text{ (m, 1H; Ph)}, 7.38 \text{ (m, 2H; Ph)}, 7.73 \text{ (m, 2H; Ph)}, 7.28 \text{ (s, 1H; triazolyl).} \\
&\text{13C NMR (150MHz, CDCl}_3\text{): } \delta 21.44 \text{ (CH}_3\text{)}, 24.61 \text{ (C3)}, 27.02 \text{ (C5)}, 28.47 \text{ (C4)}, 41.28 \text{ (C6)}, 65.01 \text{ (C2)}, 69.52 \text{ (C1)}, 126.02, 126.34, 126.92 \text{ (CH; Ph)}, 126.98 \text{ (CH; triazolyl)}, 131.28, 131.88 \text{ (CH; Ph)}, 133.69 \text{ (C; Ph)}, 149.24 \text{ (C; triazolyl).} \\
&\text{HRMS: } \text{C}_{15}\text{H}_{20}\text{N}_3\text{O}^+ \text{[M+H]}_{\text{cal}} m/z 258.1601; \text{[M+H]}_{\text{exp}} m/z 258.1609.
\end{align*}
\]
Compounds 33b and 34b were prepared in the same reaction. Reaction occurred in a mixture of azides 30a and 30b with phenylacetylene. Products remained a mixture and were NOT separated by column chromatography to give yellow crystals of both 33b and 34b with a yield of 193 mg (91%). Rf: 0.46 (Hex:EtOAc, 3:2). Products 33b and 34b exist in a 1:1 ratio in the reaction mixture.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-methylcyclohexyl acetate (33b)

\[
\begin{align*}
\text{H} & \text{C} \\
\text{N} & \text{N} \\
\text{O} & \text{O}
\end{align*}
\]

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.12 ($t, J = 3.6$ Hz, 3H; CH$_3$), 1.70 (m, 4H; H5ax, H5eq, H6ax, H6eq), 1.91 (s, 3H; CH$_3$), 2.01 (m, 1H; H4), 2.19 (m, 2H; H3ax, H3eq), 4.78 (m, 1H; H2), 5.15 ($td, J = 9.3, 4.6$ Hz, 1H; H1), 7.32 (s, 1H; triazolyl) 7.40 (m, 2H; Ph), 7.81 (m, 3H; Ph). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 21.36 (CH$_3$), 22.67 (COCH$_3$), 23.96 (C3), 27.88 (C6), 29.04 (C5), 32.83 (C4), 61.27 (C2), 71.07 (C1), 122.66 (CH; triazolyl), 125.23, 125.87, 128.93, 129.11, 129.94 (CH; Ph), 131.55 (C; Ph), 136.94 (C; triazolyl), 170.27 (C=O). HRMS: C$_{17}$H$_{30}$N$_3$O$_2^+$ $[M+H]_{\text{Cal}} m/z$ 300.1707; $[M+H]_{\text{exp}} m/z$ 300.1732.
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-methylcyclohexyl acetate (34b)

\[
\begin{align*}
&\text{H NMR (600 MHz, CDCl}_3): \delta 1.14 (t, J = 3.6 \text{ Hz}, 3\text{H; CH}_3), 1.70 (m, 4\text{H; H4ax, H4eq,}
\end{align*}
\]

H6ax, H6eq), 1.93 (s, 3H; CH3), 2.01 (m, 1H; H5), 2.21 (m, 2H; H3ax, H3eq), 4.53 (m, 1H; H2), 5.40 (td, J = 9.4, 4.4 Hz, 1H; H1), 7.30 (s, 1H; triazolyl), 7.40 (m, 2H; Ph), 7.81 (m, 3H; Ph).

\[
\text{13C NMR (150MHz, CDCl}_3): \delta 21.31 (\text{CH}_3), 22.94 (\text{COCH}_3), 24.14 (\text{C3}), 29.92 (\text{C5}), 30.21 (\text{C4}), 37.36 (\text{C6}), 61.27 (\text{C2}), 71.12 (\text{C1}), 123.01 (\text{CH; triazolyl}), 125.23, 125.87, 128.93, 129.11, 129.94 (\text{CH; Ph}), 130.79 (\text{C; Ph}), 137.36 (\text{C; triazolyl}), 170.10 (\text{C=O}). \text{ HRMS: C}_{17}\text{H}_{30}\text{N}_3\text{O}_2^+ [M+H]_{\text{Cal}} m/z 300.1707; [M+H]_{\text{exp}} m/z 300.1732.
\]

Compounds 26a and 27a were prepared in the same reaction. Reaction occurred in a mixture of azides 22a and 22b with 1-octyne. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 26a and 27a with a yield of 141 mg (83%). Products 26a and 27a exist in a 1:1 ratio in the reaction mixture.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-phenylcyclohexanol (26a)

\[
\begin{align*}
&\text{H NMR (600 MHz, CD}_3\text{OD): } \delta 0.87 (t, J = 5.7 \text{ Hz}, 3\text{H; CH}_3), 1.32 (m, 6\text{H; CH}_2), 1.65 (m, 2\text{H; CH}_2), 1.87 (m, 2\text{H; H5ax, H5eq}), 1.98 (m, 1\text{H; H6eq}), 2.05 (s, 3\text{H; CH}_3), 2.14 (m, 2\text{H; H5ax, H6ax}), 2.51 (m, 1\text{H; H3ax}), 2.55 (m, 1\text{H; H3eq}), 2.72 (t, J = 7.8 \text{ Hz}, 2\text{H; CH}_2), 3.25
\end{align*}
\]
(sept, \( J = 3.6 \) Hz, 1H; H4), 4.15 (dt, \( J = 7.4, 3.7 \) Hz, 1H; H1), 4.46 (m, 1H; H2), 7.21 (m, 1H; Ph), 7.36 (m, 2H; Ph), 7.41 (m, 2H; Ph), 7.52 (s, 1H; triazolyl). \(^{13}\)C NMR (150MHz, CD\(_3\)OD): \( \delta \) 13.82 (CH\(_3\)), 20.67, 21.24 (CH\(_2\)), 23.32 (C5), 24.63 (CH\(_2\)), 25.49 (C6), 26.89, 31.31 (CH\(_2\)), 32.35 (C3), 35.28 (C4), 63.38 (C2), 70.02 (C1), 123.02 (CH; triazolyl), 126.38 (CH; Ph), 128.23, 129.02 (2CH; Ph), 146.09 (C; triazolyl), 148.33 (C; Ph). HRMS: C\(_{20}\)H\(_{30}\)N\(_3\)O\(^+\) [M+H]\(_{\text{cal}}\) m/z 328.2383; [M+H]\(_{\text{exp}}\) m/z 328.2376.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-phenylcyclohexanol (27a)

\(^1\)H NMR (600 MHz, CD\(_3\)OD): \( \delta \) 0.88 (t, \( J = 5.7 \) Hz, 3H; CH\(_3\)), 1.30 (m, 4H; CH\(_2\)), 1.38 (m, 2H; CH\(_2\)), 1.74 (m, 2H; CH\(_2\)), 1.85 (m, 1H; H6eq), 1.95 (m, 1H; H5eq), 2.01 (s, 3H; CH\(_3\)), 2.09 (m, 1H; H6ax), 2.21 (m, 1H; H5ax), 2.46 (m, 1H; H3ax), 2.57 (m, 1H; H3eq), 2.89 (t, \( J = 7.8 \) Hz, 2H; CH\(_2\)), 3.33 (sept, \( J = 3.8 \) Hz, 1H; H4), 4.27 (dt, \( J = 7.5, 3.6 \) Hz, 1H; H1), 4.43 (m, 1H; H2), 7.26 (m, 1H; phenyl), 7.32 (m, 2H; Ph), 7.37 (m, 2H; Ph), 7.58 (s, 1H; triazolyl). \(^{13}\)C NMR (150MHz, CD\(_3\)OD): \( \delta \) 13.21 (CH\(_3\)), 21.89, 22.27, 23.47 (CH\(_2\)), 26.52 (C5), 26.88 (C6), 27.99, 32.36 (CH\(_2\)), 33.86 (C3), 34.97 (C4), 62.35 (C2), 71.84 (C1), 125.01 (CH; triazolyl), 128.31 (CH; Ph), 129.29, 129.66 (2CH; Ph), 147.20 (C; triazolyl), 149.84 (C; Ph). HRMS: C\(_{20}\)H\(_{30}\)N\(_3\)O\(^+\) [M+H]\(_{\text{cal}}\) m/z 328.2383; [M+H]\(_{\text{exp}}\) m/z 328.2376.

Compounds 35a and 36a were prepared in the same reaction. Reaction occurred in a mixture of azides 31a and 31b with 1-octyne. Products were separated by column
chromatography (silica gel; Hex:EtOAc, 7:3) to give a colorless oil for both 35a and 36a.

Products 35a and 36a exist in a 1:1 ratio in the reaction mixture.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-phenylcyclohexyl acetate (35a)

Compound 35a was isolated a colorless oil with a yield of 93 mg (42%). Rf: 0.74

(Hex:EtOAc, 7:3). 1H NMR (600 MHz, CDCl3): δ 0.89 (t, J = 5.7 Hz, 3H; CH₃), 1.30 (m, 4H; CH₂), 1.38 (m, 2H; CH₂), 1.74 (m, 2H; CH₂), 1.85 (m, 1H; H6eq), 1.95 (m, 1H; H5eq), 2.01 (s, 3H; CH₃), 2.09 (m, 1H; H6ax), 2.21 (m, 1H; H5ax), 2.46 (m, 1H; H3ax), 2.57 (m, 1H; H3eq), 2.89 (t, J = 7.8 Hz, 2H; CH₂), 3.33 (sept, J = 3.8 Hz, 1H; H4), 4.73 (dt, J = 11.0, 3.7 Hz, 1H; H2), 5.24 (dt, J = 10.7, 3.5 Hz, 1H; H1), 7.26 (m, 1H; Ph), 7.32 (m, 2H; Ph), 7.37 (m, 2H; Ph), 7.58 (s, 1H; triazolyl). 13C NMR (150MHz, CDCl3): δ 14.10 (CH₃), 21.00 (CH₃), 22.58, 24.37 (CH₂), 26.37 (C6), 26.97 (C5), 28.81, 28.88, 31.45 (CH₂), 34.27 (C3), 36.35 (C4), 60.52 (C2), 71.84 (C1), 122.18 (CH; triazolyl), 126.77 (CH; Ph), 126.90, 128.95 (2CH; Ph), 142.45 (C; triazolyl), 146.38 (C; Ph), 169.98 (C=O). HRMS: C_{22}H_{32}N₃O₂⁺ [M+H]_{Cal} m/z 370.2489; [M+H]_{exp} m/z 370.2499.
Compound 36a was isolated a colorless oil with a yield of 69 mg (31%). Rf: 0.74 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.86 ($t$, $J = 6.1$ Hz, 3H; CH$_3$), 1.30 (m, 6H; CH$_2$), 1.64 (m, 2H; CH$_2$), 1.95 (m, 1H; H4ax, H4eq), 2.05 (s, 3H; CH$_3$), 2.20 (m, 3H; H3ax, H3eq, H6eq), 2.44 (m, 1H; H6ax), 2.72 ($t$, $J = 7.6$ Hz, 2H; CH$_2$), 3.20 ($sept$, $J = 3.8$ Hz, 1H; H5), 4.63 (m, 1H; H2), 5.39 (m, 1H; H1), 7.22 (m, 1H; Ph), 7.32 (m, 1H; triazolyl), 7.34 (m, 4H; Ph). $^{13}$C NMR (150MHz, CDCl$_3$): δ 14.12 (CH$_3$), 21.10 (COCH$_3$), 22.61 (CH$_2$), 25.21 (C3), 26.95, 28.70, 28.93 (CH$_2$), 29.20 (C4), 31.56 (CH$_2$), 33.24 (C6), 36.83 (C5), 60.57 (C2), 70.92 (C1), 120.59 (CH; triazolyl), 126.55 (CH; Ph), 127.03, 128.82 (2CH; Ph), 143.12 (C; triazolyl), 143.29 (C; Ph), 170.16 (C=O). HRMS: C$_{22}$H$_{32}$N$_3$O$_2$ $^+ [M+H]_{Cal m/z}$ 370.2489; $[M+H]_{exp m/z}$ 370.2496.

Compounds 26b and 27b were prepared in the same reaction. Reaction occurred in a mixture of azides 22a and 22b with phenylacetylene. Products remained a mixture and were NOT separated by column chromatography to give white crystals of both 26b and 27b with a yield of 138 mg (72%). Products 26b and 27b exist in a 1:1 ratio in the reaction mixture.
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-phenylcyclohexanol (26b)

![Chemical Structure Image]

$^1$H NMR (600 MHz, CD$_3$OD): δ 1.85 (m, 1H; H4ax), 1.96 (m, 1H; H4eq), 2.13 (m, 1H; H3eq), 2.35 (m, 1H; H3ax), 2.50 (m, 1H; H6eq), 2.60 (m, 1H; H6ax), 3.34 (m, 1H; H5), 4.31 (m, 1H; H1), 4.41 (m, 1H; H2), 7.29 (m, 2H; Ph), 7.33 (m, 2H; Ph), 7.36 (s, 1H; triazolyl), 7.39 (m, 2H; Ph), 7.75 (m, 4H; Ph). $^{13}$C NMR (150MHz, CD$_3$OD): δ 26.3 (C4), 29.48 (C6), 30.82 (C3), 43.25 (C5), 64.85 (C2), 70.38 (C1), 125.55, 125.61, 125.64, 125.68 (4CH; Ph), 126.83, 126.94 (2CH; Ph), 128.41 (CH; triazolyl), 128.70 (C; Ph), 128.83, 128.91, 129.22, 129.52 (4CH; Ph), 140.23 (C; Ph), 145.20 (C; triazolyl). HRMS: C$_{20}$H$_{22}$N$_3$O$^+$ [M+H]$^+_{\text{cal}}$ m/z 320.1757; [M+H]$^+_{\text{exp}}$ m/z 320.1752.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-phenylcyclohexanol (27b)

![Chemical Structure Image]

$^1$H NMR (600 MHz, CD$_3$OD): δ 1.96 (m, 1H; H5ax), 2.13 (m, 1H; H5eq), 2.24 (m, 1H; H6ax), 2.35 (m, 1H; H6eq), 2.50 (m, 1H; H3eq), 2.68 (m, 1H; H3ax), 2.98 (m, 1H; H4), 4.40 (m, 1H; H1), 4.41 (m, 1H; H2), 7.26 (m, 2H; Ph), 7.33 (m, 2H; Ph), 7.35 (s, 1H; triazolyl), 7.39 (m, 2H; Ph), 7.75 (m, 4H; Ph). $^{13}$C NMR (150MHz, CD$_3$OD): δ 21.84 (C3), 28.97 (C4), 33.36 (C6), 42.21 (C5), 65.33 (C2), 69.94 (C1), 125.55, 125.62, 125.64, 125.68 (4CH; Ph), 126.83, 126.93 (2CH; Ph), 128.39 (CH; triazolyl), 128.62 (C; Ph), 128.83, 128.91, 129.22, 129.53 (4CH; Ph),
Compounds 35b and 36b were prepared in the same reaction. Reaction occurred in a mixture of azides 31a and 31b with phenylacetylene. Products were separated by column chromatography (silica gel; Hex:EtOAc, 7:3) to give white crystals for both 35b and 36b. Products 35b and 36b exist in a 1:1 ratio in the reaction mixture.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-phenylcyclohexyl acetate (35b)

Compound 35b was isolated a colorless oil with a yield of 77 mg (71%). Rf: 0.74 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.88 (m, 1H; H6ax), 1.95 (m, 1H; H5ax), 2.03 (s, 3H; CH$_3$), 2.18 (m, 2H; H5eq, H6eq), 2.55 (m, 2H; H3ax, H3eq); 3.38 (sept, $J = 4.0$ Hz, 1H; H4), 4.74 (m, 1H; H2), 5.37 (dt, $J = 9.8$, 3.3 Hz, 1H), 7.25 (m, 1H; triazolyl), 7.35 (m, 5H; Ph), 7.43 (m, 2H; Ph), 7.84 (m, 3H; Ph). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 21.13 (C6), 26.42 (COCH$_3$), 27.20 (C5), 34.45 (C3), 36.67 (C4), 58.77 (C2), 72.00 (C1), 119.14, 125.80 (C; Ph), 126.56 (CH; triazolyl), 127.02 (C; Ph), 128.30 (2C, Ph), 128.82 (C; Ph), 128.95 (2C; Ph), 130.58 (C; triazolyl), 143.46, 147.60 (C; Ph), 170.15 (C=O). HRMS: C$_{22}$H$_{24}$N$_3$O$_2^+$ [M+H]$_{cal}$ m/z 362.1863; [M+H]$_{exp}$ m/z 362.1867.
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-phenylcyclohexyl acetate (36b)

Compound 36b was isolated a colorless oil with a yield of 96 mg (88%). Rf: 0.66 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.98 (m, 2H; H4ax, H6ax), 2.07 (s, 3H; CH$_3$), 2.28 (m, 3H; H3ax, H3eq, H4eq), 2.50 (m, 1H; H6eq), 3.22 (sept, $J = 4.1$ Hz, 1H; H5), 4.71 (m, 1H; H2), 5.48 (td, $J = 6.5$, 3.6 Hz, 1H), 7.23 (m, 1H; triazolyl), 7.33 (m, 1H; Ph), 7.35 (m, 4H; Ph), 7.42 (m, 2H; Ph), 7.78 (s, 1H; Ph), 7.82 (m, 2H; Ph). $^{13}$C NMR (150MHz, CDCl$_3$): δ 21.17 (C4), 27.12 (COCH$_3$), 28.77 (C6), 33.26 (C3), 36.97 (C5), 52.28 (C2), 71.08 (C1), 117.95, 121.99 123.02 (C; Ph), 125.94 (CH; triazolyl), 126.94, 127.05 (C; Ph), 129.34 (2C, Ph), 130.59 (2C; Ph), 131.33 (C; triazolyl), 147.56 (C; Ph), 170.26 (C=O). HRMS: C$_{22}$H$_{24}$N$_3$O$_2$ $^+ [M+H]_{Cal}$ m/z 362.1863; $[M+H]_{exp}$ m/z 362.1889.

Compounds 28a and 29a were prepared in the same reaction. Reaction occurred in a mixture of azides 23a and 23b with 1-octyne. Products remained a mixture and were NOT separated by column chromatography to give a yellow oil of both 28a and 29a with a yield of 157 mg (74%). Rf: 0.38 (Hex:EtOAc, 7:3). Products 28a and 29a exist in a 1:1 ratio in the reaction mixture.
2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-(tert-butyl)-cyclohexanol (28a)

\[
\begin{align*}
\text{H NMR} & \ (600 \text{ MHz, CD}_3\text{OD}): \ \delta \ 0.85 \ (s, \ 9H; \ C(\text{CH}_3)_3), \ 0.91 \ (m, \ 3H; \ \text{CH}_3), \ 1.33 \ (m, \ 4H; \ \text{CH}_2), \ 1.57 \ (m, \ 3H; \ \text{H5ax, H5eq, H6ax}), \ 1.68 \ (m, \ 3H; \ \text{H4, CH}_2) \ 1.87 \ (m, \ 1H; \ \text{H6eq}), \ 2.25 \ (m, \ 3H; \ \text{H3ax, H3eq CH}_2), \ 2.69 \ (m, \ 2H; \ \text{CH}_2), \ 4.43 \ (m, \ 1H; \ \text{H1}), \ 4.48 \ (m, \ 1H; \ \text{H2}), \ 7.79 \ (s, \ 1H; \ \text{triazolyl}). \\
\text{C NMR} & \ (150\text{MHz, CD}_3\text{OD}): \ \delta \ 13.02 \ (\text{CH}_3), \ 20.18 \ (\text{CH}_2), \ 22.14 \ (\text{C3}), \ 23.21 \ (\text{C5}), \ 26.83 \ (3\text{CH}_3), \ 29.38, \ 29.47 \ (\text{CH}_2), \ 30.89 \ (\text{C6}), \ 31.43, \ 32.09 \ (\text{CH}_2), \ 33.43 \ (\text{C}(\text{CH}_3)_3), \ 42.78 \ (\text{C4}), \ 60.78 \ (\text{C2}), \ 68.65 \ (\text{C1}), \ 122.90 \ (\text{CH}; \ \text{triazolyl}), \ 147.39 \ (\text{C}; \ \text{triazolyl}). \ \text{HRMS}: \ \text{C}_{18}\text{H}_{34}\text{N}_3\text{O}^+ \\
\text{[M+H]}_{\text{Cal}} \ m/z : 308.2696; \ [\text{M+H}]_{\text{exp}} \ m/z : 308.2702.
\end{align*}
\]

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-(tert-butyl)-cyclohexanol (29a)

\[
\begin{align*}
\text{H NMR} & \ (600 \text{ MHz, CD}_3\text{OD}): \ \delta \ 0.89 \ (s, \ 9H; \ C(\text{CH}_3)_3), \ 0.91 \ (m, \ 3H; \ \text{CH}_3), \ 1.33 \ (m, \ 4H; \ \text{CH}_2), \ 1.80 \ (m, \ 3H; \ \text{H5, H6ax, H6eq}), \ 2.03 \ (m, \ 1H; \ \text{H4ax}), \ 2.16 \ (m, \ 3H; \ \text{H4eq, CH}_2), \ 2.31(m, \ 4H; \ \text{H3ax, H3eq CH}_2), \ 2.69 \ (m, \ 2H; \ \text{CH}_2), \ 4.37 \ (m, \ 1H; \ \text{H1}), \ 4.57 \ (q, \ J = 3.4 \text{ Hz}, \ 1H; \ \text{H2}), \ 7.76 \ (s, \ 1H; \ \text{triazolyl}). \ \text{C NMR} & \ (150\text{MHz, CD}_3\text{OD}): \ \delta \ 13.02 \ (\text{CH}_3), \ 21.38, \ 22.28 \ (\text{CH}_2), \ 23.28 \ (\text{C3}), \ 26.37 \ (\text{C4}), \ 28.75 \ (3\text{CH}_3), \ 30.68 \ (\text{CH}_2), \ 34.36 \ (\text{C6}), \ 33.43 \ (\text{C}(\text{CH}_3)_3), \ 35.25, \ 36.98(\text{CH}_2), \ 47.23
\end{align*}
\]
Compounds 37a and 38a were prepared in the same reaction. Reaction occurred in a mixture of azides 32a and 32b with 1-octyne. Products remained a mixture and were NOT separated by column chromatography to give a colorless oil of both 37a and 38a with a yield of 188 mg (89%). Rf: 0.64 (Hex:EtOAc, 7:3). Products 37a and 38a exist in a 1:1 ratio in the reaction mixture.

2-(4-hexyl-1H-1,2,3-triazol-1-yl)-4-(tert-butyl)-cyclohexyl acetate (37a)

\[\text{1H NMR (600 MHz, CD}_3\text{OD)}: } \delta \text{ 0.86 (s, 3H; CH3), 0.89 (s, 9H; C(CH}_3\text{)3), 1.35 (m, 1H; H4), 1.45 (m, 2H; CH}_2\text{), 1.65 (m, 6H; CH}_2\text{), 1.92, (m, 2H; H6ax, H6eq), 2.10, (s, 3H; CH}_3\text{), 2.11 (m, 3H; H3eq, H5ax, H5eq), 2.30 (m, 1H; H3ax), 2.70 (t, } J = 7.7 \text{ Hz, 2H; CH}_2\text{), 4.58 (m, 1H; H2), 5.52 (m, 1H; H1), 7.81 (m, 1H; triazolyl).}\]

\[\text{13C NMR (150MHz, CD}_3\text{OD)}: } \delta \text{ 13.24 (CH}_3\text{), 19.68 (CH}_3\text{), 21.07, 21.34 (CH}_2\text{), 22.30 (C5), 26.18 (C3), 26.30 (3CH}_3\text{), 26.74, 28.52, 31.35 (CH}_2\text{), 31.70 (C(CH}_3\text{)3), 40.73 (C4), 57.25 (C2), 71.12 (C1), 121.37 (CH; triazolyl), 147.65 (C; triazolyl), 170.36 (C=O).}\]

\[\text{HRMS: C}_{20}\text{H}_{36}\text{N}_3\text{O}_2^+ [M+H]^{\text{Cal/m/z 350.2802; [M+H]}^{\text{exp/m/z 350.2814.}}}\]
2-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-(tert-butyl)-cyclohexyl acetate (38a)

$^1$H NMR (600 MHz, CD$_3$OD): δ 0.86 (s, 3H; CH$_3$), 0.90 (s, 9H; C(CH$_3$)$_3$), 1.35 (m, 6H; CH$_2$), 1.51 (m, 2H; CH$_2$), 1.54 (m, 1H; H5), 1.90, (m, 2H; H3ax, H3eq), 2.12, (s, 3H; CH$_3$), 2.11 (m, 2H; H4ax, H4eq), 2.25 (m, 1H; H6eq), 2.32 (m, 1H; H6ax), 2.70 (t, $J = 7.7$ Hz, 2H; CH$_2$), 4.71 (m, 1H; H2), 5.44 (m, 1H; H1), 7.84 (m, 1H; triazolyl). $^{13}$C NMR (150MHz, CD$_3$OD): δ 13.04 (CH$_3$), 20.65 (CH$_3$), 21.07, 21.45 (CH$_2$), 24.87 (C4), 26.18 (C3), 26.36 (3CH$_3$), 27.45, 29.18, 31.35 (CH$_2$), 31.70 ($C$(CH$_3$)$_3$), 40.88 (C5), 58.57 (C2), 69.34 (C1), 121.54 (CH; triazolyl), 147.55 (C; triazolyl), 170.36 (C=O). HRMS: C$_{20}$H$_{36}$N$_3$O$_2$ $^{[M+H]}_{Cal}$ m/z 350.2802; $^{[M+H]}_{exp}$ m/z 350.2814.

Compounds 28b and 29b were prepared in the same reaction. Reaction occurred in a mixture of azides 23a and 23b with phenylacetylene. Products remained a mixture and were NOT separated by column chromatography to give colorless crystals of both 28b and 29b with a yield of 148 mg (71%). Rf: 0.25 (Hex:EtOAc, 7:3). Products 28b and 29b exist in a 1:1 ratio in the reaction mixture.
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-(tert-butyl)-cyclohexanol (28b)

1H NMR (600 MHz, CD3OD): δ 0.88 (s, 9H; C(CH3)3), 1.48 (m, 1H; H5eq), 1.61 (m, 3H; H4, H5ax, H6eq), 1.86 (m, 2H; H3eq, H6ax), 2.08 (m, 1H; H3ax), 4.52 (q, J = 3.5 Hz, 1H; H1), 4.55 (q, J = 3.3 Hz, 1H; H2), 7.35 (m, 1H; Ph), 7.44 (m, 2H; Ph), 7.84 (m, 2H; Ph), 8.40 (m, 1H; triazolyl). 13C NMR (150MHz, CD3OD): δ 20.08 (C3), 25.56 (C5), 26.47 (3CH3), 28.49 (C6), 31.73 (C(CH3)3), 39.80 (C4), 62.05 (C2), 68.19 (C1), 120.63 (CH; triazolyl), 125.35 (2C; Ph), 127.99 (C; Ph), 128.64 (2C; Ph), 130.42 (C; Ph), 147.03 (C; triazolyl). HRMS: C18H26N3O+ [M+H]cal m/z 300.2070; [M+H]exp m/z 300.2068.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-(tert-butyl)-cyclohexanol (29b)

1H NMR (600 MHz, CD3OD): δ 0.92 (s, 9H; C(CH3)3), 1.68 (m, 3H; H5, H4ax, H6eq), 1.86 (m, 2H; H4eq, H6ax), 2.35, (m, 2H; H3ax, H3eq), 4.42 (q, J = 3.2 Hz, 1H; H1), 4.66 (q, J = 3.6 Hz, 1H; H2), 7.35 (m, 1H; Ph), 7.44 (m, 2H; Ph), 7.84 (m, 2H; Ph), 8.37 (m, 1H; triazolyl). 13C NMR (150MHz, CD3OD): δ 21.44 (C3), 26.47 (3CH3), 26.73 (C4), 29.24 (C6), 31.96 (C(CH3)3), 41.22 (C5), 62.91 (C2), 66.70 (C1), 120.45 (CH; triazolyl), 125.35 (2C; Ph), 127.99 (C; Ph), 128.64 (2C; Ph), 130.42 (C; Ph), 147.03 (C; triazolyl). HRMS: C18H26N3O+ [M+H]cal m/z 300.2070; [M+H]exp m/z 300.2068.
Compounds 37b and 38b were prepared in the same reaction. Reaction occurred in a mixture of azides 32a and 32b with phenylacetylene. Products remained a mixture and were NOT separated by column chromatography to give white crystals of both 37b and 38b with a yield of 167 mg (78%). Rf: 0.72 (Hex:EtOAc, 7:3). Products 37b and 38b exist in a 1:1 ratio in the reaction mixture.

2-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-(tert-butyl)-cyclohexyl acetate (37b)

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{H} \\
\text{CH}_3 & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[\text{O} \quad \text{O}\]

$^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.85 (s, 9H; C(CH$_3$)$_3$), 1.52 (m, 2H; H5ax, H5eq), 1.62 (m, 1H; H4), 1.71 (m, 2H; H3ax, H6ax), 2.10 (s, 3H; CH$_3$), 2.18 (m, 1H; H3eq), 2.36, (m, 2H; H6eq), 4.58 (m, 1H; H2), 5.52 (m, 1H; H1), 7.33 (m, 1H; Ph), 7.42 (m, 2H; Ph), 7.78 (m, 2H; Ph), 8.36 (m, 1H; triazolyl). $^{13}$C NMR (150MHz, CD$_3$OD): $\delta$ 21.54 (CH$_3$), 22.94 (C3), 23.79 (C5), 26.08 (C6), 27.02 (3CH$_3$), 32.21 (C(CH$_3$)$_3$), 43.67 (C4), 61.99 (C2), 72.14 (C1), 121.97 (CH; triazolyl), 122.48 (2C; Ph), 126.85 (C; Ph), 128.86 (2C; Ph), 130.05 (C; Ph), 147.62 (C; triazolyl), 172.34 (C=O). HRMS: C$_{20}$H$_{28}$N$_3$O$_2$+$ [M+H]$Cal m/z 342.4547; [M+H]$exp m/z 342.4552.$
2-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-(tert-butyl)-cyclohexyl acetate (38b)

\[
\text{\begin{center}
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\end{center}}
\]

\(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 0.88 (s, 9H; C(CH\(_3\))\(_3\)), 1.55 (m, 2H; H4ax, H6ax), 1.71 (m, 1H; H5), 1.93 (m, 3H; H4eq, H6eq, H3ax), 2.10 (s, 3H; CH\(_3\)), 2.18 (m, 1H; H3eq), 4.67 (m, 1H; H2), 5.58 (m, 1H; H1), 7.33 (m, 1H; Ph), 7.42 (m, 2H; Ph), 7.78 (m, 2H; Ph), 8.38 (m, 1H; triazolyl). \(^{13}\)C NMR (150MHz, CD\(_3\)OD): \(\delta\) 21.05 (CH\(_3\)), 23.64 (C4), 24.07 (C3), 27.02 (3CH\(_3\)), 28.24 (C6), 32.21 (C(CH\(_3\))\(_3\)), 42.03 (C5), 63.21 (C2), 70.24 (C1), 121.36 (CH; triazolyl), 122.48 (2C; Ph), 126.85 (C; Ph), 128.86 (2C; Ph), 129.34(C; Ph), 146.38 (C; triazolyl), 171.58(C=O).

HRMS: C\(_{20}\)H\(_{28}\)N\(_3\)O\(_2\)+ [M+H]Cal m/z 342.4547; [M+H]exp m/z 342.4552.

Diethyl-5-(4-hexyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (11a)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}}
\]

Product was purified by column chromatography (silica gel; Hex:EtOAc, 4:1) to give 1.61 g (84%) of colorless oil of pure triazole. \(^1\)H NMR (600 MHz, CD\(_3\)OD): \(\delta\) 0.90 (t, \(J=7.0\) Hz, 3H; CH\(_3\); hexyl), 1.28 (t, \(J=7.0\) Hz, 3H; CH\(_3\)), 1.29 (t, \(J=7.0\) Hz, 3H; CH\(_3\)), 1.36 (m, 6H; CH\(_2\); hexyl), 1.68 (quintet, \(J=7.0\) Hz, 2H; CH\(_2\); hexyl), 1.80 (ddd, \(J=13.7, 9.2, 4.7\) Hz, H3ax), 2.33 (m, 2H, H3eq, H6ax), 2.42 (m, 1H, H6eq), 2.70 (t, \(J=7.6\) Hz, 2H; CH\(_2\); hexyl), 3.32 (m, 2H, H1, H2), 4.09 (m, 1H; H4), 4.14 (m, 4H; OCH\(_2\)), 4.48 (ddd, \(J=9.2, 8.5, 4.5\) Hz, 1H; H5), 7.81 (s,
1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 13.04 (CH$_3$, hexyl), 13.12 (CH$_3$, Et), 22.28, 25.06, 29.14, 28.62 (CH$_2$, hexyl), 28.72 (C6), 31.36 (CH$_2$, hexyl) 31.64 (C3), 40.27 (C2), 40.36 (C1), 60.92, 60.99 (OCH$_2$), 62.07 (C5), 67.97 (C4), 122.61 (CH; triazolyl), 126.67(C; triazolyl), 173.24, 173.43(C=O). HRMS: C$_{20}$H$_{34}$N$_3$O$_5$ [M+H]$^{+}$ m/z 396.2493; [M+H]$^{+}$ exp m/z 396.2511.

Diethyl-5-(4-hexyl-1,2,3-triazolyl)-4-acetoxy-1,2-cyclohexanedicarboxylate (11b)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 4:1) to give 2.19 g (77%) of colorless oil of pure triazole. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.87 (t, $J = 7.1$ Hz, CH$_3$), 1.28 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.29 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.32 (m, 2H; CH$_2$; hexyl), 1.70 (m, 2H; CH$_2$, hexyl), 1.82 (m, 1H, H3ax), 2.29 (m, 2H, H3eq, H6ax), 2.48 (m, 1H, H6eq), 2.68 (t, $J = 7.6$ Hz, 2H; CH$_2$, hexyl), 3.26 (q, $J = 5.1$ Hz, 1H, H2), 3.38 (q, $J = 5.1$ Hz, 1H, H1), 4.20 (m, 4H; OCH$_2$), 4.63 (td, $J = 8.3$, 4.0 Hz, 1H; H5), 5.25 (td, $J = 8.2$, 4.0 Hz, 1H; H4), 7.34(s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CDCl$_3$): $\delta$ 12.25 (CH$_3$, hexyl), 13.95 (CH$_3$, Et), 20.17 (CH$_3$-Acetyl), 22.54, 25.85, 29.64, 28.64 (CH$_2$, hexyl), 29.01 (C6), 31.54 (CH$_2$, hexyl) 31.78 (C3), 40.67 (C2), 40.92 (C1), 61.28, 61.39 (OCH$_2$), 65.28 (C5), 71.36 (C4), 123.68 (CH; triazolyl), 129.58(C; triazolyl), 168.34, 172.54, 173.95 (C=O). HRMS: C$_{22}$H$_{36}$N$_3$O$_6$+ [M+H]$^{+}$ m/z 438.2599; [M+H]$^{+}$ exp m/z 438.2595.
Diethyl- 5-(4-phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (12a)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 2:1) to give 1.84 g (81%) of white crystals of pure triazole. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.25 (t, $J$=7.0 Hz, 3H; CH$_3$), 1.29 (t, $J$=7.1 Hz, 3H; CH$_3$), 1.85 (ddd, $J$=13.6, 11.7, 5.3 Hz, 1H; H3ax), 2.47 (dtd, $J$=13.5, 4.3, 1.4 Hz 1H; H6ax), 2.57 (m, 2H; H3eq, H6eq), 2.93 (dt, $J$=12.8, 4.2 Hz, 1H, H1), 3.43 (m, 1H, H2), 4.03 (ddd, $J$=11.6, 10.1, 4.4 Hz, 1H; H4), 4.18 (m, 4H; OCH$_2$), 4.42 (ddd, $J$=12.6, 10.0, 4.4 Hz, 1H; H5), 7.34 (m, 1H; Ph), 7.43 (m, 2H; Ph), 7.83 (m, 2H; Ph), 8.32 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 13.06 (CH$_3$), 13.14 (CH$_3$), 29.75 (C6), 34.93 (C3), 41.36 (C2), 41.89 (C1), 60.66, 60.77 (OCH$_2$), 65.50 (C5), 68.55 (C4), 120.82 (CH; triazolyl), 125.34 (2C; Ph), 127.92 (1C; Ph), 128.62 (2C; Ph), 130.54 (1C; Ph), 146.95 (C; triazolyl), 172.46, 172.82 (C=O). HRMS: C$_{20}$H$_{26}$N$_3$O$_5$ $^+$ [M+H]$_{\text{Cal}}$ m/z 388.1867; [M+H]$_{\text{exp}}$ m/z 388.1895.

Diethyl- 5-(4-phenyl-1,2,3-triazolyl)-4-acetoxy-1,2-cyclohexanedicarboxylate (12b)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 4:1) to give 1.67 g (75%) of colorless oil of pure triazole. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.29 (t, $J$=7.1 Hz, 3H; CH$_3$), 1.30 (t, $J$=7.1 Hz, 3H; CH$_3$), 1.94 (m, 1H; H3ax), 1.95(s, 3H, CH$_3$), (dtd, $J$=13.5,
4.3, 1.4 Hz 1H; H6ax), 2.57 (m, 2H; H3eq, H6eq), 3.31 (dt, J = 12.8, 4.2 Hz, 1H, H1), 3.43 (m, 1H, H2), 4.03 (ddd, J = 11.6, 10.1, 4.4 Hz, 1H; H4), 4.18 (m, 4H; OCH2), 4.48 (m, 1H; H5), 5.38 (ddd, J = 12.6, 10.0, 4.4 Hz, 1H; H4), 7.34 (m, 1H; Ph), 7.43 (m, 2H; Ph), 7.83 (m, 2H; Ph), 8.32 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD3OD): δ 14.14 (CH3), 14.18 (CH3), 20.82 (CH3; Acetyl), 28.85 (C3), 29.15 (C6), 40.07 (C1), 40.020 (C2), 58.64 (C5), 61.43, 61.46 (OCH2), 70.25 (C4), 118.76 (CH; triazolyl), 125.71 (2C; Ph), 128.23 (1C; Ph), 128.83 (2C; Ph), 130.40 (1C; Ph), 147.59 (C; triazolyl), 169.47, 172.60, 172.85 (C=O). HRMS: C22H27N3O6$^+ [M+H]$ Cal m/z 430.1978; [M+H] exp m/z 430.1945.

*Dimethyl-5-(4-hexyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (53a)*

A crude product initially of 0.41 g was obtained. Product was purified by column chromatography (Hex:EtOAc/ 4:2) to give 282 mg (72%) of colorless oil of pure triazole. $^1$H NMR (600 MHz, CDCl3): δ 0.88 (t, J = 7.0 Hz, 3H; CH3, hexyl), 1.31 (m, 6H; CH2, hexyl), 1.62 (quintet, J = 7.6 Hz, 2H; CH2, hexyl), 2.04 (dt, J = 13.2, 11.5 Hz, 1H; H3ax), 2.29 (ddd, J = 13.7, 12.7, 5.0 Hz, 1H; H6ax), 2.49 (dt, J = 13.7, 4.7 Hz, 1H; H3eq), 2.57 (dt, J = 13.7, 3.5 Hz, 1H; H6eq), 2.63 (dd, J = 9.2, 7.2 Hz, 2H; CH2, hexyl), 2.77 (dt, J = 13.0, 4.0 Hz, 1H; H2), 3.42 (q, J = 4.0 Hz, 1H; H1), 3.69 (m, OH), 3.72 (S, 3H; OCH3), 3.73 (S, 3H; OCH3), 4.15 (ddd, J = 11.2, 9.7, 4.7 Hz, 1H; H4), 4.30 (ddd, J = 12.1, 9.7, 4.2 Hz, 1H; H5), 7.33 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CDCl3): δ 14.13 (CH3, hexyl), 22.62, 25.65, 29.05, 29.36 (CH2, hexyl), 31.50 (C3), 31.64 (CH2, hexyl) 32.04 (C6), 41.02 (C1), 42.01 (C2), 52.27, 52.38 (OCH3), 62.64 (C5), 71.43 (C4), 121.52
(CH; triazolyl), 147.87(C; triazolyl), 172.55, 172.69(C=O). HRMS: C\textsubscript{18}H\textsubscript{36}N\textsubscript{3}O\textsubscript{5}\textsuperscript{+} [M+H]\textsubscript{Cal} m/z 368.2180; [M+H]\textsubscript{exp} m/z 368.2194.

*Dimethyl(1R\textsuperscript{*,}2R\textsuperscript{*,}4S\textsuperscript{*,}5S\textsuperscript{*})-5-(4-phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (53b)*

![Chemical structure of Dimethyl(1R\textsuperscript{*,}2R\textsuperscript{*,}4S\textsuperscript{*,}5S\textsuperscript{*})-5-(4-phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (53b)](image)

A crude product initially of 351 mg was obtained. Product was purified by column chromatography (Hex:EtOAc/4:2) to give 0.30 g (75%) of colorless oil of pure triazole. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): $\delta$ 2.07 (q, $J$ =12.8 Hz, 1H; H\textsubscript{3ax}), 2.41 (td, $J$ =13.1, 4.9, 1H; Hz, H6ax), 2.54 (dt, $J$ =13.6, 3.9 Hz, 1H; H3eq), 2.60 (dt, $J$ =13.6, 3.3 Hz, 1H; H6eq), 2.81 (dt, $J$ =12.9, 4.0 Hz, 1H; H2), 3.45 (q, $J$ =4.1 Hz, 1H; H1), 3.73 (S, 3H; OCH\textsubscript{3}), 3.75 (S, 3H; OCH\textsubscript{3}), 4.20 (m, 1H; H4), 4.21 (m, 1H; OH), 4.37 (ddd, $J$ =12.6, 9.2, 4.1 Hz, 1H; H5), 7.29 (m, 1H; Ph), 7.34 (m, 2H; Ph), 7.59 (m, 2H; Ph), 7.73 (s, 1H; triazolyl). \textsuperscript{13}C NMR (600 MHz, CDCl\textsubscript{3}): $\delta$ 31.59 (C3), 31.87 (C6), 41.06 (C1), 42.11 (C2), 52.30, 52.41 (OCH\textsubscript{3}), 63.32 (C5), 71.54 (C4), 120.90 (CH; triazolyl), 125.50 (2C; Phenyl), 128.22 (2C; Ph), 128.86 (C; Ph), 130.06 (C; Ph), 146.85(C; triazolyl), 172.53, 172.66(C=O). HRMS: C\textsubscript{18}H\textsubscript{22}N\textsubscript{3}O\textsubscript{5}\textsuperscript{+} [M+H]\textsubscript{Cal} m/z 360.1554; [M+H]\textsubscript{exp} m/z 360.1571.
Cyclohexyl-4-hexyl-1H-1,2,3-triazole (40a)

Product was isolated as colorless oil with a yield of 180 mg (81%). Rf: 0.64 (Hex:EtOAc, 9:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 6.9$ Hz, 3H; CH$_3$), 1.33 (m, 4H; CH$_2$), 1.55 (m, 2H; H4ax, H4eq), 1.51 (m, 4H; H3ax, H5ax), 1.78 (m, 4H; CH$_2$), 1.92 (m, 2H; H3eq, H5eq), 2.13 (m, 2H; H2ax, H6ax), 2.67 (m, 2H; H2eq, H6eq), 2.75 (t, $J = 7.1$Hz, 2H; CH$_2$), 4.44 (tt, $J = 11.8$, 3.9 Hz, 1H; H1), 7.78 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CDCl$_3$): 14.13 (CH$_3$), 22.83 (CH$_2$), 25.14 (C4), 25.93 (C3), 26.01(C5), 27.03, 28.93, 29.11, 30.34 31.95 (CH$_2$), 31.02 (C6), 31.98 (C2), 60.81 (C1) 128.14 (CH; triazolyl), 145.21 (C; triazolyl). HRMS: C$_{14}$H$_{26}$N$_3$ [M+H]$^+$cal $m/z$ 236.2121; [M+H]$^+$exp $m/z$ 236.2209.

Cyclohexyl-4-phenyl-1H-1,2,3-triazole (40b)

Product was isolated as white crystals with a yield of 175 mg (85%). Rf: 0.62 (Hex:EtOAc, 9:1). $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.35 (m, 1H; H4ax), 1.55 (m, 2H; H3ax, H5ax), 1.80 (m, 1H; H4eq), 1.92 (m, 4H; H2ax, H6ax, H3eq, H5eq), 2.22 (m, 2H; H2eq, H6eq), 4.53 (tt, $J = 11.7$, 3.9 Hz, 1H; H1), 7.33 (m, 1H; Ph), 7.43 (m, 2H; Ph), 7.82 (m, 2H; Ph), 8.36 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD): 25.31 (C3), 25.86 (C5), 26.01 (C4), 31.13(C2), 31.95 (C6), 59.34 (C1), 125.34, 126.91 (2CH; Ph), 127.91 (CH; Ph), 129.00 (C; Ph), 129.18 (CH; triazolyl), 148.17 (C; triazolyl). HRMS: C$_{14}$H$_{18}$N$_3$ [M+H]$^+$cal $m/z$ 228.1495; [M+H]$^+$exp $m/z$ 228.1520.
Compounds exist as a mixture of cis and trans configurational isomers of 43a. Column chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded a colorless oil 134 mg (62%) of both isomers. Rf: 0.42 (Hex:EtOAc, 5:2).

**43a-cis**  
\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 0.89 (t, \(J = 7.1\) Hz, 3H; CH\(_3\)), 1.00 (d, \(J = 6.5\) Hz, 1H, H4), 1.32 (m, 6H; CH\(_2\)), 1.41 (m, 2H; H3eq, H5eq), 1.64 (m, 4H; H3ax, H5ax, CH\(_2\)), 1.64 (m, 2H, CH\(_2\)), 1.82 (m, 1H; H4), 1.93 (m, 2H; H2eq, H6eq), 2.24 (m, 2H; H2ax, H6ax), 2.67 (t, \(J = 7.5\) Hz, 1H; CH\(_2\)), 4.49 (septet, \(J = 4\) Hz, 1H; H1), 7.78 (s, 1H; triazolyl).  
\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 14.12 (CH\(_3\)), 22.21 (CH\(_3\)), 23.10, 25.09, 29.84, 31.24, 32.86 (CH\(_2\)), 32.15 (C4), 33.99 (C2, C6), 34.28 (C3, C5), 61.38 (C1), 121.28 (CH; triazolyl), 148.36 (C; triazolyl).

HRMS: C\(_{15}\)H\(_{28}\)N\(_3\) [M+H]\(_{\text{cal}}\) m/z 250.2278; [M+H]\(_{\text{exp}}\) m/z 250.2271.

**43a-trans**  
\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 0.89 (t, \(J = 7.1\) Hz, 3H; CH\(_3\)), 0.97 (d, \(J = 6.5\) Hz, 1H,H4) 1.21 (m, 2H; H3ax, H5ax), 1.32 (m, 6H; CH\(_2\)), 1.53 (m, 1H; H4), 1.64 (m, 2H, CH\(_2\)), 1.86 (m, 4H; H3eq, H5eq, H2ax, H6ax), 2.14 (m, 2H; H2eq, H6eq), 2.66 (m, 2H; CH\(_2\)), 2.72 (t, \(J = 7.7\) Hz, 1H; CH\(_2\)), 4.41 (tt, \(J = 12.0, 4.1\) Hz, 1H; H1), 7.74 (s, 1H; triazolyl).  
\(^{13}\)C NMR (600 MHz, CDCl\(_3\)): \(\delta\) 14.38 (CH\(_3\)), 22.37 (CH\(_3\)), 23.62, 26.34, 29.96, 30.59, 32.70 (CH\(_2\)), 32.92 (C4), 34.32 (C2, C6), 34.88 (C3, C5), 61.46 (C1), 121.06 (CH; triazolyl), 148.87 (C; triazolyl).

HRMS: C\(_{15}\)H\(_{28}\)N\(_3\) [M+H]\(_{\text{cal}}\) m/z 250.2278; [M+H]\(_{\text{exp}}\) m/z 250.2271.
Compounds exist as a mixture of cis and trans configurational isomers of 43b. Column chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded a colorless oil 174 mg (66%) of both isomers. Rf: 0.51 (Hex:EtOAc, 3:2).

43b-cis $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.82 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.75 (m, 2H; H3ax, H5ax), 1.80 (m, 1H; H4), 1.93 (m, 2H; H3eq, H5eq), 2.11 (m, 2H; H2ax, H6ax), 2.59 (m, 2H; H2eq, H6eq), 4.61 (m, 1H; H1), 7.15 (m, 3H; Ph), 7.23 (m, 2H; Ph), 7.78 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 14.12 (CH$_3$), 32.22 (C4), 34.69 (C2, C6), 35.26 (C3, C5), 61.21 (C1), 121.28 (CH; triazolyl), 119.53, 126.23, 126.99, 127.01 (CH; Ph), 127.31 (CH; triazolyl), 128.52 (C; Ph), 145.36 (C; triazolyl). HRMS: C$_{15}$H$_{20}$N$_3$ [M+H]$_{cal}$ m/z 242.1652; [M+H]$_{exp}$ m/z 242.1684.

43b-trans $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.62 (m, 2H; H3ax, H5ax), 1.80 (m, 1H; H4), 1.95 (m, 2H; H3eq, H5eq), 2.07 (m, 2H; H2ax, H6ax), 2.34 (m, 2H; H2eq, H6eq), 4.62 (m, 1H; H1), 7.29 (m, 3H; Ph), 7.33 (m, 2H; Ph), 7.92 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 14.12 (CH$_3$), 32.22 (C4), 34.69 (C2, C6), 35.26 (C3, C5), 61.21 (C1), 119.53, 126.23, 126.99, 127.01 (CH; Ph), 127.31 (CH; triazolyl), 128.52 (C; Ph), 145.36 (C; triazolyl). HRMS: C$_{15}$H$_{20}$N$_3$ [M+H]$_{cal}$ m/z 242.1652; [M+H]$_{exp}$ m/z 242.1684.
 Compounds exist as a mixture of cis and trans configurational isomers of 44a. Column chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded a colorless oil 219 mg (68%) of both isomers. Rf: 0.37 (Hex:EtOAc, 3:2).

44a-cis $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.88 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.32 (m, 4H; CH$_2$), 1.67 (m, 2H; H3ax, H5ax), 1.89 (m, 4H; H3eq, H5eq, CH$_2$), 2.05 (m, 2H; H2ax, H6ax), 2.46 (m, 2H; H2eq, H6eq), 2.72 (t, $J = 7.7$ Hz, 2H; CH$_2$), 2.77 (m, 1H; H4), 4.64 (quintet, $J = 4.3$ Hz, 1H; H1), 7.20 (m, 3H; Ph), 7.29 (m, 2H; Ph), 7.35 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CDCl$_3$): $\delta$ 14.18 (CH$_3$), 22.67, 25.84, 28.64, 28.74 (CH$_2$), 29.08 (C3), 29.94 (CH$_2$), 29.57 (C5), 30.14 (C2), 31.80 (C6), 41.81 (C4), 55.90 (C1), 119.53, 126.23, 126.99, 127.01 (CH; Ph), 128.52 (C; Ph), 145.82, 148.12 (C; triazolyl). HRMS: C$_{20}$H$_{30}$N$_3$ [M+H]$_{\text{cal}}$ m/z 312.2434; [M+H]$_{\text{exp}}$ m/z 312.2429.

44a-trans $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.86(t, $J = 7.1$ Hz, 3H; CH$_3$), 1.31 (m, 4H; CH$_2$), 1.65 (m, 2H; H3ax, H5ax), 1.90 (m, 4H; H3eq, H5eq, CH$_2$), 2.04 (m, 2H; H2ax, H6ax), 2.44(m, 2H; H2eq, H6eq), 2.72 (t, $J = 7.7$ Hz, 1H; CH$_2$), 2.75 (m,1H; H4), 4.52 (tt, $J = 12.1$, 3.9 Hz, 1H; H1), 7.24 (m, 3H; Ph), 7.31(m, 2H; Ph), 7.39 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz,
CDCl$_3$: $\delta$ 14.18 (CH$_3$), 22.67, 25.84, 28.64, 28.94 (CH$_2$), 29.08 (C3), 29.814 (CH$_2$), 29.57 (C5), 30.14 (C2), 31.80 (C6), 41.81 (C4), 55.90 (C1), 119.53, 126.23, 126.99, 127.01 (CH; Ph), 128.52 (C; Ph), 145.82, 148.12 (C; triazolyl). HRMS: C$_{20}$H$_{29}$N$_3$ [M+H]$^{+}$ cal m/z 312.2434; [M+H]$^{+}$ exp m/z 312.2429.

(4-methylcyclohexyl)-4-phenyl-1H-1,2,3-triazole (44b)

Compound exists as a mixture of cis and trans configurational isomers of 44b. Column chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded a white solid 0.134mg (68%) of both isomers. Rf: 0.42 (Hex:EtOAc, 3:2).

44a-cis $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.27 (m, 2H; H3ax, H5ax), 1.90 (m, 4H; H3eq, H5eq, H2ax, H6ax), 2.59 (m, 2H; H2eq, H6eq), 2.83 (m, 1H; H4), 4.51 (quintet, $J = 2.84$ Hz, 1H; H1), 7.12-7.33 (m, 8H; Ph), 7.50 (m, 2H; Ph), 7.85 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 20.05 (C4), 27.86 (C3), 29.73 (C5), 32.29 (C2), 32.95 (C6), 41.81 (C4), 56.34 (C1), 125.59-127.47 (8CH, Ph), 128.48, 129.22 (C; Ph), 146.06, 147.40 (C; triazolyl). HRMS: C$_{20}$H$_{22}$N$_3$ [M+H]$^{+}$ cal m/z 304.1808 [M+H]$^{+}$ exp m/z 304.1822.

44a-trans $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.23 (m, 2H; H3ax, H5ax), 1.82(m, 4H; H3eq, H5eq, H2ax, H6ax), 2.62 (m, 2H; H2eq, H6eq), 2.74 (ttt, $J = 12.3$, 3.3 Hz, 1H; H4), 4.46 (tt, $J =
12.0, 4.0 Hz, 1H; H1), 7.18-7.31 (m, 8H; Ph), 7.42 (m, 2H; Ph), 7.82 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): δ 19.94 (C4), 25.17 (C3), 29.73 (C5), 32.29 (C2), 32.95 (C6), 41.81 (C4), 56.34 (C1), 125.12-127.10 (8CH, Ph), 128.48, 129.22 (C; Ph), 147.01, 147.62 (C; triazolyl). HRMS: C$_{20}$H$_{22}$N$_3$ [M+H]$_{\text{cal}}$ m/z 304.1808 [M+H]$_{\text{exp}}$ m/z 304.1822.

(4-methylcyclohexyl)-4-hexyl-1H-1,2,3-triazole (45a)

Compound exists as a mixture of cis and trans configurational isomers of 45a. Column chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded a colorless oil 141mg (77%) of both isomers. Rf: 0.65 (Hex:EtOAc, 3:2).

45a-cis $^1$H NMR (600 MHz, CDCl$_3$): δ 0.81 (s, 9H; C(CH$_3$)$_3$), 0.93 (m, 3H; CH$_3$), 1.13 (m, 4H; H3ax, H5ax, CH$_2$), 1.36 (m, 6H; H3eq, H5eq, H2ax, H6ax, CH$_2$), 1.67 (m, 3H; H4, CH$_2$), 2.52 (m, 2H; H2eq, H6eq), 2.71 (t, J = 7.5 Hz, 2H; CH$_2$), 4.57 (m, 1H; H1), 7.34 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): δ 18.24 (3CH$_3$), 19.36 (CH$_3$), 21.02, 21.42, 21.69 (CH$_2$), 23.10 (C5), 24.01 (C3), 24.52 (C4), 25.41 (CH$_2$), 30.01 (C6), 31.61 (C2), 33.72 (C(CH$_3$)$_3$), 59.82 (C1), 120.36, 139.24 (C; triazolyl). HRMS: C$_{18}$H$_{34}$N$_3$ [M+H]$_{\text{cal}}$ m/z 292.2747 [M+H]$_{\text{exp}}$ m/z 292.2747.

45b-trans $^1$H NMR (600 MHz, CDCl$_3$): δ0.89(s, 9H; C(CH$_3$)$_3$), 0.93 (m, 3H; CH$_3$), 1.13 (m, 4H; H3ax, H5ax, CH$_2$), 1.36 (m, 6H; H3eq, H5eq, H2ax, H6ax, CH$_2$), 1.84 (m, 3H; H4,
CH₂), 1.94 (m, 2H; H2eq, H6eq), 2.26 (m, 2H; CH₂), 2.69 (m, 2H; CH₂), 4.36 (ttt, J = 12.1, 3.4
1H; H1), 7.25 (s, 1H; triazolyl). ¹³C NMR (150MHz, CDCl₃): δ 18.31 (3CH₃), 19.24 (CH₃),
21.02, 21.42, 21.69 (CH₂), 23.51 (C5), 24.57 (C3), 24.52 (C4), 25.81 (CH₂), 30.01 (C6), 31.61
(C2), 33.72 (C(CH₃)₃), 60.57 (C1), 120.01, 139.28 (C; triazolyl). HRMS: C₁₈H₃₄N₃ [M+H]⁺ cal
m/z 292.2747 [M+H]⁺ exp m/z 292.2747.

(4-methylcyclohexyl)-4-phenyl-1H-1,2,3-triazole (45b)

Compound exists as a mixture of cis and trans configurational isomers of 45b. Column
chromatography (silica gel; Hex:EtOAc, 3:2) was done and yielded brown crystals 182mg (81%)
of both isomers. Rf: 0.56 (Hex:EtOAc, 3:2).

45b-cis ¹H NMR (600 MHz, CDCl₃): δ 0.91 (s, 9H; C(CH₃)₃), 1.21 (m, 2H; H3ax, H5ax),
1.43 (m, 4H; H3eq, H5eq, H2ax, H6ax), 1.57 (m, 1H; H4), 2.57 (m, 2H; H2eq, H6eq), 4.67
(m,1H; H1), 7.12-7.21 (m, 3H; phenyl), 7.59 (m, 2H; phenyl), 7.99 (s, 1H; triazolyl). ¹³C NMR
(150MHz, CDCl₃): δ 18.24 (3CH₃), 23.64 (C5), 24.36 (C3), 26.17 (C4), 30.24 (C6), 32.29 (C2),
34.25 (C(CH₃)₃), 58.30 (C1), 119.36, 121.62, 121.97, 122.08, 122.67 (CH, phenyl), 129.34 (C;
phenyl), 134.08, 142.64 (C; triazolyl). HRMS: C₁₈H₂₆N₃ [M+H]⁺ cal m/z 284.2121 [M+H]⁺ exp m/z
284.2108.
45b-trans $^1$H NMR (600 MHz, CDCl$_3$): δ 0.94 (s, 9H; C(CH$_3$)$_3$), 1.23 (m, 2H; H3ax, H5ax), 1.41 (m, 4H; H3eq, H5eq, H2ax, H6ax), 1.58 (ttt, $J = 12.4$, 3.2 Hz, 1H; H4), 2.35 (m, 2H; H2eq, H6eq), 4.67 (ttt, $J = 12.1$, 3.4 Hz, 1H; H1), 7.22 (m, 3H; phenyl), 7.62 (m, 2H; phenyl), 8.18 (s, 1H; triazolyl). $^{13}$C NMR (150MHz, CDCl$_3$): δ 18.36 (3CH$_3$), 23.64 (C5), 24.36 (C3), 26.17 (C4), 30.24 (C6), 33.08 (C2), 34.25 (C(CH$_3$)$_3$), 58.30 (C1), 119.36, 121.62, 121.37, 122.08, 122.85 (CH, phenyl), 129.21 (C; Ph), 134.08, 143.21 (C; triazolyl). HRMS: C$_{18}$H$_{26}$N$_3$ [M+H]$^{\text{cal}}$ m/z 284.21.21 [M+H]$^{\text{exp}}$ m/z 284.2108.

General procedure for synthesis of triazoles through toluene reflux

Azide (2 mmol) was dissolved in 20 mL of toluene. Alkyne (3 mmol) was dissolved in the mixture and stirred for 72 hours while checking for completion with TLC. After completion, all solvent was removed by rotary evaporator and the crude product was dissolved in EtOAc. Solution was dried with anhydrous Na$_2$SO$_4$ crystals for 12 hours. Na$_2$SO$_4$ crystals were filtered off and rotary evaporator condensed crude product.
Azide 10a reacted with ethyl-2-butynoate to give a crude mixture of 15a and 16a that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

**Diethyl 3-methyl-4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-7,8-dicarboxylate (15a)**

![Chemical Structure](image)

Compound 15a was isolated as colorless oil with a yield of 271 mg (50%). Rf: 0.52 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.28 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.32 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 2.11 (m, 2H; H3ax, H6ax), 2.21 (m, 1H; H3eq), 2.59 (s, 3H; CH$_3$), 2.73 (m, 1H; H6eq), 3.52 (m, 1H; H2), 4.19 (m, 4H, OCH$_2$), 4.41 (td, $J$ = 10.9, 4.2 Hz, 1H; H5), 4.47 (td, $J$ = 11.0, 4.5 Hz, 1H; H4). $^{13}$C NMR (150MHz, CDCl$_3$): δ 11.28 (CH$_3$), 14.25, 14.31 (CH$_3$), 25.20 (C3), 27.63 (C6), 39.74 (C2), 40.57 (C1), 56.24 (C5), 61.03 (OCH$_2$), 61.03, 62.04 (OCH$_2$), 77.11 (C4), 121.99, 149.72 (C; triazolyl). 156.70, 172.01, 172.07 (C=O). HRMS: C$_{16}$H$_{22}$N$_3$O$_6$+$^+$ [M+H]$_{\text{cal}}$ m/z 352.1503; [M+H]$_{\text{exp}}$ m/z 352.1438.

**Diethyl 4-hydroxy-5-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16a)**

![Chemical Structure](image)

Compound 16a was isolated as yellow oil with a yield of 322 mg (63%). Rf: 0.24 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): δ 1.28 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.30 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.38 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.84 (m, 1H; H3ax), 2.32 (m, 1H; H6ax), 2.46 (s,
3H; CH₃), 2.50 (m, 1H; H3eq), 2.55 (m, 1H, H6e), 2.90 (d, J = 5.6 Hz, 1H; OH), 3.36 (m, 1H; H1), 3.42 (m, 1H; H2), 4.22 (m, 4H, OCH₂), 4.28 (spt, J = 5.1 Hz, 1H; H4), 4.38 (m, 2H; OCH₂), 5.24 (m, 1H; H5). ¹³C NMR (150MHz, CDCl₃): δ 12.58 (CH₃), 14.23, 14.29 (CH₃), 21.15 (CH₃), 29.78 (C3), 32.16 (C6), 40.70 (C2), 40.87 (C1), 60.47 (OCH₂), 61.41, 61.70 (OCH₂), 62.10 (C5), 69.50 (C4), 125.78, 147.77 (C; triazolyl), 171.29, 172.85, 172.92 (C=O). HRMS: C₁₈H₂₈N₃O₇⁺ [M+H]_{Cal} m/z 398.1922; [M+H]_{exp} m/z 398.1902.

Azide 10a reacted with methyl-2-hexynoate to give a crude mixture of 15b and 16b that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

_Diethyl 3-propyl-4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-7,8-dicarboxylate (15b)_

![Diagram of 15b]

Compound 15b was isolated as colorless oil with a yield of 296 mg (56%). Rf: 0.64 (Hex:EtOAc, 1:1). ¹H NMR (600 MHz, CDCl₃): δ 0.97 (t, J = 7.0 Hz, 3H; CH₃), 1.29 (t, J = 7.1 Hz, 3H; CH₃), 1.31 (t, J = 7.1 Hz, 3H; CH₃), 1.76 (m, 2H; CH₂), 2.03 (m, 1H; H6eq), 2.07 (m, 1H; H3eq), 2.71 (m, 1H; H6ax), 2.94 (t, J = 8.2 Hz 2H; CH₂), 3.44 (m, 1H; H3ax), 3.50 (m, 2H; H1; H2), 4.18 (m, 4H, OCH₂), 4.43 (td, J = 10.8, 4.2 Hz, 1H; H5), 4.45 (td, J = 11.1, 4.3 Hz, 1H; H4). ¹³C NMR (150MHz, CDCl₃): δ 13.88 (CH₃), 14.25, 14.30 (CH₃), 22.21 (CH₂), 25.20 (C6), 27.50 (C6), 39.75 (C2), 40.55 (C1), 56.42 (C5), 61.96, 62.03 (OCH₂), 77.74 (C4), 121.65, 153.98 (C; triazolyl). 156.59, 172.01, 172.11 (C=O). HRMS: C₂₀H₂₆N₃O₅⁺ [M+H]_{Cal} m/z 380.1816; [M+H]_{exp} m/z 380.1806.
Diethyl-4-hydroxy-5-(4-(methoxycarbonyl)-5-propyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16b)

Compound 16b was isolated as yellow oil with a yield of 342 mg (60%). Rf: 0.41 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.96 (t, $J$ = 7.0 Hz, 3H; CH$_3$), 1.30 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.31 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.72 (m, 2H; CH$_2$), 1.86 (ddd, $J$ = 13.7, 11.0, 5.2 Hz, 1H; H$_3$ax), 2.31 (ddd, $J$ = 14.1, 11.2, 5.0 Hz, 1H; H$_3$ax), 2.55 (m, 2H; H$_3$ex, H$_6$ex), 2.86 (m, 2H; CH$_2$), 3.93 (s, 3H; CH$_3$), 3.37 (m, 1H; H$_1$), 3.41 (m, 1H; H$_2$), 4.24 (m, 4H, OCH$_2$), 4.35 (m, 1H; H$_4$), 5.22 (ddd, $J$ = 11.3, 9.2, 4.2 Hz, 1H; H$_5$). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 13.01 (CH$_3$), 14.05, 14.27 (CH$_3$), 22.48, 28.45 (CH$_2$), 29.88 (C6), 32.10 (C3), 40.69 (C2), 40.85 (C1), 52.44 (OCH$_2$), 61.48, 62.24 (OCH$_2$), 62.30 (C4), 69.39 (C5), 125.25, 152.12 (C; triazolyl), 160.19, 172.88, 172.90 (C=O). HRMS: C$_{19}$H$_{30}$N$_3$O$_7^+$ [M+H]$^+$Cal m/z 412.2078; [M+H]$^+$exp m/z 412.2074.
Azide 10a reacted with methyl-2-octynoate to give a crude mixture of 15c and 16c that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

*Diethyl 3-pentyl-4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-7,8-dicarboxylate (15c)*

![Structure of 15c]

Compound 15c was isolated as colorless oil with a yield of 354 mg (61%). Rf: 0.68 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.93 (t, $J$ =7.0 Hz, 3H; CH$_3$), 1.28 (t, $J$ =7.1 Hz, 3H; CH$_3$), 1.30 (t, $J$ =7.1 Hz, 3H; CH$_3$), 1.74 (m, 4H; CH$_2$), 2.00 (m, 1H; H6eq), 2.05 (m, 3H; H3eq, CH$_2$), 2.79 (m, 1H; H6ax), 2.91 (t, $J$ = 7.9 Hz 2H; CH$_2$), 3.38 (m, 1H; H3ax), 3.47 (m, 2H; H1, H2), 4.19 (m, 4H, OCH$_2$), 4.41 (td, $J$ =11.2, 4.0 Hz, 1H; H5), 4.48 (td, $J$ =11.0, 4.2 Hz, 1H; H4). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 12.10 (CH$_3$), 14.22, 14.28 (CH$_3$), 21.24, 21.86, 22.91, 23.14 (CH$_2$), 25.16 (C6), 26.83 (C6), 38.27 (C2), 40.02 (C1), 58.36 (C5), 61.09, 61.18 (OCH$_2$), 77.64 (C4), 121.34, 149.79 (C; triazolyl), 156.59, 171.84, 172.18 (C=O). HRMS: C$_{20}$H$_{30}$N$_3$O$_6^+$ [M+H]$^+$ Cal $m/z$ 408.2129; [M+H]$^+$ exp $m/z$ 408.2284.
Diethyl-4-hydroxy-5-(4-(methoxycarbonyl)-5-pentyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16c)

Compound 16c was isolated as colorless oil with a yield of 451 mg (63%). Rf: 0.49 (Hex:EtOAc, 1:1). ¹H NMR (600 MHz, CDCl₃): δ 0.95 (t, J = 7.0 Hz, 3H; CH₃), 1.29 (t, J = 7.1 Hz, 3H; CH₃), 1.30 (t, J = 7.1 Hz, 3H; CH₃), 1.52 (m, 2H; CH₂), 1.56 (m, 2H; CH₂), 1.71 (m, 2H; CH₂), 1.92 (ddd, J = 13.5, 11.3, 4.9 Hz, 1H; H3ax), 2.30 (ddd, J = 14.0, 11.4, 5.1 Hz, 1H; H3ax), 2.51 (m, 1H; H3ex), 2.55 (m, 1H; H6ex), 2.74 (m, 2H; CH₂), 3.35 (m, 1H; H1), 3.42 (m, 1H; H2), 3.96 (s, 3H; CH₃), 4.23 (m, 4H, OCH₂), 4.36 (m, 1H; H4), 5.22 (ddd, J = 11.4, 9.2, 4.0 Hz, 1H; H5). ¹³C NMR (150MHz, CDCl₃): δ 11.62 (CH₃), 14.09, 14.38 (CH₃), 22.31, 22.91, 23.37, 28.45 (CH₂), 29.15 (C6), 32.91 (C3), 40.44 (C2), 41.02 (C1), 57.34 (OCH₂), 60.91, 61.38 (OCH₂), 62.28 (C4), 69.31 (C5), 125.38, 148.39 (C; triazolyl), 162.33, 172.36, 172.60 (C=O). HRMS: C₂₁H₃₄N₃O₇⁺ [M+H]cal m/z 440.2391; [M+H]exp m/z 440.2382.
Azide 10a reacted with methyl-2-nonynoate to give a crude mixture of 15d and 16d that were separated by column chromatography (silica gel; Hex:EtOAc, 7:3).

*Diethyl 3-hexyl-4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-7,8-dicarboxylate (15d)*

![Chemical Structure](image)

Compound 15d was isolated as colorless oil with a yield of 162 mg (70%). Rf: 0.67 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.29 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.30 (t, $J$ = 7.0 Hz, 3H; CH$_3$), 1.71 (m, 4H; CH$_2$), 1.98 (m, 3H; H6eq, CH$_2$), 2.09 (m, 3H; H3eq, CH$_2$), 2.68 (m, 1H; H6ax), 2.90 (t, $J$ = 8.0 Hz 2H; CH$_2$), 3.31 (m, 1H; H3ax), 3.42 (m, 2H; H1, H2), 4.18 (m, 4H, OCH$_2$), 4.35 (td, $J$ = 11.2, 4.2 Hz, 1H; H5), 4.51 (td, $J$ = 10.7, 4.4 Hz, 1H; H4). $^{13}$C NMR (150MHz, CDCl$_3$): δ 12.05 (CH$_3$), 14.23, 14.26 (CH$_3$), 21.34, 21.79, 22.53, 23.14 (CH$_2$), 25.16 (C6), 26.31 (C6), 38.27 (C2), 41.24 (C1), 58.56 (C5), 61.08, 61.0 (OCH$_2$), 78.24(C4), 121.24, 148.24 (C; triazolyl), 157.32, 171.84, 172.38 (C=O). HRMS: C$_{21}$H$_{32}$N$_3$O$_6$+ [M+H]$_{Cal}$ m/z 422.2286; [M+H]$_{exp}$ m/z 422.2309.
Diethyl-4-hydroxy-5-(4-(methoxycarbonyl)-5-hexyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16d)

Compound 16d was isolated as colorless oil with a yield of 186 mg (60%). Rf: 0.21 (Hex:EtOAc,7:3). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.99 (t, $J = 7.0$ Hz, 3H; CH$_3$), 1.28 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.29 (t, $J = 7.0$ Hz, 3H; CH$_3$), 1.51 (m, 4H; CH$_2$), 1.58 (m, 2H; CH$_2$), 1.69 (m, 2H; CH$_2$), 1.93 (ddd, $J = 13.4$, 11.3, 5.0 Hz, 1H; H3ax), 2.28 (m, 1H; H3ax), 2.52 (m, 1H; H3ex), 2.60 (m, 1H; H6ex), 2.82 (m, 2H; CH$_2$), 3.34 (m, 1H; H1), 3.43 (m, 1H; H2), 4.01 (s, 3H; CH$_3$), 4.25 (m, 4H, OCH$_2$), 4.36 (m, 1H; H4), 5.25 (ddd, $J = 11.6$, 9.0, 4.1 Hz, 1H; H5). $^{13}$C NMR (150MHz, CDCl$_3$): δ 11.63 (CH$_3$), 14.12, 14.23 (CH$_3$), 22.30, 22.82, 23.01, 23.49, 28.75 (CH$_2$), 29.28 (C6), 23.54 (C3), 40.28 (C2), 41.12 (C1), 58.39 (OCH$_2$), 60.81, 61.59 (OCH$_2$), 62.34 (C4), 70.21 (C5), 124.69, 143.54 (C; triazolyl), 162.34, 171.35, 172.86 (C=O). HRMS: C$_{22}$H$_{36}$N$_3$O$_7$$^+$ [M+H]$_{\text{cal}}$ m/z 454.2548; [M+H]$_{\text{exp}}$ m/z 454.2548.
Diethyl-5-(5-hexyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (11c)

11c was synthesized with 11a and could not be separated. Product was cleaned by column chromatography (silica gel; hexane:EtOAc, 4:1) to give 0.82 g (42%) of colorless oil of 11c. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.92 (t, $J$=7.0 Hz, 3H; CH$_3$, hexyl), 1.26 (t, $J$=7.0 Hz, 3H; CH$_3$), 1.28 (t, $J$=7.0 Hz, 3H; CH$_3$), 1.32 (m, 6H; CH$_2$, hexyl), 1.68 (quintet, $J$=7.0 Hz, 2H; CH$_2$, hexyl), 1.80 (m, 2H; H3ax, H3eq), 2.34 (m, 1H, H6ax), 2.42 (m, 1H, H6eq), 2.71 (t, $J$=7.5 Hz, 2H; CH$_2$, hexyl), 3.44 (m, 1H, H1), 3.46 (m, 1H, H1; H2), 4.14 (m, 4H; OCH$_2$), 4.33 (m, 1H; H4), 4.43 (m, 1H; H5), 7.79 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 13.03 (CH$_3$, hexyl), 13.12 (CH$_3$, Et), 22.28, 25.06, 29.14, 28.62 (CH$_2$, hexyl), 28.72 (C6), 31.36 (CH$_2$, hexyl) 31.64 (C3), 40.27 (C2), 40.36 (C1), 60.92, 60.99 (OCH$_2$), 62.07 (C5), 67.97 (C4), 122.61 (CH; triazolyl), 126.67(C; triazolyl), 173.24, 173.43(C=O). HRMS: C$_{20}$H$_{34}$N$_3$O$_5$ [M+H]$_{\text{Cal}}$ m/z 396.2493; [M+H]$_{\text{exp}}$ m/z 396.2511.
Diethyl-5-(5-phenyl-1,2,3-triazolyl)-4-hydroxy-1,2-cyclohexanedicarboxylate (12c)

12c was synthesized with 12a and could not be separated. Product was cleaned by column chromatography (silica gel; hexane:EtOAc, 4:1) to give 0.92 g (46%) of colorless oil of 12c. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.25 (t, $J$ = 7.0 Hz, 3H; CH$_3$), 1.29 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.85 (ddd, $J$ = 13.6, 11.7, 5.3 Hz, 1H; H3ax), 2.45 (dtd, $J$ = 13.5, 4.3, 1.4 Hz 1H; H6ax), 2.57 (m, 2H; H3eq, H6eq), 2.93 (dt, $J$ = 12.8, 4.2 Hz, 1H, H1), 3.44 (m, 1H, H1), 3.46 (m, 1H; H2) 4.18 (m, 4H; OCH$_2$), 4.33 (ddd, $J$ = 11.6, 10.1, 4.4 Hz, 1H; H4), 4.44 (ddd, $J$ = 12.6, 10.0, 4.4 Hz, 1H; H5), 7.34 (m, 1H; Ph), 7.43 (m, 2H; Ph), 7.83 (m, 2H; Ph), 8.32 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 13.06 (CH$_3$), 13.14 (CH$_3$), 29.75 (C6), 34.93 (C3), 41.36 (C2), 41.89 (C1), 60.66, 60.77 (OCH$_2$), 65.50 (C5), 68.55 (C4), 120.82 (CH; triazolyl), 125.34 (2C; Ph), 127.92 (1C; Ph), 128.63 (2C; Ph), 130.54 (1C; Ph), 146.95 (C; triazolyl), 172.46, 172.82 (C=O). HRMS: C$_{20}$H$_{26}$N$_3$O$_5$$^+$ [M+H]$_{\text{cal}}$ m/z 388.1867; [M+H]$_{\text{exp}}$ m/z 388.1895.
Diethyl 4-(4,5-diphenyl-1H,1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylate (13)

Compound 13 was isolated as white crystals with a yield of 186 mg (69.9%). Rf: 0.27 (Hex:EtOAc, 7:3). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.24 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.26 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.85 (ddd, $J$ = 13.2, 11.1, 5.0 Hz, 1H; H3ax), 2.01 (m, 1H; H3eq), 2.52 (m, 1H; H6ex), 3.35 (m, 2H; H1, H2), 4.12 (m, 1H; H5), 4.22 (m, 4H, OCH$_2$), 4.56 (ddd, $J$ = 11.4, 9.0, 4.1 Hz, 1H; H5). 7.28 (m, 4H; Ph), 7.34 (m, 2H; Ph), 7.39 (m, 4H; Ph). $^{13}$C NMR (150MHz, CDCl$_3$): $\delta$ 14.04, 14.09 (CH$_3$), 23.24 (C6), 26.97 (C3), 41.39 (C2), 41.44 (C1), 60.04, 60.97 (OCH$_2$), 62.13 (C4), 70.55 (C5), 124.30 (C;triazolyl), 125.64, 125.67, 125.94, 126.02, 126.34, 126.41, 126.57, 126.75, 126.82, 127.36 (CH; Ph), 135.26, 136.27 (C; Ph), 145.36 (C;triazolyl), 171.24, 171.89 (C=O). HRMS: C$_{22}$H$_{36}$N$_3$O$_7$ $^+_{[M+H]}$Cal m/z 464.2180; $^+_{[M+H]}$exp m/z 464.1280.

Diethyl-5-(5-hexyl-1,2,3-triazolyl)-4-acetoxy-1,2-cyclohexanedicarboxylate (11d)

11d was synthesized with 11b and could not be separated. Product was cleaned by column chromatography (silica gel; Hex:EtOAc, 4:1) to give 0.78 g (41%) of colorless oil of
11d. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J = 7.1$ Hz, CH$_3$), 1.29 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.31 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.33 (m, 2H; CH$_2$hexyl), 1.71 (m, 2H; CH$_2$ hexyl), 1.82 (m, 1H, H3ax), 2.29 (m, 2H, H3eq, H6ax), 2.48 (m, 3H, H6eq, CH$_2$, hexyl), 3.41 (m, 1H, H2), 3.48 (m, 1H, H1), 4.20 (m, 4H; OCH$_2$), 4.68 (m, 1H; H5), 5.52 (td, $J = 8.1$, 4.0 Hz, 1H; H4), 7.32 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CDCl$_3$): $\delta$ 12.25 (CH$_3$, hexyl), 13.95 (CH$_3$, Et), 20.17 (CH$_3$-Acetyl), 22.54, 25.85, 29.64, 28.64 (CH$_2$, hexyl), 29.01 (C6), 31.54 (CH$_2$, hexyl) 31.78 (C3), 40.67 (C2), 40.92 (C1), 61.28, 61.39 (OCH$_2$), 65.28 (C5), 71.36 (C4), 123.68 (CH; triazolyl), 129.58(C; triazolyl), 168.34, 172.59, 173.95 (C=O). HRMS: C$_{22}$H$_{36}$N$_3$O$_6^+$ [M+H]$^+$ cal m/z 438.2599; [M+H]$^+$ exp m/z 438.2595.

*Diethyl- 5-(5-phenyl-1,2,3-triazolyl)-4-acetoxy-1,2-cyclohexanedicarboxylate (12d)*

![Chemical structure](image)

12d was synthesized with 12b and could not be separated. Product was cleaned by column chromatography (silica gel; Hex:EtOAc, 4:1) to give 0.72g (40%) of colorless oil of 12d.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.96 (t, $J = 7.0$ Hz, 3H; CH$_3$), 1.29 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.30 (t, $J = 7.1$ Hz, 3H; CH$_3$), 1.94 (m, 1H; H3ax), 1.95 (s, 3H, CH$_3$), (m, 1H; H6ax), 2.57 (m, 2H; H3eq, H6eq), 3.44 (m, 1H, H2), 3.53 (m, 1H, H1), 4.18 (m, 4H; OCH$_2$), 4.77 (ddd, $J = 12.6$, 10.0, 4.4 Hz, 1H; H5), 5.59 (m, 1H; H4), 7.34 (m, 1H; phenyl), 7.43 (m, 2H; phenyl), 7.83 (m, 2H; phenyl), 8.32 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 14.14 (CH$_3$), 14.18 (CH$_3$), 20.82 (CH$_3$; Acetyl), 28.85 (C3), 29.15 (C6), 40.07 (C1), 40.020 (C2), 58.64 (C5), 61.43, 61.46 (OCH$_2$), 70.25 (C4), 118.76 (CH; triazolyl), 125.71 (2CH; Ph), 128.23 (1CH; Ph), 128.83 (2CH;
Phenyl, 130.40 (1C; Ph), 147.59 (C; triazolyl), 160.24, 172.60, 172.85 (C=O). HRMS: 

\[ C_{22}H_{27}N_3O_6^+ \quad [M+H]_{\text{Cal}} \ m/z \ 430.1978; \quad [M+H]_{\text{exp}} \ m/z \ 430.1945. \]

*Diethyl 4-acetoxy-5-(4,5-diphenyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (14)*

![Diagram of compound 14]

Compound 14 was isolated as colorless with a yield of 0.94 g (82%). Rf: 0.28 (Hex:EtOAc, 5:4). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.92 (t, $J$ = 6.9 Hz, 3H; CH$_3$), 1.28 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.30 (t, $J$ = 7.1 Hz, 3H; CH$_3$), 1.84 (s, 3H, CH$_3$), 1.96 (m, 2H; H3ax, H6ax), 2.41 (m, 2H; H3eq, H6eq), 3.22 (m, 1H, H2), 3.39 (m, 1H, H1), 4.14 (m, 4H; OCH$_2$), 4.44 (ddd, $J$ = 12.6, 10.0, 4.4 Hz, 1H; H5), 5.59 (m, 1H; H4), 7.31 (m, 2H; phenyl), 7.34 (m, 4H; phenyl), 7.62 (m, 4H; phenyl), 8.07 (s, 1H; triazolyl). $^{13}$C NMR (600 MHz, CD$_3$OD): $\delta$ 14.14 (CH$_3$), 14.18 (CH$_3$), 20.82 (CH$_3$; Acetyl), 28.85 (C3), 29.15 (C6), 40.07 (C1), 40.020 (C2), 58.64 (C5), 61.43, 61.46 (OCH$_2$), 70.25 (C4), 118.76 (CH; triazolyl), 125.01, 125.34. 125.69, 125.87, 126.24, 126.59, 128.08, 128.83 (CH; Phenyl), 130.40, 132.04 (1C; Phenyl), 147.36 (C; triazolyl), 159.64, 170.36, 173.67 (C=O). HRMS: C$_{28}$H$_{32}$N$_3$O$_6^+$ $[M+H]_{\text{Cal}} \ m/z$ 506.2286; $[M+H]_{\text{exp}} \ m/z$ 506.2261.
Azide 10a reacted with ethyl-2-butynoate to give a crude mixture of 57a and 58a that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

$3$-methyl-$5,6,7,8,9,9$-hexahydro-$4\text{H}-\text{benzo}(1,2,3)\text{triazolo}(1,5-\text{d})(1,4)\text{oxazin}-4$-one (57a)

Compound 57a was isolated as a white crystal with a yield of 0.263 g (52%). Rf: 0.49 (Hex:EtOAc, 3:7). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.50 (m, 2H; H4eq, H5eq), 1.71 (m, 1H; H5ax), 1.79 (m, 1H; H4ax), 2.01 (m, 2H; H3eq, H6eq), 2.35 (m, 1H; H3ax), 2.61 (s, 3H; CH$_3$), 3.06 (m, 1H; H6ax), 4.19 (td, $J = 11.0, 4.3$ Hz, 1H; H2), 4.31 (td, $J = 11.0, 4.4$ Hz, 1H, H1). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 11.24 (CH$_3$), 23.20 (C5), 23.54 (C4), 26.88 (C6), 29.50 (C3), 59.74 (C2), 81.41 (C1), 121.97, 149.36 (2C; triazolyl), 156.96 (C=O). HMRS: C$_{10}$H$_{14}$N$_3$O$_2$$^+$ [M+H]$^\text{cal}$ m/z 208.1081; [M+H]$^\text{exp}$ m/z 208.1096.

Ethyl 1-(2-hydroxycyclohexyl)-$5$-methyl-$1\text{H}-1,2,3$-triazole-$4$-carboxylate (58a)

Compound 58a was isolated as colorless oil with a yield of 0.52 g (62%). Rf: 0.36 (Hex:EtOAc, 3:7). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.40 (t, $J = 7.2$ Hz, 3H; CH$_3$), 1.41 (m, 1H; H5ax), 1.49 (m, 2H; H3ax, H4ax), 1.88 (m, 2H; H4eq, H5eq), 1.99 (m, 1H; H6eq), 2.12 (qd, $J = 13.0, 3.6$ Hz, 1H; H6ax), 2.21 (m, 1H; H3eq), 2.57 (s, 1H; OH), 2.60 (s, 3H; CH$_3$), 3.97 (ddd, $J = 12.9, 8.8, 3.6$ Hz, 1H; H2), 4.27 (td, $J = 10.1, 4.7$ Hz, 1H; H1), 4.45-4.36 (m, 2H; OCH$_2$). $^{13}$C
NMR (150 MHz, CD$_3$OD): $\delta$ 9.20, 14.38 (CH$_3$), 24.18 (C4), 24.90 (C5), 31.28 (C6), 34.09 (C3), 61.00 (OCH$_2$), 64.74 (C1), 72.52 (C2), 135.67, 139.31 (C; triazolyl), 161.57 (C=O). HMRS: C$_{12}$H$_{20}$N$_3$O$_3^+$ [M+H]$_{cal}$ m/z 254.1499; [M+H]$_{exp}$ m/z 254.1512.

Azide 10a reacted with methyl-2-hexynoate to give a crude mixture of 57b and 58b that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

3-propyl-5,6,7,8,9,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazin-4-one (57b)

![Chemical structure of 57b]

Compound 57b was isolated as a white crystal with a yield of 0.1 g (22%). Rf: 0.47 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.97 (t, $J = 7.4$ Hz, 3H; CH$_3$), 1.50 (m, 2H; H4ax, H5ax), 1.75 (m, 4H; H3eq, H6eq, CH$_2$), 2.01 (m, 2H; H4eq, H5eq), 2.33 (m, 1H; H3ax), 2.94 (t, $J = 7.7$ Hz, 2H; CH$_3$), 3.06 (m, 1H; H6ax), 4.18 (td, $J = 11.0$, 4.3 Hz, 1H; H1), 4.30 (td, $J = 11.0$, 4.4 Hz, 1H; H2). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 13.87 (CH$_3$), 22.20 (CH$_2$), 23.22 (C4), 23.55 (C5), 26.88 (C6), 27.52 (CH$_2$), 29.49 (C3), 59.62 (C1), 81.15 (C2), 121.54, 153.71 (C; triazolyl), 157.24 (C=O). HMRS: C$_{12}$H$_{18}$N$_3$O$_2^+$ [M+H]$_{cal}$ m/z 236.1394; [M+H]$_{exp}$ m/z 236.1385.
Methyl 1-(2-hydroxycyclohexyl)-5-propyl-1H-1,2,3-triazole-4-carboxylate (58b)

\[
\begin{align*}
\text{HO} & \quad \text{N} \quad \text{N} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{N} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[\begin{align*}
\text{H}_3\text{C} \quad \text{O} \\
\end{align*}\]

\[^1\text{H} \text{NMR} (600 \text{ MHz}, \text{CDCl}_3): \delta 0.95 (t, J = 7.3 \text{ Hz}, 3\text{H}; \text{CH}_3), 1.39 (m, 1\text{H}; \text{H}5\text{ax}), 1.62-1.45 (m, 4\text{H}; \text{H}3\text{ax}, \text{H}4\text{ax}, \text{CH}_2), 1.90 (m, 3\text{H}; \text{H}4\text{eq}, \text{H}5\text{eq}, \text{H}6\text{ax}), 2.18 (m, 2\text{H}; \text{H}3\text{eq}, \text{H}6\text{eq}), 2.93 (m, 1\text{H}; \text{CH}_2), 3.04 (m, 1\text{H}; \text{CH}_2), 3.82 (s, 1\text{H}; \text{OH}), 3.86 (s, 3\text{H}; \text{CH}_3), 3.92 (m, 1\text{H}; \text{H}1), 4.22 (m, 1\text{H}; \text{H}2). \quad \text{\[^{13}\text{C} \text{NMR} (150 \text{ MHz}, \text{CDCl}_3): \delta 13.90 (\text{CH}_3), 22.39 (\text{CH}_2), 24.06 (\text{C}4), 24.71 (\text{C}5), 25.21 (\text{CH}_2), 31.67 (\text{C}6), 34.12 (\text{C}3), 51.89 (\text{CH}_3), 64.83 (\text{C}1), 72.47 (\text{C}2), 134.92, 143.50 (\text{C}; \text{triazolyl}), 161.88 (\text{C}=\text{O}). \quad \text{HRMS: } \text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_3^+ [\text{M+H}]_{\text{Cal}} m/\text{z} 268.1656; [\text{M+H}]_{\text{exp}} m/\text{z} 268.1645.}
\end{align*}\]

Azide 10a reacted with methyl-2-octynoate to give a crude mixture of 57b and 58b that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

3-pentyl-5,6,7,8,9,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazin-4-one (57c)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Compound 57c was isolated as a white crystal with a yield of 0.30 g (42%). Rf: 0.51 (Hex:EtOAc, 1:1). \[^1\text{H} \text{NMR} (600 \text{ MHz}, \text{CDCl}_3): \delta 0.98 (t, J = 7.3 \text{ Hz}, 3\text{H}; \text{CH}_3), 1.38 (m, 2\text{H}; \text{H}4\text{ax}, \text{H}5\text{ax}), 1.71 (m, 8\text{H}; \text{H}3\text{eq}, \text{H}6\text{eq}, 2\text{CH}_2), 1.97 (m, 1\text{H}; \text{H}4\text{eq}), 2.03 (m, 3\text{H}; \text{H}5\text{eq}, \text{CH}_2), 2.12 (m, 1\text{H}; \text{H}3\text{ax}), 2.18 (t, J = 7.5 \text{ Hz}, 2\text{H}; \text{CH}_2), 3.01 (m, 1\text{H}; \text{H}6\text{ax}), 4.17 (td, J = 11.0, 4.1 \text{Hz}, 1\text{H}; \text{H}1), 4.28 (td, J = 11.0, 4.2 \text{Hz}, 1\text{H}; \text{H}2). \quad \text{\[^{13}\text{C} \text{NMR} (150 \text{ MHz}, \text{CDCl}_3): \delta 13.87 (\text{CH}_3),}
\end{align*}\]
22.04, 22.18 (CH$_2$), 23.07 (C4), 23.25 (C5), 24.67 (CH$_2$), 25.37 (C6), 26.47 (CH$_2$), 28.26 (C3), 60.48 (C1), 79.98 (C2), 120.47, 150.37 (C; triazolyl), 161.04 (C=O). HMRS: C$_{14}$H$_{22}$N$_3$O$_2$$^+$ [M+H]$_{\text{cal}}$ m/z 264.1707; [M+H]$_{\text{exp}}$ m/z 264.1714.

*Methyl 1-(2-hydroxycyclohexyl)-5-pentyl-1H-1,2,3-triazole-4-carboxylate (58c)*

![Methyl 1-(2-hydroxycyclohexyl)-5-pentyl-1H-1,2,3-triazole-4-carboxylate (58c)](image)

Compound 58c was isolated as colorless oil with a yield of 0.52 g (64%). Rf: 0.38 (Hex:EtOAc, 1:1). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J$=7.0 Hz, 3H; CH$_3$, pentyl), 1.47 (m, 9H; H4ax, H5ax, H6ax, 3CH$_2$, pentyl), 1.88 (m, 2H; H4eq, H5eq), 1.97 (m, 1H; H3eq), 2.14 (qd, $J$=13.1, 3.7 Hz, 1H; H3ax), 2.23 (m, 1H; H6eq), 2.96 (ddd, $J$=14.0, 9.9, 6.0 Hz, 1H; CH$_2$ pentyl), 3.04 (ddd, $J$=14.1, 9.9, 6.0 Hz, 1H; CH$_2$ pentyl), 3.91 (S, 3H; COOCH$_3$), 3.95 (m, 1H; H1), 4.30 (m, 1H; H2). $^{13}$C NMR (600 MHz, CDCl$_3$): $\delta$ 13.95 (CH$_3$, pentyl), 22.30, 22.84 (CH$_2$, pentyl), 24.19 (C3), 25.09 (CH$_2$, pentyl) 28.66 (C5), 31.48 (CH$_2$, pentyl), 32.00 (C3), 34.13 (C6), 51.90 (OCH$_3$), 62.72 (C1), 72.40 (C2), 130.85, 143.64 (C; triazolyl), 162.05 (C=O). HRMS: C$_{15}$H$_{26}$N$_3$O$_3$$^+$ [M+H]$_{\text{cal}}$ m/z 296.1969; [M+H]$_{\text{exp}}$ m/z 296.1955.
Azide 10a reacted with methyl-2-nonynoate to give a crude mixture of 57d and 58d that were separated by column chromatography (silica gel; Hex:EtOAc, 1:1).

3-hexyl-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazin-4-one (57d)

Compound 57d was isolated as a white crystal with a yield of 0.38 g (44%). Rf: 0.53 (Hex:EtOAc, 1:1). 1H NMR (600 MHz, CDCl3): δ 0.97 (t, J = 7.3 Hz, 3H; CH3), 1.21 (m, 4H; CH2), 1.27 (m, 1H; H4ax), 131 (m, 1H: H5ax), 1.54 (m, 2H; H3eq, H6eq), 1.59 (m, 2H; CH2), 1.82 (m, 1H; H6eq), 1.94 (m, 3H; H5eq, CH2), 2.07 (m, 1H; H3ax), 2.18 (m, 2H; CH2), 3.05 (m, 1H; H6ax), 4.19 (td, J = 11.0, 4.0 Hz, 1H; H1), 4.26 (td, J = 10.8, 4.2 Hz, 1H; H2). 13C NMR (150 MHz, CDCl3): δ 10.34 (CH3), 20.24, 20.55, 20.74 (CH2), 20.87 (C4), 22.47 (C5), 22.52 (CH2), 25.00 (C6), 26.64 (CH2), 27.94 (C3), 61.51 (C1), 80.26 (C2), 124.66, 148.34 (C; triazolyl), 164.67 (C=O). HMRS: C15H24N3O2+ [M+H]cal m/z 278.1863; [M+H]exp m/z 278.1892.

Methyl 1-(2-hydroxycyclohexyl)-5-hexyl-1H-1,2,3-triazole-4-carboxylate (58d)

Compound 58d was isolated as colorless oil with a yield of 0.57 g (62%). Rf: 0.39 (Hex:EtOAc, 1:1). 1H NMR (600 MHz, CDCl3): δ 0.84 (t, J = 7.0 Hz, 3H; CH3, hexyl), 1.24 (m, 4H; CH2), 1.31 (m, 5H; H4ax, H5ax, H6ax, CH2, pentyl), 1.67 (m, 1H; H4eq) 1.72 (m, 1H; H5eq), 1.92 (m, 1H; H3eq), 2.14 (m, 2H; H3ax, H6eq), 2.84 (m, 2H; CH2 hexyl), 3.13 (ddd, J
=14.1, 9.9, 6.0 Hz, 1H; CH₂ hexyl), 3.85 (S, 3H; COOCH₃), 3.97 (m, 1H; H1), 4.24 (m, 1H; H2).

¹³C NMR (600 MHz, CDCl₃): δ 13.04 (CH₃, hexyl), 19.24, 19.98, 20.04 (CH₂, hexyl), 22.64 (C3), 24.67 (CH₂, hexyl) 27.68 (C5), 30.24 (CH₂, hexyl), 31.47 (C6), 33.33 (C3), 54.37 (OCH₃), 63.24 (C1), 74.27 (C2), 131.36, 141.67 (C; triazolyl), 163.47 (C=O). HRMS: C₁₆H₂₈N₃O₃⁺ [M+H]_{Cal} m/z 310.2125; [M+H]_{exp} m/z 310.2118.

*Methyl 4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-3-carboxylate (57e)*

![Chemical structure](image)

Compound 57e was synthesized from azide 10a and dimethyl acetylenedicarboxylate. Product was isolated as a white crystal with a yield of 310 mg (88%). Rf: 0.35 (Hex:EtOAc, 2:3). ¹H NMR (600 MHz, CDCl₃): δ 1.53 (m, 2H; H4ax, H5ax), 1.77 (m, 2H; H3ax, H6ax), 2.02 (m, 2H; H4eq, H5eq), 2.36 (m, 1H; H6eq), 3.10 (m, 1H; H3eq), 3.99 (s, 3H; CH₃), 4.29 (td, J = 11.0, 4.3 Hz, 1H; H2), 4.36 (td, J = 11.0, 4.3 Hz, 1H; H1). ¹³C NMR (150 MHz, CDCl₃): δ 22.86 (C5), 23.34 (C4), 27.17 (C3), 29.18 (C6), 53.28 (CH₃), 60.27 (C2), 81.11 (C1), 125.95, 141.46 (C=O), 153.46, 160.21 (C; triazolyl). HMRS: C₁₁H₁₄N₃O₄⁺ [M+H]_{Cal} m/z 252.0979; [M+H]_{exp} m/z 252.0951.
Ethyl 4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-3-carboxylate (57f)

Compound 57f was synthesized from azide 10a and diethyl acetylenedicarboxylate. Product was isolated as a white crystal with a yield of 283 mg (76%). Rf: 0.25 (Hex:EtOAc, 3:2). ¹H NMR (600 MHz, (CD₃)₂CO): δ 1.35 (t, J = 7.1 Hz, 3H; CH₃), 1.56 (qt, J = 13.2, 3.5 Hz, 1H; H5ax), 1.66 (qt, J = 13.4, 3.6 Hz, 1H; H4ax), 1.84 (m, 2H; H3ax, H6ax), 2.00 (m, 2H; H4eq, H5eq), 2.29 (m, 1H; H6eq), 3.01 (m, 1H; H3eq), 4.39 (m, 2H; OCH₂), 4.62 (td, J = 11.0, 4.4 Hz, 1H; H2), 4.71 (td, J = 11.0, 4.4 Hz, 1H; H1). ¹³C NMR (150 MHz, (CD₃)₂CO): δ 13.61 (CH₃), 23.00 (C6), 23.19 (C5), 26.48 (C4), 26.72 (C3), 59.63 (C2), 61.36 (OCH₂), 80.67 (C1), 126.06, 141.11 (C=O), 153.74, 159.77 (C; triazolyl). HMRS: C₁₂H₁₆N₃O₄⁺ [M+H]⁺ m/z 266.1135; [M+H]exp m/z 266.1153.

General procedure for synthesis of 5-triazolyl-4-hydroxy-1,2-cyclohexanedicarboxylic acids (hydrolysis of esters).

5-triazolyl-4-hydroxy-1,2-cyclohexanedicarboxylates (3 mmol) was dissolved in 3 mL of MeOH, and 1M KOH (10 mL) was added. The mixture was stirred at room temperature till consumption of the starting material (6 h). Aqueous layer was washed 2 x 10 mL of DCM. Reaction mixture was concentrated to 1/3 of the volume by rotary evaporator, and acidified with 6 M HCl to pH ~ 1. The aqueous layer was separated and extracted 4 x 8 mL EtOAc. Combined organic extracts were dried over anhydrous Na₂SO₄ for 12 hours and the product was concentrated with rotary evaporator. Carboxylic acids were purified by chromatography (Hex:EtOAc:Acetic Acid - 7:3:0.5).
(1S,2S,4S,5S)-4-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylic acid (47a)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 1:1 (with 2% acetic acid)) to give 128 mg (34%) of colorless oil of pure acid. $^1$H NMR (600 MHz, CD$_3$OD):

$\delta$ 0.95 (t, $J$ = 7.0 Hz, 3H; CH$_3$, hexyl), 1.42 (m, 6H; CH$_2$, hexyl), 1.68 (m, 2H; CH$_2$), 1.88 (m, H3ax), 2.34 (m, 2H, H3eq, H6ax), 2.53 (m, 1H, H6eq), 2.70 (t, $J$ = 7.6 Hz, 2H; CH$_2$), 3.35 (m, 1H; H1, H2), 3.38 (m, 1H; H1), 4.12 (m, 1H; H4), 4.75 (ddd, $J$ = 9.4, 8.4, 4.3Hz, 1H; H5), 7.81 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 13.04 (CH$_3$, hexyl), 22.28, 25.06, 29.14, 28.67 (CH$_2$, hexyl), 28.72 (C6), 30.37 (CH$_2$, hexyl) 31.22 (C3), 40.17 (C2), 40.36 (C1), 62.07 (C5), 67.97 (C4), 121.73 (CH; triazolyl), 126.34 (CH; triazolyl). HRMS: C$_{16}$H$_{26}$N$_3$O$_5$ [M+H]$^+$ cal m/z 340.1867; [M+H]$_{exp}$ m/z 340.1879.

(1S,2S,4S,5S)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylic acid (47b)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 1:1 (with 2% acetic acid) to give 102 mg (23%) of white crystals of pure acid. $^1$H NMR (600 MHz, CD$_3$OD):

$\delta$ 1.85 (m, 1H; H3ax), 2.36 (m, 3H; H3eq, H6ax, H6eq), 3.24 (m, 1H, H1), 3.34 (m, 1H, H2), 3.56 (ddd, $J$ =11.8, 10.0, 4.1 Hz, 1H; H4), 4.62 (m, 1H; H5), 7.21 (m, 1H; phenyl), 7.33 (m, 2H; phenyl), 7.83 (m, 2H; phenyl), 8.36 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD):
27.03 (C6), 29.34 (C3), 42.36 (C2), 42.39 (C1), 65.31 (C5), 69.27 (C4), 118.32 (CH; triazolyl), 124.39 (2C; Phenyl), 127.34 (1C; Phenyl), 128.02 (2C; Phenyl), 129.94 (1C; Phenyl), 146.99 (C; triazolyl). HRMS: \( \text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_5^+ \) \([\text{M}+\text{H}]_{\text{Cal}} m/z \) 332.1241; \([\text{M}+\text{H}]_{\text{exp}} m/z \) 332.1257.

\((1S,2R,4R,5R)-4-(4\text{-hexyl-}1\text{H}-1,2,3\text{-triazol-1-yl})-5\text{-hydroxycyclohexane-1,2-dicarboxylic acid} \) (55a)

Product was purified by column chromatography (silica gel; hexane:EtoAc, 1:1 (with 2% acetic acid)) to give 191 mg (46%) of colorless oil of pure acid. \(^1\)H NMR (600 MHz, \( \text{CD}_3\text{OD} \)): \( \delta \) 0.93 (t, \( J =7.0 \text{ Hz} \), 3H; CH\(_3\), hexyl), 1.44 (m, 4H; CH\(_2\), hexyl), 1.47 (m, 2H; CH\(_2\), hexyl) 1.60 (m, 2H; CH\(_2\), hexyl), 1.86 (m, H\(3ax\)), 2.28 (m, 2H, H\(3eq\), H\(6ax\)), 2.59 (m, 1H, H\(6eq\)), 2.70 (t, \( J =7.5 \text{ Hz} \), 2H; CH\(_2\)), 3.30 (m,1H; H1, H1), 3.48 (m, 1H; H2), 4.11 (m, 1H; H4), 4.62 (ddd, \( J = 9.7, 8.0, 4.3 \text{ Hz} \), 1H; H5), 7.79 (s, 1H; triazolyl). \(^{13}\)C NMR (150 MHz, \( \text{CD}_3\text{OD} \)): \( \delta \) 16.47 (CH\(_3\), hexyl), 24.34, 25.06, 28.61, 28.88 (CH\(_2\), hexyl), 28.97 (C6), 30.92 (CH\(_2\), hexyl) 33.24 (C3), 43.45 (C2), 46.24 (C1), 63.57 (C5), 72.94 (C4), 122.34 (CH; triazolyl), 139.24 (CH; triazolyl). HRMS: \( \text{C}_{16}\text{H}_{26}\text{N}_3\text{O}_5^+ \) \([\text{M}+\text{H}]_{\text{Cal}} m/z \) 340.1867; \([\text{M}+\text{H}]_{\text{exp}} m/z \) 340.1879.
(1S,2R,4R,5R)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylic acid (55b)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 1:1 (with 2% acetic acid)) to give 102 mg (23%) of white crystals of pure acid. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 1.85 (m, 1H; H3ax), 2.36 (m, 3H; H3eq, H6ax, H6eq), 3.24 (m, 1H, H1), 3.34 (m, 1H, H2), 4.07 (ddd, $J$ = 11.8, 10.0, 4.1 Hz, 1H; H4), 4.62 (m, 1H; H5), 7.21 (m, 1H; phenyl), 7.33 (m, 2H; phenyl), 7.83 (m, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD): 27.03 (C6), 29.34 (C3), 42.36 (C2), 42.39 (C1), 65.31 (C5), 69.27 (C4), 118.32 (CH; triazolyl), 124.39 (2C; Phenyl), 127.34 (1C; Ph), 128.02 (2C; Ph), 129.94 (1C; Ph), 146.99 (C; triazolyl). HRMS: C$_{16}$H$_{18}$N$_3$O$_5$ $^[M+H]_{\text{Cal}} m/z$ 332.1241; $^[M+H]_{\text{exp}} m/z$ 332.1257.

(1R,2S,4S,5S)-4-(4-hexyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylic acid (56a)

Product was purified by column chromatography (silica gel; Hex:EtOAc, 1:1 (with 2% acetic acid)) to give 214 mg (53%) of colorless oil of pure acid. $^1$H NMR (600 MHz, CD$_3$OD): $\delta$ 0.91 (t, $J$ = 6.8 Hz, 3H; CH$_3$, hexyl), 1.31 (m, 4H; CH$_2$, hexyl), 1.39 (m, 2H; CH$_2$, hexyl), 1.51 (m, 2H; CH$_2$, hexyl), 1.91 (m, 2H; H3ax, H6ax), 2.14 (m, 1H, H3eq), 2.62 (m, 1H, H6eq), 2.78 (t, $J$ = 7.5 Hz, 2H; CH$_2$), 3.34 (m, 1H; H1, H2), 3.48 (m, 1H; H1), 4.03 (m, 1H; H4), 4.62 (m, 1H; H5), 7.96 (s, 1H; triazolyl). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 14.37 (CH$_3$, hexyl), 23.47, 24.06,
26.30, 27.94 (CH₂, hexyl), 28.34 (C6), 31.24 (CH₂, hexyl) 33.47 (C3), 44.34 (C2), 46.64 (C1), 63.44 (C5), 73.64 (C4), 123.47 (CH; triazolyl), 140.20 (CH; triazolyl). HRMS: C₁₆H₂₆N₃O₅ [M+H]Cal m/z 340.1867; [M+H]exp m/z 340.1854.

(1R,2S,4S,5S)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylic acid (56b)

Product was purified by column chromatography (silica gel; Hex:EtOAc,1:1 (with 2% acetic acid) to give 204 mg (50%) of white crystals of pure acid. ¹H NMR (600 MHz, CD₃OD): δ 1.80 (m, 1H; H3ax), 2.14 (m,1H; H3eq), 2.34 (m, 1H; H6ax), 2.82 (m,1H; H6eq), 3.28 (m, 1H, H2), 3.41 (m, 1H, H1), 4.15 (m,1H; H4), 4.62 (ddd, J =11.6, 9.8, 4.1 Hz, 1H; H5), 7.28 (m, 1H; Ph), 7.31 (m, 2H; Ph), 7.45 (m, 2H; Ph), 8.14 (s, 1H; triazolyl). ¹³C NMR (150 MHz, CD₃OD): 30.21 (C6), 30.63 (C3), 41.54 (C2), 43.12 (C1), 69.36 (C5), 74.27 (C4), 122.67 (CH; triazolyl), 123.24, 124.25 (CH; Ph), 127.34 (CH; Ph), 129.94, 131.67 (CH; Ph), 130.69 (C; Ph), 147.36 (C; triazolyl). HRMS: C₁₆H₁₈N₃O₅⁺ [M+H]Cal m/z 332.1241; [M+H]exp m/z 332.1254.
NMR Analysis of pH-dependent Conformational Equilibrium

Azaaryl compound was dissolved in CD$_3$OD (0.02-0.03 M), and the change in chemical width and the chemical shifts of the protons geminal to the azaaryl groups, hydroxyl group and the ethyl ester-lipid tails were monitored by $^1$H NMR spectra (600 MHz) during titration of the solution with $d$-trifluoroacetic acid ($d$-TFA). Acid was dissolved in CD$_3$OD (1 M) and added to the solution of azaaryl-lipid in an NMR tube (0.6 mL) in small portions (1-5 μL). After every addition the solution was mixed thoroughly by gentle shaking, and its pH (pD) was measured using a micro combination pH electrode for NMR cells (9826BN, Thermo Scientific). Shaking and measuring was repeated 3-4 times until a constant value of pD reading was constant. After recording the $^1$H NMR spectrum, pD was measured again: the original and final values matched within 0.05 units. The spin-spin coupling constants between several pairs of vicinal protons attached to the cyclohexane moiety are strongly conformation-dependent, which allowed an assignment of a predominant conformation and an estimation of a position of the conformational equilibrium as described previously.$^{18,25-29,37,99}$

Calculations for Conformational Preference of Triazolylicyclohexanes

As a model compound, methyl, phenyl and triazole substituted cyclohexanes were used for the computational studies. All the calculations are performed using Gaussian 09 program package. The MP2 method$^{84}$ was utilized for geometry optimization in which the structure or geometry with the lowest potential energy was obtained. This optimization accounted for all rotamers, isomers of a molecule that can be obtained by rotation of a substituent at a particular bond, of each structure. The geometry optimizations were performed at MP2 level with 6-311+G(d,p) basis set. For each optimized structure, vibrational frequency calculations were carried out to confirm if it was a minimum with no imaginary frequency and to obtain
thermodynamic correction terms including zero-point vibration energy, thermal correction ($C_p$) to enthalpy ($\Delta H_{298}$), and entropy ($\Delta S$). For more accurate description of thermodynamics of the axial and equatorial conformers, coupled cluster CCSD(T) method was used for single point energy calculation based on the MP2 optimized geometries of each structure. This was done to find the lowest potential energy for the already optimized structures while accounting for all excitations, i.e. up to triple excitations (T). The single point energy calculations were carried out at MP2/6-311++G(3df,3pd) and CCSD(T)/6-311+G(d,p) levels. In order to mimic the experimental environment, the single-point energy calculations were carried out using the conductor polarizable continuum model (CPCM) at the B3LYP/6-311+G(3df,2p) level with methanol as a solvent. Finally, to estimate more accurate energetics, the CCSD(T)/6-311+G(d,p) level energies were extrapolated to CCSD(T)/6-311++G(3df,3pd) level using basis set effect obtained at MP2 level via following equation: 

$$\text{CCSD(T)/6-311++G(3df,3pd)} = \text{CCSD(T)/6-311+G(d,p)} + \text{MP2/6-311++G(3df,3pd)} - \text{MP2/6-311+G(d,p)}$$

**Procedure for Glycosidase Inhibition**

The enzyme activities ($\beta$-D-galactosidases and $\beta$-D-glucosidases) were assayed using multi-enzyme complexes isolated from fungi P. canescens and A. oryzae as described before. All assays were performed in a standard way by monitoring spectrophotometrically (with Beckman Du-65 spectrometer) the release of p-nitrophenol from the corresponding p-nitrophenyl glycosides at 30°C. One unit of enzyme activity was defined as the amount of enzyme that releases 1 µmol of p-nitrophenol per minute. Enzyme and substrate concentrations were selected so that the degree of hydrolysis was never more than 20%, and in most cases was less than 10%, over the course of the assay. The method used to measure the rate of the reaction assumes that the amount
of the substrate is high enough, such that the disappearance over a given period is insignificant, that is the rate of the reaction is close to linear for the first stage of the reaction.

For the preliminary estimation, the enzyme solutions (100 µL with activities 750±150 µU) were mixed with a set of inhibitor/activator solutions (100 µL, 10 mM), then diluted with 700 µL of 0.2 M acetic buffer (pH 4.2), and the mixture was incubated for 1 h at 30°C. The reaction was initiated with addition of a proper substrate (100 µL of 20 mM p-nitrophenyl glycopyranoside), and aliquots were taken after 5 and 10 min. The reaction was terminated by addition of 1 mL of 1 M Na2CO3 to 0.5 mL of aliquot solution. The concentration of the released p-nitrophenol was determined at 400 nm using molar extinction coefficient 18.3 mM-1 cm-1. The inhibition/activation was estimated as a loss/increase of enzymatic activity in %.
REFERENCES


38. Samoshin, A. V.; Veselov, I. S.; Chertkov, V. A.; Yaroslavov, A. A.; Grishina, G. V.; Samoshina, N. M.; Samoshin, V. V. Flaposomes: New Amphiphiles Based on Trans-3,4-Bis(Acyloxy)-Piperidine Able to Perform a PH-Triggered Conformational Flip and Cause an Instant Cargo Release from Liposomes. Tetrahedron Lett. 2013, 54 (41), 5600–5604.


APPENDIX A: SELECTED $^1$H NMR TITRATION DATA
Titration $^1$H NMR Data and Conformational Parameters for 3c.\textsuperscript{a)}

![Diagram](image)

<table>
<thead>
<tr>
<th>$pD$</th>
<th>$H^1 (O)$</th>
<th>$H^1 (S)$</th>
<th>$H^2$</th>
<th>$H^2$</th>
<th>$n_B(n_{BD})$, $\Delta G_{B-A}$</th>
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<td>3.92 \textsuperscript{c)}</td>
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\textsuperscript{a)} 600 MHz; 0.02-0.03 M solutions at 294K; b) d-trifluoroacetic acid was added in large excess (x10\textsuperscript{15}) to CD\textsubscript{3}OD solution; c) Partially or completely overlapped with other signals; d) Unresolved signal (a width at 1/3 of its height is shown); e) Poorly resolved signal;
Titration $^1$H NMR Data and Conformational Parameters for 3d.\textsuperscript{a)}

\[
\begin{array}{|c|c|c|c|c|c|c|c|c|c|c|}
\hline
pD & H^1 (O) & H^1 (S) & H^2 & n_B(n_B^*) & \Delta G_{B-A} \\
\hline
\delta & W, Hz & \delta & W, Hz & \delta & W, Hz & \% & kJ/mol \\
\hline
7.29 & 3.97 & 11.01 & 3.76 & 12.30 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.1 \\
7.29 & 3.97 & 11.01 & 3.76 & 12.30 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.1 \\
6.97 & 3.97 & 11.01 & 3.76 & 12.30 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.1 \\
6.17 & 3.97 & 11.01 & 3.76 & 12.30 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.1 \\
5.96 & 3.97 & 11.01 & 3.76 & 12.30 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.1 \\
5.55 & 3.97 & 11.01 & 3.76 & 12.34 & 2.94 & 25.10 & 3.10 & 25.22 & 16 & 4.0 \\
5.42 & 3.97 & 11.06 & 3.76 & 12.36 & 2.94 & 25.05 & 3.10 & 25.21 & 16 & 4.0 \\
5.20 & 3.97 & 11.11 & 3.76 & 12.37 & 2.94 & 25.01 & 3.10 & 25.18 & 16 & 4.0 \\
4.98 & 3.97 & 11.18 & 3.77 & 12.40 & 2.94 & 24.87 & 3.11 & 25.08 & 17 & 3.9 \\
4.74 & 3.97 & 11.23 & 3.77 & 12.54 & 2.95 & 24.67 & 3.11 & 24.98 & 18 & 3.8 \\
4.46 & 3.97 & 11.41 & 3.79 & 12.70 & 2.95 & 24.56 & 3.12 & 24.81 & 19 & 3.6 \\
3.97 & 3.96 & 12.34 & 3.82 & 13.63 & 2.97 & 23.54 & 3.14 & 23.76 & 24 & 2.8 \\
3.76 & 3.96 & 12.96 & 3.85 & 14.10 & 2.98 & 23.02 & 3.16 & 23.24 & 27 & 2.4 \\
3.47 & 3.96 & 13.56 & 3.87 & 14.77 & 3.00 & 22.33 & 3.18 & 22.62 & 31 & 2.0 \\
3.17 & 3.96 & 14.06 & 3.89 & 15.29 & 3.01 & 21.69 & 3.19 & 22.02 & 34 & 1.6 \\
2.84 & 3.96 & 14.43 & 3.91 & 15.72 & 3.02 & 21.39 & 3.20 & 21.67 & 36 & 1.4 \\
2.67 & 3.96 & 14.54 & 3.91 & 15.81 & 3.02 & 21.20 & 3.21 & 21.53 & 37 & 1.3 \\
2.36 & 3.95 & 14.85 & 3.91 & 16.02 & 3.02 & 20.95 & 3.21 & 21.8 & 39 & 1.1 \\
2.02 & 3.95 & 15.10 & 3.91 & 16.19 & 3.02 & 20.68 & 3.21 & 20.94 & 40 & 1.0 \\
1.89 & 3.94 & 15.24 & 3.91 & 16.33 & 3.02 & 20.53 & 3.21 & 20.79 & 41 & 0.9 \\
1.53 & 3.94 & 15.50 & 3.91 & 16.51 & 3.02 & 20.30 & 3.21 & 20.59 & 42 & 0.8 \\
1.27 & 3.93 & 15.70 & 3.91 & 16.60 & 3.02 & 20.10 & 3.21 & 20.50 & 43 & 0.7 \\
\hline
\end{array}
\]

\textsuperscript{a)} 600 MHz; 0.02-0.03 M solutions at 294K; b) \(d\)-trifluoroacetic acid was added in large excess (\(10^{15}\)) to CD\(_3\)OD solution; c) Partially or completely overlapped with other signals; d) Unresolved signal (a width at 1/3 of its height is shown); e) Poorly resolved signal; f) Used as \(W_A\)
Titration $^1$H NMR Data and Conformational Parameters for 3f.\textsuperscript{a})

\begin{table}[h]
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
$pD$ & $H^1$ (O) & $H^2$ (S) & $H^3$ & $H^4$ & $n_{pH}$ & $\Delta G_{B-A}$, kJ/mol \\
\hline
\hline
7.41 & 3.88 & 10.70 & 3.46 & 11.30 & 2.95 & 25.40 & 3.04 & 25.53 & 13 & 4.6 \\
7.23 & 3.88 & 10.70 & 3.46 & 11.30 & 2.95 & 25.40 & 3.04 & 25.53 & 13 & 4.6 \\
6.63 & 3.88 & 10.70 & 3.46 & 11.30 & 2.95 & 25.40 & 3.04 & 25.53 & 13 & 4.6 \\
6.52 & 3.88 & 10.70 & 3.46 & 11.30 & 2.95 & 25.40 & 3.04 & 25.53 & 13 & 4.6 \\
6.34 & 3.85 & 10.72 & 3.46 & 11.31 & 2.95 & 25.38 & 3.04 & 25.51 & 13 & 4.6 \\
6.18 & 3.85 & 10.76 & 3.46 & 11.33 & 2.96 & 25.36 & 3.04 & 25.50 & 13 & 4.5 \\
5.72 & 3.85 & 10.84 & 3.46 & 11.39 & 2.97 & 25.20 & 3.04 & 25.36 & 14 & 4.4 \\
5.24 & 3.84 & 11.04 & 3.47 & 11.67 & 2.97 & 24.94 & 3.05 & 25.16 & 15 & 4.2 \\
5.05 & 3.84 & 11.23 & 3.48 & 11.95 & 2.98 & 24.70 & 3.05 & 24.89 & 17 & 3.9 \\
4.90 & 3.84 & 11.66 & 3.48 & 12.22 & 2.98 & 24.47 & 3.06 & 24.59 & 19 & 3.6 \\
4.60 & 3.83 & 12.33 & 3.5 & 13.12 & 2.99 & 23.85 & 3.07 & 24.00 & 23 & 3.0 \\
4.29 & 3.83 & 13.25 & 3.53 & 14.21 & 3.01 & 22.86 & 3.1 & 23.02 & 28 & 2.3 \\
3.95 & 3.82 & 14.29 & 3.57 & 15.32 & 3.03 & 21.80 & 3.12 & 21.94 & 34 & 1.6 \\
3.37 & 3.81 & 15.45 & 3.6 & 16.49 & 3.05 & 20.60 & 3.15 & 20.81 & 41 & 0.9 \\
2.92 & 3.80 & 15.93 & 3.61 & 17.04 & 3.05 & 19.87 & 3.16 & 20.00 & 45 & 0.5 \\
2.44 & 3.80 & 16.44 & 3.62 & 17.51 & 3.06 & 19.45 & 3.16 & 19.60 & 47 & 0.3 \\
2.13 & 3.80 & 16.68 & 3.62 & 17.74 & 3.06 & 19.26 & 3.16 & 19.39 & 49 & 0.1 \\
1.71 & 3.80 & 16.94 & 3.62 & 17.90 & 3.06 & 19.06 & 3.16 & 19.21 & 50 & 0.0 \\
1.51 & 3.80 & 17.02 & 3.62 & 18.11 & 3.07 & 19.04 & 3.17 & 19.17 & 50 & 0.0 \\
1.37 & 3.80 & 17.04 & 3.62 & 18.11 & 3.08 & 18.96 & 3.18 & 19.09 & 50 & 0.0 \\
\hline
\end{tabular}
\end{table}

a) 600 MHz; 0.02-0.03 M solutions at 294K; b) d-trifluoroacetic acid was added in large excess (x10$^{15}$) to CD$_3$OD solution; c) Partially or completely overlapped with other signals; d) Unresolved signal (a width at 1/3 of its height is shown); e) Poorly resolved signal; f) Used as $W_A$
Titration $^1$H NMR Data and Conformational Parameters for 3k.\textsuperscript{a)}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|}
\hline
$pD$ & $H^1$ & $H^2$ & $\delta$ & $W$, Hz & $\delta$ & $W$, Hz & $\delta$ & $W$, Hz & $\%$ & $\Delta G_{B-A}$, kJ/mol \\
\hline
7.61 & 4.03 & 10.09 & 4.01 & 10.89 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.5 \\
7.54 & 4.03 & 10.09 & 4.01 & 10.89 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.5 \\
6.27 & 4.03 & 10.11 & 4.01 & 10.92 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.4 \\
5.65 & 4.03 & 10.15 & 4.01 & 10.96 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.4 \\
5.34 & 4.03 & 10.22 & 4.01 & 11.00 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.3 \\
5.23 & 4.03 & 10.23 & 4.01 & 11.03 & 2.94 & 26.25 & 3.08 & 26.34 & 7 & 6.3 \\
4.85 & 4.03 & 10.27 & 4.01 & 11.07 & 2.95 & 26.22 & 3.08 & 26.34 & 7 & 6.2 \\
4.63 & 4.03 & 10.33 & 4.01 & 11.09 & 2.95 & 26.09 & 3.08 & 26.28 & 8 & 6.1 \\
4.43 & 4.03 & 10.37 & 4.01 & 11.10 & 2.95 & 26.00 & 3.08 & 26.21 & 8 & 6.0 \\
4.17 & 4.02 & 10.42 & 4.02 & 11.17 & 2.95 & 25.94 & 3.08 & 26.05 & 8 & 5.8 \\
4.01 & 4.02 & 10.53 & 4.02 & 11.48 & 2.96 & 25.70 & 3.08 & 25.95 & 10 & 5.5 \\
3.72 & 4.01 & 10.82 & 4.01 & 12.01 & 2.96 & 25.56 & 3.09 & 25.72 & 11 & 5.0 \\
3.41 & 4.00 & 11.65 & 4.00 & 13.14 & 2.98 & 24.79 & 3.11 & 24.88 & 17 & 3.9 \\
2.98 & 3.97 & 14.05 & 3.99 & 15.21 & 3.02 & 23.10 & 3.14 & 23.32 & 28 & 2.3 \\
2.36 & 3.93 & 16.21 & 3.99 & 17.29 & 3.09 & 20.21 & 3.20 & 20.38 & 43 & 0.7 \\
1.90 & 3.92 & 17.34 & 3.98 & 18.20 & 3.12 & 18.83 & 3.22 & 19.01 & 50 & 0.0 \\
1.63 & 3.91 & 17.68 & 3.98 & 18.75 & 3.12 & 18.05 & 3.23 & 18.34 & 53 & -0.3 \\
1.43 & 3.80 & 17.97 & 3.61 & 19.05 & 3.05 & 17.64 & 3.16 & 17.92 & 55 & -0.5 \\
1.23 & 3.89 & 18.04 & 3.96 & 19.26 & 3.15 & 17.59 & 3.25 & 17.84 & 56 & -0.6 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a)} 600 MHz; 0.02-0.03 M solutions at 294K; b) $d$-trifluoroacetic acid was added in large excess ($x10^{15}$) to CD$_3$OD solution; c) Partially or completely overlapped with other signals; d) Unresolved signal (a width at 1/3 of its height is shown); e) Poorly resolved signal; f) Used as $W_A$
APPENDIX B: SELECTED $^1$H NMR SPECTRA
Diethyl cis-4-hydroxy-trans-5-(pyridine-2-yl-thio)cyclohexane-trans-1,2-dicarboxylate (3c) in CD$_3$OD
Diethyl cis-4-hydroxy-trans-5-((1H-benzoimidazol-2-ylthio)cyclohexane-trans-1,2-dicarboxylate (3k) in CDCl₃
trans-2-(phenylthio)cyclohexanol (5a) in CDCl₃
trans-2-(pyridin-2-ylthio)cyclohexanol (5c) in CD$_3$OD

$W = 23.0 \text{ Hz}$

$W = 22.5 \text{ Hz}$
Diethyl-5-azido-4-hydroxy-1,2-cyclohexanedicarboxylate (10a) in CDCl₃
Diethyl-5-azido-4-acetoxy-1,2-cyclohexanedicarboxylate (10b) in CDCl₃
4-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexyl acetate (35b) in CDCl₃
Diethyl 4-(4,5-diphenyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylate (13) in CDCl₃
Diethyl-4-hydroxy-5-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16a) in CD$_3$OD
Ethyl 4-oxo-5,6,7,8,9-hexahydro-4H-benzo(1,2,3)triazolo(1,5-d)(1,4)oxazine-3-carboxylate (57f) in CDCl₃
APPENDIX C: SELECTED $^{13}$C NMR SPECTRA
2-(4-hexyl-1H-1,2,3-triazol-1-yl)cyclohexanol (18a) in CDCl₃
2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexanol (18b) in CDCl₃
4-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexyl acetate (35b) in CDCl₃
APPENDIX D: SELECTED MASS SPECTRA
Diethyl cis-4-hydroxy-trans-5-(pyridine-2-yl-thio)cyclohexane-trans-1,2-dicarboxylate (3c)
Diethyl-4-hydroxy-t-5-((1-methyl-1H-imidazol-2-yl)thio)cyclohexane-r-1,t-2-dicarboxylate (3g)
Diethyl 4-(4,5-diphenyl-1H-1,2,3-triazol-1-yl)-5-hydroxycyclohexane-1,2-dicarboxylate (13)

\[ [\text{M+H}^+] \text{ cal} = 464.2180 \]

\[ [2\text{M+H}^+] \]

\[ \text{cal} = 927.4364 \]
Diethyl-4-oxo-3-methyl-5,6,7,8,9-hexahydro-4H-benzo[b][1,2,3]triazolo[1,4]oxazine-7,8-dicarboxylate (15a)
Diethyl-4-hydroxy-5-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16a)
Diethyl-4-oxo-3-propyl-5,6,7,8,9-hexahydro-4H-benzo[b][1,2,3]triazolo[1,4]oxazine-7,8-dicarboxylate (15a)
Diethyl-4-hydroxy-5-(4-(methoxycarbonyl)-5-propyl-1H-1,2,3-triazol-1-yl)cyclohexane-1,2-dicarboxylate (16b)
(1R,2R,4S)-4-(tert-butyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclohexanol (28b)
4-hexyl-1-(4-phenylcyclohexyl)-1H-1,2,3-triazole (43a)
Cyclohexyl-4-phenyl-1H-1,2,3-triazole (40b)

\[[M+H]^+\]_{cal} = 228.1495

\[[2M+H]^+\]
Ethyl 1-(2-hydroxycyclohexyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (58a)