Design and Synthesis of Dendrimers by Combination of ‘Click’ Chemistry and A³-Coupling

by

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Abstract

Over the recent years, dendrimers have found applications in an extended range of fields due to their unique features and properties, such as their core, backbone, internal cavities and surface groups. Synthetic elaboration of dendrimers to enhance their efficacy in carrying out different functions continues to be a topical area of research. In this thesis, a new methodology to synthesize dendrimers was developed using a combination of two important reactions: copper catalyzed alkyne-azide and A₃-coupling reactions. The so called ‘click’ CuAAC reaction has been widely used in the synthesis of dendrimers, while A₃-coupling had never been employed for such a purpose. Through a combination of these reactions, we aimed to streamline their synthesis, and make it more versatile. The divergent synthesis of dendrimers, employing almost exclusively A₃-coupling, proved to be troublesome due to the rapid increase in polarity of the generated macromolecules. The convergent methodology, on the other hand, where the dendrimers synthesis was achieved through a combination of ‘click’ CuAAC and A₃-coupling reactions, was found to be more promising for their synthesis. Using these coupling methodologies, various dendrimers with differing cores and backbones have been prepared and characterized. Dendrimers (1), (2), (4) and (5) were synthesized through the divergent approach, while the protected generation 1 dendrimer (10), its unprotected counterpart (19) and the protected generation 2 dendrimer (18) were afforded from the convergent methodology.
Résumé

Au cours des dernières années, les dendrimères ont trouvé des applications dans une gamme étendue de domaines. Ces macromolécules ont des caractéristiques et propriétés uniques, telles qu’un noyau central, l’embranchement, les cavités internes et les groupements fonctionnelles le long de leur surface. L’élaboration synthétique de dendrimères pour améliorer leur efficacité afin d’obtenir des fonctionnalités variés continue d’être un domaine d'actualité de la recherche. Dans cette thèse, une nouvelle méthodologie pour synthétiser des dendrimères a été développée en utilisant une combinaison de deux réactions importantes: l’addition cyclique alcyne-azide catalysée par le cuivre (I) et l’accouplement A3 (aldéhyde-alcyne-amine). La réaction couramment appelée CuAAC a été régulièrement utilisé dans la synthèse de dendrimères, tandis que l’accouplement A3 n’avait jamais été utilisé auparavant à de telles fins. Grâce à une combinaison de ces réactions, nous avons cherché à expédier leur synthèse et à la rendre plus polyvalente. La synthèse divergente des dendrimères, employant presque exclusivement l’accouplement A3, s’est avérée difficile en raison de l'augmentation rapide de la polarité de la macromolécule générée. Quant à la méthodologie convergente, la synthèse des dendrimères a été atteinte grâce à une combinaison des réactions de type «clic» CuAAC et de couplage A3; celle-ci a été jugée plus prometteuse pour la synthèse puisque différentes générations de dendrimère ont été synthétisées. Grâce à l’utilisation de ces méthodes d'accouplement, plusieurs dendrimères avec de différents coeurs centraux et
embranchements ont été préparés et caractérisés. Les dendrimères (1), (2), (4) et (5) ont été synthétisés par l'approche divergente, tandis que la version protégée de première génération de dendrimère (10), son homologue non protégé (19) et la version protégée de la deuxième génération de dendrimère (18) ont été préparé à partir de la méthode convergente.
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<tbody>
<tr>
<td>ATP</td>
<td>Adenosine-5′-triphosphate</td>
</tr>
<tr>
<td>Ar</td>
<td>Argon gas</td>
</tr>
<tr>
<td>A^3-coupling</td>
<td>Aldehyde-alkyne-amine coupling</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
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<td>CuAAC</td>
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<td>Copper(I) iodide</td>
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<tr>
<td>DA</td>
<td>Diels-Alder cycloaddition</td>
</tr>
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<td>DCM</td>
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<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
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<td>Triethylamine</td>
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<td>FITC</td>
<td>Fluorescein-5-thiosemicarbazide</td>
</tr>
<tr>
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<td>Potassium hydroxide</td>
</tr>
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<td>Acetonitrile</td>
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<td>Sodium ascorbate</td>
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<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>NP</td>
<td>Nanoparticle</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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</tr>
<tr>
<td>PAMAM</td>
<td>Poly(amidoamine)</td>
</tr>
<tr>
<td>PEG</td>
<td>Poly(ethylene glycol)</td>
</tr>
<tr>
<td>PPI</td>
<td>Poly(propylene imine)</td>
</tr>
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<td>Tetrabutylammonium fluoride</td>
</tr>
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<tr>
<td>tBOC</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
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<td>Thio-Ene coupling</td>
</tr>
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<td>Triisopropylsilyl</td>
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<td>Thin-Layer-Chromatography</td>
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Chapter 1

1.0 Introduction

1.1 General overview

Dendrimers are hyperbranched and monodisperse macromolecules that are generally spherical in shape.¹ Their structural features include a multi-arm core, linking units branching out of the core, and numerous surface groups at the periphery of these macromolecules (Figure 1.1-1).¹ These macromolecules have intriguing properties that are accounted for by their composition, shape, size and surface groups.¹ These macromolecules are generally generated in a layer-by-layer method where the synthesis of each new layer on the dendrimer, i.e. the generation, is highly controlled, thus yielding monodisperse molecules with a large number of peripheral groups.¹ The structure of a dendrimer can often include the presence of internal cavities, especially in higher generations, resulting from the flexibility of the core’s arms and the linking units bonded there.² For instance, when the core’s arms are quite rigid, a dendrimer with an open structure and no well-defined cavities will be afforded.²,³ On the other hand, in the case of a flexible core and building blocks, the overall structural conformation of the dendrimer will allow for the formation of cavities as the dendrimer’s branches will be able to fold back on themselves.²,³ This structural feature of the dendrimer is of tremendous importance due to its potential application for encapsulation of small moieties of interest.³
1.2 Synthetic methodologies

The assembly of ‘cascade’ molecules, as dendrimers were then called, was first achieved in 1978 by Vögtle et al. by connecting repeating linking units to an aromatic or aliphatic core to form one of the most known dendrimers, the PPI dendrimers. Almost a decade later, Tomalia and coworkers realized the first divergent synthesis of monodisperse hyperbranched macromolecules and labelled them dendrimers. Through recurring Michael addition of methyl acrylate to amines and amidation of the ensuing esters with ethylenediamine (EDA), they accomplished the synthesis of poly(amidoamine) (PAMAM) dendrimers which are now widely used and commercially available (Figure 1.2-1). Later on, in 1990, Hawker and Fréchet were successful in generating dendrimers through the convergent methodology. The Fréchet-type dendrons were built by synthesizing

Figure 1.1-1: Structural conformation of a dendrimer.
benzyl ethers from phenols and benzylic halides, the periphery of the dendritic wedge, in very good yields (Figure 1.2-2). Upon multiple iterations of bromination and condensation, the desired generation of the dendron was achieved and subsequently attached to a core.

Figure 1.2-1: PAMAM dendrimer synthesized via the divergent methodology by Tomalia. Reproduced with permission from Ref 5, Copyright 1985 Nature Publishing Group.
There are two main pathways to the synthesis of dendrimers; namely the divergent and the convergent methodologies as mentioned above. The divergent process involves the growth of these hyperbranched macromolecules from the core towards the periphery of the molecule (the inside-out approach). With each iteration of the synthesis, a new generation is added onto the polyfunctional core thereby increasing the number of surface groups on the dendrimer. In this method, the building blocks or linking units are reacted with the peripheral groups of the previous generation to afford a new one. It is worth noting that the divergent methodology generally requires the activation of its peripheral groups through deprotection before any new layer of building blocks can be attached to the growing dendrimer. At any generation synthesized along this pathway, the peripheral groups can be activated towards the addition of functional molecules to
afford a monofunctional dendrimer. The divergent approach has multiple advantages that are worth mentioning.\textsuperscript{1} Firstly, this method offers complete control on the development of the dendrimer and tolerates the synthesis of elevated generations until steric hinderance at the surface of the macromolecule inhibits reactions occurring at the periphery of the dendrimer. Nonetheless, the divergent method also has drawbacks that need to be taken into account.\textsuperscript{1} For instance, with higher generations becoming more and more crowded at the edge of the dendrimer, the existence of structural defects due to incomplete reactions are known to happen.\textsuperscript{8} The need to use excess amount of the building block to ensure the formation of a generation and the presence of structurally similar defects also renders the purification a hassle in the divergent method. As mentioned earlier, the synthesis of a higher generation involves the activation/deprotection of the surface groups and, in the instance where the desired dendrimer is quite large, this would considerably lengthen its synthetic scheme. Lastly, the divergent approach does not easily allow for the introduction of multiple functionalities at the dendrimer’s surface since the peripheral groups are identical and have similar reactivity.\textsuperscript{1}

The convergent strategy, on the other hand, implies the synthesis of dendrons or dendritic wedges that will only be attached to the core of the dendrimer through their focal point once the desired generation has been achieved (the outside-in approach).\textsuperscript{9a} Dendrons being much smaller than their dendrimer counterparts, their synthesis and subsequent purification are significantly simpler. One of the most interesting aspects to consider with the convergent methodology
is the fact that the synthesis of multifunctional dendrimers are much more feasible in this manner since the dendrons used can be built with differing functionalities at the surface. These dendrons can then be linked to a core provided that the arms of the core differ in reactivity and that the dendrons’ focal point is equipped with the correct chemical moiety for the intended core’s arm. Above mentioned benefits make the convergent approach quite attractive. However, the convergent method also has shortcomings that are noteworthy. As such, steric limitations might inhibit the linkage of the dendron to the core at its focal point and the need to use excess amounts of higher generation dendrons to drive forward the generation of the dendrimer is deemed to be a significant waste from a synthetic point of view.

Over the years, many examples of dendrimers decorated with interesting functional groups have been reported. Monofunctional dendrimers are the ones where only one type of functional group has been attached to the periphery of the molecule. For instance, PPI dendrimer, one of the most studied hyperbranched molecules, has been coupled with many fluorescent molecules such as dansyl. The adornment of 32 units of dansyl was achieved by reacting the fourth generation PPI dendrimer with dansyl chloride (Figure 1.2-3) and quenching of the fluorescent units could later be done with one Co^{2+} ion instead of more at lower generation. This demonstrated that dendrimers decorated with fluorescent units could be used as sensors for complexation of metal ions with signal amplification and superior sensitivity towards quenching. Other types of dendrimers that have been developed are the multifunctional ones where more
than one type of functional group has been attached to the periphery of the macromolecule. The synthesis of such moieties can be quite difficult to achieve as it implies having either diverging reactive units at the surface or the selective protection of part of the end groups and their subsequent activation prior to reacting with the desired functional groups. Fréchet and coworkers were able to synthesize a polyether-based dendrimer with two distinct end functionalities; namely poly(ethyleneglycol) (PEG) and model drugs (Figure 1.2-4). To generate this bifunctional dendrimer, a polyether framework holding five free benzylic alcohols and five tert-butylchlorodiphenyl silyl (TBDPS) protected phenols was exploited. After deprotection of the phenols groups, the Williamson ether synthesis was used to attach mesylate-terminated PEG chains at the phenol ends allowing various model drugs to be subsequently attached to the benzylic alcohols. The coupling of model drugs such as cholesterol, phenylalanine and tryptophan could be achieved by carbonate, ester and carbamate linkages respectively. This type of bifunctional macromolecule perfectly demonstrates how having different peripheral groups will modify the properties of a dendrimer. For instance, PEG units here will provide aqueous solubility even in the case of extreme hydrophobicity, such as with cholesterol, and potential targeting with drugs.
Figure 1.2-3: Vögtle’s fourth generation PPI dendrimers with 32 dansyl units at its periphery.
Functionalization of dendrimers can also be done at the core of the macromolecule thus achieving specific properties that would otherwise be hard to obtain. Being able to reproduce naturally occurring biological functions is a goal that is often of great interest in science; the approach often drawn on is thus to mimic the molecules that are required for these biological functions. Based on multiple studies showing that metalloporphyrin cores require steric shielding to accomplish biological tasks, Aida et al. were able to covalently attach hydrophobic Fréchet-type dendrons to zinc or iron 5,10,15,20-tetrakis(3’,5’-
dihydroxyphenyl)porphyrin core by employing an alkali-mediated coupling reaction (Figure 1.2-5). With this synthesis, they were able to show that a dendrimer’s core can be modified to be the component of interest in the macromolecule, and that the dendrimer’s arms could be used as shields to achieve functions comparable to those seen in biological systems and were able to protect the dioxygen adduct forming at the metal’s active site thereby improving its half-life. Effectively, subsequent changes on the arms with esters, ethers, positively or negatively charged moieties were shown to afford aqueous solubility, electron-transfer, oxygen (O₂) binding as well as other media interactions.

**Figure 1.2-5: Porphyrin core shielded with Fréchet-type dendrons.**
Reproduced with permission from Ref. 13g, Copyright 2005 American Chemical Society.
1.3 Applications

Dendrimers have been found useful in numerous fields over time. This mostly originates from the fact that the structure of a dendrimer can be modified at the core, backbone or surface groups depending on the application pursued. As discussed previously, the dendrimer’s multivalency at its periphery is another crucial aspect of the desired purpose as it has the ability to be decorated with many functional moieties, whether they are differing or not, that will be available for interaction. The use of dendrimers in catalysis has been an appealing idea to the scientific community as encompassing catalytic metal centers to the dendrimer’s structure, either at the core or the periphery, can provide advantages of both homogeneous and heterogeneous catalysis. As such, a better solubility and high selectivity under mild conditions will be afforded while still maintaining easier separation techniques and sturdiness from heterogeneous catalysis. Other aspects to consider are the enhanced mechanical and thermal stability of the dendrimer-based catalyst as well as the added simplicity of the overall system. In the case of the catalyst being incorporated at the dendrimer’s core or in the cavities, selective catalysis could also be achieved depending on the reactant’s size and the cavities’ exposure. The first example of a successful dendrimer-based catalyst was developed by van Koten and coworkers. In this instance, they were able to garnish the periphery of a polysilane dendrimer with diaminoaryl nickel(II) pincer species (Figure 1.3-1). This dendrimer was confirmed to catalyze the Kharasch addition of polyhaloalkanes to alkenes.
Interestingly, the possibility of using this catalytic system for a continuous process using a membrane reactor was deemed feasible.

Figure 1.3-1: van Koten’s polysilane dendrimer with diaminoarylnickel(II) pincer complexes for catalytic purposes. Reproduced with permission from Ref. 23b, Copyright 2001 American Chemical Society.

Drug delivery is another field in which dendrimers have been extensively used. There are two structural features of dendrimers that renders their use extremely interesting for drug delivery; the presence of internal cavities and the multivalency for functional groups at the periphery. With high generation dendrimers, the inner nooks of the macromolecule can be used for encapsulating a drug moiety that can later on be released in the body. Meijer and coworkers demonstrated this possibility by encapsulating four rose Bengal molecules in a
fifth generation PPI dendrimer (Figure 1.3-2).\textsuperscript{17} By forming a rigid, bulky shell at the surface of the PPI dendrimer, the entrapment of rose Bengal in the internal cavities was ensured. Further studies on the release of the entrapped molecule were also done by the Meijer group. It was noted that upon insertion of a smaller guest molecule, \( p \)-nitrobenzoic acid, the release of the molecule was possible by slightly puncturing the shell. Only the complete abstraction of the bulky covering would allow the release of the rose Bengal molecules from the dendrimer’s cavities due to their substantial size. This example clearly demonstrates that encapsulation of therapeutic drugs could be achieved while effectively protecting them from interacting with the outside environment as probable in the body, and that their discharge was successful and could be controlled.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Encapsulation of rose Bengal molecules in generation five PPI dendrimer by formation of a rigid, bulky tert-butyloxy carbonyl (tBOC)-protected N-hydroxysuccinimide ester shell. Reproduced with permission from Ref. 17d, Copyright 1996 Nature Publishing Group.}
\end{figure}
Using the possibility of attaching different functional groups at a dendrimer’s periphery has also been exploited in the application of these macromolecules for drug delivery. This technique has the advantage of allowing the attachment of moieties such as a drug for therapeutic purposes, a targeting agent for receptor recognition as well as a fluorescent unit for monitoring. Baker and coworkers demonstrated the generation of such a drug delivery system by conjugating folic acid (FA), the targeting agent, methotrexate (MTX), the therapeutic drug, and fluorescein-5-thiosemicarbazide (FITC), the fluorescent sensor, to a fifth generation PAMAM dendrimer (Figure 1.3). Such a dendrimer was designed by making use of covalent linkages like an ester bond for attaching MTX, an amide bond for FA, a thiourea link for FITC while deactivating the terminal amine units by partial acetylation so as to diminish toxicity and preventing non-specific bonding. This trifunctional dendrimer was shown to bind in a specific manner to FA receptor-expressing KB cells during in vitro experiments and to impede the growth of these cells.
Figure 1.3-3: Generation five PAMAM dendrimer functionalized with folic acid (FA), methotrexate (MTX), and fluorescein-5-thiosemicarbazide (FITC) at the periphery. Reproduced with permission from Ref. 21a, Copyright 2005 American Chemical Society.

The application of dendrimers has also been extended to redox sensors.\textsuperscript{22} Astruc \textit{et al.} notably demonstrated the design of a polysilane-based dendrimer with free alkyne moieties at the periphery of the molecule (Figure 1.3-4).\textsuperscript{23} When decorated with ‘clicked’ ferrocenyl groups via 1,2,3-triazole rings, this dendrimer showed the ability to recognize and bind oxo anions (e.g. $\text{H}_2\text{PO}_4^-$, $\text{ATP}_2^-$), and metal cations (e.g. $\text{Pd}^{2+}$, $\text{Pt}^{2+}$). This system acquired improved stability and enhanced redox potentials of the ferrocenyl groups as observed with cyclic voltammetry. Dendrimers with tertiary and free amines at the surface, such as PPI and PAMAM dendrimers, have been found to be extremely useful in the
formation of metallic nanoparticles (NPs) as they have the ability to complex various metal ions. In these instances, the dendrimer’s facile modification of the peripheral units, its internal amines and cavities allow for control in the shape and size of the NPs while providing a stable, protected environment for the NPs.24

**Figure 1.3-4: Astruc’s polysilane/triazole dendrimer. Reproduced with permission from Ref 23a, Copyright 2007 John Wiley and Sons.**

1.4 Scope and goals of thesis

1.4.1 Scope of thesis

Dendrimer synthesis being an iterative process, there are several drawbacks that need to be overcome to render their synthesis less challenging.
The issues commonly arise from the chemistry that involves many protecting and activating steps, the formation of side products, such as structural defects at higher generations due to steric hinderance, and the purification that is often long, hard and costly. Thus, the reactions employed to afford these macromolecules should be high yielding ones with little by-products, be consistent and versatile enough to withstand a wide range of different substrates. As such, three reactions, commonly referred to as part of the ‘‘click’’ chemistry, have recently been added to the repertoire of reactions most often used for the development of dendrimers; these include the Cu$^{1}$-catalyzed Alkyne Azide [3 + 2] Cycloaddition (CuAAC), the Diels-Alder cycloaddition (DA) and the Thio-Ene coupling (TEC) (Figure 1.4-1). The CuAAC is, by far, deemed to be the most valuable and used of these three reactions due to its simplicity, efficacy, robustness and various green properties. For instance, this reaction requires mild conditions, little excess of the reagents; it generates no side products, and the desired regio- and chemoselective product (1,4-disubstituted 1,2,3-triazole) is obtained in nearly quantitative yields with very simple work-up techniques (e.g. simple filtration for the removal of the Cu-catalyst). Furthermore, this reaction is known to be water compatible and can tolerate various functional groups on the substrates to yield a wide range of triazoles. The only shortcoming to the CuAAC is the fact that it requires the use of copper, a metal, to mediate the reaction. Since dendrimers are often applied in a biological context, the use of any type of metal often becomes a concern due to their toxicity.
Figure 1.4-1: Click reactions: a) Cu$^1$-catalyzed Alkyne Azide [3 + 2] Cycloaddition (CuAAC), b) Diels-Alder cycloaddition (DA), c) Thio-Ene coupling (TEC).

Although never used towards this end, the aldehyde-alkyne-amine ($A^3$) coupling reaction is another reaction that could be of great use in dendrimer synthesis. It involves the catalytic addition of alkynes to imines, formed in situ from amines and aldehydes, and yields propargyl amines in a one-step process (Scheme 1.4-1).$^{28,29}$ This reaction is an effective way of covalently bonding together small units that can carry a number of different functional moieties while affording a molecule containing an alkyne group and a nitrogen that could be extremely useful for potential applications. It should be noted that only primary and secondary amines can be used as substrates in $A^3$-coupling, as water is a by-product of the reaction. The synthesis of propargyl amines was formerly done by reacting metal acetylides with imines in a stepwise fashion. It initially involved the generation of sensitive alkali metal acetylides where stoichiometric amounts of reactive organometallic reagents would deprotonate the alkyne under harsh conditions. The preparation of the imine substrate had to be then done in a
separate flask before addition of the metal acetylide due to its preferred affinity with the electrophilic aldehyde.\textsuperscript{30}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_1.4-1.png}
\end{center}

**Scheme 1.4-1: Aldehyde-alkyne-amine (A\textsuperscript{3}) coupling reaction to generate propargyl amines.**

The mechanism of A\textsuperscript{3}-coupling (Scheme 1.4-2) involves 2 critical steps.\textsuperscript{29,31} The first one is the formation of the metal acetylide through the C-H activation of the alkyne by the metal catalyst in a \(\pi\)-metal-alkyne complex. Secondly, the attack of the amine on the aldehyde will occur to generate the formation of the imine or iminium ion, in the case of a secondary amine. This imine will then be prone to a nucleophilic attack from the electron rich metal acetylide to give the desired propargyl amine followed by regeneration of the metal catalyst to complete the catalytic cycle. Interestingly, using formaldehyde allows the rapid formation of a very reactive imine and using a secondary amine generates an iminium ion that is much more susceptible to nucleophilic attack than an imine. In these two cases, further electrophilic activation is not required for the reaction to occur.\textsuperscript{32}
Scheme 1.4-2: General mechanism for $A^3$-coupling reactions.

The $A^3$-coupling reaction is extremely versatile as it can be performed under various conditions and with a variety of transition metals to catalyze it. Some common transition metals used to catalyze $A^3$-coupling are gold, silver, copper, a combination of ruthenium and copper, iron, etc. Both organic solvents and water can be used, and the reaction’s scope has been extended to include almost all types of amines, aldehydes and alkynes. $A^3$-coupling is also known to be an atom economic reaction with no side products generated except water and is very efficient with good yields. For all these reasons, $A^3$-coupling could be a reaction of great use for the generation of dendrimers.

1.4.2 Goals of thesis

One of the objectives of this thesis is to develop a versatile synthetic methodology for dendrimers which combines two highly efficient reactions, the CuAAC ‘click’ and the aldehyde-alkyne-amine ($A^3$) coupling. Since both CuAAC and $A^3$-coupling are simple, robust and high yielding reactions that have been
extensively studied and performed under various conditions, it was proposed that they would be ideal reactions to incorporate in the scheme for generating these macromolecules. The generations of dendrimers achieved in this project would have alkyne moieties, nitrogen atoms and triazole rings incorporated in their backbone due to the nature of the reactions used for their synthesis. This methodology will yield macromolecules which could then be functionalized at the periphery with various desired groups such as model drugs (e.g. lipoic acid) or fluorescent units like BODIPY for applications in biology.

1.5 References


Chapter 2

2.0 Synthesis of dendrimers using a combination of CuAAC and A³-coupling

2.1 Introduction

Dendrimers have attracted a considerable amount of attention in the biological and medicinal field due to their structural properties that have demonstrated enormous potential over their macromolecular counterparts.¹⁻³, ² For instance, their monodispersity, resulting from a layer-by-layer synthesis, is sought after, as it ensures a structurally controlled macromolecule with a high density of surface groups that can be functionalized with a variety of small moieties, depending on the desired applications.¹⁻² Dendrimer synthesis can be somewhat challenging as the growth of the macromolecule usually requires the use of multiple building blocks that need to be prepared. The chemistry employed for the synthesis of these building blocks often proves to be difficult as it needs to be efficient enough that there is little to no by-products formed.² Because the building blocks are prepared over many steps, protections and deprotections become necessary so as to retain some important chemical moieties in the structure. These, however, tend to lengthen the synthesis and the purification process of the building blocks, and to make them more costly.³⁻⁴ Thus, finding a methodology that uses economical and cost-effective reactions is greatly desired for the synthesis of dendrimers.

Herein, we report the synthesis of dendrimers by employing two highly efficient reactions, namely the Cu¹-catalyzed alkyne azide [3 + 2] cycloaddition
(CuAAC) ‘click’ reaction and the aldehyde-alkyne-amine (A³) coupling reaction. These reactions have been selected for their interesting features that can notably streamline the synthesis of dendrimers, and provide macromolecules that could be easily functionalized with desired moieties. The CuAAC reaction is considered, out of the three reactions comprised in ‘click’ chemistry and frequently used for dendrimers synthesis, to be the extremely useful because of its simplicity and efficacy. Effectively, this reaction is extremely versatile as it only requires the conception of azide and alkyne-terminated molecules that can be ‘clicked’ in an AB₂ (A: azide and B: alkyne) manner to generate a building block consisting of the two substrates linked together by triazole rings. This chemistry can be performed under mild conditions and yields almost quantitative amounts of product with no side products. It also has the added advantage of being chemoselective and regioselective, when copper is employed as the catalyst, generating 1,4-disubstituted 1,2,3-triazole exclusively as the product. The A³-coupling is the second reaction that was considered for the synthesis of dendrimers. It involves the catalytic connection of an alkyne unit to an amine with an aldehyde as the bridging unit. It has, to the best of our knowledge, never been used for the synthesis of dendrimers but it has many advantages that could render it extremely useful for this purpose. A³-coupling being an efficient, atom economical reaction which only generates water as a by-product, its use for the synthesis of dendrimers ensures that a reliable process with good yields will be incorporated to the methodology. It should also be noted that this reaction is a one-pot process, thus very simple, that can be done under various mild conditions with different
metal catalysts and has an extensive scope for all of its substrates.\textsuperscript{6} Furthermore, the alkyne and amine moieties incorporated in the structure could offer tremendous potential for applications in numerous fields.

### 2.2 Results and discussion

As previously stated, dendrimers can be synthesized through two methods; the divergent and the convergent approach. The former method entails adding building units onto the core of the dendrimer in an inside-out manner, while the latter requires the generation of dendrons that will be coupled to the core after activation of their focal point.\textsuperscript{2} The divergent synthesis was the first process that we decided to tackle. For this procedure, it was decided that aldehyde-alkyne-amine (A\textsuperscript{3}) coupling would be the reaction mostly used to generate the growth of the dendrimer. As the name of the reaction states it, aldehyde, alkyne and amine moieties would have to be present on the core and/or building blocks chosen for this synthesis. The dendrimers synthesized through the inside-out approach had \(p\)-xylylenediamine as the core with formaldehyde, due to its increased reactivity, and N-Boc-propargylamine as the building blocks (Scheme 2.2-1). As previously stated, A\textsuperscript{3}-coupling is a one-step process; as such, the three afore mentioned compounds were simply combined together with copper iodide, the metal catalyst, in an Ar-purged reaction vial and left to react following the conditions mentioned in Scheme 2.2-1. The first generation of the dendrimer (I) was ensued after purification of the crude mixture which merely involved its filtration over a silica plug for the removal of the metal catalyst.\textsuperscript{7} In order to synthesize the next
generation, compound (1) had to first undergo deprotection of its four tert-butylxoycarbonyl protecting groups to obtain free amines that could once again couple with formaldehyde and N-Boc-propargylamine in the next iteration of this scheme. The deprotection was achieved by reacting (1) with hydrogen chloride solution in dioxane to generate compound (2) as a salt after multiple ether washes meant to remove excess HCl/dioxane solution. It should be noted that we selected HCl/dioxane as the deprotecting agent due to the generation of the HCl salt of an amine after the occurrence of the deprotection. Effectively, previous studies\(^7\) had shown that these amine salts could be directly incorporated into the one-step \(A^3\)-coupling process, since the free amines of the salts were generated in situ, when sodium bicarbonate (NaHCO\(_3\)) was added to the reaction. Subsequently, the second iteration of the dendrimer’s synthesis (3) was attempted by directly performing another \(A^3\)-coupling reaction between compound (2), formaldehyde and N-Boc-propargylamine under similar basic conditions. This reaction, however, proved to be unsuccessful in the presence of NaHCO\(_3\). This was most likely due to the fact that the free amines were not generated, and \(A^3\)-coupling would thus not have occurred. Multiple variations in the type and quantity of base used during the reaction were also tried but led to no success (Table 2.2-1). Different solvents were also evaluated for this reaction as it was observed that compound (2) did not dissolve well in the solvent of choice, acetonitrile (MeCN) but to no avail. The high polarity of the salt (2) and its insolubility in a solvent suitable for \(A^3\)-coupling became an obstacle to the growth of the dendrimer through this method.
Scheme 2.2-1: Divergent synthesis of dendrimers by $A^3$-coupling with p-xylylenediamine as the core.

<table>
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<th>Base</th>
<th>Equivalents used</th>
<th>Solvent</th>
</tr>
</thead>
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<tr>
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<td>NaHCO$_3$</td>
<td>6</td>
<td>MeCN</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO$_3$</td>
<td>6.5</td>
<td>MeCN</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO$_3$</td>
<td>7</td>
<td>MeCN</td>
</tr>
<tr>
<td>4</td>
<td>NaHCO$_3$</td>
<td>6</td>
<td>CHCl$_3$&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>KOH</td>
<td>6</td>
<td>MeCN/DMF&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>KOH</td>
<td>6</td>
<td>H$_2$O</td>
</tr>
</tbody>
</table>
Table 2.2-1: Various conditions used for attempts at synthesizing compound (3).

Upon noticing the solubility issues occurring with this first design for dendrimers, it was decided that the original core, \( p \)-xylylenediamine, would be changed to piperazine instead. The building blocks, formaldehyde and \( N \)-Boc-propargylamine, used so far in the divergent methodology were nonetheless kept unchanged. This new core containing only secondary amines, the number of protected propargylamine arms would be lower, and thus the polarity of the molecules prepared would be lessened and their solubility altered to our advantage. Thus, compound (4), the central part of the growing dendrimer with piperazine at its core, was synthesized by combining this particular substrate with afore mentioned building blocks and copper iodide, the metal catalyst (Scheme 2.2-2). This intermediate was then purified by simple filtration of the reaction mixture over a small silica plug. Deprotection of compound (4) was achieved by treating it with hydrogen chloride solution or trifluoroacetic acid to afford (5), an amine salt (the salt being HCl or HTFA) in its pure form after multiple ether washes. The synthesis of the first generation of dendrimer with piperazine at its
core, compound (6), was performed through A³-coupling with the selected building blocks under similar basic conditions as mentioned before but, once again, unsuccessfully. Yet again, solubility issues were encountered at low generation of the prepared macromolecules due to their high polarity, originating from the numerous nitrogens present in their structure, and further reactions were all fruitless.

Scheme 2.2-2: Divergent synthesis of dendrimers by A³-coupling with piperazine as the core.
With the divergent synthesis of dendrimers being ineffective, we decided to focus our attention on the convergent approach instead. In this method, the dendritic wedges would be synthesized through the ‘click’ Cu\(^{1}\)-catalyzed alkyne azide [3 + 2] cycloaddition (CuAAC), and their focal point would later on be activated prior to connection to the piperazine core through A\(^{3}\)-coupling. The dendron required for the first generation was synthesized in two steps (Scheme 2.2-3). To begin with, Sonogashira coupling was done on 3,5-dibromobenzyl alcohol (7) to attach (triisopropylsilyl)acetylene at the bromo positions yielding (8) after purification by column chromatography. Compound (8) was then esterified with 4-pentyneic acid in the presence of DMAP and EDC to give 3,5-bis((triisopropylsilyl)ethynyl)benzyl pent-4-ynoate (9), after purification by column chromatography. With this latter reaction, the dendritic wedge (9) is now equipped with an alkyne moiety inserted in its structure and can be used as one of the three components required for A\(^{3}\)-coupling. First generation dendrimer, compound (10), was thus synthesized by coupling (9), formaldehyde and piperazine together by A\(^{3}\) reaction while using copper iodide (CuI) as the metal catalyst in a one step process. The purification of compound (10) involved column chromatography with 1:2 hexanes:EtOAc as the eluent.
Scheme 2.2-3: Convergent synthesis of first generation dendrimer (10).

The convergent synthesis of dendrimers by combination of ‘click’ CuAAC and A³-coupling was also extended to the second generation (Scheme 2.2-4). In this case, compound (8) generated in the synthesis of first generation dendrimer (10) (Scheme 2.2-3) underwent bromination to yield (11). No purification was necessary at this step as the intermediate was pure enough to carry on after working-up the reaction. Azidation was then done on (11) by using sodium azide (NaN₃) in DMF to afford compound (12) in a pure enough form that further purification by chromatography was not necessary. In parallel, ethynyltrimethylsilane was coupled to 3,5-dibromobenzyl alcohol (7) by
Sonogashira coupling to give (13) after purification by column chromatography. The trimethylsilyl (TMS) protecting groups on (13) were then removed by mild deprotection with potassium carbonate (K$_2$CO$_3$) to yield (14) after doing a column for purification. Compounds (12) and (14) were then coupled together by CuAAC using copper sulfate pentahydrate (CuSO$_4$.5H$_2$O) and sodium ascorbate to generate, after purification by column, (15), where two units of (12) had ‘clicked’ onto (14), and (16), where only one unit of (12) ‘clicked’ at one of the acetylene moiety of (14) leaving the other one free. Although this ‘click’ reaction did not work out as planned due to the incompletion of the reaction in the occurrence of compound (16), this molecule could be of synthetic importance for the generation of a dendritic wedge to be used for the multifunctionalization of the dendrimer synthesized. Nevertheless, (16) was kept for future use while compound (15) was esterified with 4-pentynoic acid, EDC and DMAP to generate (17) which was purified by column chromatography. Compound (17) being now furnished with an alkyne at its end, it was subsequently reacted with formaldehyde and piperazine through A$^3$-coupling with copper iodide, as the reaction’s catalyst, to afford the dendrimer of second generation (18) after purification by column.
The image contains a chemical reaction scheme. The reactions are as follows:

1. Reaction of 7 with H-TIPS under PdCl₂(PPh₃)₂, PPh₃, CuI (5 mol%), C₆H₅·Et₃N, 80°C, 18h, to obtain 8 in 91% yield.
2. Reaction of 8 with CBr₄, PPh₃ in THF, r.t., 18h, to obtain 11 in 92% yield.
3. Reaction of 11 with NaN₃ in DMF, r.t., 18h, to obtain 12 in 94% yield.
4. Reaction of 7 with H-TMS under PdCl₂(PPh₃)₂, PPh₃, CuI (5 mol%), C₆H₅·Et₃N, 80°C, 18h, to obtain 13 in 90% yield.
5. Reaction of 13 with K₂CO₃ in Acetone:THF:H₂O, 3 days, to obtain 14 in quantitative yield.
6. Reaction of 14 with 12 under CuSO₄·5H₂O, Na ascorbate, DMF, THF, H₂O, r.t., 18h, to obtain 15 in 38% yield.
7. Reaction of 16 with 15 under CuSO₄·5H₂O, Na ascorbate, DMF, THF, H₂O, r.t., 18h, to obtain 16 in 27% yield.
8. Reaction of 15 with propargyl alcohol under DMAP, EDC, DCM, r.t., 24h, to obtain 17 in 80% yield.
Scheme 2.2-4: Convergent synthesis of second generation dendrimer (18).

With the divergent synthesis of dendrimers of generation 1 and 2 done, their potential functionalization was a prospect that was considered. This would first entail the removal of the protecting groups decorating the periphery of the dendrimers. Thus, the deprotection of first generation dendrimer (10) (Scheme 2.2-5) would have to be done with a strong enough deprotecting agent to remove the triisopropylsilyl groups without damaging any other part of the dendrimers components. As such, it was decided that the reaction would involve the removal of the triisopropylsilyl groups with tetrabutylammonium fluoride (TBAF) at a low temperature to prevent the cleavage of the ester bonds present in first generation
dendrimer (10). Due to the harshness of the deprotecting agent and the sensitivity of the ester bond, care had to be taken on the reaction’s temperature and time as well as on its work-up. It was crucial that the addition of TBAF was done at -60°C and that the reaction’s mixture temperature did not rise above 0°C so as to avoid the cleavage of the ester bonds; this was achieved by allowing the time of reaction to be only of 1.5-2 hours. When the reaction was left to stir overnight and the temperature reached room temperature, no desired product was observed as it had completely decomposed to compound (7). The work-up of this deprotection also proved to be challenging as the removal of the reaction’s solvent, THF, by evaporation led to the decomposition of the product to (7). This was remedied by first quenching the reaction mixture with water and performing extractions with EtOAc before the removal of any solvent used for the reaction. The organic extractions allowed the product and TBAF to be separated before being heated during evaporation thus preventing any further reactions to occur between them. After following this procedure, the deprotection of first generation dendrimer (10) was successful and compound (19), containing four free acetylenes as the terminal groups, was obtained in high yields after purification by flash column chromatography.
Scheme 2.2-5: Synthesis of compound (19) through deprotection of first generation dendrimer (10).

2.3 Conclusions

In conclusion, we have developed a synthetic methodology to dendrimers by combining ‘click’ CuAAC and A$^3$-coupling reactions. Although both the divergent and the convergent approaches were attempted, the latter was the method that proved to be the most promising. Synthesizing the dendrimers through the divergent methodology proved to be challenging as performing multiple A$^3$-coupling reactions on the same scaffold caused many solubility issues that were hard to overcome. The problems encountered with this approach were resolved by adopting the convergent methodology for the synthesis of the dendrimers. In this scheme, dendrons had to first be built with ‘click’ chemistry,
and then attached to an amine-bearing core with formaldehyde by $\text{A}^3$-coupling. These dendrimers of generations 1 and 2 have alkyne groups at the periphery, and offer the potential to covalently link a variety of groups such as lipoic acid, a drug, and BODIPY, a fluorescent dye, using CuAAC for potential applications in the biological field. This coupling methodology is currently being explored.

2.4 Materials and Experimental

2.4.1 Materials

Copper(II) sulfate pentahydrate ($\text{CuSO}_4.5\text{H}_2\text{O}$) (>98.0%), sodium ascorbate ($\text{NaAsc}$) (crystalline, 98%), tetrabutylammonium fluoride solution ($\text{TBAF}$) ($\text{Bu}_4\text{NF}$) (1.0 M in THF), carbon tetrabromide ($\text{CBr}_4$) (99%), potassium carbonate ($\text{K}_2\text{CO}_3$) (>99%), copper(I) iodide ($\text{CuI}$) (98%), bis(triphenylphosphine)palladium(II) dichloride ($\text{PdCl}_2(\text{PPh}_3)_2$), triphenylphosphine (TPP), (triisopropylsilyl)acetylene (97%), ethynyltrimethylsilane (98%), piperazine (99%), $p$-xylylenediamine (99%), 4-pentyanoic acid (95%), paraformaldehyde (powder, 95%), formaldehyde solution (37 wt. % in $\text{H}_2\text{O}$), 4-(dimethylamino)pyridine (DMAP) (>99%), $N$-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide hydrochloride (EDC) (crystalline), $N$-Boc-propargylamine (97%), hydrogen chloride solution (HCl/dioxane) (4.0M in dioxane), trifluoroacetic acid (TFA) (99%) and sodium azide ($\text{NaN}_3$) (>99.5%) were purchased from Sigma-Aldrich Canada, and used as received. 3,5-Dibromobenzyl alcohol was purchased from Alfa Aeser, and used as received. Benzene ($\text{C}_6\text{H}_6$) was dried over molecular sieves, tetrahydrofuran (THF),
dichloromethane (DCM) and triethylamine (Et$_3$N) were distilled. All other solvents were used as received in their anhydrous forms.

2.4.2 Synthesis of dendrimers by the divergent method

Synthesis of generation 1 dendrimer with $p$-xylylenediamine (1)

$p$-Xylylenediamine (28.09 mg, 0.21 mmol), N-Boc-propargylamine (155.47 mg, 1.0 mmol) and catalytic amount (ca. 20 mol\%) of CuI were dissolved in acetonitrile (0.5 mL) in a reaction vial. Formaldehyde (75 μL, 1.0 mmol at 37 wt. % in H$_2$O) was added to the stirring solution, and the reaction mixture was flushed with Ar for 10 min. The reaction vial was sealed and left to stir at 60°C for 24 h. The reaction mixture was then dissolved in 10:1 DCM:MeOH and the solution filtered over a small silica plug to remove the catalyst and any solids formed during the reaction. The solvent was evaporated to afford a yellow oil (43.91 mg, 26\%) after purification by preparative thin-layer-chromatography (TLC) using 2:1 hexanes:EtOAc as the eluent. $^1$H NMR (300MHz, Acetone-$d_6$): δ (ppm) 1.42 (s, 36H, -CO-O-(CH$_2$)$_3$), 3.34 (s, 8H, N-CH$_2$-C≡C), 3.65 (s, 4H, Ar-CH$_2$-N), 3.90-3.92 (m, 8H, NHBoc-CH$_2$-C≡C), and 7.30 (s, 4H, ArH). $^{13}$C($^1$H) NMR (75MHz, Acetone-$d_6$): δ (ppm) 27.7, 29.9, 41.6, 56.3, 77.1, 78.3, 82.3, 129.0, 137.4, 155.4 and 205.3. HRMS (EI): Theoretical Mw = 805.01 g/mol. Found Mw$^+$ = 805.49 g/mol.

Synthesis of generation 1 dendrimer salt with $p$-xylylenediamine (2)
Compound (1) (158.1 mg, 0.20 mmol) was stirred in excess amount of HCl/dioxane (5 mL) for 24 h. The acidic solution was evaporated and multiple diethyl ether washes were carried out on the residue to remove the remaining HCl/dioxane solution. The solvent was evaporated to yield a red-brown solid in quantitative yield (122.42 mg). $^1$H NMR (300MHz, Methanol-d$_4$): $\delta$ (ppm) 4.00 (s, 8H, N-CH$_2$-C=C), 4.29 (s, 8H, C≡C-CH$_2$-NH$_3^+$), 4.64 (s, 4H, Ar-CH$_2$-N), and 7.82 (s, 4H, ArH). $^{13}$C{${^1}$H} NMR (75MHz, Methanol-d$_4$): $\delta$ (ppm) 29.0, 41.8, 55.9, 75.8, 81.7, and 137.1.

Synthesis of generation 0 dendrimer with a piperazine core (4)

Piperazine (51.98 mg, 0.60 mmol), N-Boc-propargylamine (233.42 mg, 1.5 mmol) and catalytic amount (ca. 10 mol%) of CuI were dissolved in acetonitrile (0.3 mL) in a reaction vial. Formaldehyde (112 $\mu$L, 1.5 mmol at 37 wt.% in H$_2$O) was added to the stirring solution, and the reaction mixture was flushed with Ar for 10 min. The reaction vial was sealed and left to stir at 60°C for 24 h. The reaction mixture was then dissolved in 10:1 DCM:MeOH and the solution filtered over a small silica plug to remove the catalyst and any solids formed during the reaction. The crude mixture was purified by column chromatography; the eluent initially consisted of pure DCM with its polarity slowly increasing by adding MeOH while monitoring the outcome on TLC and the pure compound was obtained at 6% MeOH. The solvent was then evaporated to afford a yellow oil in quantitative yield (253.78 mg). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 1.43 (s, 18H, -CO-O-(CH$_2$)$_3$), 2.58 (s, 8H, N-CH$_2$-CH$_2$-N), 3.24-
3.25 (m, 4H, N-CH₂-C≡C), and 3.89 (s, 4H, NHBOC-CH₂-C≡C). HRMS (EI): Theoretical Mw = 420.55 g/mol. Found Mw⁺ = 421.28 g/mol.

Synthesis of generation 0 dendrimer salt with piperazine (5)

Compound (4) (170.7 mg, 0.41 mmol) was stirred in excess amount of HCl/dioxane (10 mL) or trifluoroacetic acid (10 mL) for up to 4 h. The acidic solution was evaporated and multiple diethyl ether washes were carried out on the residue to remove the remaining HCl/dioxane solution. The solvent was evaporated to yield a red-brown solid in quantitative yield (148.62 mg). ¹H NMR (300MHz, D₂O): δ (ppm) 3.25 (s, 8H, N-CH₂-CH₂-N), 3.77 (s, 4H, N-CH₂-C≡C), and 3.82 (s, 4H, C≡C-CH₂-NH₃⁺). ¹³C {¹H} NMR (75MHz, D₂O): δ (ppm) 28.8, 45.3, 48.9, 76.3, and 80.8.

2.4.3 Synthesis of dendrimers by the convergent method

Synthesis of 3,5-bis(triisopropylsilylethynyl)benzyl alcohol (8)

This compound was prepared by an adaptation of a procedure published earlier.⁸

Triisopropylsilylacetylene (6.4 mL, 2.82 mmol) and catalytic amounts (ca. 5 mol%) of CuI, [PdCl₂(PPh₃)₂] and PPh₃ were added to a solution of 3,5-dibromo benzyl alcohol (1) (2.5 g, 9.40 mmol) in benzene (20 mL) and triethylamine (20 mL). The reaction mixture was left to reflux overnight while stirring under Ar. The solvent was then evaporated and the black residue was
dissolved in diethyl ether. The solution was filtered over celite in a fritted glass funnel to remove the different catalysts and water washings (3x50 mL) were performed on the filtrate. The organic phase was dried over MgSO₄ and the solvent was evaporated again. The crude mixture was purified by column chromatography; the eluent initially consisted of pure hexanes with its polarity slowly increasing by adding EtOAc while monitoring the outcome on TLC and the pure compound was obtained at 10% EtOAc. The solvent was then removed under vacuum to yield a pale yellow oil (3.9939 g, 91%). ¹H NMR (300MHz, CDCl₃): δ (ppm) 1.12(s, 42H, -Si(C₃H₇)₃), 4.66 (s, 2H, -CH₂-OH), 7.42 (s, 2H, ArH), and 7.48 (s, 1H, ArH). ¹³C{¹H} NMR (75MHz, CDCl₃): δ (ppm) 11.3, 18.7, 64.4, 91.4, 105.9, 123.9, 130.2, 134.3, and 141.1.

Synthesis of 3,5-bis((triisopropylsilyl)ethynyl)benzyl pent-4-ynoate (9)

4-pentynoic acid (267.3 mg, 2.72 mmol) and DMAP (279.5 mg, 2.2 mmol) were added to a stirring solution of compound (2) (1.0645 g, 2.27 mmol) in anhydrous DCM (7 mL) under Ar. EDC (653.0 mg, 3.41 mmol) was added last to the reaction flask due to its hygroscopic nature. The reaction was left to stir at room temperature under Ar for 18 h. The reaction mixture was dissolved in extra DCM and water washes (3x25 mL) were performed on it. The organic phase was washed with brine (3x25 mL) and dried over MgSO₄. The crude compound was purified by column chromatography; the eluent initially consisted of pure hexanes with its polarity slowly increasing by adding EtOAc while monitoring the outcome on TLC and the pure compound was obtained at 2% EtOAc. The solvent was removed under vacuum to yield a pale yellow oil (1.0849 g, 87%). ¹H NMR
(300MHz, CDCl$_3$): δ (ppm) 1.13 (s, 42H, -Si(C$_3$H$_7$)$_3$), 2.00 (s, 1H, C≡C-H), 2.53-2.62 (m, 4H, C≡C-CH$_2$-CH$_2$-CO), 5.08 (s, 2H, Ar-CH$_2$-O), 7.40 (s, 2H, ArH), and 7.51 (s, 1H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): δ (ppm) 11.3, 14.4, 18.7, 33.3, 65.4, 69.3, 82.3, 91.8, 105.6, 131.5, 135.0, 136.1 and 171.4. HRMS (EI): Theoretical Mw = 548.95 g/mol. Found Mw$^+$ = 549.36 g/mol.

Synthesis of generation 1 dendrimer (10)

Piperazine (38.0 mg, 0.44 mmol), compound (9) (484.9 mg, 0.88 mmol) and catalytic amount (ca. 10 mol%) of CuI were dissolved in acetonitrile (2.5 mL) in a reaction flask. Paraformaldehyde (26.8 mg, 0.88 mmol) was added last to the stirring solution and the reaction mixture was flushed with Ar for 10 min. The reaction flask was attached to a condenser before being lowered into an oil bath set at 85°C and was left to stir overnight under Ar. The reaction mixture was then dissolved in 10:1 DCM:MeOH and the solution filtered over a small silica plug to remove the catalyst and any solids formed during the reaction. The crude product was purified by flash column chromatography; the eluent initially consisted of pure hexanes with its polarity increasing by adding EtOAc while monitoring the outcome on TLC and the pure compound was obtained at 20% EtOAc. The solvent was removed under vacuum to yield a bright yellow oil (447.8 mg, 84%).

$^1$H NMR (300MHz, CDCl$_3$): δ (ppm) 1.12 (s, 84H, -Si(C$_3$H$_7$)$_3$), 2.54-2.59 (m, 16H, C≡C-CH$_2$-CH$_2$-CO and N-CH$_2$-CH$_2$-N), 3.23 (s, 4H, N-CH$_2$-C≡C), 5.05 (s, 4H, Ar-CH$_2$-O), 7.37 (s, 4H, ArH), and 7.50 (s, 2H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): δ (ppm) 11.3, 14.6, 18.7, 33.6, 47.0, 51.5, 65.4, 75.2, 83.7,
HRMS (EI): Theoretical Mw = 1208.05 g/mol. Found Mw$^+$ = 1208.80 g/mol.

Synthesis of 3,5-bis(triisopropylsilyl)ethynyl)benzyl bromide (11):

This compound was prepared by an adaptation of a procedure published earlier.\textsuperscript{8}

Carbon tetrabromide (1.087 g, 3.28 mmol) was added to a stirring solution of compound (8) (1.0220 g, 2.18 mmol) in dry THF (9 mL), under Ar, and placed on an ice bath after stirring at room temperature for 5 min. PPh$_3$ (858.5 mg, 3.27 mmol) was slowly added to the solution in small portions. The reaction mixture was removed from the ice bath after 15 minutes and was left to stir at room temperature for 18 h. The reaction was then quenched with water and the THF was evaporated. The aqueous phase was extracted with DCM (3x15 mL) and the organic phase was then dried over MgSO$_4$. The crude product was purified by column chromatography using hexanes as the eluent while monitoring the outcome on TLC. The solvent was evaporated to yield the product as a colourless oil (1.0637 g, 92%). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 1.17 (s, 42H, -Si(C$_3$H$_7$)$_3$), 4.41 (s, 2H, -CH$_2$-Br), 7.45 (s, 2H, ArH), and 7.51 (s, 1H, ArH). $^{13}$C\{$_1^H$\} NMR (75MHz, CDCl$_3$): $\delta$ (ppm) 11.3, 18.7, 31.8, 92.0, 105.4, 124.4, 132.3, 135.0 and 138.1.

Synthesis of 3,5-bis(triisopropylsilyl)ethynyl)benzyl azide (12):
This compound was prepared by adaptation of a procedure published earlier.8

NaN₃ (651.6 mg, 10.0 mmol) was added to a solution of compound (11) (1.0637 g, 2.0 mmol) in dry DMF 8 (mL) that was left to stir at room temperature for 18 h. The reaction mixture was extracted with EtOAc (3x30 mL). The organic phase was then washed with water (3x30 mL), brine (3x30 mL) and dried over MgSO₄. The solvent was then removed under vacuum to yield a pale yellow oil (931.4 mg, 94%) without further purification. ¹H NMR (300MHz, CDCl₃): δ (ppm) 1.14 (s, 42H, -Si(C₃H₇)₃), 4.32 (s, 2H, -CH₂-N₃), 7.37 (s, 2H, ArH), and 7.53 (s, 1H, ArH). ¹³C{¹H} NMR (75MHz, CDCl₃): δ (ppm) 11.3, 18.7, 54.0, 92.1, 105.5, 124.3, 131.3, 134.9, and 135.9.

Synthesis of 3,5-bis(trimethylsilylethynyl)benzyl alcohol (13)

This compound was prepared by an adaptation of a procedure published earlier.8

Ethynyltrimethylsilane (1.1 mL, 7.52 mmol) and catalytic amounts (ca. 5 mol%) of CuI, [PdCl₂(PPh₃)₂] and PPh₃ were added to a solution of 3,5-dibromo benzyl alcohol (7) (500.39 mg, 1.88 mmol) in benzene (5 mL) and triethylamine (5 mL). The reaction mixture was left to reflux overnight while stirring under Ar. The solvent was then evaporated and the black residue was dissolved in diethyl ether. The solution was filtered over celite in a fritted glass funnel to remove the different catalysts and water washings (3x15 mL) were performed on the filtrate. The organic phase was dried over MgSO₄ and the solvent was evaporated again.
The crude compound was purified by column chromatography; the eluent initially consisted of pure hexanes with its polarity slowly increasing by adding EtOAc while monitoring the outcome on TLC and the pure compound was obtained at 8% EtOAc. The solvent was then removed under vacuum to yield a pale yellow oil (508.4 mg, 90%). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 0.23 (s, 18H, -Si(CH$_3$)$_3$), 4.63 (s, 2H, -CH$_2$OH), 7.41 (s, 2H, -ArH), and 7.50 (s, 1H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): $\delta$ (ppm) -0.1, 64.0, 95.0, 104.0, 123.4, 130.0, 134.3 and 141.2.

**Synthesis of 3,5-diethynylbenzyl alcohol (14):**

This compound was prepared by an adaptation of a procedure published earlier.  

A solution of K$_2$CO$_3$ (808.3 mg, 5.85 mmol) was prepared in H$_2$O (2.5 mL) and was added to a solution of compound (13) (351.3 mg, 1.17 mmol) in acetone (2.5 mL) and THF (2.5 mL). The biphasic mixture was stirred overnight at room temperature for 48 h. Acetone and THF were evaporated from the reaction mixture and the remaining aqueous phase was then extracted with EtOAc (3x 15 mL). Water washings (3x 15 mL) were done on the organic layer which was then dried over MgSO$_4$. The solvent removed by vacuum to afford a beige needle-like solid in quantitative yield without further purification (0.1996 g). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 3.09 (s, 2H, -C≡C-H), 4.66 (s, 2H, -CH$_2$-OH), 7.47 (s, 2H, ArH), and 7.53 (s, 1H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): $\delta$ (ppm) 64.2, 78.0, 82.4, 122.7, 130.7, 134.7 and 141.4. HRMS (EI): Theoretical Mw = 156.18 g/mol. Found Mw$^+$ = 155.05g/mol.
Synthesis of compounds (15) and (16):

Sodium ascorbate (10.0 mg, 0.05 mmol, 20 mol%) was added to a solution of compounds (14) (39.8 mg, 0.26 mmol) and (12) (276.1 mg, 0.56 mmol) dissolved in THF (2 mL). An aqueous solution (1 mL) of CuSO$_4$.5H$_2$O (6.5 mg, 0.026 mmol, 10 mol%) was added dropwise to the reaction mixture that was then left to stir overnight at room temperature. After 18 h, THF and DMF were evaporated from the reaction mixture and the remaining aqueous phase was extracted with EtOAc (3x20 mL). The organic phase was washed with brine (3x20 mL), dried over MgSO$_4$, and the solvent was evaporated. The crude product was purified by column chromatography; the eluent initially consisted of pure hexanes with its polarity slowly increasing by adding EtOAc while monitoring the outcome on TLC and the pure compound was obtained at 35% EtOAc. The solvent was removed under vacuum to yield the desired product, compound (15), as a yellow oil (109.7 mg, 38%). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 1.11 (s, 84H, -Si(C$_3$H$_7$)$_3$), 4.77 (s, 2H, CH$_2$-OH), 5.50 (s, 4H, N-CH$_2$-Ar), 7.38 (s, 4H, ArH), 7.54 (s, 2H, ArH), 7.79 (s, 4H, C=CH-N and ArH) and 8.14 (s, 1H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): $\delta$ (ppm) 11.2, 18.7, 53.6, 64.8, 92.8, 105.0, 120.1, 121.9, 123.8, 124.8, 131.0, 131.5, 134.7, 135.7, 142.5 and 147.8. HRMS (ES): Theoretical Mw= 1143.93 g/mol. Found [M + Na]$^+$ = 1166.71 g/mol.

The purification of the crude mixture also revealed that the ‘click’ reaction had occurred at only one of the two acetylene sites to afford compound (16) (80.1 mg, 27%) under the previously mentioned conditions at 30% EtOAc. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ (ppm) 1.12 (s, 42H, -Si(C$_3$H$_7$)$_3$), 3.08 (s, 1H, C=C-H), 4.70
(s, 2H, CH₂-OH), 5.49 (s, 2H, N-CH₂-Ar), 7.37 (s, 2H, ArH), 7.42 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.69 (s, 1H, ArH) and 7.80 (s, 2H, C=CH-N and ArH).

\[^{13}\text{C} \{^{1}\text{H}\}\text{ NMR (75MHz, CDCl}_3\}: \delta \text{ (ppm) 11.2, 18.7, 53.6, 64.5, 83.1, 93.0, 105.0, 119.9, 122.8, 124.5, 124.8, 128.4, 130.1, 130.7, 131.5, 134.6, 135.7 and 142.0.}\]

HRMS (ES): Theoretical Mw = 649.39 g/mol. Found [M + Na]⁺ = 672.38 g/mol.

**Synthesis of compound (17):**

4-pentynoic acid (14.4 mg, 0.15 mmol) and DMAP (14.5 mg, 0.11 mmol) were added to a stirring solution of compound (15) (130.6 mg, 0.11 mmol) in anhydrous DCM (0.6 mL) under Ar. EDC (34.3 mg, 0.18 mmol) was added at the end to the reaction flask due to its hygroscopic nature. The reaction was left to stir at room temperature under Ar for 18 h. The reaction mixture was dissolved in extra DCM and water washes (3x20 mL) were performed on it. The organic phased was washed with brine (3x20 mL) and dried over MgSO₄. The crude product was purified by simply flushing it over a small silica plug using 2:1 hexanes:EtOAc as the eluent. The solvent was removed under vacuum to yield a pale yellow oil (111.2 mg, 80%). \(^1\text{H} \text{ NMR (300MHz, CDCl}_3\): \delta \text{ (ppm) 1.11 (s, 84H, -Si(C}_3\text{H}_7)_3\), 1.95 (s, 1H, C=C-H), 2.51-2.61 (m, 4H, C=C-CH}_2\text{-CH}_2\text{-CO), 5.19 (s, 2H, O-CH}_2\text{-Ar), 5.51 (s, 4H, N-CH}_2\text{-Ar), 7.38 (s, 4H, ArH), 7.54 (s, 2H, ArH), 7.79-7.82 (m, 4H, C=CH-N and ArH) and 8.17 (s, 1H, ArH).}^{13}\text{C} \{^{1}\text{H}\}\text{ NMR (75MHz, CDCl}_3\): \delta \text{ (ppm) 11.2, 14.3, 18.7, 33.3, 53.6, 66.1, 69.2, 82.4, 92.9, 105.0, 120.0, 122.7, 124.9, 125.2, 131.3, 131.5, 134.7, 135.7, 137.2, 147.6 and 171.6.} \text{HRMS (EI): Theoretical Mw = 1222.01 g/mol. Found [M + Na]⁺ = 1246.74 g/mol.}
Synthesis of generation 2 dendrimer (18)

Piperazine (2.80 mg, 0.033 mmol), compound (17) (79.8 mg, 0.065 mmol) and catalytic amount (ca. 10 mol%) of CuI were dissolved in acetonitrile (0.35 mL) in a reaction flask. Paraformaldehyde (2.0 mg, 0.066 mmol) was added last to the stirring solution and the reaction mixture was flushed with Ar for 10 min. The reaction flask was attached to a condenser before being lowered into an oil bath set at 85°C and was left to stir overnight under Ar. The reaction mixture was then dissolved in 10:1 DCM:MeOH and the solution filtered over a small silica plug to remove the catalyst and any solids formed during the reaction. The product was purified by preparative TLC using 1:1 EtOAc:hexanes as the eluent. The solvent was removed under vacuum to yield a yellow oil (77.0 mg, 93%). $^1$H NMR (300MHz, CDCl$_3$): δ (ppm) 1.11 (s, 168H, -Si(C$_3$H$_7$)$_3$), 2.51-2.58 (m, 16H, C≡C-CH$_2$-CH$_2$-CO and N-CH$_2$-CH$_2$-N), 3.20 (s, 4H, N-C$_6$H$_4$-C≡C), 5.17 (s, 4H, O-CH$_2$-Ar), 5.51 (s, 8H, N-CH$_2$-Ar), 7.38 (s, 8H, ArH), 7.54 (s, 4H, ArH), 7.81 (m, 8H, C=CH-N and ArH) and 8.16 (s, 2H, ArH). $^{13}$C{$^1$H} NMR (75MHz, CDCl$_3$): δ (ppm) 11.4, 14.6, 18.6, 33.6, 47.1, 51.6, 53.6, 66.1, 69.2, 82.4, 92.9, 105.0, 120.0, 122.7, 124.8, 125.2, 131.3, 131.5, 134.7, 135.7, 137.2, 147.6 and 171.8. HRMS (EI): Theoretical Mw = 2557.26 g/mol. MALDI-TOF, [M + Li]$^+$ = 2557.26 g/mol.

Synthesis of compound (19)

Tetrabutylammonium fluoride solution (TBAF) (1.0 M in THF) (0.35 mL, 0.35 mmol) was added dropwise to a stirring solution of compound (10) (100.76
mg, 0.084 mmol) in dry THF (9 mL) placed in a dry ice/acetone bath. Once the addition had been performed at -60°C, the reaction mixture was left to stir for 1.5-2h while the oil bath slowly warmed up to 0°C. The reaction was then quenched with water (5 mL) and extracted with EtOAc (3x15 mL). Water washings (3x15 mL) were performed on the organic phase which was then dried on anhydrous MgSO₄. Due to the miscibility of THF in water, brine had to be added during the extractions and the washings to eliminate the emulsions occurring. The solvent was removed under vacuum and the crude product was purified by preparatory thin-layer chromatography (TLC) using 2:1 EtOAc:hexanes as the eluent to afford a brown oil (43.8 mg, 90%). ¹H NMR (300MHz, CDCl₃): δ (ppm) 2.51-2.59 (m, 16H, C≡C-CH₂-CH₂-CO and N-CH₂-CH₂-N), 3.11 (s, 4H, C≡C-), 3.23 (s, 4H, N-CH₂-C≡C), 5.07 (s, 4H, Ar-CH₂-O), 7.43 (s, 4H, ArH) and 7.54 (s, 2H, ArH). ¹³C{¹H} NMR (75MHz, CDCl₃): δ (ppm) 14.7, 33.6, 46.9, 51.5, 65.1, 75.5, 78.4, 82.2, 83.5, 122.8, 131.8, 135.3, 136.6 and 171.6. HRMS (EI): Theoretical Mw = 582.69 g/mol. Found Mw⁺ = 583.26 g/mol.

2.5 References

Chapter 3

3.0 Conclusions and Future Outlook

3.1 Summary and Conclusions

Dendrimers have become valuable assets in a wide range of fields due to their extensive range of applicability. Dendrimer’s features are unique due to their layer-by-layer synthesis that allow control on the macromolecule’s structure and provide monodisperse molecules with a high density of surface groups. Effectively, structural components such as the core, the backbone and the peripheral groups can be varied to accommodate entities that will considerably change the properties of the dendrimer and thus provide it with a specific function. Encapsulation of moieties in the dendrimer’s cavities and their subsequent release is also one interesting feature that has attracted substantial attention in the scientific community, more specifically in the medical field. Although dendrimers are highly desired molecules, their synthesis can prove to be quite challenging and costly as a result of all the components that need to be incorporated in their structure and the multiple steps that is required for high generation dendrimers.

In this thesis, we have elaborated a synthetic scheme that allows for the synthesis of dendrons and dendrimers in few chemical steps. This was done by employing two crucial reactions; the first one being the ‘click’ Cu¹-catalyzed Alkyne Azide [3 + 2] Cycloaddition (CuAAC) and the second being the aldehyde-amine-alkyne (A³) coupling. Out of the three ‘click’ reactions used for
dendrimer’s synthesis, the CuAAC reaction is the most commonly employed one due to its robustness, effectiveness and versatility. Although not generally used for dendrimer’s synthesis, A³-coupling has the added advantage of being a simple one-step process that is high yielding, atom-economical, green and modular. An amine-containing core was used as it was proposed that A³-coupling would be employed to grow the dendrimer in an inside-out approach (divergent methodology) as well as for attaching the dendrons onto the core of the dendrimer in the convergent approach. When employing a tetrafunctional core for the divergent approach, difficulties were encountered early on during the synthesis due to the rapidly increasing polarity of the dendrimers even at small generations. It was proposed that by modifying the core to a bifunctional one, the growing dendrimer would be less polar and more soluble in organic solvents as it contained less amines; but this proved to still be a major issue, and we decided to focus our attention on the convergent approach. Nevertheless, dendrimers of small generations in their protected and salt forms, compounds (1), (2), (4) and (5), were synthesized through this method.

The dendrons used for the convergent approach were synthesized with CuAAC from building blocks containing the appropriate acetylene and azide end groups, and were subsequently decorated with a free alkyne moiety that could then be simply linked to the bifunctional core by A³-coupling through formaldehyde. The acetylene-terminated building blocks contained a free alcohol at its other end that could undergo esterification with 4-pentynoic acid to incorporate a free alkyne necessary for A³-coupling with the core. The azide-
terminated building blocks were decorated with protected acetylenes groups that could then be deprotected for functionalization after linkage to the core. With these key components in place, dendrimers of generation 1 (compounds (10) and (19)) and generation 2 (compound (18)) were built in a convergent method through a combination of ‘click’ CuAAC and A^3-coupling.

3.2 Future Outlooks

Since the divergent synthesis of dendrimers of generation 1 and 2 was successful, their functionalization should be contemplated. After removal of the protecting groups at the surface of these molecules, different moieties such as dyes or drugs could be coupled to the peripheral acetylene groups. These functionalized dendrimers could then be evaluated for potential applications.

It would also be important to synthesize further generations of these dendrimers through the convergent methodology. With higher generation dendrimers, important features of the macromolecules such as the density of surface groups and the presence of cavities start to be notable. For instance, an increase in the amount of surface groups on the dendrimer could lead to interesting effects on the properties of the growing dendrimer; while, the presence of cavities in the structural conformation of the dendrimer would allow small moieties to be entrapped and safely delivered to their target.