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Synthesis and Characterization of Sugar Based Low Molecular Weight Gelators and the Preparation of Chiral Sulfinamides

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SYNTHESIS AND CHARACTERIZATION OF SUGAR BASED LOW MOLECULAR WEIGHT GELATORS AND THE PREPARATION OF CHIRAL SULFINAMIDES

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ABSTRACT

SYNTHESIS AND CHARACTERIZATION OF SUGAR BASED LOW MOLECULAR WEIGHT GELATORS AND THE PREPARATION OF CHIRAL SULFINAMIDES

Hari Prasad Reddy Mangunuru
Old Dominion University, 2014
Director: Dr. Guijun Wang

Low molecular weight gelators (LMWGs) have received considerable attention in the field of chemistry from last few decades. These compounds form self-assembled fibrous networks like micelles, cylindrical, sheets, fibers, layers and so on. The fibrous network entraps the solvent and forms gel, because of the self-assembly phenomenon and their demonstrated potential uses in a variety of areas, ranging from environmental to medicinal applications.

Sugars are good starting materials to synthesize the new class of LMWG's, because these are different from some expensive materials, these are natural products. We have synthesized and characterized the LMGS's based on D-glucose and D-glucosamine. D-glucosamine is the versatile starting material to make different peptoids and triazoles. Several series of compounds were synthesized using compounds 1-3 as starting material and studied the gelation behavior all the compounds.

We have studied the self-assembling properties of a new class of tripeptoids, synthesized by one-pot Ugi reaction from simple starting materials. Among the focused library of tripeptoids synthesized, we found that several efficient low molecular weight organogelators were obtained for aqueous DMSO and ethanol mixtures.

We have also synthesized and characterized a series of monosaccharide triazole derivatives. These compounds were synthesized from N-acetyl glucosamine and *D*-glucose via a Cu(I) catalyzed azide/alkyne cycloaddition reaction (CuAAc). The compounds have been screened for their gelation properties and several efficient low molecular weight organo/hydro gelators were obtained, among these compounds, five per-acetyl glucosamine derivatives and one peracetyl glucose derivative were able to form gels in water. These new molecules are expected to be useful in drug delivery and tissue engineering.
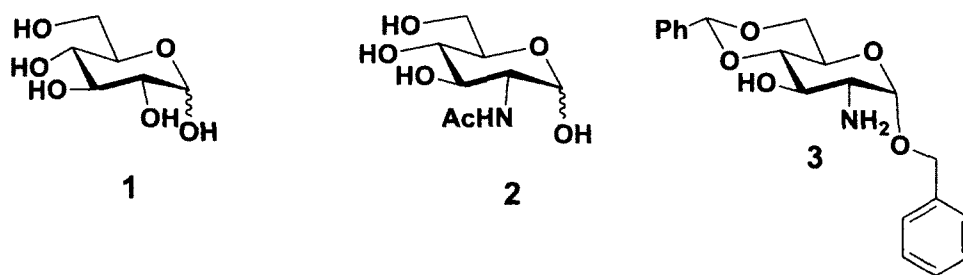
Asymmetric synthesis of chiral amines is a challenging in synthetic organic chemistry. The development of new catalysts for asymmetric organic transformations is a very important research goal in modern synthetic organic chemistry. We have synthesized a new class of chiral oxathiozinone from chiral amino phenol. From this synthesized chiral sulfinamides, ketimines followed by reducing the ketimines synthesized the highly hindered chiral amines.

Dedicated to:

My father & mother: Mangunuru Siva Reddy , Venkataravama

My wife Anusha

My brother Hanimi reddy

My uncle& aunt: Hanimi reddy, Seetharavamma

My uncle& aunt: Rajashekar reddy, leelavathi

My uncle & aunt: Eswara reddy, Kamala Kumari

My uncle & aunt: Krishna reddy, Vijaya Lakshmi

Friends & family members

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I want to give my deepest thanks to my wonderful wife Anusha. Her patience, help, love and support mean to the world to me.

NOMENCLATURE

Ac   Acetyl

Bn   Benzyl

Bz   Benzoyl

DMF   *N,N*-Dimethylformamide

DMSO   Dimethylsulfoxide

DCM   Dichloromethane

DIEA   Diisopropyl ethyl amine

LHMDS   Lithium hexamethyldisilazide

PTSA   p-toluenesulfonic acid

TFA   Trifluoroacetic acid

THF   Tetrahydrofuran

TIPPSA   Triisopropyl phenyl sulfonamide

*t*BSA   Tetrabutyl sulfinamide

TOSMIC   Toluenesulfonylmethyl isocyanide

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CHAPTER 1

INTRODUCTION TO LMWG's AND SULFINAMIDES

1.1. INTRODUCTION TO GELATORS

There has been a rapid growth of research on low molecular weight gelators (LMWGs), because of potential applications of these materials. An organo/hydrogel is typically formed by entrapment of solvent molecules by the trapped three dimensional self-assembled fibrillar networks (SAFINs) formed from low molecular weight organo/hydro gelators.[1-4] The supramolecular association are mainly formed due to the weak non covalent interactions such as H-bonding, π–π stacking, van der Waal forces, donor–acceptor interactions. The formation of such an organo/ hydrogel is a thermo reversible process as the "gel" can be melted to a "sol" (solution) by heating above a characteristic gel melting temperature (Tg). Many researchers are trying to correlate properties of the gels and the structures of gelators. The chemical structure of many gelators looks rather diverse, therefore it is difficult to exactly predict the structural requirement of molecules to show gelation. Serendipity is the main reasoning behind gel formation, which is how many of the gelators are found during the last few decades.[5-8]

Due to the molecular weight difference in polymers and low molecular weight gelators these can be categorized in two ways. Polymers attracted much interest because of the versatility of a wide range of applications. Their use ranges from thermoplastics, elastomers, and plastomers as well as thermoplastic elastomers. Polymer gels consist of a cross-linked polymer network inflated with a solvent such as water. They have the ability

to reverse, swell or shrink due to small changes in their environment (pH, temperature, electric field, stimuli responses).[9-10]

Polymer based gels have been studied for many years. The advantage of these polymer gels are strong chemical bonds and mechanical properties. The main disadvantages of polymer hydrogels are they need more gelator (gelator/solvent ratio is relatively high) and they are typically thermally irreversible. **Figure 1** shows the structures of two polymeric gels.[15-16]

1   2
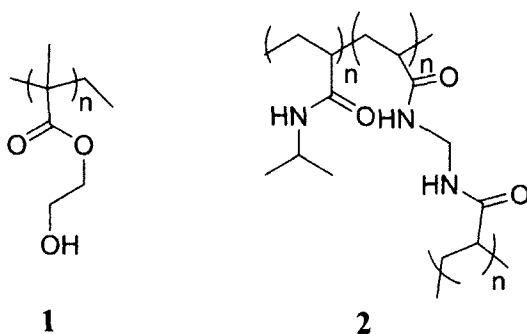
Figure 1. Examples of polymer gelators.

The main difference between the polymer gel and low molecular weight gel is the mechanism of gelation. Low molecular weight gelators have been classified based on the self-assembly of gelator molecules in solvent systems. If the gelator molecules self-assemble in the organic solvent those are called organo gelators, where as if the molecules self-assemble in water mediated system those are called hydrogelators. On the other hand, polymer gels are assembled based upon their crosslinkage, and solvent entrapment.

1.1.1. LOW MOLECULAR WEIGHT GELATORS

Low molecular weight gelators (LMWGs) are small molecules that can form gel in organic solvents and/or water. The gels are mostly liquid trapped in to a three-dimensional networks with non covalent interactions such as hydrogen bonding, donor-acceptor, π-π,[2] hydrophobic and Vander walls interaction's.[11-14] Low molecular weight gelators are classified into two types, one is organogelators (LMOG's) and the second one is hydrogelators (LMHG's).[15-21] There is a big difference in the intermolecular interactions of these two types. In case of hydrogelators, they mainly rely on hydrogen bonding and hydrophobic interactions and for the organo gelators the main driving force is hydrophobic interactions, rather than hydrogen bonding.[22]

The chemical structure of many of the gelators looks rather simple, it is difficult to precisely predict the structural requirements for molecules to show gelation property. However, considerable amount of research has been done so far from many researchers, the information gained from a variety of different types of gelators helped in rationalizing the general structural requirements of molecular gelators. These molecules are generally showes gelation behavior in presence of functional groups such as hydroxyl, amide, urea and carboxylic acid. These functional groups are capable of forming hydrogen bonded assemblies and they have been proved to be essential for gelation. The general functional groups for gelator molecules are shown in **Figure 2.**
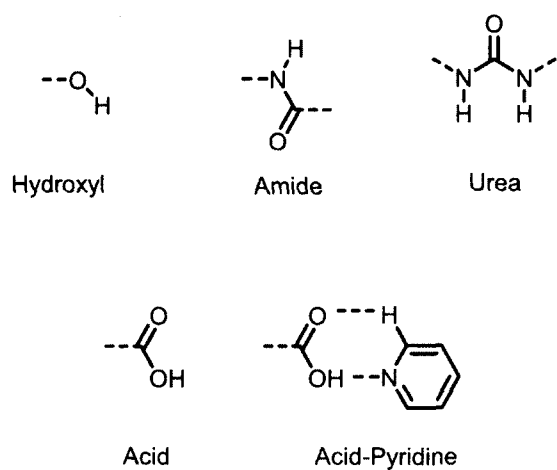
Figure 2. General functional group requirements for the design of gelators.

The molecules with structural functionality such as amino acids, peptides, peptoids, cholesterol, sugar, cyclohexyl, chiral aliphatic/oligiethylene chains have been found to facilitate the gelation of variety of solvents shown in **Figure 3**.
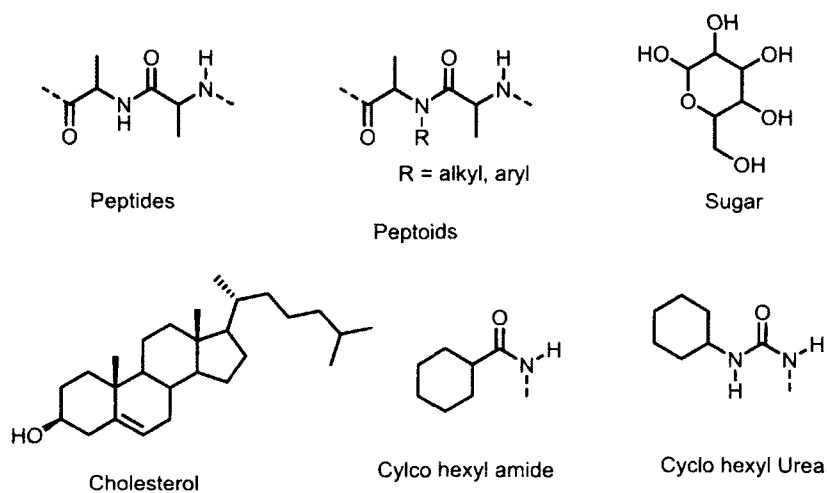
Figure 3. General structures facilitates for the design of gelators.

Numerous examples are there for the LMWG's, researchers are able to find gelators from

different classes of compounds including ureas, amides, acids, carbamates, esters,

carbohydrates, steroids, nucleotides, nucleosides, amino acids, alcohols etc. Some

examples are shown in **Figure 4**. [23-28]
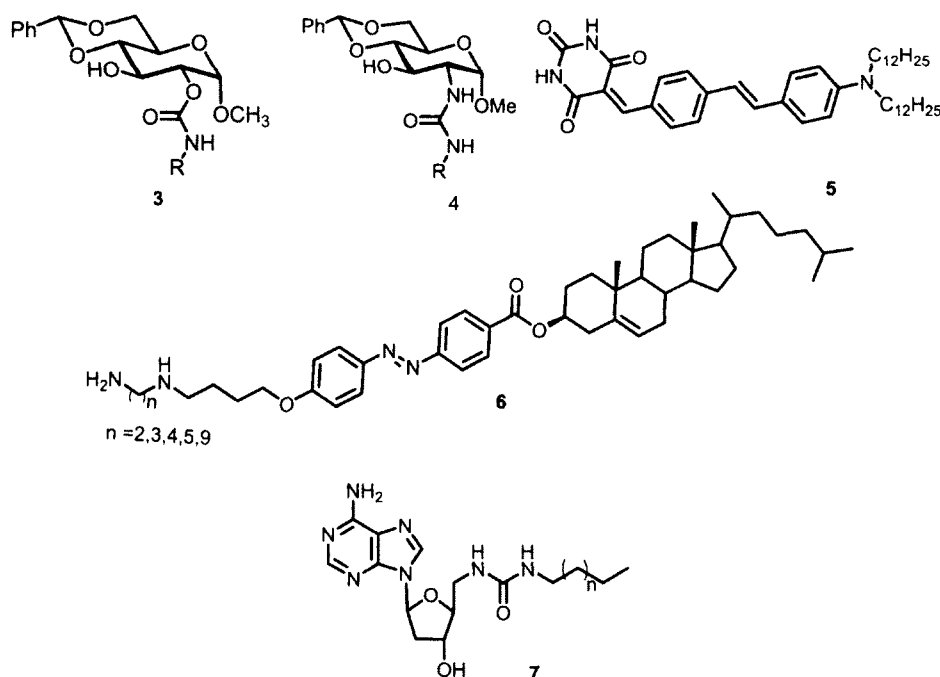
Figure 4. Structures of some organo/hydrogelators.

1.1.2. LOW MOLECULAR WEIGHT ORGANO GELATORS (LMOGs)

There are many reports for the LMOGs, being an important class of soft materials, they

have evolved to be one of the most attractive subjects bridging supramolecular chemistry

and material sciences due to their structural diversity and associated physical properties.

Myriad applications in fields such as optoelectronics, light harvesting, environmental science, and regenerative medicine are being envisaged.[29-43]

Presence of an aromatic group that helps $\pi-\pi$ stacking is another features for the design of organogelators. Molecules that facilitate dipole–dipole and donor–acceptor interactions can also lead to the gelation of solvents. These compounds have been around for a long time, particularly in lubricants, and the cosmetics industry, where they exist as hydrocarbon or fatty acid suspensions. As stated earlier, organogels differ from hydrogels, not only by the solvent being gelated, but also by the way the molecules self-assemble, which is the main driving force for gelation.

Pyrene Based LMOG's:

Ziessel *et al.* reported an efficient organogelator based on the phenylethynyl pyrene skeleton comprising of amide functional groups.[26] The double substitution of 4-ethynylphenylaminoacyl on pyrene renders gel formation in organic solvents such as toluene, cyclohexane, and DMF, the bisamide-pyrene compound **8** shown in **Figure 5** was able to form thermally reversible transparent gels with cyclohexane and turbid gels with toluene and DMF.[26]
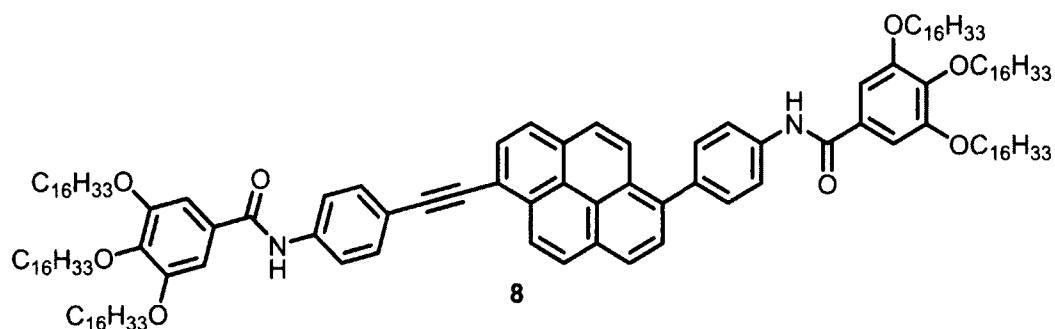
Figure 5. Bisamide-pyrene containing organo gelator.

Takashi and Yuko studied the reverse mode fluorescence color switching of the oligopeptide functionalized pyrene gelators shown in **Figure 6**.[29] The cyclohexane gel of pyrene monoglutamate derivatives **9, 10** showed monomer like emission because of the hydrogen bonded arrays of the oligopeptide moieties which suppress the formation of pyrene excimers. The reverse way is encountered in the case of compound **11** that exhibited excimer emission of pyrene.[29]
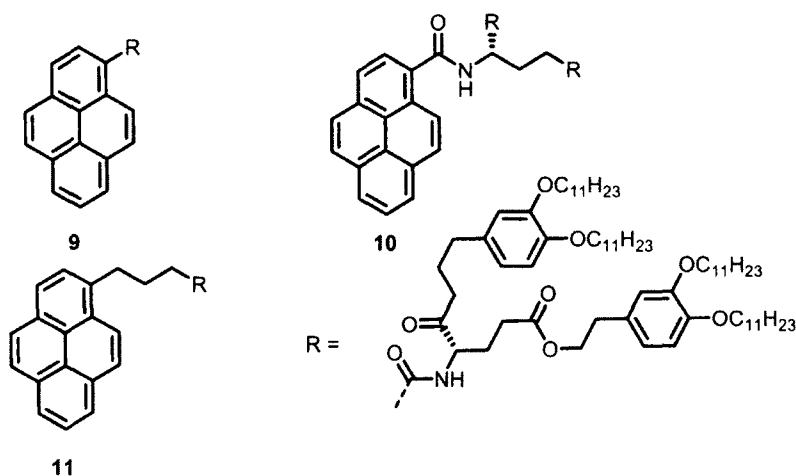
Figure 6. Structures of Pyrene-Containing Oligopeptide Derivatives.

Azobenzene based LMOG's:

Photoresponsive organo gelators have gained considerable attention from last few decades. These chromophores are of great interest because their properties can be modulated using light as an external trigger. For example, upon photo irradiation, gel can be transformed into a viscous liquid or a solution. In many cases, the size and shape of the xerogel morphology can be manipulated with light, leading to a change in their electronic properties. Such change in photoinduced physical processes can be achieved by trans–cis isomerization, 2 + 2 dimerization, photoscission, or photopolymerizations of the chromophore derived gelators.[30a-g] Shinkai and co-workers have synthesized many of these azobenzene containing molecules. They made significant contributions to azobenzene derived gelators. The two types of gelators **12–14** shown in **Figure 7** with steroid skeletons having either the natural (S) configuration or the inverted (R) configuration have been studied. Among them, the gelator with p-alkoxy azobenzene moiety is the most efficient and can gelate either nonpolar solvents.[30a-b]

12

13

14

R = CH$_3$, C$_4$H$_9$, C$_2$H$_5$, C$_{10}$H$_{21}$, C$_3$H$_7$
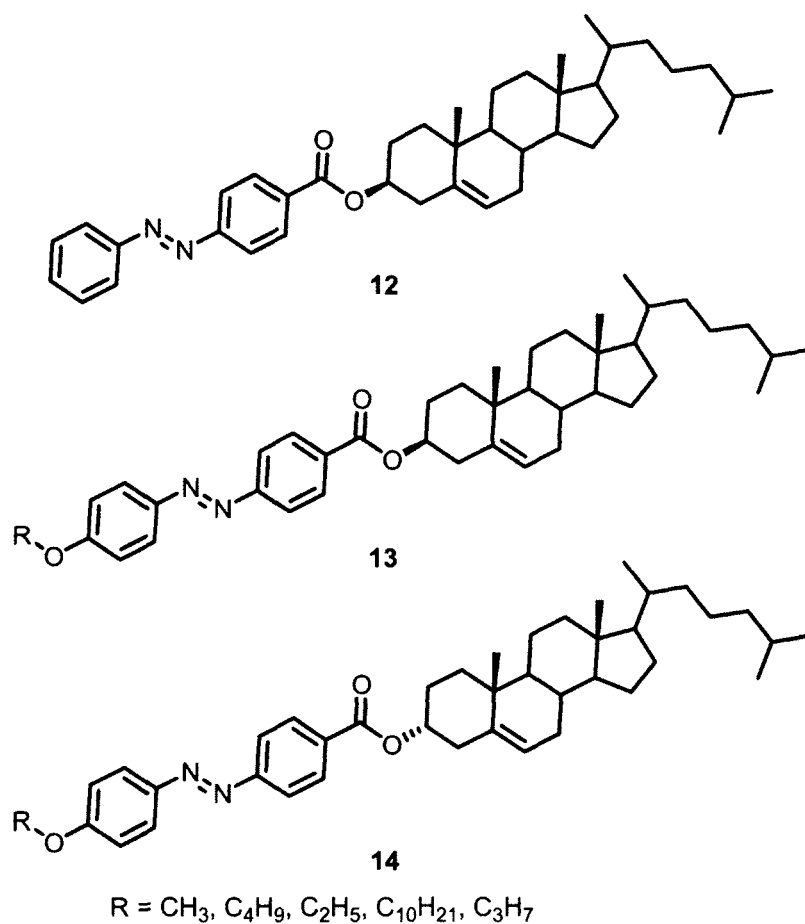
Figure 7. Azobenzene containing steroid molecular organogelators.

Feringa and co-workers have reported chiral recognition in hybrid gel assemblies of alkyl substituted 1,2-bis-(uriedocyclohexane) derivatives as shown in **Fig 8.**[31a]
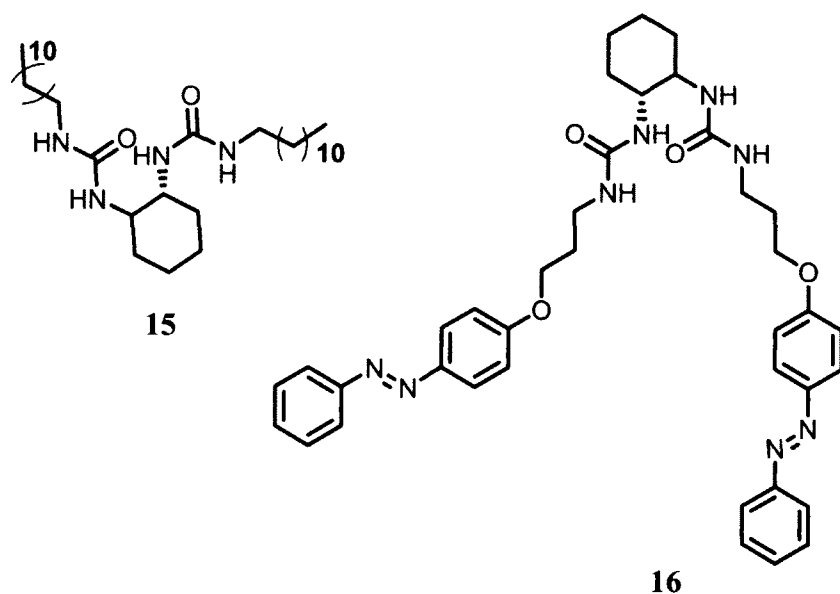
Figure 8. Azobenzene containing chiral amino molecular organogelators.

Yagai and coworkers developed azobenzene-functionalized diaminopyrimidinone derivatives **17** and **18** shown in **Figure 9** hierarchically organize into lamellar superstructures to form organogels in nonpolar media, which undergo photoinduced disruption and reformation. [31c]
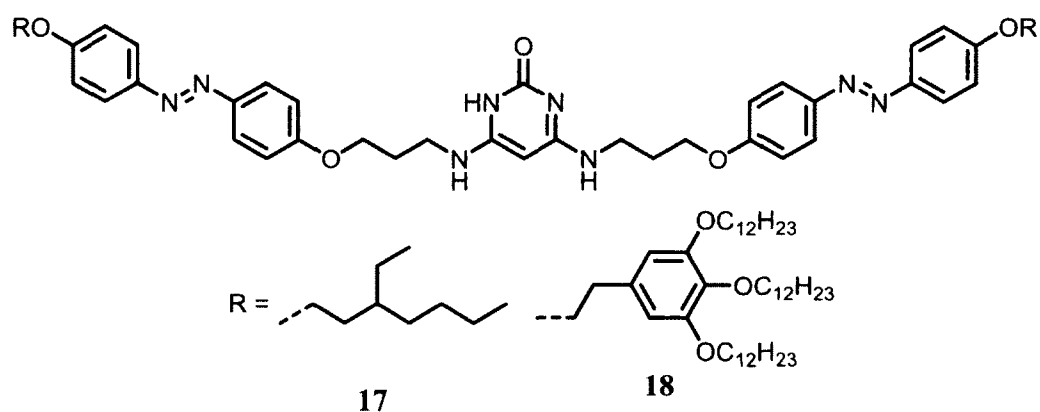
Figure 9. Azobenzene containing diaimno pyrimidione organogelators.

Diacetylene Based LMOG's:

From last few decades, there has been considerable interest focused in the self-assembly study of diacetylene derivatives. Gel forming diacetylenes are particularly interesting because the gel network which is stabilized by the noncovalent interactions can be permanently supported by strong covalent bonds. The covalent fixation of supramolecular assemblies through photo polymerization reactions to give polydiacetylenes, which are attractive candidates as conducting nanowires. Kim and his co-workers synthesiszed and characterized a series of polymerization and stabilization of the supramolecular nanostructures formed by the urethane-amide dendrons **19** and **20** in **Fig 10** with diacetylenes moieties at the alkyl periphery have been reported.[31d]
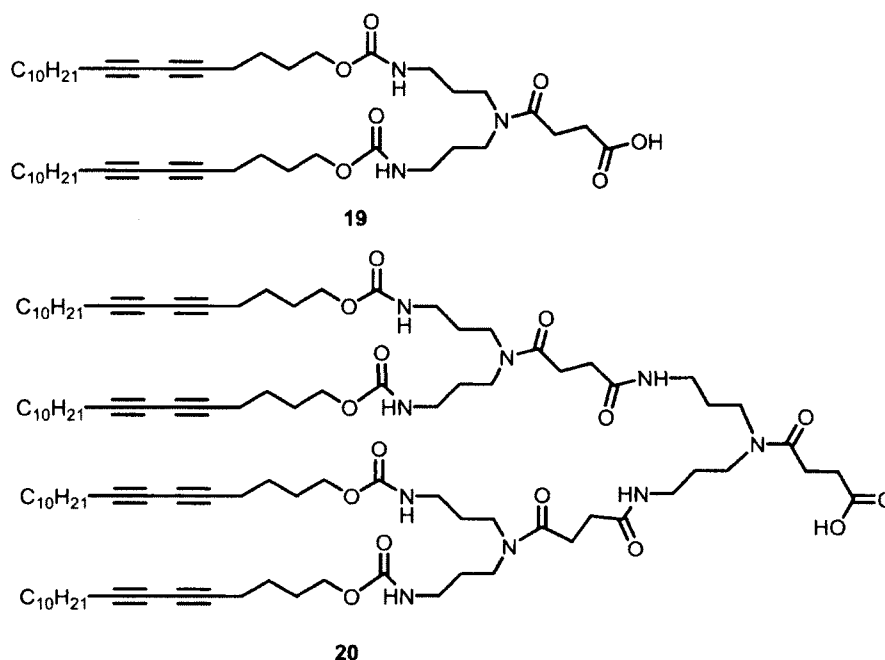
Figure 10. Diacetylene containing urethane amide dendrons.

Jean-Francois Morin and his coworkers synthesized a high molecular weight polydiacetylenes with low polydispersity index (PI = 1.8) has been achieved in good yield from a butadiyne derivative **21** (in **Figure 11**), having sterically demanding phenyl groups, using a light-promoted topo chemical reaction. [31e]
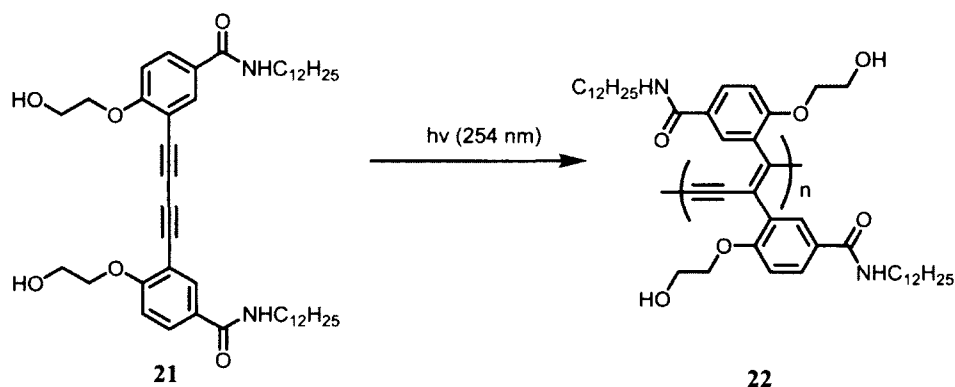
Figure 11. Poly diacetylene containing butadiyne derivatives.

Porphyrine Based LMOG's:

Porphyrins are a class of macrocyclic dyes exhibiting intense absorption bands in the visible region and are deeply colored. They have attracted considerable attention in the field of photosynthesis, porphyrins have tunable electronic properties depending on the exocyclic modifications and coordinated metal ion. Photosynthetic antenna complexes consisting of self-assembled arrays of porphyrinic and carotenoid pigments have been a motivation for chemists to design and develop new molecules and assemblies to mimic the natural photosynthetic processes.

Kimura and his coworkers reported that a mixture of the zinc porphyrin dimer compound

23 shown in **Figure 12** and an optically active (1R, 2R)-trans-1,2-bis(aklylamide) cyclo-

-hexane form an optically transparent gel with well resolved fibrous architecture.[31f]
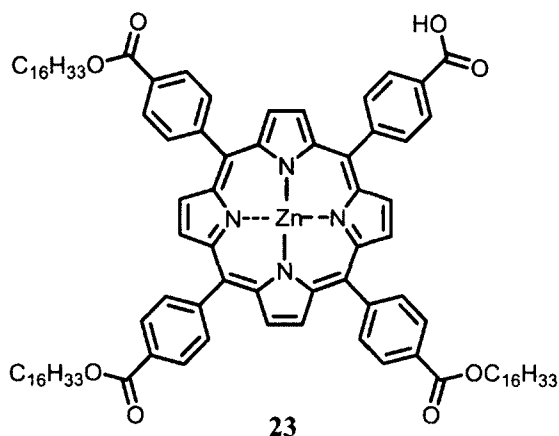
Figure 12. Porphyrin based LMOG's.

Lazzaroni, De Feyter, Amabilino, and co-workers have investigated the effect of the

number of stereogenic centers on gelation of **24** in **Fig 13**. The interactions between

molecules were interrupted by the methyl group attached to the stereogenic center that

increased solubility and hence decreased the gelation ability. [31g]
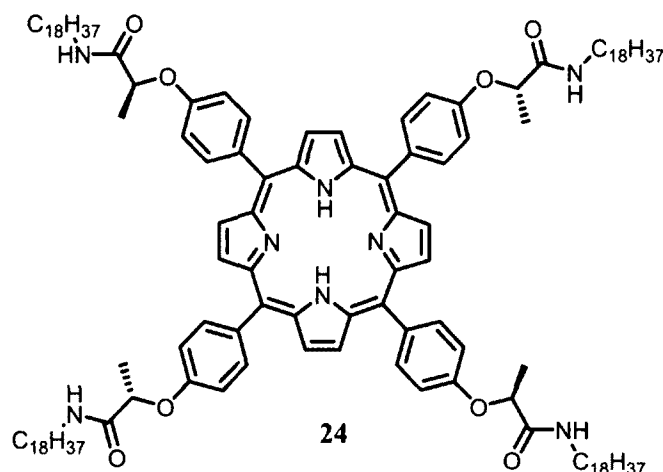
Figure 13. Porphyrin based LMOG's.

Thiophene Based LMOG's:

From last few decades thiophenes based LMOG's have attained considerable attention because of their molecular arrangement among large number of π-conjugated systems. Due to their high charge carrier mobility and chemical stability, conjugated oligomers and polymers of thiophenes have been used in applications such FETs, LEDs, PVDs, and chemical sensors.[31h-i] Feringa and his coworkers studied the bisurea appended oligo(thiophene)s, shown in **Figure 14**. These molecules were self-assemble in solvents such as tetralin and 1, 2-dichloroethane leading to the formation of organogels.[31j]

n = 1, 2

25
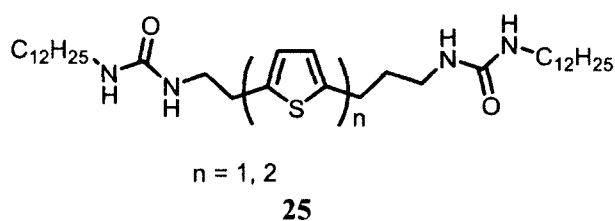
Figure 14. Bis urea appended oligo(thiophene)s LMOG's.

Samuel and his coworkers designed and synthesized a series of phenyl-quater(thiophene), ter(phenylene vinylene), and quater(phenylene) segments (**Figure 15**) as part of the rod segment of the DRC structure. The self-assembly of the conjugated molecules into supramolecular ribbon nanostructures leads to enhanced electronic conductivity due to improved orbital overlap. Furthermore, these supramolecular polymers can be oriented macroscopically in external fields. The iodine doped films were prepared from toluene gel exhibited a conductivity value of 7.9×10^{-5} S cm^{-1} whereas that of the monomer solution showed only 8.0×10^{-8} S cm^{-1}.[31k]

26

R =
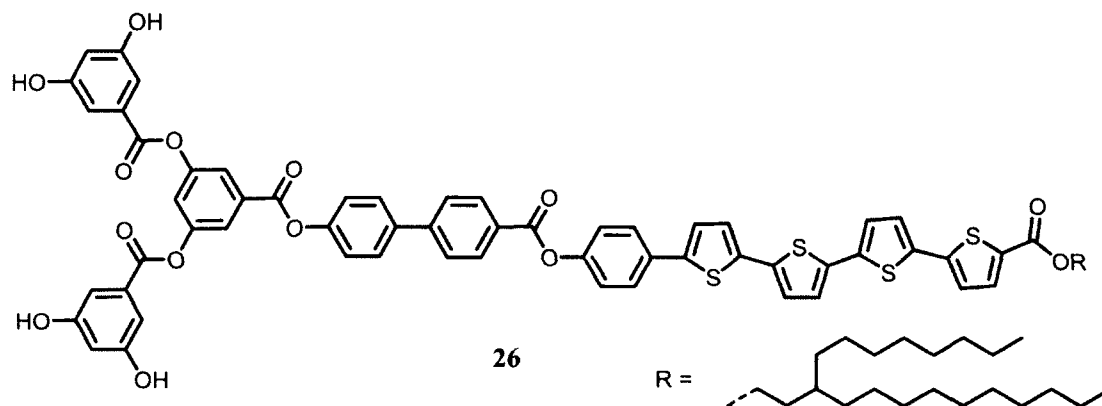
Figure 15. Phenyl-quater(thiophene) LMOG's.

1.1.3. LOW MOLECULAR WEIGHT HYDRO GELATORS (LMHGs)

Low molecular weight hydrogelators are typically made by dissolving a small amount (0.1-20 wt%) of the gelator molecule in water and heating until the gelator dissolves. [17] Rapid cooling of heated gelator molecules forms hydrogels after cooling below the sol-gel temperature (T_{gel}). The immobilization of the solvent is obtained by the formation of a fibrous network and taking advantage of water's relatively high external rigidity.[32-34] LMHGs are placed in a different category from their organogelator counterparts primarily because of the biocompatibility, the solvent also causes a different method of association used to assemble with other molecules. When designing LMHGs it becomes imperious to control the hydrophobic interactions, which lack the directionality of hydrogen bonding. When a dry hydrogel begins to absorb water, the first water molecule entering the matrix will hydrate the most polar, hydrophilic groups, leading to primary bound. Once the water molecule is bound to the various interactions with the gelator molecule then the gelators become saturated.[35]

The structure of hydrogelators mainly consists of contrasting polar and nonpolar regions, in which polar groups mainly include amino acids or sugars, while the nonpolar regions mainly include long alkyl chains or aromatic rings. **Figure 16** shows the structures of several compounds (**27-30**) that can form gels in water.[36-39]

R = H
-OH
-CH2COOH

27

28

29

30
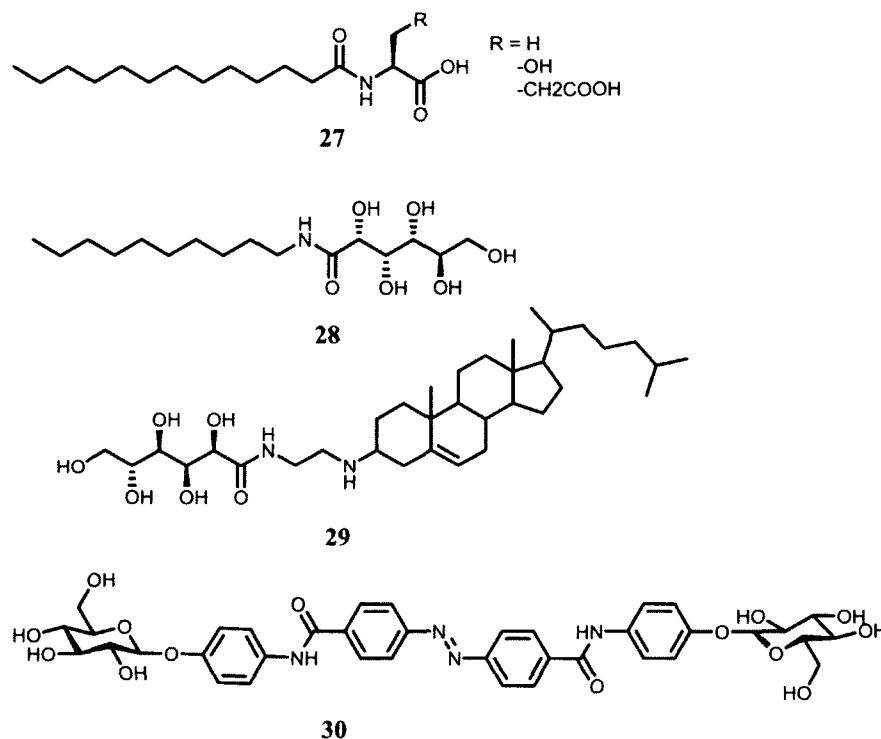
Figure 16. Examples of amphiphilic and bolamphiphilic hydrogelators.

1.1.4. CARBOHYDRATE BASED LMWGs

Carbohydrate based LMWG's have attracted considerable attention from last few decades. The abundance and availability of these compounds are not the only reason; structures of these compounds also give people different functional groups to work with. These molecules have several hydroxyl groups which are available for introducing other functional groups like urea, amide, carbamate.[23-24] The hydroxyl groups are very good hydrogen bonding donors, which will be useful in gel formation. The presence of multiple chiral centers can be used in the separation of enantiomers or a heterogeneous catalyst used for enantioselective reactions. Carbohydrate based materials are also important from medicinal point of view, because these molecules are natural products

and are biocompatible like amino acids. The presence of large number of hydroxyl group in carbohydrates can make the compounds soluble in water.

Shinkai and his coworkers first started glucose, galactose and mannose protected monosaccharides at 4, 6 position using benzaldehyde and $ZnCl_2$. The structure of those molecules are shown in **Figure 17**.[40-42]
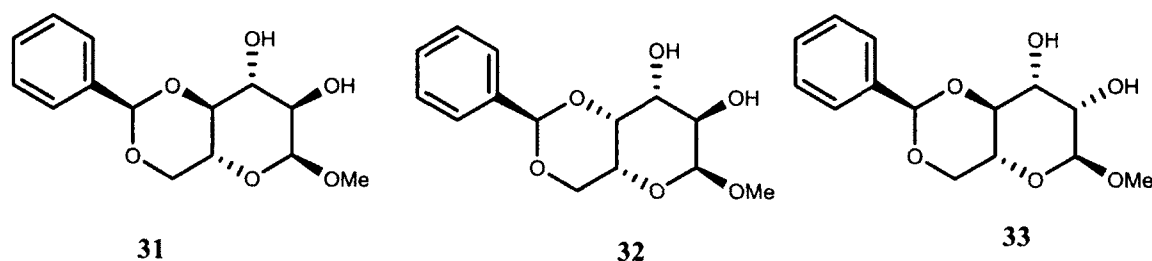
Figure 17. The product of a 4,6 position protected sugar.

Shinkai, Hamachi, and the Shimizu groups have produced much advancement in this area of C-LMWGs. LMHGs, such as the azobenzene derivatives. Shown here is one example of azobenzene derivative with a sugar head group. The LMHG's were found by combinatorial synthesis using solid phase glycolipid synthesis developed by Hamachi and Shinkai. Several alkyl and cycloalkyl ester derivatives show very good gelators at very low concentration as low as 4 mM shown in **Figure 18**.[39, 43]

34

35

n = 6,9,10,11,12,13,14

36
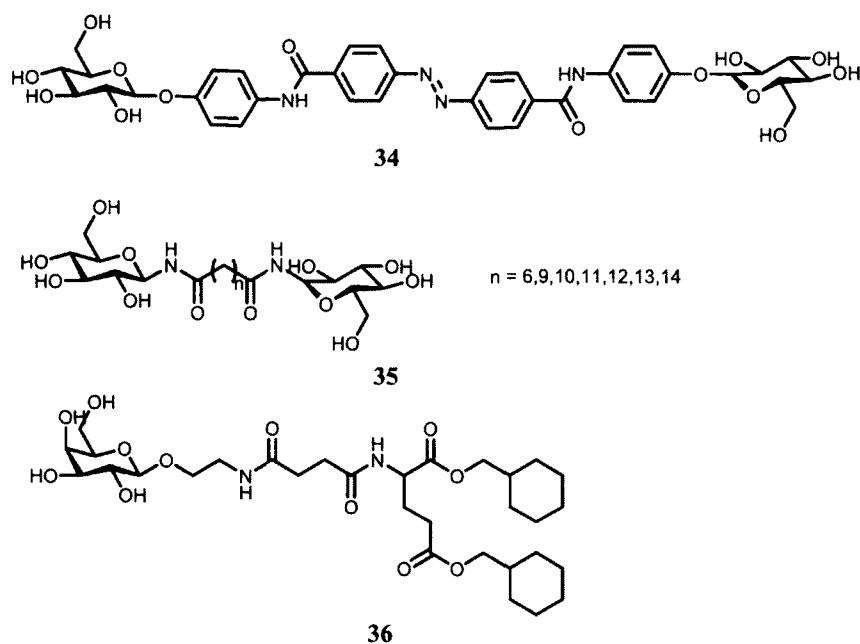
Figure 18. The sugar based LMWG's.

Colema and his co-workers showed that β-cyclodextrin has ability to form gel in pyridine itself or in combination with toluene, chloroform, or tetrahydrofuran.[44] Exposing this system to water disrupts the hydrogen bonding and causes the molecules to crystallize, forming a ternary crystal complex of β-cyclodextrin, pyridine, and water. The cyclodextrin structure is shown in **Figure 19**.
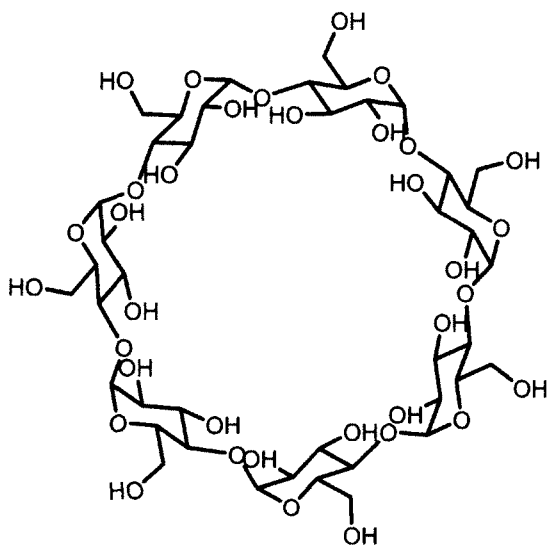
37

Figure 19. The sugar based β-cyclodextrin LMWG's.

Wang's group has studied a variety of sugar based compounds for the LMWG's. [23-24] Shinkai group mainly worked on the 4,6 position protected sugars for their studies,[33] Wang's group have focused on the functionalization of the anomeric, 2 and 3 position of the sugar moiety. The syntheses of these amide, urea, carbamate, diacetylene containing compounds have been studied. Stimuli responsive polydiacetylenes were also prepared by the cross-linking of the diacetylene-containing glycolipids shown in **Figure 20**.[46]
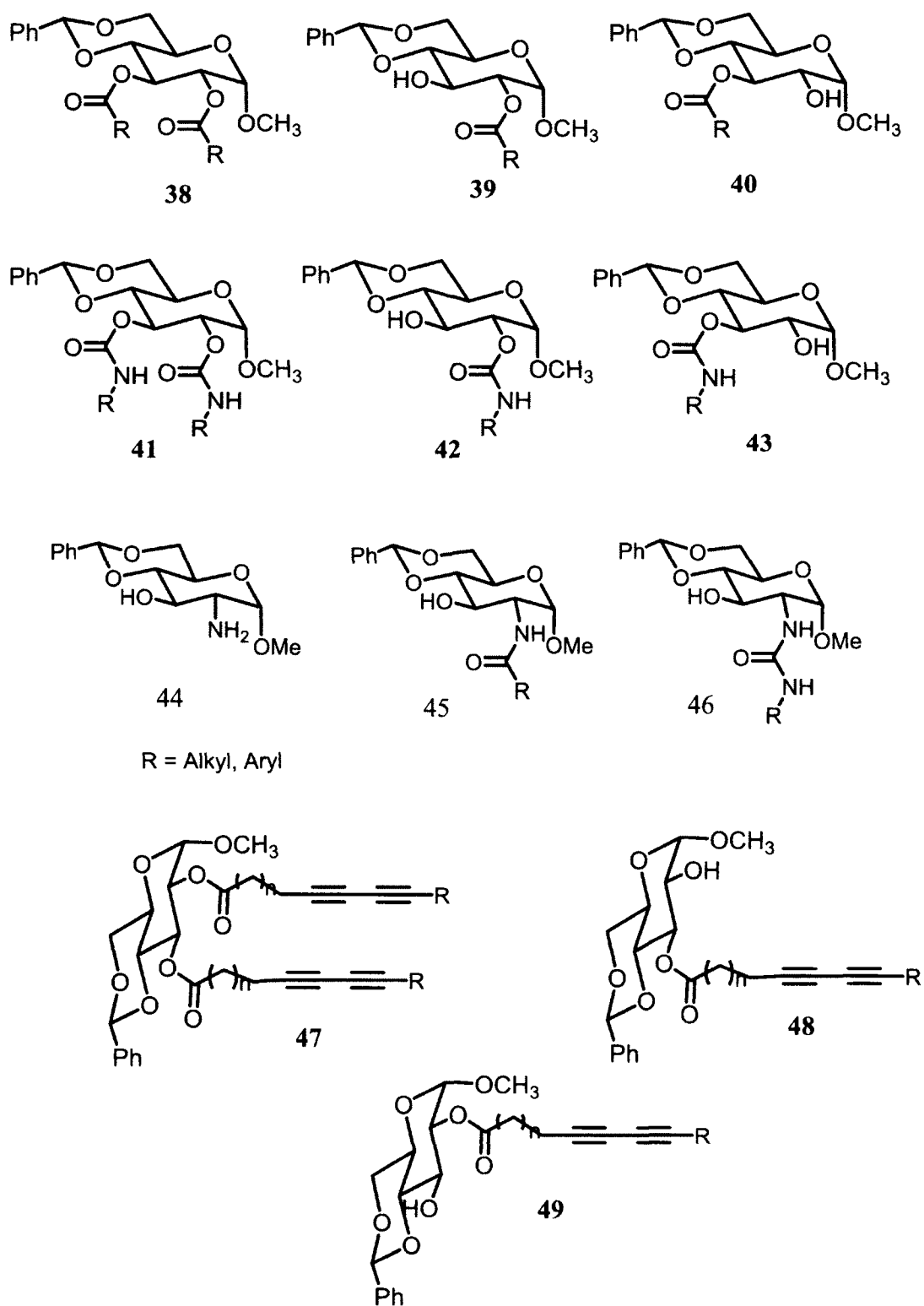
Figure 20. The sugar based amide, urea, carbamate, diacetylene based LMWG's.

1.1.5. PEPTOIDS

Peptoids, oligomers of N-substituted glycines, are described as a motif for the generation of chemically diverse libraries of novel molecules. The main difference between peptoids and peptides is the side chain is connected to the nitrogen of the peptide backbone, instead of the α-carbon as in peptides. Notably, peptoids lack the amide hydrogen which is responsible for many of the secondary structural elements in peptides and proteins as shown in **Figure 21**.[49-51]
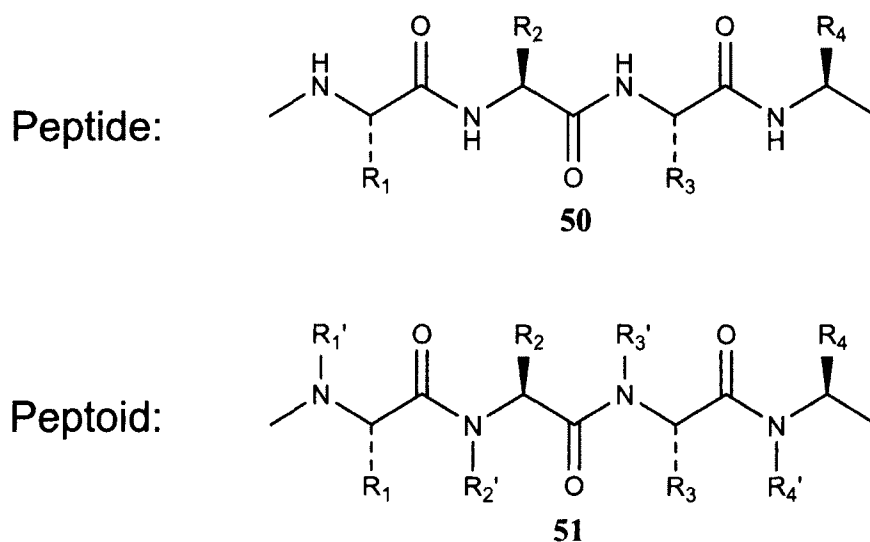
Figure 21. Schematic comparison between peptides and peptoids.

1.1.6. APPLICATIONS OF LMWGs

The special interests in LMWG's are associated with their inherent electronic properties such as fluorescence, charge carrier mobilities, electronic conductivities, nanomaterials, biological areas *etc*. Therefore, in recent years, considerable effort has been put in by the

scientific community to the design of LMWG's for specific application in the field of advanced materials. Supramolecular organization of chromophores attained through gelation approach induces strong electronic communication between the individual gelators, resulting in remarkable modulation of the electronic properties. A few good applications are discussed below.

Material Applications:

The recent development LMWG's in the field of conducting nanowires of functional π-conjugated molecules are attracted the considerable attention because of their potential candidates in organic electronic devices. Self-assembled 1-D structures of organogelators show enhanced conductivity due to electron hopping through intermolecular interactions. In many cases, conducting properties of organogels were investigated in the film states obtained from the xerogels on different substrates.

Stupp and his coworkers synthesized the thiophene based organogealtors for the conducting nanowires.[31k] The iodine doped xeogel film of the oligo (thiophene) DRC molecule exhibits very good conductivity. The oligo(thiophene) is shown in **Figure 22.**
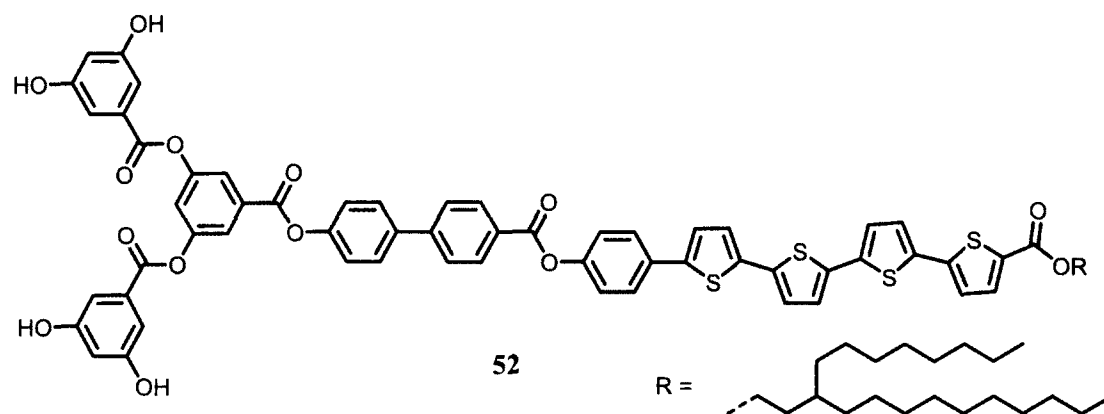
Figure 22. Conducting nanowired organo π gelator.

Shinkai and his coworkers synthesized and characterized a series of redox responsive chiral gels based on quater-, quinque-, and sexi-thiophenes bearing cholesteryl groups at the α-position, as shown in **Figure 23.** In addition to the unique thermochromic properties, sol–gel phase transition has been achieved by the addition of oxidizing and reducing reagents such as $FeCl_3$ and L-ascorbic acid respectively.[47]
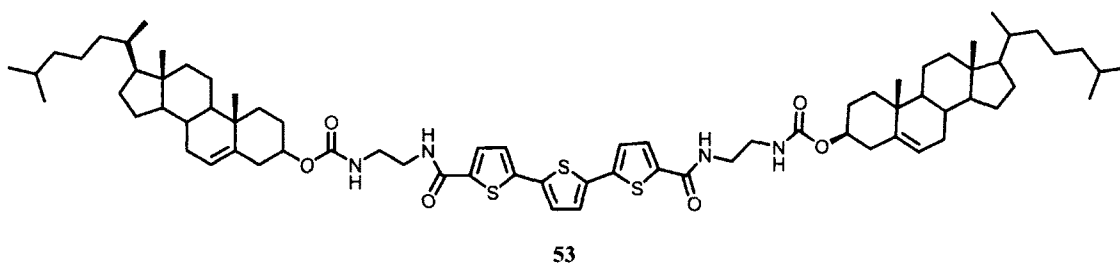
Figure 23. A thiophene based organo π gelator.

Biological applications:

Bing Xu's group have developed an enzyme based trigger and control the self-assembly of small molecules for hydrogelation, which takes place in vitro or in vivo, extra- or intra cellularly.[48] Using phosphatase, they illustrated the design and application of enzyme-catalyzed or regulated formation of supramolecular hydrogels that offer a new strategy for detecting the activity of enzymes, screening for enzyme inhibitors, typing bacteria, drug delivery systems, and controlling the fate of cells. Since the expression and distribution of enzymes differ by the types and states of cells, tissues, and organs, using an enzymatic reaction to convert precursors into hydrogelators that self-assemble into nanofibers as the matrices of the hydrogel, one can control the delivery, function, and response of a hydrogel according to a specific biological system.

Compound **54** have tyrosine phosphate to the C-terminal end of the amino acid derivative afforded the precursor, which served as a substrate for the phosphatases in the hydrogelation. The use of enzymes to trigger and control the self-assembly of small molecules for hydrogelation, which takes place *in vitro* or *in vivo*, extra- or intracellularly After being treated with a tyrosine phosphatase, hydrolyzed into a hydrogelator (**Scheme 1**).[48]
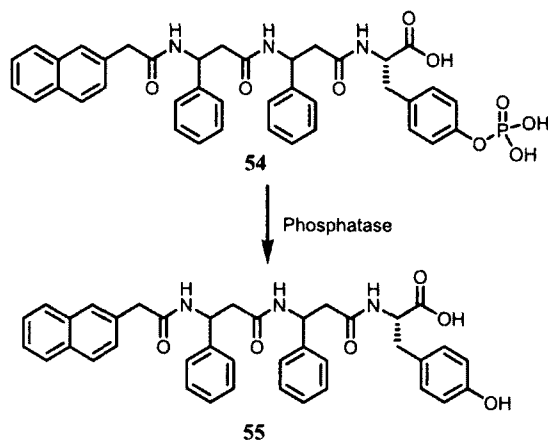
Scheme 1. The process for using phosphatase to control the balance between hydrophilic and hydrophobic interactions that leads to the formation of a hydrogel.

Bing Xu's group also studied the formation of a hydrogel within a cell, an endogenous enzyme should convert a soluble precursor, which does not necessarily self-assemble and gel extracellularly, into a hydrogelator that self-assembles into nanofibers. The design and synthesis of **56** as an esterase substrate was shown in **Scheme 2**. Mammalian cells take in **57** by diffusion, their endogenous esterases convert **56** to **57**, and the molecules of **57** self-assemble to form nanofibers, resulting in a supramolecular hydrogel inside the cells.[48]
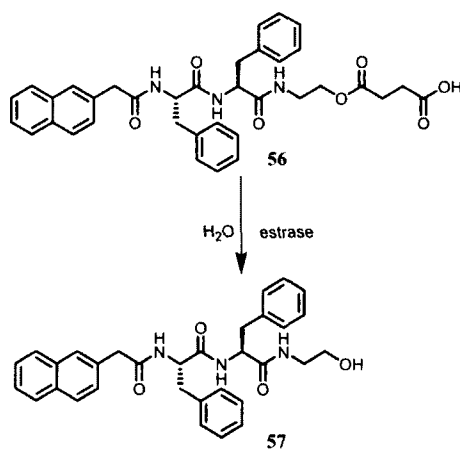
Scheme 2. An esterase to convert precursor molecule.

1.2. INTRODUCTION TO SULFINAMIDE

The development of new asymmetric catalysts for organic transformations is an important research goal in modern synthetic organic chemistry. The synthesis of enantiomerically pure chiral amines and their derivatives is also very important. There are so many methods developed for the preparation of chiral amine derivatives from chiral N-tert-butyl sulfinamide. The extensive study is focused on the N-tert-butyl sulfinamide because of its important in pharmaceutical, biological, and synthetic chemistry. The use of chiral ligands as a source of asymmetric induction in metal-catalyzed reactions has been a traditional focus of this field.[52]

Some of the available drug molecules were synthesized using the N-tert-butyl sulfonamide shown in **Fig 24**.[164a]

Sesquiterpenes: the
lead compound of anti-tumor
58

The frist selectivity 5-HT4 receptor
antagonist: the lead compound of
antidepressant
59

Gemcitabine: antitumor and antiviral
It is used to treatment of pancreatic
cancer, non-small cell lung cancer
60
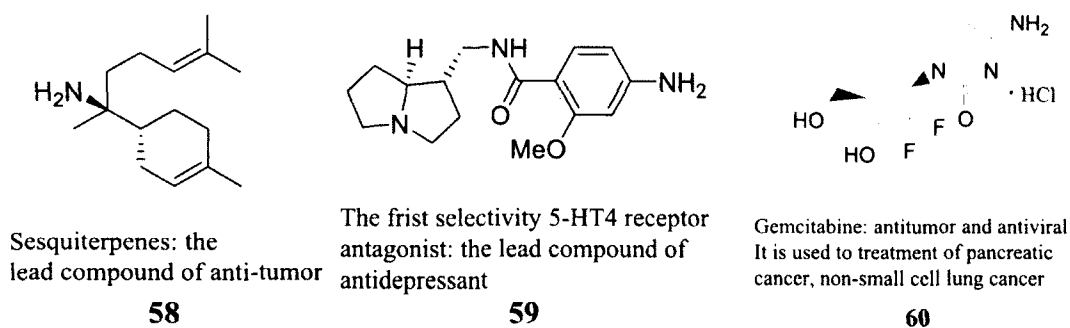
Figure 24. Drug molecules with chiral amine.

Ellman and his coworkers first synthesized and isolated the enantiomerically pure tert-butanesulfinamide.[164b] Since then, several different approaches to the synthesis of this

compound have been reported, including enantioselective oxidation, resolution of racemic material, diastereoselective synthesis utilizing stoichiometric chiral auxiliaries shown in **Scheme 3**.[164b]

Scheme 3. First synthesis of tert-butanesulfinamide

Ligand (a) (0.26 mmol %)
VO(acac)$_2$ (0.25 mol %)

H$_2$O$_2$ (1.1 equiv), 30 wt%
in H$_2$O, CHCl$_3$, 40h, 15-20 °C

1. LiNH$_2$/NH$_2$, THF,
   -78 °C

2. Crystalization

61

62

77 %
> 99 % ee
63

Ligand (a)
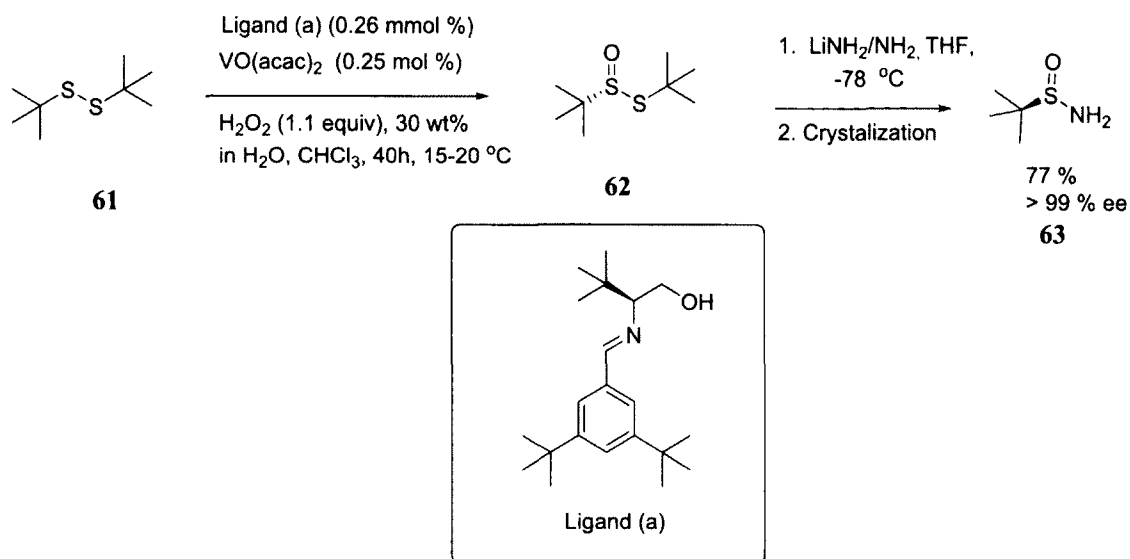
Senanayake and co-workers developed a chiral auxiliary-based method for the synthesis of diverse chiral sulfoxides and sulfinamides, including tert-butanesulfinamide from amino indanol, norphedrine, and quinine (**Figure 25**).[53a-c]
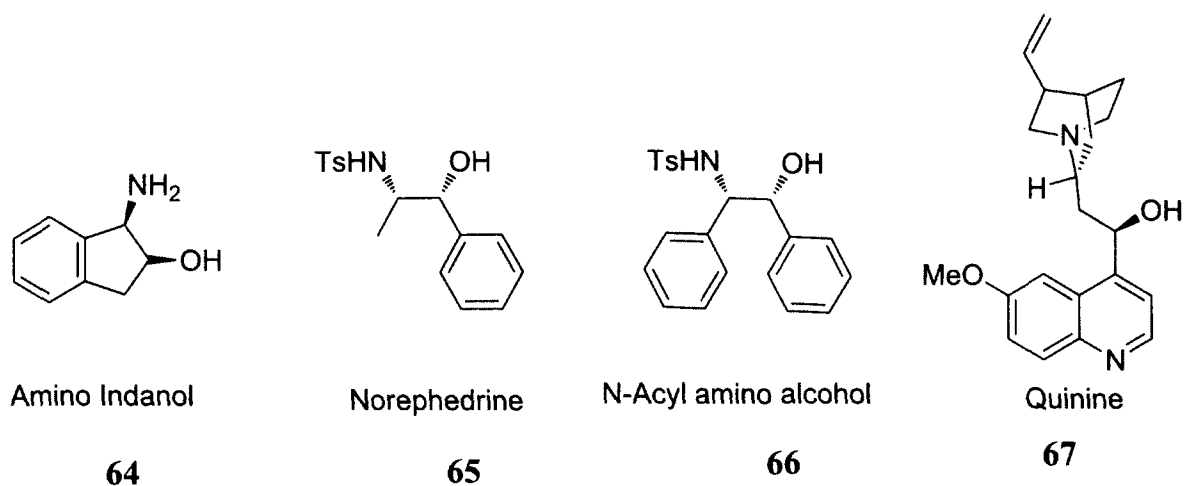
Figure 25. Different chiral auxiliaries for synthesis of tert-butanesulfinamide.

1.2.1. APPLICATIONS OF SULFINAMIDE

Synthesis of SC-53116

Ellman and his coworkers developed a self-condensation methodology for the aldimines in a diastereoselective intermolecular self-condensation reaction was used for the synthesis of the highly potent and selective serotonin 5-HT4 agonist SC-53116 (**59**) (**Scheme 4**). For the self-condensation of **68**, lithium hexamethyldisilazide (LHMDS) was identified as the optimal base, and **69** was generated in 55% yield as a 91:5:4:0 mixture of diastereomers. After condensation, microwave irradiation of N-sulfinyl imine **69** produced nitrile **70** which was separated from the minor diastereomers by column chromatography and was subsequently reduced to the primary amine **71**. Amide-bond formation yielded intermediate **72** in 80% yield. Removal of the sulfinyl and acetal protecting groups and cyclization to form the pyrrolizidine core was achieved under

acidic reducing conditions. This highly efficient synthesis of **59** was completed in five

steps and 29% overall yield from the *N-tert*-butanesulfinyl imine **68**.[54]

Scheme 4. Synthesis of 5-HT4 receptor antagonist

The frist selectivity 5-HT4 receptor
antagonist: the lead compound of
antidepressant **59**
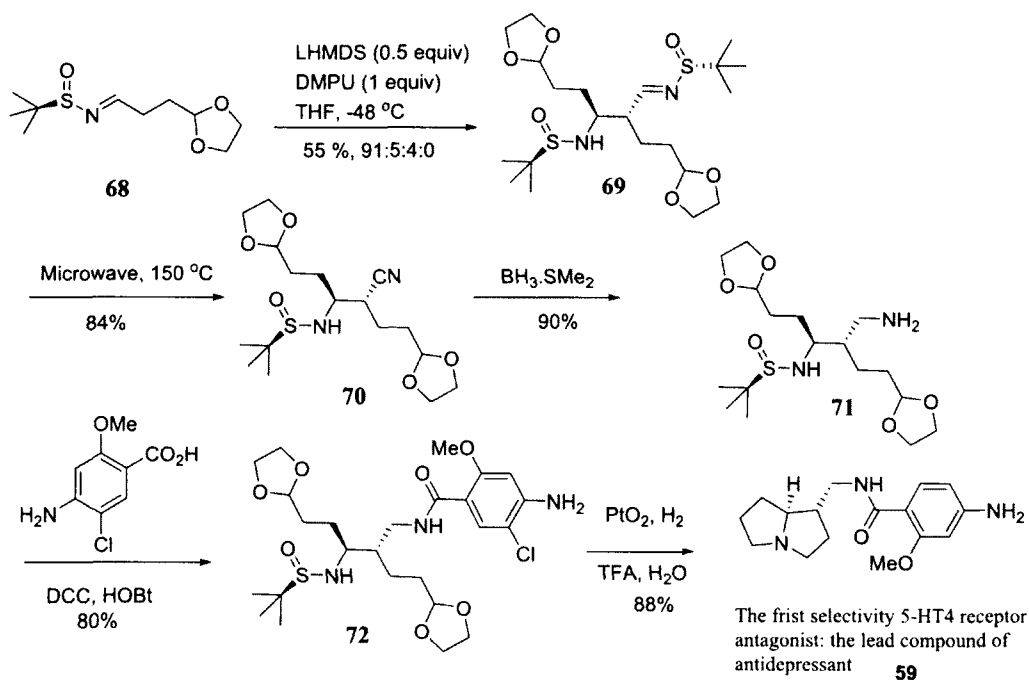
Synthesis of α-Branched amines:

For the synthesis of α-branched amines from imines can be easily accomplished by using

chiral t-butylsulfinamide. The additions of organometalic reagents or different

nucleophiles have proven to get good diastereo selectivity of chiral amine using this

auxiliraies. Ellman and his coworker reported the first Grignard reagent to attack the N-

tert-butanesulfinyl aldimines shown in **scheme 5**.[164a]

Scheme 5. Addition of aliphatic Grignard reagent to aldimines
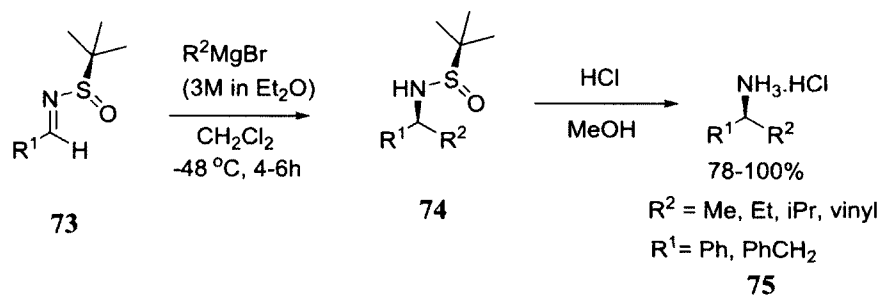
Senanayake and coworkers used the aryl Grignards for the addition of aryl aldimines in the synthesis of (S)-cetirizine dihydrochloride as shown in **scheme 6**.[55]

Scheme 6. Synthesis of (S)-Cetirizine Dihydrochloride

(S)-Cetirizine Hydrochloride
81
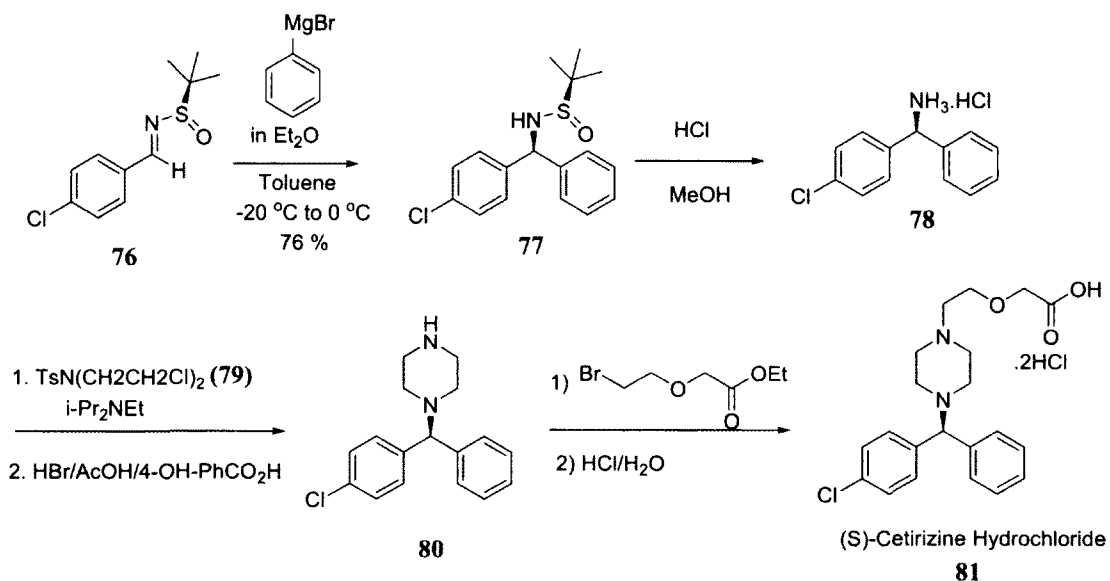
Synthesis of α-Amino acid derivatives:

Davis and co-workers published the first report on alpha amino acids synthesis by addition of Grignard reagent to N-tert-butanesufinyl imino esters. The addition of

BnMgCl to the N-tert-butanesufinyl aldimine (**82**) in presence of 2 equiv.of BF$_3$.OEt$_2$ will provide amino acid derivatives (**83**) with good diastero selectivity as shown in **Scheme 7**.[56]

Scheme 7. Synthesis of α-Amino acid derivatives

70%, 94:6   70%, 84:16   27%, 99:1   59%, 83:17
84   **85**   **86**   **87**
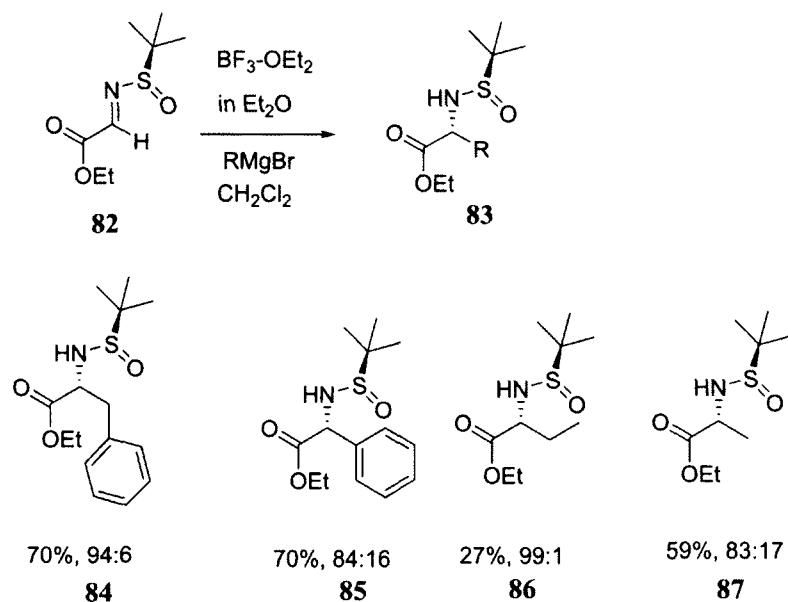
Yus and coworkers developed the asymmetric synthesis for the synthesis of α,α-disubstituted amino acids from N-tert-butanesulfinyl imino esters. Reaction of triorgano zincate reagent with the N-tert-butanesulfinyl imino esters will give the highly substituted amino acid derivatives shown in **Scheme 8**.[57-58]

Scheme 8. Synthesis of α,α – disubstituted amino acid derivatives

R= Et, 96%, 96:4 dr

R= iPr, 82%, 79:21 dr
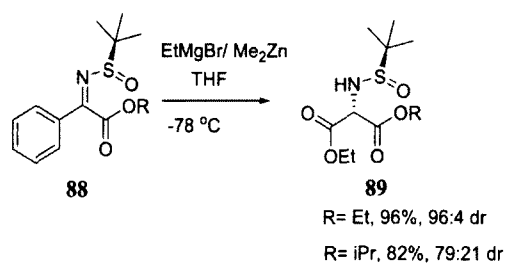
Synthesis of β-Amino acid derivatives:

Ellman and coworkers developed the asymmetric synthesis for the synthesis of β-amino acids from N-tert-butanesufinyl imino esters.[59-60] For these compounds high diastereoselectivty can be obtained from up on addition of TiCl(OiPr)$_3$ shown in **Scheme 9.**

Scheme 9. Synthesis of β-Amino acid derivatives
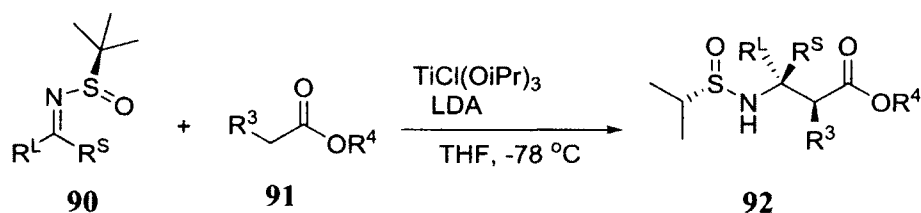
Synthesis of 1,2-Diamino derivatives:

Ando and co-workers reported the stereoselective addition of aryl Grignard reagent to R-amino imine **95** to provide chiral protected diamine **97** in 77% yield. Compound **97**, which was ultimately converted to an imidazolines for SAR studies on the inhibition of neuropeptide Y5 receptor shown in **Scheme 10.**[61]

Scheme 10. Synthesis of 1,2-diamino derivatives
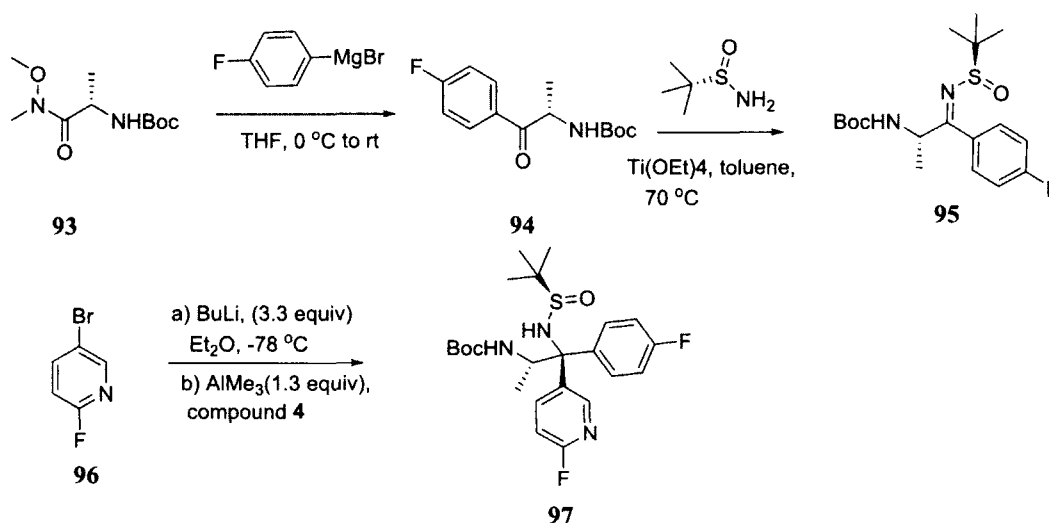
Total Synthesis of (-)-Melotenine A :

Andrade and coworkers synthesized the (-)-Melotenine A is a monoterpene indole alkaloid belonging to the Aspidosperma class of natural products. The synthesis of (-)-melotenine A is outlined in **Scheme 11**, began by condensing commercial N-tosyl indole-3-carboxaldehyde **98** and (R)-N-tert-butanesulfinamide with Ti-(OEt)$_4$ and In[0]. Addition of allyl bromide resulted in formation of an allyl indium species which stereoselectively added to the preformed N-sulfinylimine to afford homoallylic sulfinamide **99** in 87% yield (d.r.=10:1). From this they transformed in to (-)-Melotenine A.[62]

Scheme 11. Total synthesis of (-)-Melotenine A staring from aldimine

108

(-)-Melotenine A
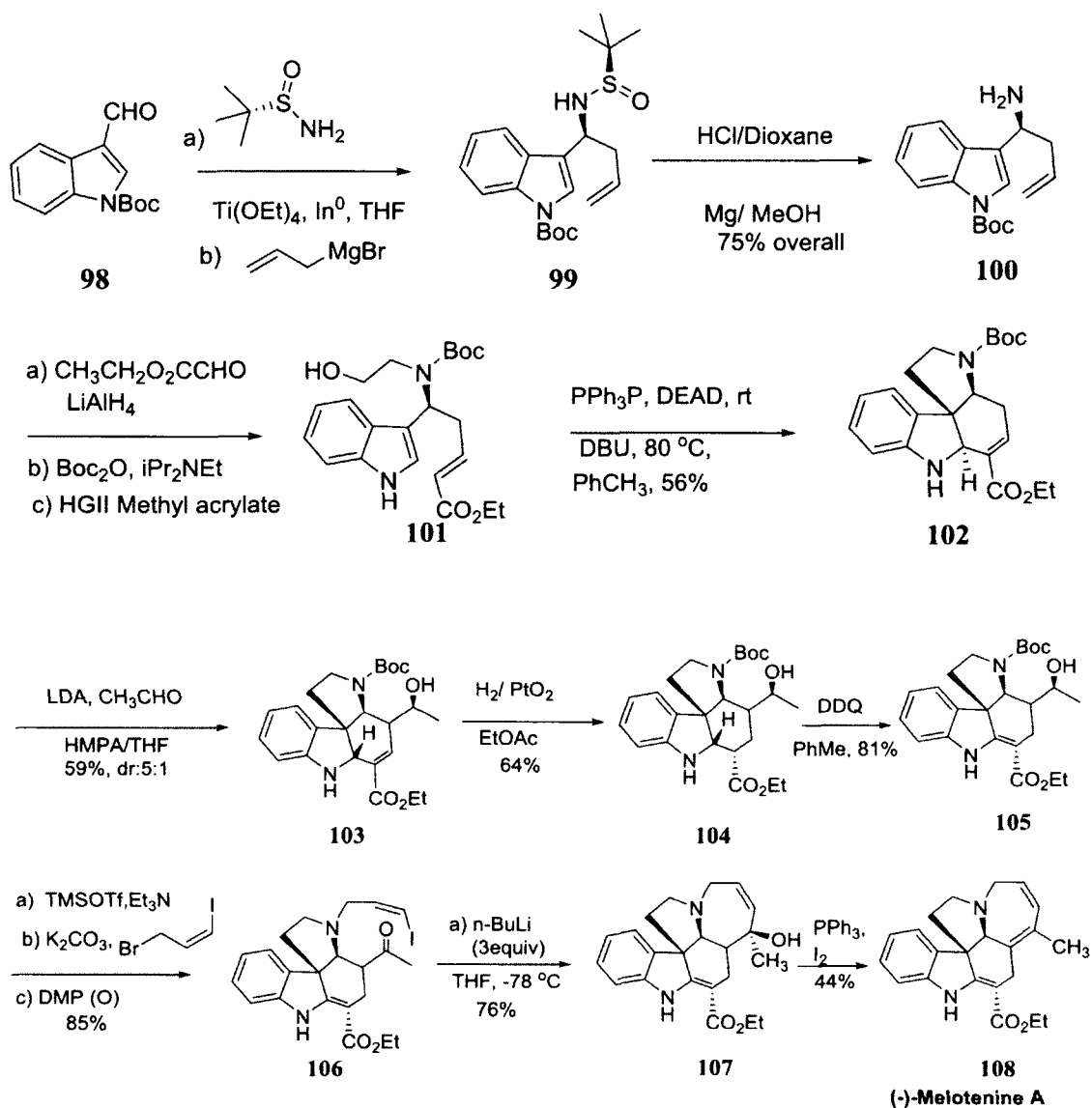
CHAPTER 2

PEPTOID BASED SMALL MOLECULE GELATORS FROM MULTI COMPONENT REACTION

2.1. INTRODUCTION

Small molecular gelators are interesting compounds that can self-assemble in organic solvents or water and form typically fibrous supramolecular architecture. These low molecular weight gelators produce thermoreversible physical gels which have potential applications in biomedical research and materials science.[1,2b,63-66] The driving forces for supramolecular gelation are non-covalent forces such as hydrogen bonding, hydrophobic interactions, π-π stacking, and Van der Waal's forces, etc. The gelation by LMWGs occurs through non-covalent interactions, the process is typically reversible which can result in advanced soft materials. Small molecule self-assembly has shown great promise as a "bottom up" approach for preparing novel functional materials.[63-73] The three-dimensional networks formed by LMWGs are useful new materials with applications in various fields, including enzyme immobilization and biocatalysis, tissue engineering and drug delivery systems, and advanced nanomaterials.[69-73] These interesting applications, a great deal of effort has been devoted to finding new types of low molecular weight gelators.[13-27] The structures of low molecular weight gelators (LMWGs) encompass a wide range of different functionalities. Several classes of organic compounds have been found to be useful building blocks for the design and synthesis of LMWGs, these include amino acids, sugars, cholesterols, amides, and ureas.[88]

These gelators obtained from bio based starting materials such as amino acids and carbohydrates will in general produce biocompatible materials or degradation products. Peptide based hydrogelators have been extensively studied and have shown great promises in tissue engineering and drug delivery.[89-104] However, peptides are endogenous compounds that are essential for many biological processes, they suffer from intrinsic problems such as rapid clearance or degradation by proteases. Therefore, peptidomimetic organo/hydrogelators that contain certain structural feature of the peptides but can withstand the proteolysis will have applications in obtaining stimuli responsive advanced materials.

Since peptide based molecular gelators have shown importance in biomedical and materials research, to prepare peptoids which are more resistant to degradation will be a useful endeavor. In this study, we have designed and synthesized a small library of tripeptoids using simple building blocks by Ugi reaction. The multiple component reactions are useful for generating a diverse array of compounds and for analyzing their properties. Ugi reaction has not been used much in preparing low molecular weight gelators, though there have been studies of using the reaction in modification of polymer gelator and recently octa-peptoids-peptide hybrids have also been shown to function as hydrogelators.[105] Peptoids have been shown to be able to self-assemble and form fibrous networks. [105-106]

As shown in Scheme 12, the Ugi reaction is a very efficient reaction involving four components in a one pot reaction, in which an acid, an isocyanide, an aldehyde or ketone

and an amine condense into a tripeptoid 1.[108] The reactions are carried out under mild conditions and usually give high yields. The tripeptoids obtained are analogous to tripeptides. This is an ideal reaction for exploring structure diversity and the discovery of novel scaffolds for drugs or new materials.

Scheme 12. Ugi one-pot four component reaction
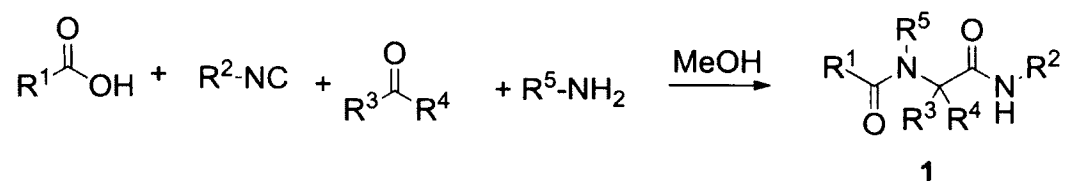
2.2. RESULTS AND DISCUSSIONS

For this study, we selected the readily available amines and carboxylic acids (2-18) as the building blocks for the Ugi reaction, as shown in **Figure 26**. In order to simplify product purification, formaldehyde was chosen as the aldehyde component, which can produce a glycine unit in the product. Among the various building blocks, the isocyanide component is the least commercially available starting materials. We selected cyclohexyl isocyanide **21**, which is based on our previous studies that compounds containing cyclohexyl group generally are effective gelators.[85-87] Ethyl 2-isocyanoacetate **22** was selected due the resulting glycine ester products. Toluenesulfonylmethyl isocyanide was selected due the presence sulfoxide group, it's very new type of functionality for gelator molecule. Protected glucosamine **5** and **6** were chosen as the amino building block, these molecules can introduce a sugar function into the peptoids. Also in our previous studies, various glucosamine derivatives have shown excellent gelation properties and a broad

range of substituents can be tolerated.[84-87] From these building blocks we synthesized a small library of peptoids as shown in **Figure 27**. The gelation properties of these compounds were then tested in several solvents and the results are shown in **Table 1**.
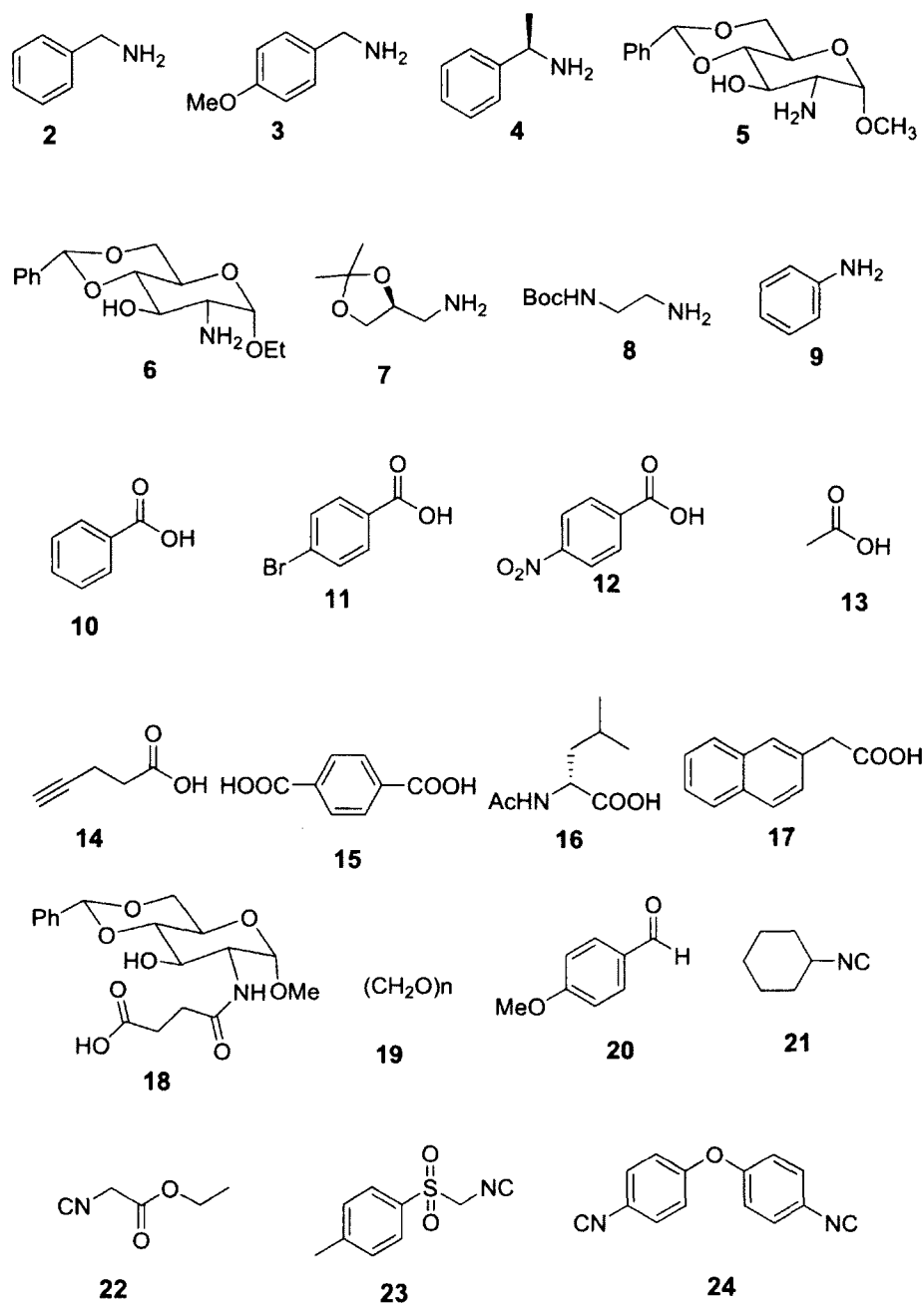
Figure 26. Structure of the starting materials chosen for the MCR reaction.

Only two aliphatic acid derivatives **25** and **26** are synthesized here. The rest of compounds contain two aromatic groups in their structures, these will introduce the a π-π interaction, which is an important factor in hydrogleators designs. From the table **1** we can see that a majority of these compounds were able to form gels in at least one of the tested solvents, several compounds turned out to be efficient gelators for ethanol aqueous solutions and DMSO aqueous solutions. The best performing compound is **32**, which forms gels at 0.2 wt% in DMSO/water (1:2) mixture. A general trend for these compounds is that branching or substitutions on the aryl group generally are necessary for gelation. The ethyl glycine series are in general more efficient gelators than those cyclohexyl series. Among the different amines used, the p-methoxylbenzylamine performed the best, and the protected glucosamine also give products that are effective gelators, unsubstituted benzyl group didn't perform well. Among the different acids tested, aryl acids are in general more efficient than aliphatic acids, and substituted aryl groups performed much better than the unsubstituted analogues.

Figure 27. The structures of peptoids synthesized by one pot reaction.

25

26

27 R = H
28 R = Br
29 R = NO₂

30

31

32

33 R = H
34 R = OMe

35 R = H
36 R = Br

37

72%, 38

83%, 39

58%, 40

Figure 27 continued

62 %, 41

62%, 42

67%, 43

75 % 44

81%, 45

84 %, 46

44%, 47

48

49a

49b

50
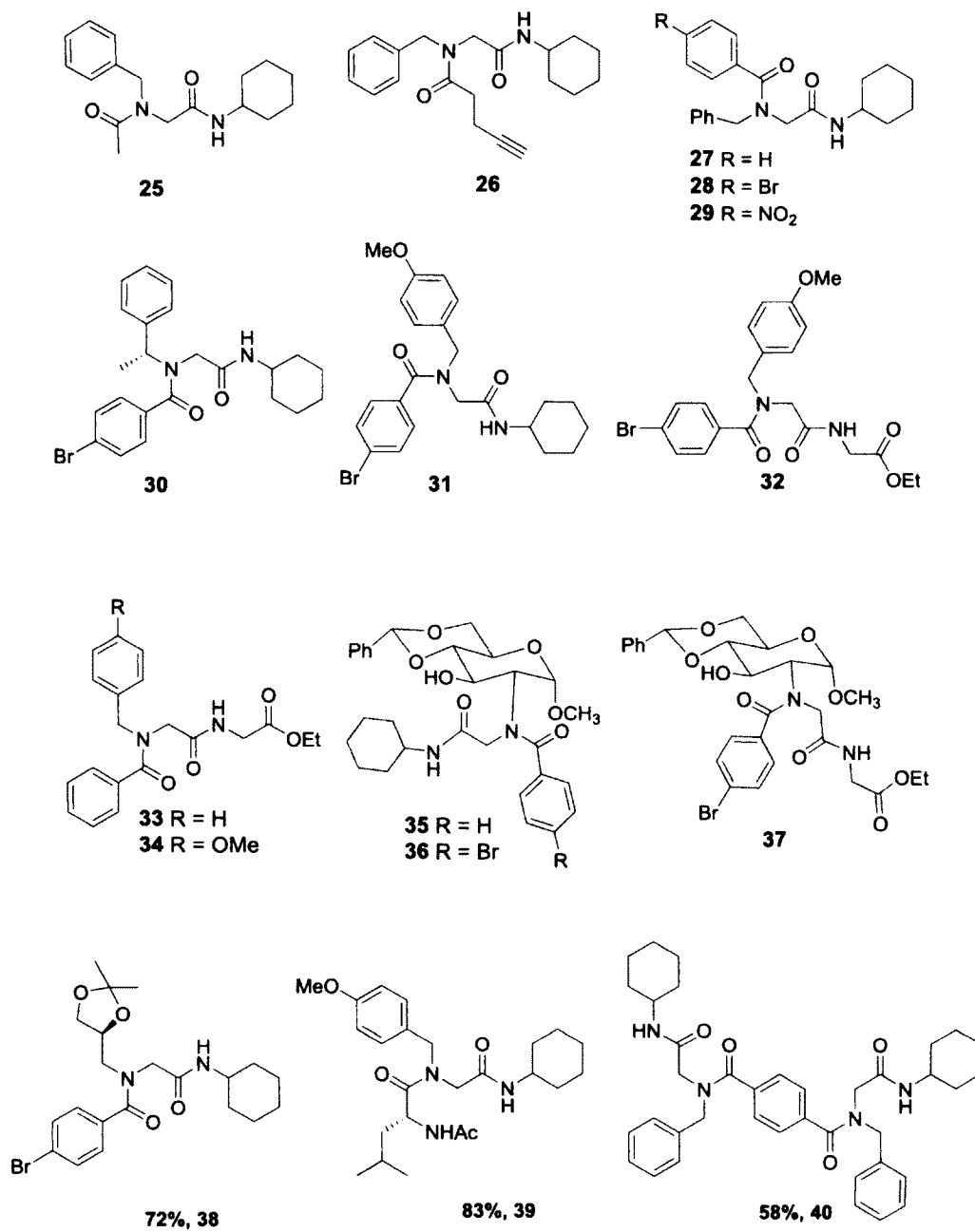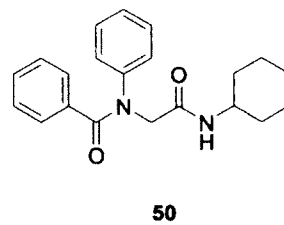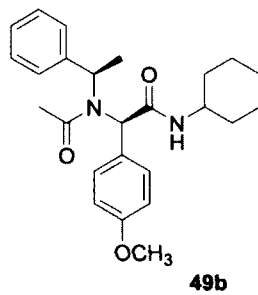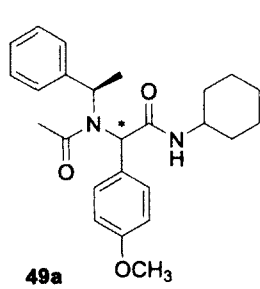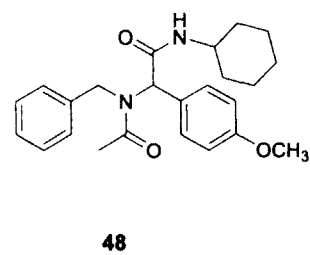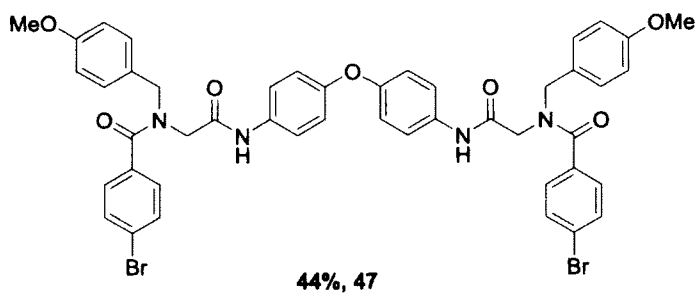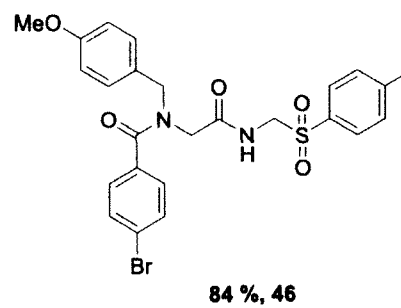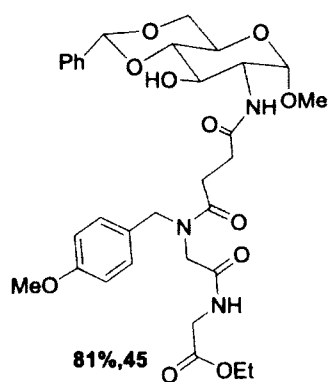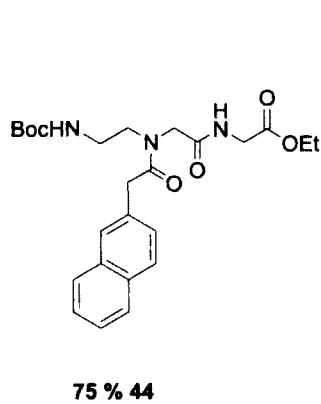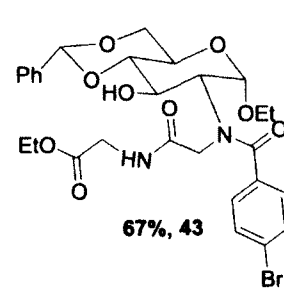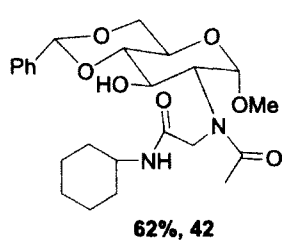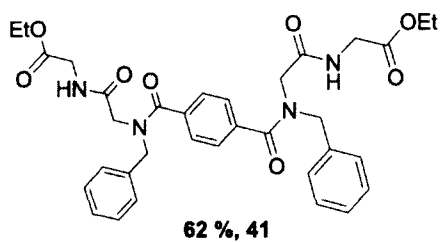
Table 1. Gelation test results for the library compounds

Compound	Hexane	Water	EtOH	DMSO:H₂O (1:1)	DMSO:H₂O (1:2)	EtOH:H₂O (1:1)	EtOH:H₂O (1:2)
25	I	P	S	S	P	S	P
26	P	S	P	P	G 20.0	G 20.0	G 20.0
27	I	I	P	P	P	P	P
28	I	P	S	G 20.0	P	G10.0	G 5.0
29	I	P	P	G 20.0	P	G 20.0	G 10.0
30	S	P	S	P	P	G 20.0	P
31	P	P	P	G 10.0	P	G 5.0	G 6.6
32	P	P	P	G 10.0	P	G 5.0	G 6.6
33	S	S	P	P	P	S	P
34	I	S	S	P	P	P	G 20
35	P	I	G 20.0	P	G	P	P
36	P	I	G 20.0	G 20.0	G 20.0	G 20.0	P
37	I	P	I	G 20.0	G 10.0	G 10.0	G 6.6

Table 1 continued

Compound	Hexane	Water	EtOH	DMSO:H$_2$O (1:1)	DMSO:H$_2$O (1:2)	EtOH:H$_2$O (1:2)
38	S	S	P	G 20.0	G 20.0	P
39	P	UG 20.0	S	UG 20.0	UG 20.0	P
40	I	UG 20.0	UG	P	G 20.0	P
41	I	I	S	P	P	P
42	I	P	G 10.0	G 10.0	G 10.0	S
43	I	P	S	G 20.0	UG 20.0	G 20.0
44	I	P	S	P	P	P
45	I	G 10.0	G 10.0	G 20.0	G 10.0	G 20.0
46	I	I	P	G 20.0	G 20.0	G 10.0
47	I	P	S	UG 20.0	P	P
48	I	UG17.0	S	ND	P	G 15.0
49a	P	UG17.0	S	ND	UG18.0	I
49b	ND	G 21.0	ND	ND	I	P
50	P	P	S	P	P	P

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL; I, insoluble; ND, not determined; C, crystallize or precipitate; S, soluble at ~20 mg/mL.
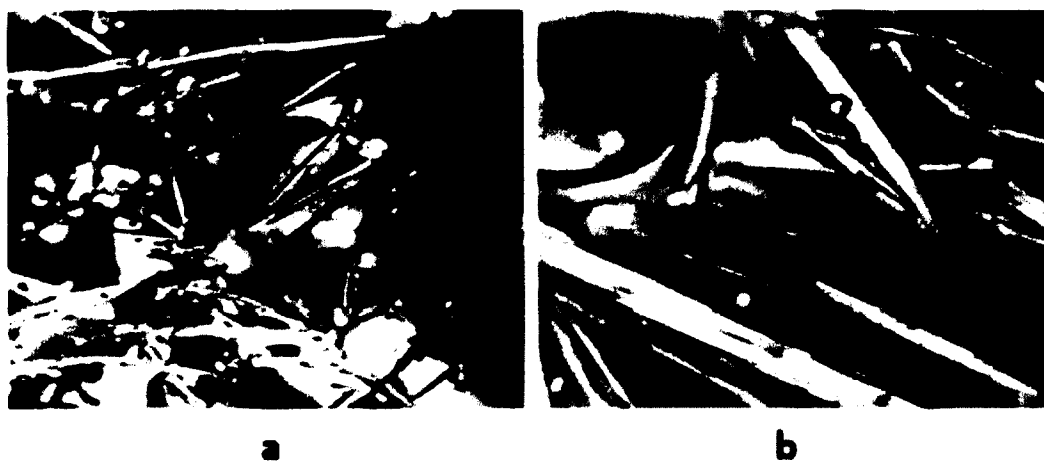
Figure 28. Optical micrographs of the gels formed by compounds **29** (a-b) solvent DMSO:H_2O (1:2) in 10 mg/mL.
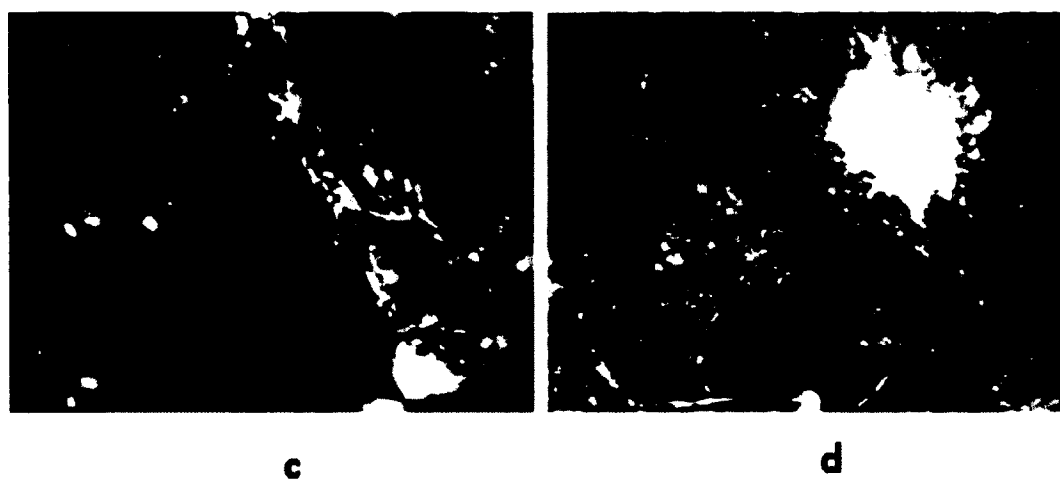
Figure 29. Optical micrographs of the gels formed by compounds **37** (c-d) in solvent DMSO: H2O (1:2) at 6.6 mg/mL.
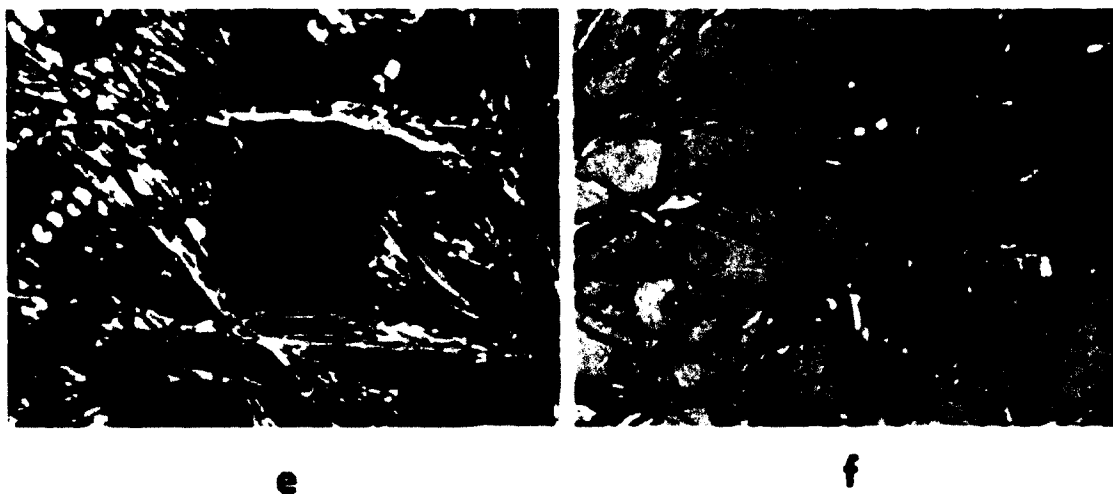
Figure 30. Optical micrographs of the gels formed by compound **32** (c-d) solvent

DMSO:H$_2$O (1:2) at 2.0 mg/mL.
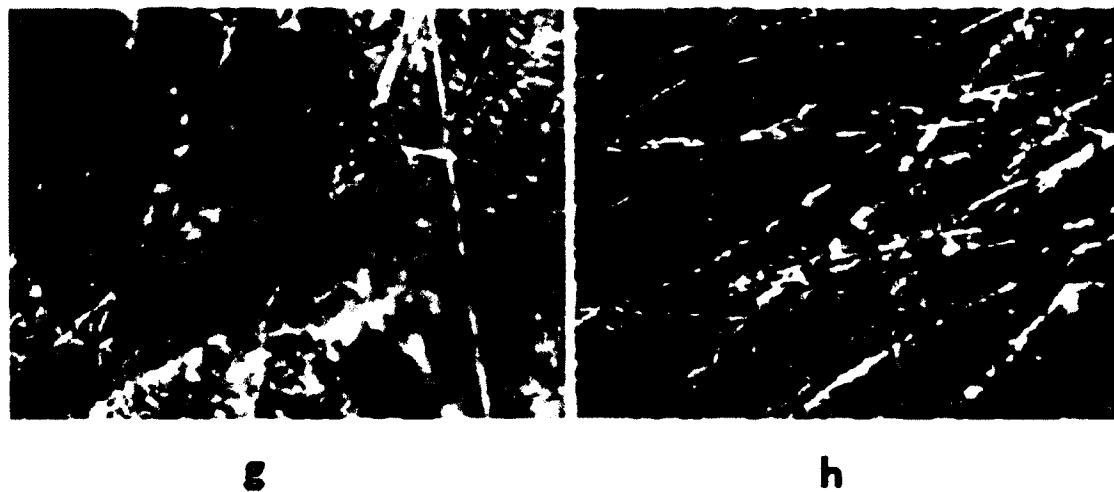
Figure 31. Optical micrographs of the gels formed by compound **32** (e-f) in solvent

EtOH:H$_2$O (1:2) at 2.8 mg/mL.

Figure 31 shows the optical micrographs of several gels. The compound **29** formed gel in DMSO aqueous mixture at 10 mg/mL, which is not a very efficient gelator, the morphology of the gel appeared as rod or sheet like feature (**Figure 28 a-b**). Compound **37** form gel in DMSO/H_2O (1:2) at 0.66 wt% which is a more efficient gelator, and the gels formed thinner fibrous assembly (**Figure 29 c-d**). The compound **32** is the most efficient gelator identified in this study, interestingly the morphology of the self-assembled structures in DMSO/H_2O and EtOH/H_2O both appeared as very long and uniform fibrous assemblies. The DMSO/H_2O gel in the edge part appeared to form a cluster of fibers bundled together during the drying process while in the mild of the sample showed more separated fibers (**Figure 30 e-f**). The EtOH/H_2O gel has shown more uniform fibrous structure with average diameter of 0.5 μm and over 300μm in length (**Figure 31 g-h**). The morphology study indicated that there is certain correlation between the gelation efficiency and the fibrous assemblies.

Table 2. Gel Melting Temperatures

Compound	MGC in DMSO:H_2O (1:2), (mg/mL)	T1 (°C)[a]	T2 (°C)[b]	T3 (°C)[c]
26	20.0	95	100	110
28	5.0	78	80	90
29	10.0	91	95	110
31	6.6	91	110	120
32	2.0	70	75	81
34	20.0	50	52	58
37	6.6	110	118	128

[a)] Temperature at which gel begins to melt.
[(b)] Temperature at which gel is approximately half melted.
[(c)] Temperature at which gel is fully melted.

The melting points were measured at their minimum gelation contractions in $DMSO:H_2O$

(1:2, volume ratio) as shown in table **2**. T1 is the temperature of the initial melting, T2 is

the temperature when the gel is estimated half melted, and T3 is the temperature when the

gel turned to clear. The melting temperature of the gel is estimated based on the

disappearance of the opaqueness of the initial gels. In general, a compound was dissolved

in a small vial at their minimum gelation concentrations and then transferred into a small

tube (such as NMR tube) using a pipette while it was still warm. The tube was then

sonicated and cooled till a stable gel is reformed. The tube was immersed in oil bath and

the temperature of the solid phase to liquid phase transition was monitored using a

thermometer.

These initial structure gelation properties from the focused small library (compounds **25-**

37) helped us to design more efficient gelators and also better understand the tripeptoid

properties in organic/aqueous mixtures. After screening these compounds, the series was

extended to different functionalities (compounds **38-50**), mainly focused on the variation

of acid and amines shown in **Figure 27**. This new peptoid series forms gels, if the

compounds contain the head group amine like **42, 43** and **45**, if there is no head group in

the peptoid system, compounds are not behaving well. Also if the compound contains

electron donor and acceptor functionality such as methoxy and bromo (example

compound **35**), those compounds shows good gelation behaviour. Still we are in a search

for the new class of system which will behave well in both organic/aqueous mixtures by

modifying amine, aldehyde, isocyanides and acid.

For all these compounds the purity was tested by ^{1}H NMR. ^{13}C NMR spectra and LC-MS. For few compounds ^{1}HNMR. ^{13}C NMR spectra were shown in **Figure 32** and **33** and their chemical shift values were discussed in experimental section.

^{1}**H NMR spectra (400 MHz, CDCl$_3$) and ^{13}C NMR spectra (100 MHz, CDCl$_3$):**
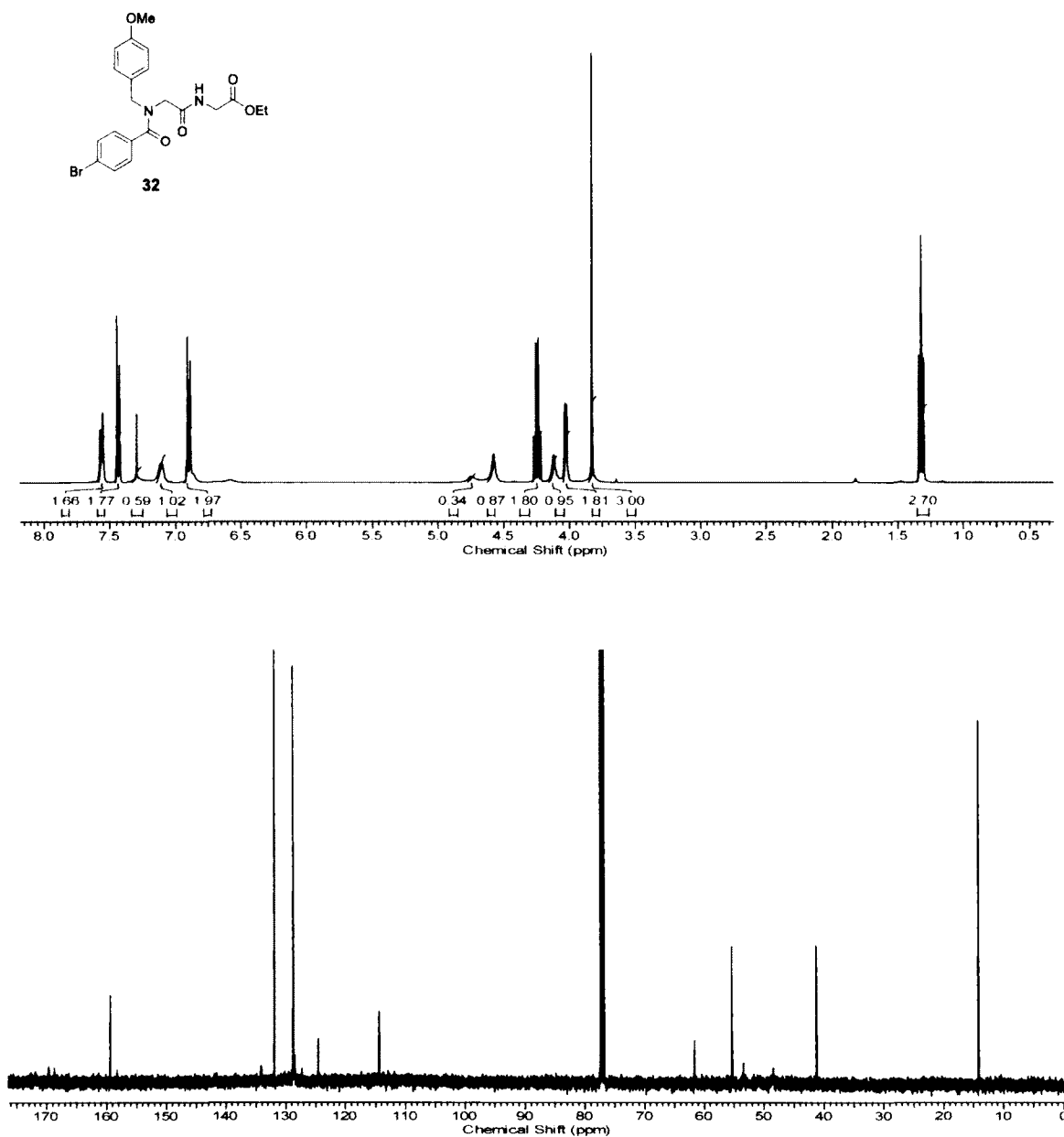
Figure 32. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) for compound **32**
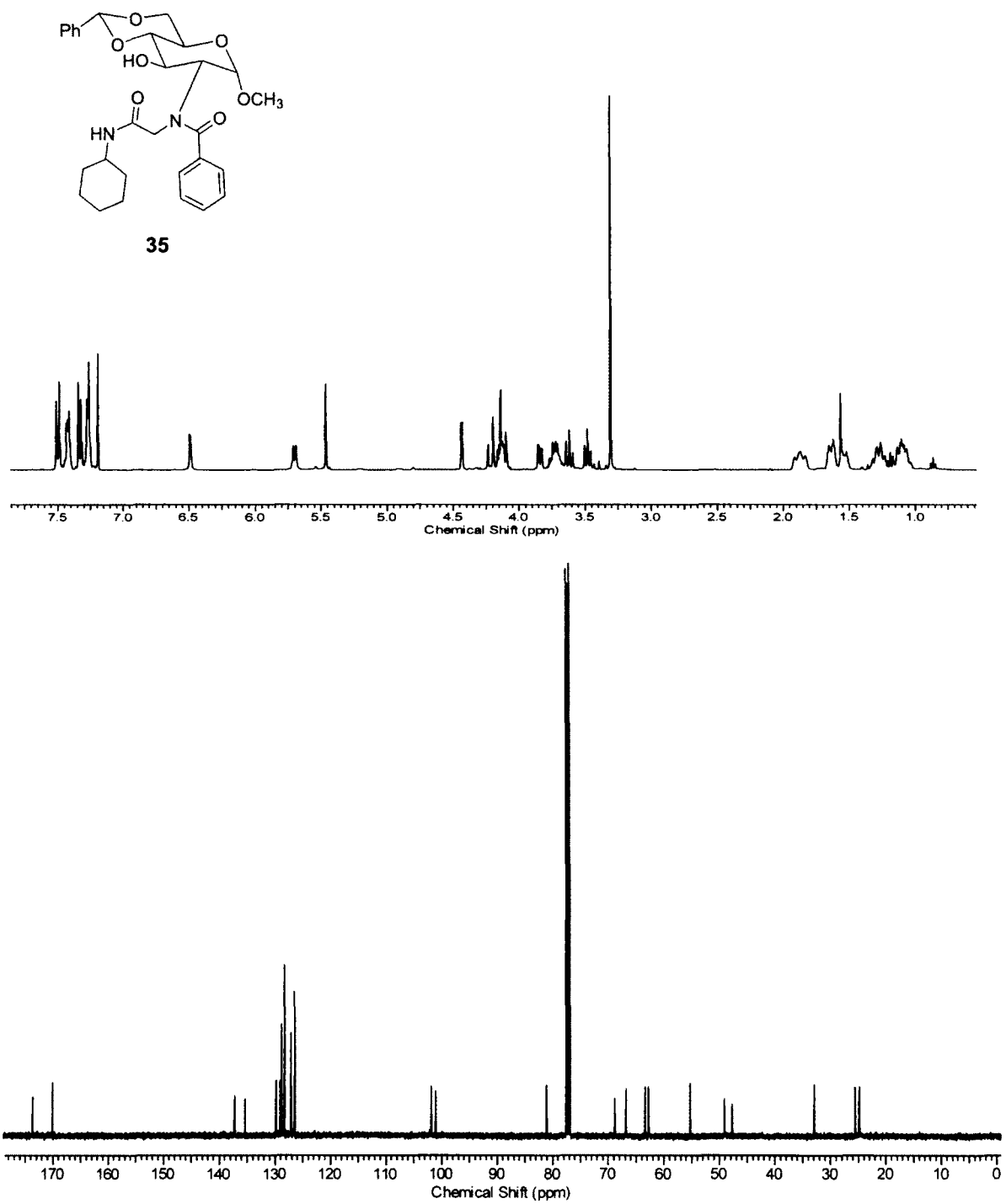
Figure 33. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers), ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) for compound **35.**

These gelators represent a new class of organo/hydrogelators and can have potential applications in medicinal chemistry and in the entrapment and delivery of drugs. These preliminary structure gelation properties from a focused small library can help us to design more efficient gelators and also to better understand the tripeptoids properties in aqueous solutions. Further structure optimization and understanding of the properties and applications of these compounds are ongoing.

2.3. CONCLUSIONS

In summary, we have designed and synthesized a series of low molecular weight tripeptoids by a one-pot Ugi reaction and obtained several effective organo/hydro gelators. These compounds are brand new class of organogelators that have not been reported before. Using MCRs to discover low molecular weight gelators is a novel method that will produce interesting structures with a variety of potential applications. Also the resulting gels should be more resistant to peptidase and this feature may be necessary for certain applications.

2.4. EXPERIMENTAL SECTION

General Methods:

Reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Acros, Fisher etc.) and used directly without any purifications. All reactions, unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. Combiflash chromatography was carried out using silicycle 230-400 mesh silcagel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates,

and visualized using UV light and phosphomolybdic (PMA) staining. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtianed with Bruker 400 MHz spectrometer in CDCl$_3$ with TMS as an internal standard. Proton and carbon spectra chemical shifts were reported using TMS and CDCl$_3$ as internal standard at 0 ppm and at 77.23 ppm, respectively.

General procedure using compound 27 as an example:

Benzyl amine (50 mg, 0.46 mmol) was added to a solution of paraformaldehyde (0.013 g, 0.46 mmol) in methanol (6 mL), the solution was stirred at room temperature for 1h. Then benzoic acid (0.055 g, 0.46 mmol) was added followed by cyclohexyl isocyanide (0.051 g, 0.46 mmol).The reaction was monitored using TLC which indicated completion after 24h. The reaction mixtrure was diluted with DCM (15 mL), washed with water (10 mL), the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified using 60% EtOAc:Hexane. The desired product was obtained as a white solid (0.145 g) in 88% of yield. All other compounds were synthesized by a similar procedure. The following are their characterization data.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)acetamide (25):

The pure compound was obtained as a white solid with 0.112 g (83 %), m.p. 122.0-124.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 0.82 (m, 2H), 1.07 (m, 4H), 1.26 (m, 4H),1.59 (m, 7H), 1.75 (m, 3H), 2.05 (s, 1H), 2.13 (s, 3H), 3.62 (m, 1H), 3.82 (s, 1H), 3.85 (s, 2H), 4.54 (s, 1H), 4.58 (s, 2H), 5.47 (d, J = 7.2 Hz, 1H), 6.15 (d, J = 7.2 Hz, 1H), 7.08 (m, 2H), 7.20-7.31 (m, 6H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ

21.4, 21.7, 24.7, 24.8, 25.3, 25.5, 32.7, 32.8, 48.1, 48.2, 50.5, 50.7, 52.5, 53.3, 126.6, 127.9, 128.0, 128.6, 129.0, 129.1,135.8, 137.0, 166.8, 167.9, 171.5, 171.9. HRMS (ESI+) calcd for $C_{17}H_{24}N_2O_2$ [M+Na]$^+$ 311.1729; found 311.1727.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)pent-4-ynamide (26):

The pure compound was obtained as a white solid with 0.109 g (71 %), m.p. 138.0-140.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 0.93 (qd, J = 11.8 Hz, 1H), 1.14 (m, 3H), 1.34 (m, 3H), 1.68 (m, 6H), 1.87 (m, 2H), 1.99 (m, 1H), 2.58 (m, 2H), 2.69 (m, 2H), 3.71 (m, 1H), 3.92 (s, 1H), 3.97 (s, 2H), 4.65 (s, 1H), 4.70 (s, 2H), 5.58 (d, J = 8.0 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.34 (m, 5H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 14.5, 14.7, 24.7, 24.8, 25.3, 25.5, 31.9, 32.3, 32.8, 32.9, 48.1, 48.4, 50.7, 50.9, 51.5, 52.4, 69.0, 69.1, 126.5, 127.9, 128.0, 128.6, 129.0, 135.6, 136.8, 166.7, 167.7, 171.9, 172.4. HRMS (ESI+) calcd for $C_{20}H_{26}N_2O_2$ [M+Na]$^+$, 349.1886; found 349.1884.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (27):

The pure compound was obtained as a white solid with 0.145 g (88 %), m.p. 104.0-106.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.10 (m, 4H),1.28 (m, 3H), 1.60 (m, 4H),1.78 (m, 3H), 3.66 (m, 2H), 3.96 (s, 2H), 4.57 (s, 2H), 4.72 (s, 1H), 5.59 (br, 1H), 6.29 (br, 1H), 7.11(m, 2H), 7.22-7.41 (m, 15H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 24.7, 25.5, 32.9, 48.1, 49.4, 54.0, 126.8, 127.1, 127.9, 128.6, 128.9, 130.1, 135.2, 135.9, 167.7, 172.9. HRMS (ESI+) calcd for $C_{22}H_{26}N_2O_2$ [M+Na]$^+$, 373.1886 found 373.1882.

N-benzyl-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (28):

The pure compound was obtained as a white solid with 0.165 g (82 %), m.p. 168.0-170.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.06 (m, 5H), 1.26 (m, 4H),

1.58 (m, 6H), 1.77 (m, 4H), 3.65 (m, 2H), 3.93 (s, 2H), 4.54(s, 2H), 4.66 (s, 1H), 5.78(br.

s, 1H), 6.22 (br. s, 1H), 7.18-7.33 (m, 9H), 7.43 (d, J = 7.5 Hz, 2H). ^{13}C (100 MHz,

CDCl$_3$): (mixture of rotamers) δ 24.7, 25.4, 32.9, 48.2, 48.4, 49.2, 49.7, 51.7, 54.0, 124.5,

127.0, 127.9, 128.6, 128.9, 131.8, 134.1, 135.8, 167.3, 171.8. HRMS (ESI+) calcd for

C$_{22}$H$_{25}$N$_2$O$_2$Br [M+Na]$^+$, 451.0991; found 451.0997.

N-benzyl-N-(2-(cyclohexylamino)-2-oxoethyl)-4-nitrobenzamide (29):

The pure compound was obtained as a white solid with 0.162 g (87 %), m.p. 190.0-192.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.10 (m, 10H), 1.67 (m, 10H),

3.59 (s, 1H), 3.68 (m, 2H), 3.98 (s, 2H), 4.52 (s, 2H), 4.73 (s, 1H), 5.22 (s, 1H), 5.89 (d, J

= 4.8 Hz, 1H), 7.08 (d, J = 6.5 Hz, 2H), 7.28 (m, 7H), 7.58 (d, J = 8.0 Hz, 2H), 7.63 (d, J

= 7.5 Hz, 2H), 8.17 (m, 2H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 24.7, 25.3,

25.4, 25.5, 30.5, 33.0, 48.4, 48.9, 53.9, 123.9, 126.9, 127.9, 128.0, 128.1, 128.2, 128.6,

128.7, 129.0, 129.1, 135.3, 141.4, 148.6, 166.8, 170.6. HRMS (ESI+) calcd for

C$_{22}$H$_{25}$N$_3$O$_4$ [M+Na]$^+$, 418.1737; found 418.1741.

(R)-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)-N-(1-phenylethyl)benzamide (30):

The pure compound was obtained as a white solid with 0.131 g (71 %), m.p. 140.0-142.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.09 (m, 3H), 1.27 (m, 3H),

1.48 (m, 2H), 1.55 (s, 2H), 1.56 (s, 3H), 1.75 (m, 2H), 3.37 (m, 2H), 3.63 (s, 3H), 4.15 (d,

J = 14.6 1H), 4.50 (s, 1H), 6.40 (br. s, 1H), 7.13 (br, 1H), 7.23 (m, 2H), 7.27 (m, 5H),

7.50 (m, 2H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 17.9, 24.6, 25.5, 32.7, 32.8,

47.1, 48.0, 57.6, 64.2, 124.2, 126.7, 127.0, 128.0, 128.7, 128.9, 132.0, 134.7, 139.1,

168.3, 171.8. HRMS (ESI+) calcd for C$_{23}$H$_{27}$N$_2$O$_2$Br [M+Na]$^+$, 465.1148; found

465.1156.

N-(4-methoxybenzyl)-4-bromo-N-(2-(cyclohexylamino)-2-oxoethyl)benzamide (31):

The pure compound was obtained as a white solid with 0.132 g (79 %), m.p. 174.0-176.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.09 (m, 4H), 1.29 (q, J = 12.0

Hz, 3H), 1.58 (m, 5H), 1.79 (m, 3H), 3.67 (m, 2H), 3.73 (s, 3H), 3.93 (s, 2H), 4.48 (s,

2H), 4.64 (s, 1H), 6.11 (d, 1H), 6.80 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 5.3 Hz, 2H), 7.29 (d,

J = 8.3 Hz, 2H), 7.46 (d, J =7.8 Hz, 2H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ

24.71, 24.74, 25.4, 48.2, 49.2, 53.5, 55.3, 114.3, 124.5, 128.4, 128.6, 131.8, 159.4, 167.4,

171.7. HRMS (ESI+) calcd for C$_{23}$H$_{27}$N$_2$O$_3$Br [M+Na]$^+$, 481.1097; found 481.1103.

Ethyl 2-(2-(N-(4-methoxybenzyl)-4-bromobenzamido)acetamido)acetate (32):

The pure compound was obtained as a white solid with 0.112 g (66 %), m.p.123.0-125.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers)) δ 1.23 (m, 3H), 3.82 (s, 3H),

4.02 (d, J = 5.3 Hz, 2H), 4.12 (br, s, 2H), 4.24 (q, J = 7.0 Hz, 2H), 4.57 (br, 2H), 6.89 (m,

2H), 7.13 (d, J = 5.0 Hz, 2H), 7.43 (m, 2H), 7.56 (d, J = 8.0 Hz, 2H). ^{13}C (100 MHz,

CDCl$_3$): (mixture of rotamers) δ 14.1, 41.2, 48.4, 53.4, 55.3, 61.6, 114.3, 124.5, 128.4,

128.7, 131.8, 134.0, 134.1, 158.2, 159.4, 168.6, 169.6, 171.9. HRMS (ESI+) calcd for

C$_{21}$H$_{23}$BrN$_2$O$_5$ [M+Na]+ , 485.0682; found 485.0680.

Ethyl 2-(2-(N-benzylbenzamido)acetamido)acetate (33):

The pure compound was obtained as a light yellow oil with 0.134 g (81). ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.22 (m, 3H), 3.67 (s, 2H), 3.91 (d, J = 3.5 Hz, 2H), 4.04 (br, s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 4.57 (br. s, 2H), 4.74 (s, 1H), 6.90 (s, 1H), 7.12 (s, 2H), 7.21-7.35 (m, 8H), 7.44 (m, 2H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 14.2, 41.0, 41.2, 48.6, 52.3, 53.9, 61.5, 126.9, 127.1, 127.9, 128.6, 128.9, 130.2, 135.1, 135.8, 168.9, 169.6, 173.0. HRMS (ESI+) calcd for; C$_{20}$H$_{22}$N$_2$O$_4$ [M+Na]$^+$, 377.1471; found 377.1471.

Ethyl 2-(2-(N-(4-methoxybenzyl)benzamido)acetamido)acetate (34):

The pure compound was obtained as a white solid with 0.094 g (67 %), m.p. 94.0-96.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of rotamers) δ 1.22 (m, 3H), 3.72 (s, 3H), 3.92 (d, J = 5.3 Hz, 2H), 4.04 (br, s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 4.57 (br, 2H),6.79 (d, J = 8.5 Hz, 2H), 6.99 (m, 1H), 7.03 (d, J = 5.5 Hz, 2H), 7.34 (m, 3H), 7.44 (m, 2H). ^{13}C (100 MHz, CDCl$_3$): (mixture of rotamers) δ 14.1, 41.2, 48.4, 53.4, 55.3, 61.5, 114.2, 126.9, 127.5, 128.3, 128.6, 130.0, 130.1, 133.1, 135.2, 159.3, 168.9, 169.6, 172.9. HRMS (ESI+) calcd for C$_{21}$H$_{24}$N$_2$O$_5$ [M+Na]$^+$, 407.1577; found 407.1575.

N-(2-(cyclohexylamino)-2-oxoethyl)-N-(8-hydroxy-6-methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxin-7-yl)benzamide (35)

The pure compound was obtained as a white solid with 0.083 g (89 %), m.p. 261.0-263.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (m, 3H), 1.27 (m, 2H), 1.58 (m, 3H), 1.87 (dd, J = 18.6, 14.1Hz, 2H), 3.30 (s, 3H), 3.46 (t, J = 9.2 Hz, 1H), 3.59 (m, 1H), 3.72 (m, 2H),

3.90 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.12 (m, 2H), 4.17 (d, *J* = 4.8 Hz, 2H), 4.45 (d, *J* = 3.5

Hz, 1H), 5.44 (s, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 1.5 Hz, 1H), 7.26 (dd, *J* = 5.0,

1.8 Hz, 3H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.42 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H). ^{13}C (100

MHz, CDCl$_3$): δ 24.6,25.4, 32.9, 47.6, 49.0, 55.2, 62.7, 63.3, 66.6, 68.7, 80.9, 100.8,

101.7, 124.1, 126.3, 128.2, 128.8, 129.0, 132.0, 134.0, 137.1, 169.7, 172.5. HRMS

(ESI+) calcd for C$_{29}$H$_{36}$N$_2$O$_7$ [M+Na]$^+$, 547.2414; found 547.2420.

4-Bromo-N-(2-(cyclohexylamino)-2-oxoethyl)-N-(8-hydroxy-6-methoxy-2-phenyl-hexahydropyrano[3,2-d][1,3]dioxin-7-yl)benzamide (36)

The pure compound was obtained as a white solid with 0.098 g (91 %), m.p. 291.0-293.0

°C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.1 (m, 3H), 1.26 (m, 2H), 1.53 (m, 1H), 1.62 (m,

2H), 1.87 (m, 2H), 3.31 (s, 3H), 3.48 (m, 1H), 3.62 (m, 1H), 3.73 (m, 2H), 3.84 (dd, *J* =

9.9, 3.6 Hz, 1H), 4.15 (m, 4H), 4.44 (d, *J* = 3.5 Hz, 1H), 5.46 (s, 1H), 5.78 (d, *J* = 8.0 Hz,

1H), 6.49 (d, *J* = 1.5 Hz, 1H), 7.27 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.33 (d, *J* = 8.3, 2H), 7.42

(m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H). ^{13}C (100 MHz, CDCl$_3$): δ 24.7, 25.4, 32.84, 32.89,

47.6, 48.9, 55.2, 62.6, 63.3, 66.7, 68.7, 80.9, 100.9, 101.7, 126.3, 127.0, 128.2, 128.7,

129.0, 129.7, 135.2, 137.1, 169.9, 173.5. HRMS (ESI+) calcd for C$_{29}$H$_{35}$N$_2$O$_7$Br

[M+Na]$^+$, 625.1519; found 625.1530.

Ethyl 2-(2-(4-bromo-N-(8-hydroxy-6-methoxy-2-phenyl-hexahydropyrano [3,2-] [1,3]dioxin-7-yl)benzamido)acetamido)acetate (37)

The pure compound was obtained as a white solid with 0.065 g (61 %), m.p. 207.0-

209.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.26 (m, 3H), 3.31 (s, 3H), 3.44 (m, 1H), 3.61

(m, 1H), 3.73 (m,1H), 3.82 (dd, J = 10.0, 3.5 Hz, 1H), 3.90 (dd, J = 18.3, 3.3 Hz, 1H),

4.08 (m, 2H), 4.15 (m, 4H), 4.32 (m, 2H), 4.47 (d, J = 3.5 Hz, 1H), 5.44 (s, 1H), 6.05 (d,

J = 2.0 Hz, 1H), 6.66 (m 1H), 7.26 (dd, J = 4.9, 1.9 Hz, 3H), 7.21 (d, J = 8.3 Hz, 2H),

7.40 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H). ^{13}C (100 MHz, CDCl$_3$): δ 14.1, 41.6, 47.0, 55.2,

61.8, 62.5, 63.3, 66.6, 68.7, 81.0, 100.7, 100.8, 124.2, 126.3, 128.2, 128.8, 129.1, 132.0,

134.0, 137.0, 169.6, 170.9, 172.6. HRMS (ESI+) calcd for $C_{27}H_{31}BrN_2O_9$ [M+Na]+ ,

629.1105; found 629.1103.

CHAPTER 3

SYNTHESIS OF A NEW CLASS OF SUGAR TRIAZOLE DERIVATIVES AS MOLECULAR GELATOR BY CLICK REACTION

3.1. INTRODUCTION

Low molecular mass organic/hydro gelators (LMOGs/LMHGs) are a new class of soft materials capable of numerous possible applications. Low molecular weight hydrogels are a common class of biomaterials utilized in a wide range of applications including as tissue engineering scaffolds, drug delivery vehicles. As a result, there is a tremendous amount of work focused in finding gelling materials.[1,2a-c] Small molecules that can self-assemble in organic solvents or water and form typically fibrous supramolecular architectures that immobilize the solvents to form organo/hydrogels. The main driving forces for supramolecular gelation are non-covalent forces such as hydrogen bonding, hydrophobic interactions, π-π stacking, and van der Waals forces, etc.[109-111]

Because gelation by LMWGs occurs through non-covalent interactions, the modification of the chemical structures of gelators is expected to affect the noncovalent interactions and consequently the properties of the corresponding gels. Intermolecular interactions, such as π-π stacking, H bonding, and hydrophobic interactions can be modulated to entrap solutes and/or solvent molecules within the supramolecular network of a gel.[112]

Low molecular weight gelators have wide variety interesting applications. Because of their interesting applications, a great deal of effort has been devoted to studying new types of low molecular weight gelators.[118-123] Organo/hydro gelators obtained from bio-based starting materials such as amino acids and carbohydrates will in general produce biocompatible materials or degradation products.[124-130]

From the time when its origin by Sharpless in 2001, the concept of click chemistry has been promptly adopted by many disciplines, perhaps most notably in materials science. From last decade triazoles have been shown to be able to self-assemble and form fibrous networks and recently a few triazole hybrids have been shown to function as hydrogelators.[113-117]

3.2. RESULTS AND DISCUSSIONS

Scheme 13. Synthesis of azide from N-acetylglucosamine
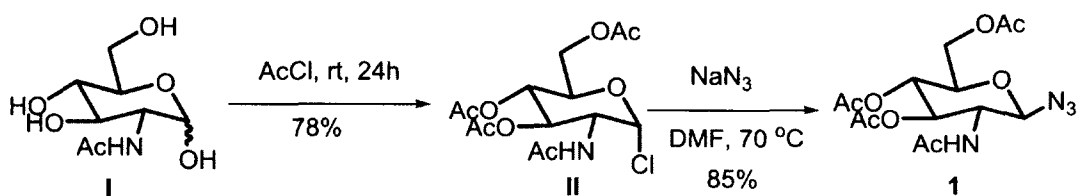
Scheme 14. Synthesis of sugar triazoles from compound **1**

Table 3. Gelation test results for the library compounds

Compound	Hexa-ne	Tolu-ene	i-PrOH	EtOH	EtOH:H₂O (1:1)	EtOH:H₂O (1:2)	DMSO:H₂O (1:1)	DMSO:H₂O (1:2)	H₂O
4	I	S	S	S	S	S	S	S	S
5	I	S	S	S	S	S	S	S	S
6	I	S	S	S	S	S	S	S	S
7	I	S	S	S	S	S	S	S	S
8	I	G 2.0	S	S	S	S	S	S	S
9	I	G 1.7	S	S	S	S	S	S	S
10	I	I	P	S	P	P	P	G 4.0	G 2.8
11	I	G 2.8	S	S	G 10.0	G 10.0	S	G 20.0	G 4.0
12	I	G 5.0	S	P	P	G 6.7	G 10.0	G 2.2	P
13	I	S	S	S	G 2.5	G 2.8	G 10.0	G 2.2	G 2.2
14	I	S	S	S	G 3.3	G 6.6	G 2.2	G 1.9	G 2.0
15	I	S	S	S	G 2.2	G 6.6	G 2.0	G 1.7	G 10.0
16	I	I	P	G 10.0	G 5.0	G 5.0	G 2.5	G 3.3	P
17	I	S	G 20.0	P	P	P	P	P	I

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL; I, insoluble; C, crystallize or precipitate; S, soluble at 20 mg/mL.

As Shown in **Scheme 14** the click chemistry is very capable of producing triazoles when reacting azide and alkyne in presence of Cu (I) and sodium ascorbate. Sodium ascorbate reduces copper (II) to copper (I) by change to H_2A in solution.[117d] This is a perfect reaction for exploring structure diversity and the discovery of novel scaffolds for drugs or new materials.[113-117]

In this study, in order to obtain the structure features of simple glucosamine derivatives for effective gelators, we synthesized and screened a small library of compounds using the click reaction. From the peracetylated glucosamine azide **1** by coupling with various alkynes, a library of triazole derivatives are obtained readily. The selection of the alkyne functional groups is based on their polarity and availability of starting materials. As shown in **Scheme 14**, we synthesized compounds **4-17**, which include the typical functional groups such as amine (**4**), alcohols (**5-10**) and aryl groups (**12-13**) and alkyl groups (**14-16**) by coupling with the corrections monoalkyne. Compound **17** was synthesized using a dialkyne starting material. These compounds were then tested for their gelation properties in several solvents. The results are shown in **Table 3**.

As shown in **Table 3**, at 20 mg/mL, all of these compounds were insoluble in hexane. But four compounds were able to gelate toluene, the short chain alchohol derivatives **8, 9**, and the acid, aryl analogy **11, 12**. A majority of the compounds were soluble in ethanol and isopropanol, only two compounds were able to form gels in the alcohols. The dimer **17** formed a gel in isopropanol and the long alkyl chain derivatives **16** formed a gel in

ethanol. Though they are no effective gelators for alcohols, we were pleased to find that many of the compounds were efficient gelators for aqueous mixtures of ethanol or DMSO, and four compounds are also effective hydrogelators. When the R group contains non-polar functional groups typically the products are able to form gels in the aqueous mixtures.

Figure 34 shows the optical micrographs of the gels formed by compounds **10** and **14**. These images are taken while the gels still contain solvents. As a general feature, these various gelators formed self-assembled fibrous networks. Compound **10** formed an opaque gel in water at 2.8 mg/mL, the morphology (**Figure 34a-c**) shows continuous fibrous assemblies. The hydrogel formed by compound **14** also exhibit self-assembled fibrous features and fibers or tubules have larger diameters (**Figure 34d-f**) the compound **14** formed gel in water showed uniform fibers or tubules, these fibers appeared to have similar widths and are less branched.

Figure 34. Optical micrographs of the gels formed by compound **10** (a-c) in H_2O 2.8

mg/mL and compound **14** (d-f) in H_2O 2.0 mg/mL.
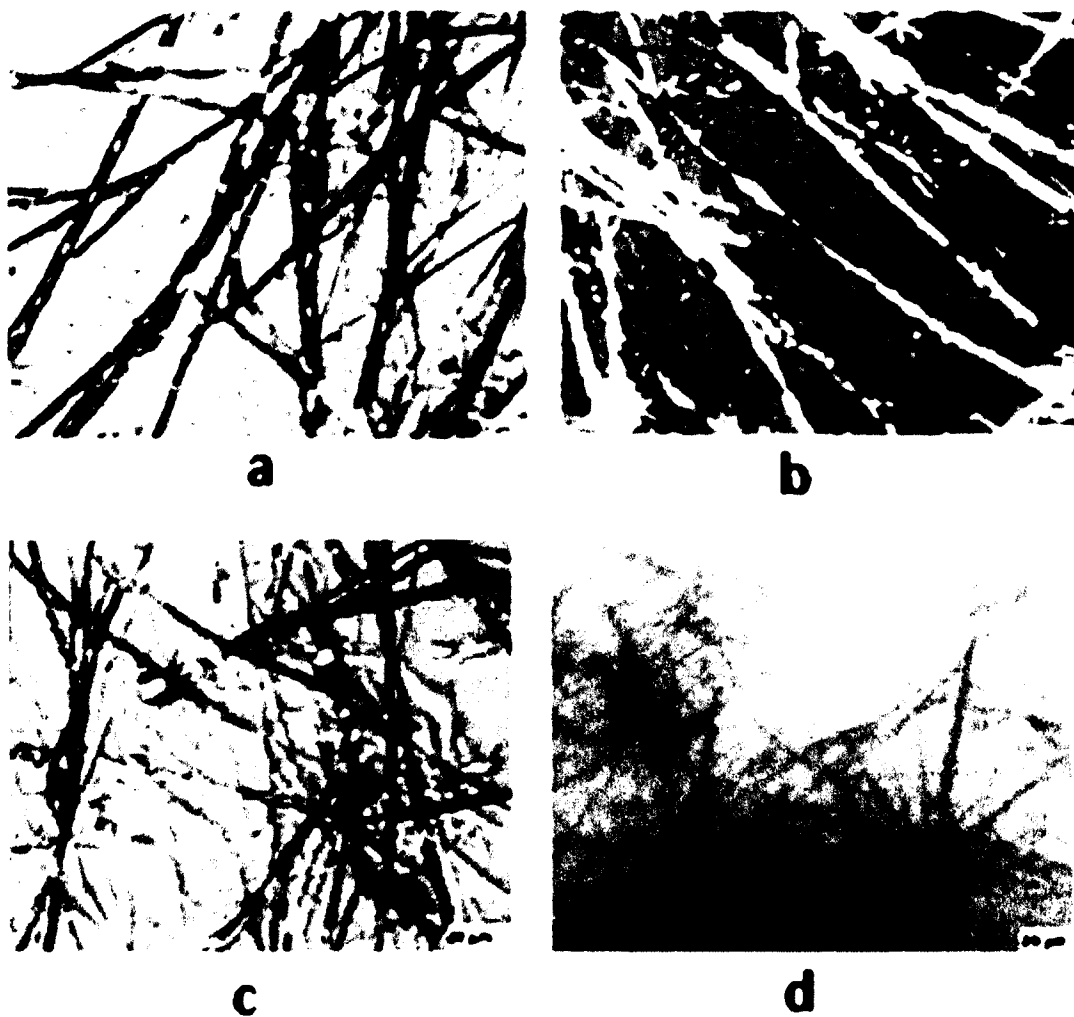
Figure 34 continued

e

f
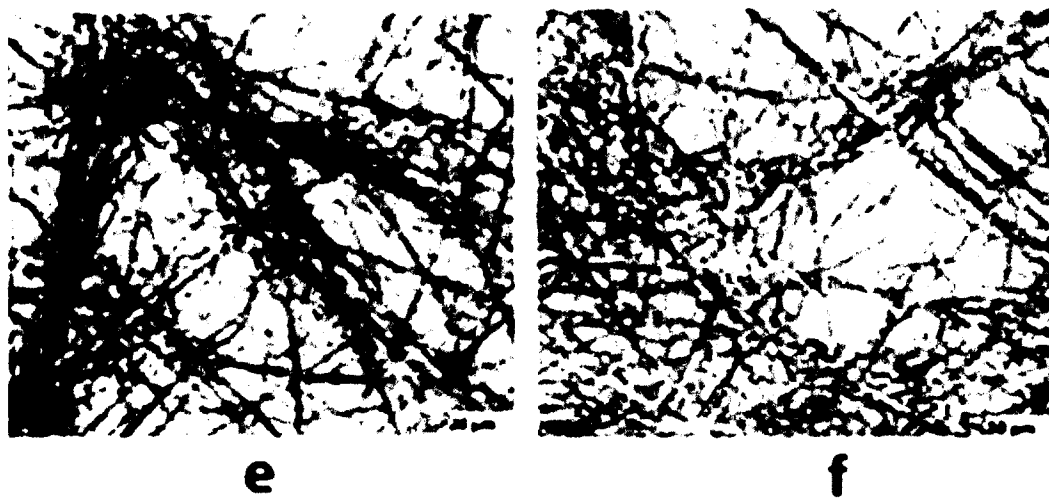
We have also studied the dynamic rheology sweep. In **Figure 35** the dynamic moduli G'

and G" are shown as a function of angular frequency ω at their minimum gelation

concentrations for compounds **10, 13** and **15**. From the **Figure 35**, observed that the

storage modulus G' is greater than the Loss modulus G" for all these compounds and

these compounds have high shear stress. The apparent rise of G' at high frequencies for

these compounds is an experimental artifact of the 25mm peltier plate geometry on the

DISCOVER HR-2 rheometer (gap loading limit) and is observed for all low viscosity

liquids.
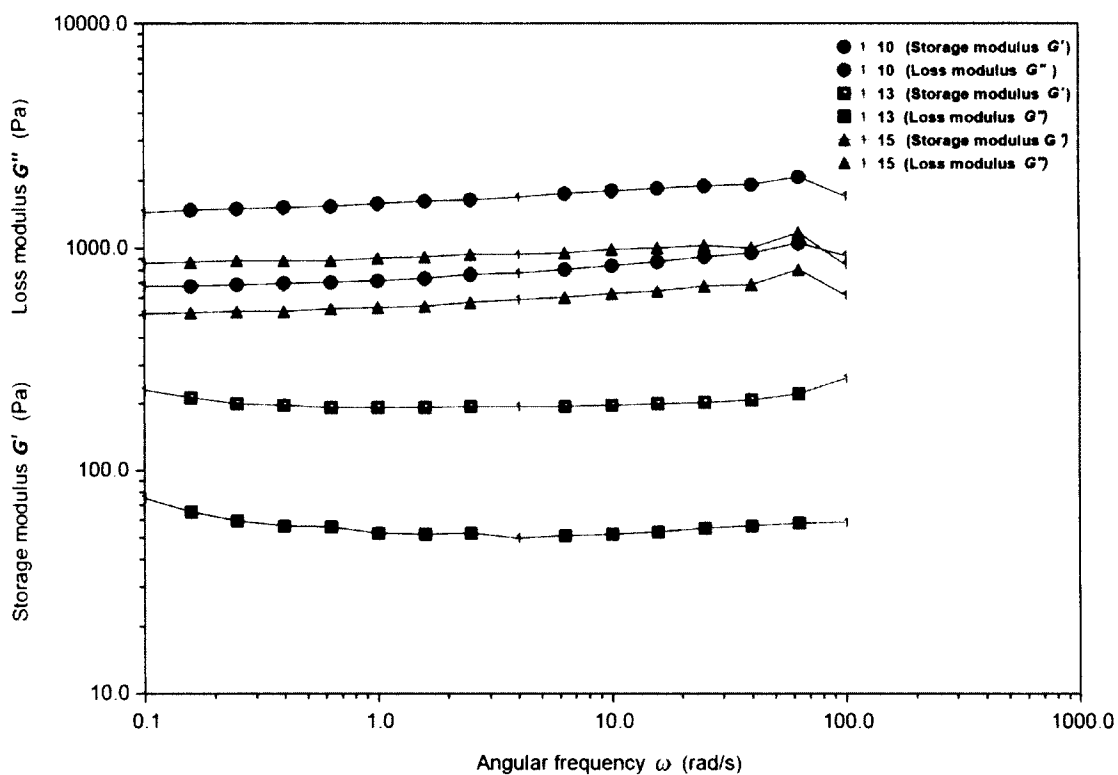
Figure 35. Viscoelastic properties of the gels formed by compounds **10** (H_2O, 2.8 mg/mL), **13** (H_2O, 2.2 mg/mL) and **15** ($DMSO:H_2O$, 1:1, 2.0 mg/mL) at their minimum gelation concentration.

After synthesizing the N-Acetyl glucosamine, we have chosen a simple starting material D-glucose for the synthesis of triazole. A series of available terminal alkyne containing alcohols, acid and free alkyne chin have chosen for this synthesis.

Scheme 15. Synthesis of sugar azide from D-glucose
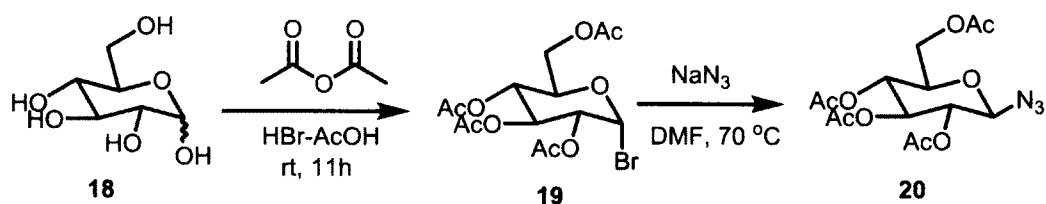
As shown in **Scheme 15**, the azide can be synthesized from the two step process from D-glucose, we fixed the azide starting material similar to previous system and altered the various alkynes (**Scheme 16**). Among the various building blocks we chose terminal acids and alcohols for the contribution of hydrogen bonding and the aliphatic chain for hydrophobic interactions.

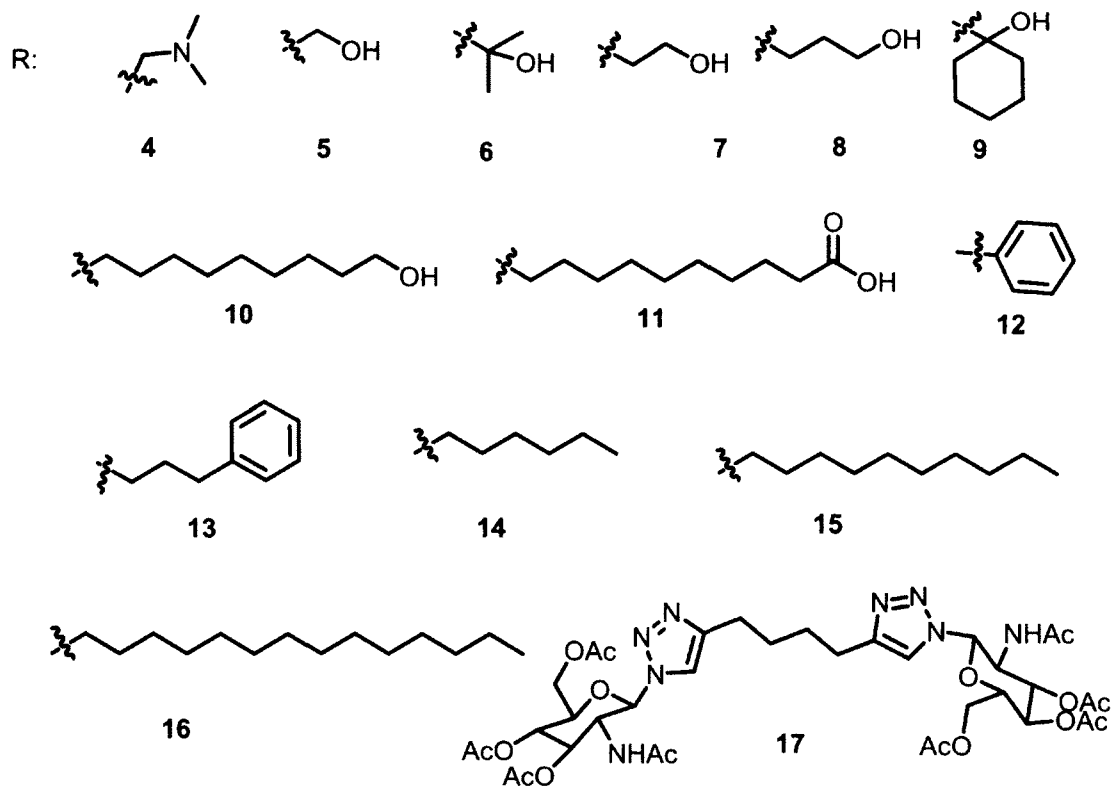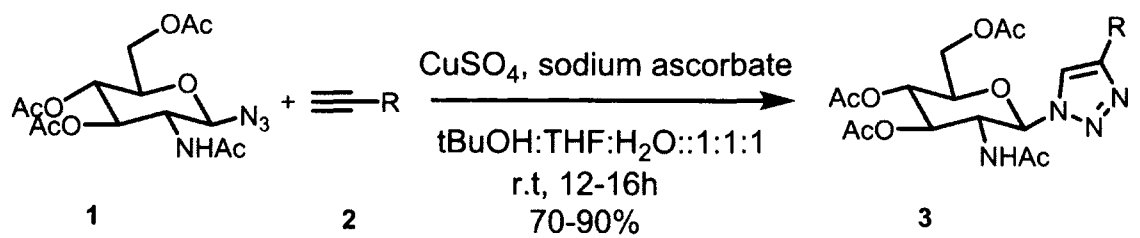**Scheme 16.** Synthesis of sugar tiazoles from compound **20**
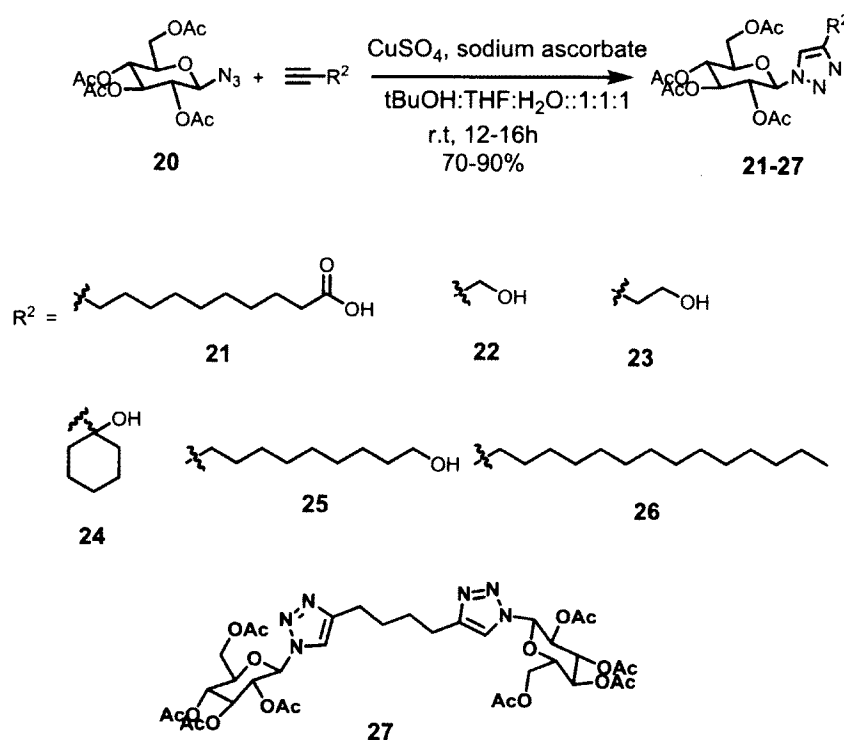
Table 4. Gelation test results for the library compounds

Compound	Hex-ane	Toluene	i-PrOH	EtOH	EtOH:H₂O (1:1)	EtOH:H₂O (1:2)	DMSO:H₂O (1:1)	DMSO:H₂O (1:2)	Water
21	I	S	S	S	S	P	G 6.6	G 2.5	S
22	I	S	S	S	S	S	S	S	S
23	I	G 20.0	S	S	S	S	S	S	S
24	I	S	P	S	G 10.0	G 6.6	G 10.0	G 6.6	P
25	I	S	S	S	S	G 6.6	G 2.0	G 2.5	G 4.0
26	I	S	P	P	S	P	G 10.0	P	S
27	I	G 6.6	P	G 10.0	G 20.0	G 5.0	P	P	P

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL; I, insoluble; C, crystallize or precipitate; S, soluble at ~20 mg/mL.
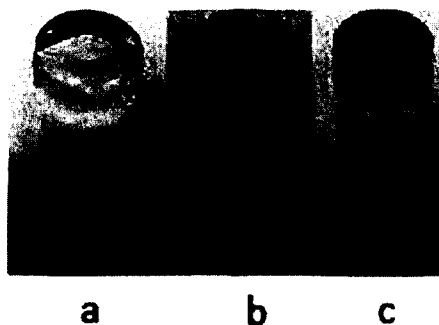
Figure 36. a) A clear gel formed by compound **22** in DMSO/H$_2$O (v1:2) at 2.5 mg/mL; b) A translucent/opaque gel formed by compound **28** in DMSO/H$_2$O (v1:2) at 2.5 mg/mL; c) A translucent/opaque gel compound **33** in EtOH/H$_2$O (v1:2) at 5.0 mg/mL.

The gels formed by these triazoles are typically translucent to opaque, some photographs of the typical gels are shown in **Figure 36**. The best performing compound is **25**, which forms gels at 0.40 wt% in water and also in the combination of organic and aqueous mixtures. Compound **25** forms nice gels because of the presence of long aliphatic chain and also the hydroxy group. Hydroxyl group will provide H-bonding and long aliphatic chain provides the hydrophobic interactions between the molecules in case of compound **25**.

Figure 37. The optical micrographs of the wet gel samples from several amides. a-c) a

gel formed by compound **25** in H_2O at 4.0 mg/mL. d) a gel formed by compound **22** in

DMSO:H_2O(1/2) at **2.5** mg/mL.

a

b

Figure 37 Continued
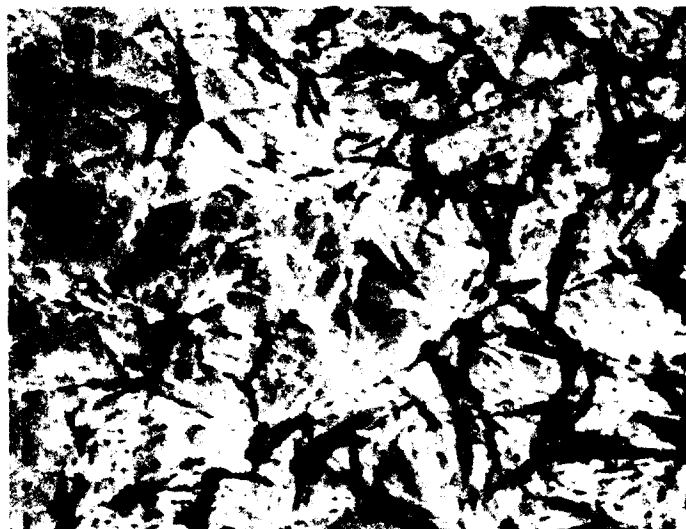
c

d

From the table **4**, we can see that compound **24** forms gel in organic/aqueous mixtures, this result the presence of cyclohexyl ring in the system. This result is similar our previous work.[30-34]because cyclohexyl ring provides strong hydrophobic interactions. We have also synthesized the dimerized compound **27** to study the effect of dimerization in

formation of gels. This compound is also forms nice gel in EtOH/water mix. the photograph of gel is shown in **Figure 36**.

The optical micrographs of the gels formed by compounds **22** and **25** were shown in **Figure 37**. These images are taken while the gels still contain solvents. As a general feature, these various gelators formed self-assembled fibrous networks. Compound **25** formed an opaque gel in water at 2.8 mg/mL, the morphology (**Figure 37a-c**) shows continuous fibrous assemblies. The assemblies are composed of many long, curvy, thin and uniform fibrous networks. The gels formed by compound **22** also exhibit self-assembled fibrous features and fibers or tubules have larger diameters **Figure 37 (d)**.
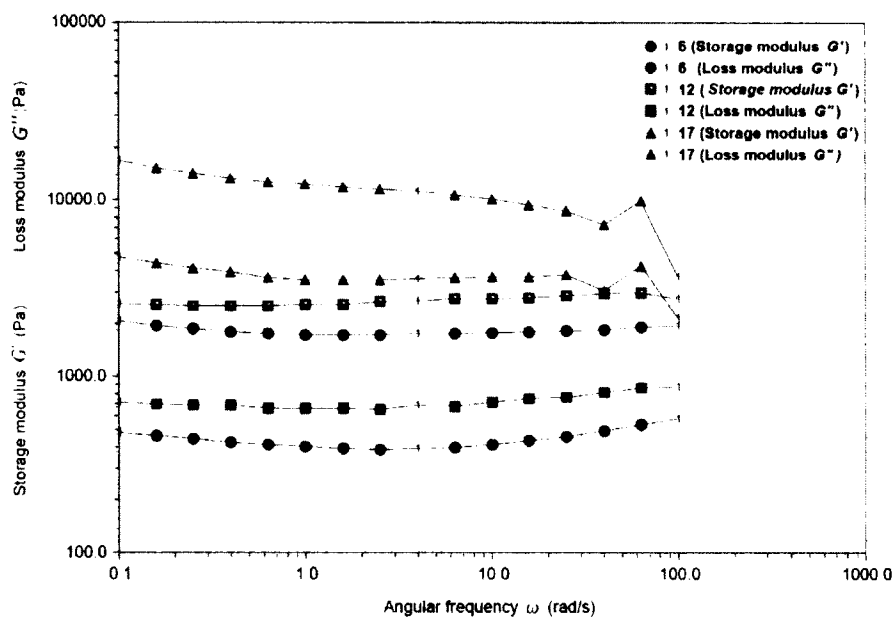
Figure 38. The viscoelastic measurement of the gels formed by compounds **21** (DMSO/H$_2$O,1/2) at 6.6 mg/mL), **25** (DMSO/H$_2$O.1/2) at 2.5 mg/mL, and urea **27** (EtOH/H$_2$O, 1/2) at 5.0 mg/mL.

We then studied the stability and elastic properties of several gels by rheology, the results are shown in **Figure 38**. For the gels formed by compounds **21**, **25** and **27**, compound **27** have the high G'/G" value than the compound **21** and **27**. This result indicated all the gels are stable and have elastic properties with the strong hydrophobic interaction between the molecules.

For all these compounds the purity was tested by ^{1}H NMR, ^{13}C NMR spectra and LC-MS. For few compounds spectra's were shown in **Figure 39**, **40**, **41**, **42** and **43**. Their chemical shift values were discussed in experimental section.

^{1}H NMR spectra (400 MHz, CDCl$_3$) and ^{13}C NMR spectra (100 MHz, CDCl$_3$):

Compound 13:
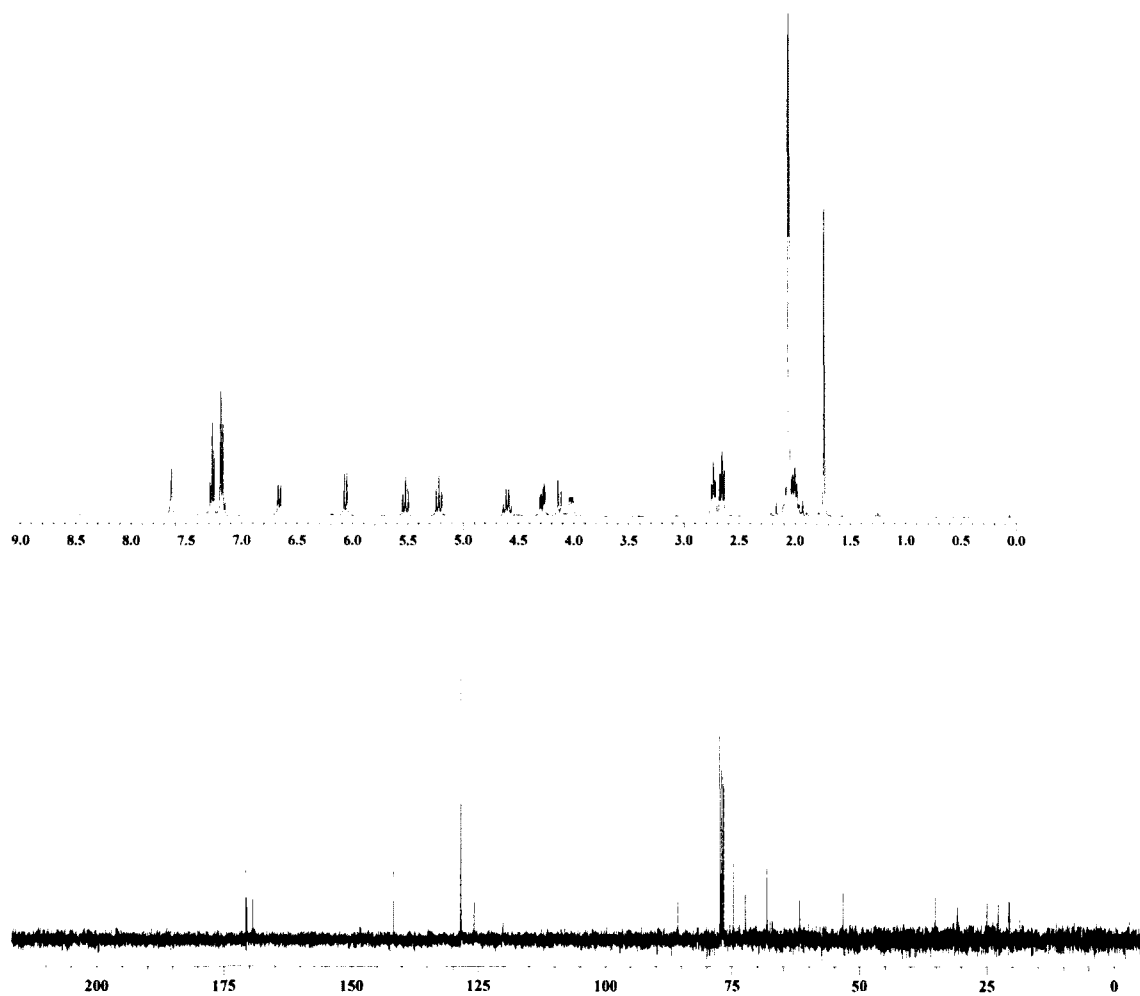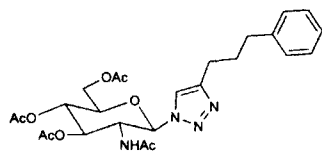
Figure 39. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra for compound **13**.

Compound 14:
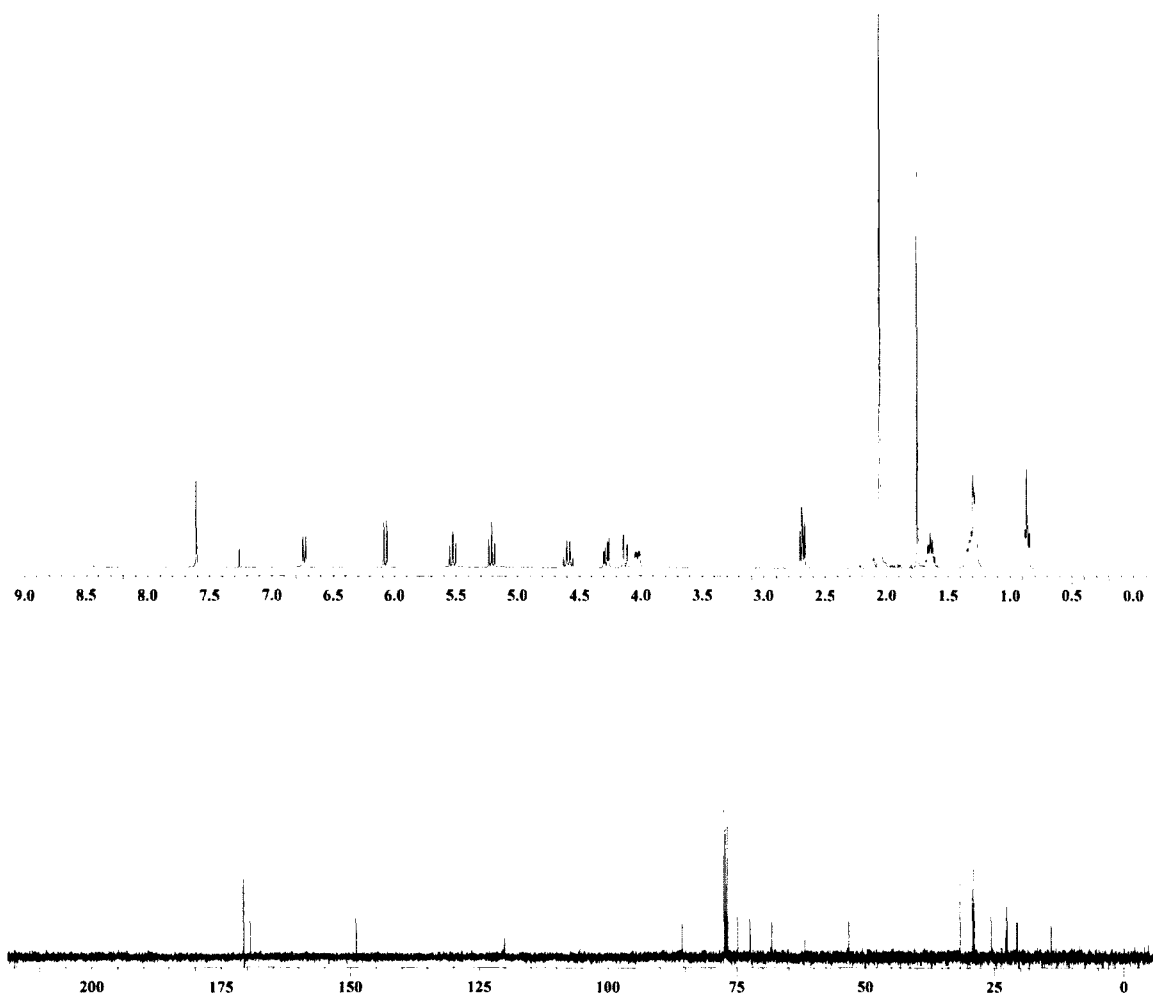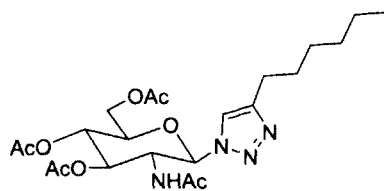
Figure 40. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra for

compound **14**.

Compound 23:
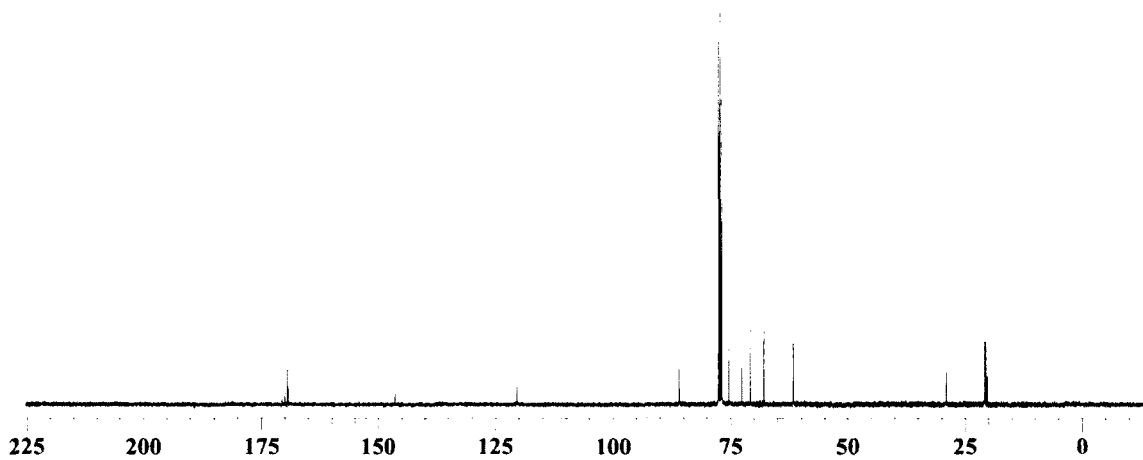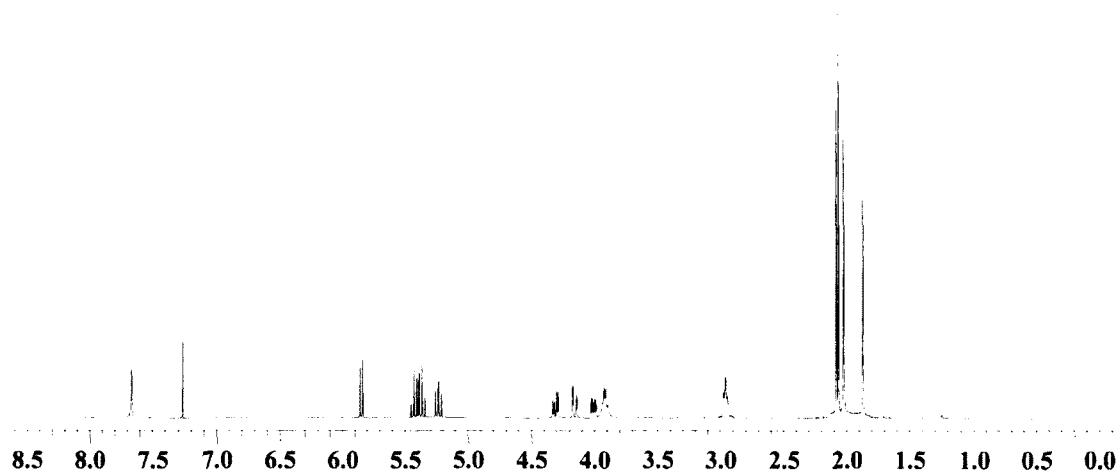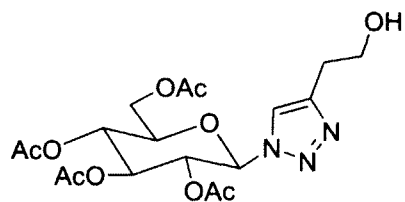
Figure 41. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra for compound **23**.

Compound 24:
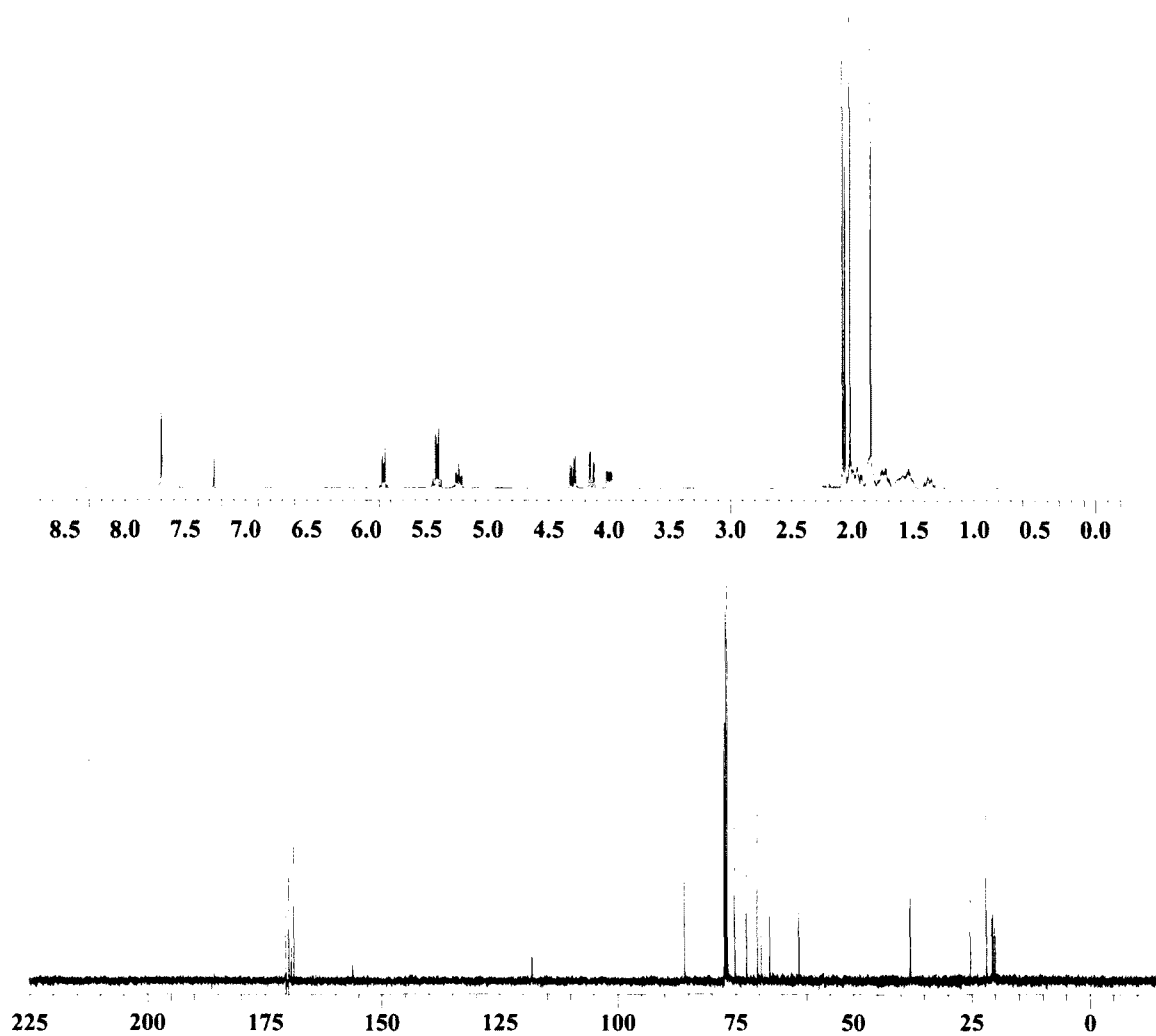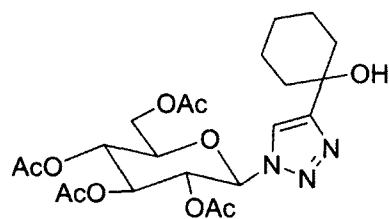
Figure 42. ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) spectra for compound **24**.

HPLC purity for compound 21:
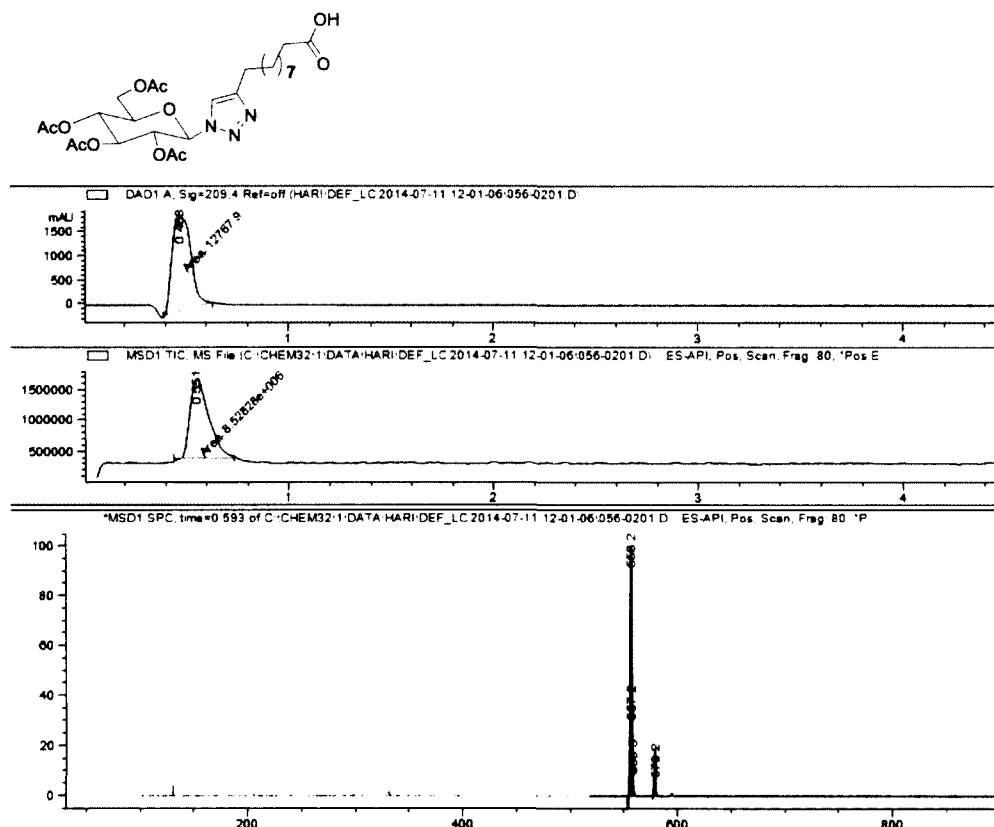
Figure 43. HPLC condition: SB-C18 column, 2.1X50 mm, 1.8μm: 0.1% formic acid in 70:30: acetonitrile/water; 1.0 mL/min; 222nm; r_t = 0.5 min.

3.3. CONCLUSIONS

In summary, we have synthesized a series of N-acetyl glucosamine and D-Glucose based triazole derivatives and studied their self-assembling properties. Among the analogues studied, we found that the compounds containing long aliphatic spacers are generally effective low molecular weight gelators, and six efficient hydrogelators have also been obtained. These sugar based hydrogels may find potential applications in biomedicical research and as advanced materials.

3.4. EXPERIMENTAL PROCEDURES

General Methods

All reactions were carried out under normal condition, reagents and solvents were obtained from commercial suppliers used directly without any purification. All the solvents were used for the reaction were purchased from Sigma-Aldrich, VWR, and Fisher. All reactions, unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. Chromatography was carried out using silicycle 230-400 mesh silcagel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates, and visualized using UV light. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with Varian 400 MHz spectrometers in CDCl$_3$. Proton and carbon spectra chemical shifts were reported using TMS and CDCl$_3$ as internal standard at 0 ppm and at 77.23 ppm, respectively.

Synthesis and characterization data:

Synthesis of compound (II):

To the N-acetyl glucosamine (500 mg, 2.26mmol) acetyl chloride (0.99 mL, 14.05 mmol) was added at room temperature. Reaction was kept at room temperature for 12h. After 12h, TLC (hexane: ethyl acetate: 1:4) indicates no starting material was left. The reaction mixture was diluted with DCM (10 mL) and then poured on to ice water (20 mL), and the organic layer was washed with saturated NaHCO$_3$ for three times then washed with brine solution. The organic layer was dried over sodium sulfate and the crude product was purified using column chromatography in (hexane: ethyl acetate: 1:4) to get the desired product as a white solid with 0.645 g.

The pure compound was obtained as a white solid with 0.645 g (78 %), m.p. 124.0-126.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 6.17 (d, 1H, J = 3.7 Hz) , 5.87 (d, 1H, J = 8.8 Hz), 5.25 (m, 2H), 2.09 (s, 3H), 2.04 (s, 6H), 1.97 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 171.5, 170.7, 170.5, 169.3, 93.8, 71.0, 70.2, 67.2, 61.3, 53.5, 23.1, 20.8, 20.7.

Synthesis of compound 1:

Compound **II** (500 mg, 1.3 mmol) was dissolved in anhydrous DMF (8 mL), followed by sodium azide (0.27 g, 4.1 mmol) was added at room temperature. Reaction was moved to 70 °C for 3h, monitored using TLC and NMR after 3h reaction was completed. DMF was removed under reduced pressure and worked up with EtOAc and water. The organic layer was dried over magnesium sulfate and the crude product was purified using column chromatography EtOAc: Hexane (2:1) to get the desired product as white solid 0.458g. The pure compound was obtained as a white solid with 0.458 g (90 %), m.p. 166.0-168.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 5.61 (d, 1H, J = 8.7 Hz) ,5.24 (t, 1H, J = 9.1 Hz), 5.10 (t, 1H, J = 9.8 Hz), 4.75 (d, 1H, J = 9.5 Hz), 4.27 (dd, 1H, J = 12.4, 4.7 Hz), 4.17 (dd, 1H, J = 9.3, 2.1 Hz), 3.91 (m, 1H), 3.78 (m, 1H), 2.10 (s, 3H), 2.04 (m, 6H), 1.98 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.1, 170.7, 170.5, 169.2, 88.3, 73.8, 72.0, 67.9, 61.8, 54.0, 23.2, 20.7, 20.67, 20.61.

General procedure for the synthesis of triazoles:

To a 50 mL of round bottom flask 100 mg of compound **(1)** (100 mg, 0.26 mmol) and 10-undecynoic acid (62 mg, 0.34 mmol) were dissolved in   tBuOH: THF: Water: 1:1:1(6 mL). To this solution copper (II) sulfate (8 mg, 0.052 mmol) and L-ascorbic sodium salt

(21 mg, 0.104 mmol) were added. Reaction was kept at room temperature for 14h. Reaction was monitored using TLC and LC-MS, shows the conversion by this time. The solvents were evaporated under reduced pressure. The resulting residue was dissolved in chloroform (10 mL), washed with water (2 mL) and the extracted crude product was purified using flash chromatography EtOAc: Hexane (95:5) (or) DCM:MeOH (97:3) to get the desired product as white solid with 0.114 g with 81%.

Compound 4:

The pure compound (4) was obtained as a white solid with 98 mg (81%), m.p. 235.0-237.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.79 (s, 1H), 7.28 (d, 1H, J = 8.5 Hz), 6.14 (d, 1H, J = 10.1 Hz), 5.56 (t, 1H, J = 10.1 Hz), 5.18 (t, 1H, J = 10.1 Hz), 4.54 (q, 1H, J = 9.3 Hz), 4.24 (dd, 1H, J = 9.3, 4.6 Hz), 4.10 (m, 1H), 4.03 (m, 1H), 3.56 (m, 2H), 2.21 (s, 6H), 2.05 (m, 9H), 1.72 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.7, 170.5, 169.3, 145.0, 122.1, 85.8, 74.6, 72.2, 68.2, 61.7, 53.9, 53.4, 44.9, 22.7, 20.67, 20.62, 20.5. (ESI+) calcd for C$_{19}$H$_{29}$N$_5$O$_8$ [M+H]$^+$, 456.4 found 456.2.

Compound 5:

The pure compound (5) was obtained as a white solid with 94 mg (82 %), m.p. 230.0-232.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.94 (s, 1H), 6.75(d, 1H, J = 9.3 Hz), 6.10 (d, 1H, J = 10.1 Hz), 5.48 (t, 1H, J = 9.3 Hz), 5.26 (t, 1H, J = 9.3 Hz),4.78 (br, s, 2H), 4.59 (q, 1H, J = 9.3 Hz), 4.28 (dd, 1H, J = 9.3, 4.6 Hz), 4.12 (m, 1H), 4.03 (m, 1H), 2.46 (br, s , 1H), 2.05 (m, 9H), 1.74 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 171.2, 170.6, 169.4, 117.4,

85.7, 74.6, 72.3, 68.1, 61.7, 55.8, 33.0, 22.5, 20.6. (ESI+) calcd for $C_{17}H_{24}N_4O_9$ [M+Na]$^+$,

451.4 found 451.1.

Compound 6:

The pure compound (6) was obtained as a white solid with 0.129 g (87 %), m.p. 245.0-

247.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 (s, 1H), 6.16 (d, 1H, J = 7.8 Hz), 6.03 (d,

1H, J = 10.1 Hz), 5.47 (t, 1H, J = 9.3 Hz), 5.25 (t, 1H, J = 9.3 Hz), 4.57 (q , 1H, J = 9.3

Hz), 4.28 (dd, 1H, J = 9.3 ,4.6 Hz), 4.12 (m, 1H), 4.03 (m, 1H), 2.87 (m, 1H), 2.05 (m,

9H), 1.90 (m, 4H), 1.71 (m, 6H), 1.55-1.34 (m, 4H). ^{13}C (100 MHz, CDCl$_3$): δ 171.5,

170.6, 169.4, 118.4, 86.0, 74.7, 72.2, 68.0, 53.1, 29.9, 22.2, 20.4. (ESI+) calcd for

$C_{19}H_{28}N_4O_9$ [M+Na]$^+$, 479.4 found 479.2.

Compound 7:

The pure compound (7) was obtained as a white solid with 0.100 g (85%), m.p. 185.0-

187.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78 (s, 1H), 7.32 (d, 1H, J = 9.3 Hz), 5.87 (d,

1H, J = 9.3 Hz), 5.35 (t, 1H, J = 9.3 Hz), 5.19 (t, 1H, J = 9.3 Hz), 4.49 (q, 1H, J = 9.3

Hz), 4.26 (dd, 1H, J =12.4, 4.6 Hz), 4.12 (m, 1H), 4.01 (m, 1H), 3.22 (m, 2H), 2.90 (m,

2H), 2.39 (m, 2H), 2.04 (m, 9H), 1.69 (m, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 171.3, 171.2,

170.7, 169.4, 145.9, 121.3, 86.1, 74.8, 72.16, 72.12, 68.6, 61.7, 61.2, 53.5, 49.6, 49.0, 28.9,

22.3, 20.6, 20.5. (ESI+) calcd for $C_{18}H_{26}N_4O_9$ [M+Na]$^+$, 465.4 found 465.1.

Compound 8:

The pure compound (**8**) was obtained as a white solid with 98 mg (82 %), m.p. 225.0-227.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$+DMSO): δ 7.59 (d, 1H, J = 9.3 Hz), 7.54 (s, 1H), 5.83 (d, 1H, J = 10.1 Hz), 5.24 (t, 1H, J = 9.3 Hz), 5.00 (t, 1H, J = 9.3 Hz), 4.43 (q, 1H, J = 9.3 Hz), 4.09 (dd, 1H, J =9.3, 4.6 Hz), 3.94(m, 1H), 3.82 (m, 1H), 3.42 (br, s , 1H), 2.6.2(m, 2H), 1.87 (m, 9H), 1.71(m, 2H), 1.54(m, 2H). ^{13}C (100 MHz, CDCl$_3$+DMSO): δ 165.5, 165.27, 165.22, 164.4, 80.8, 69.6, 67.8, 63.4, 56.9, 56.0, 47.6, 26.9, 17.8,17.1, 15.8, 15.6. (ESI+) calcd for C$_{19}$H$_{28}$N$_4$O$_9$ [M+Na]$^+$, 479.4 found 479.2.

Compound 9:

The pure compound (**9**) was obtained as a white solid with 0.114 g (86%), m.p. 231.0-233.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (s, 1H), 7.08(d, 1H, J = 9.3 Hz), 6.15 (d, 1H, J = 10.1 Hz), 5.52(t, 1H, J = 9.3 Hz), 5.24(t, 1H, J = 9.3 Hz), 4.61(q, 1H, J = 9.3 Hz), 4.30 (dd, 1H, J =9.3, 4.6 Hz), 4.13 (m, 1H), 4.07 (m, 1H), 2.73 (t, 1H, J = 7.8 Hz), 2.69 (t, 1H, J = 7.8 Hz), 2.05 (m, 9H), 1.75 (s, 3H), 1.64 (m, 2H), 1.29 (m, 6H), 0.86 (t, 3H, J = 7.0 Hz). ^{13}C (100 MHz, CDCl$_3$): δ 170.8, 170.7, 170.6, 169.3, 155.8, 119.4, 85.7, 74.6, 72.3, 69.2, 68.1, 61.7, 53.3, 37.9, 37.7, 25.3, 22.6, 21.8, 20.67, 20.63, 20.5. (ESI+) calcd for C$_{22}$H$_{32}$N$_2$O$_2$ [M+Na]$^+$, 519.5 found 519.2.

Compound 10:

The pure compound (**10**) was obtained as a white solid with 0.120g (82 %), m.p. 188.0-190.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.72 (s, 1H), 6.02 (m, 2H), 5.42 (t, 1H, J = 9.3 Hz), 5.23 (t, 1H, J = 9.3 Hz), 4.60 (m, 1H) , 4.29 (dd, 1H, J = 9.3, 4.6 Hz), 4.14 (m, 1H),

3.97 (m, 1H), 3.63 (m, 2H), 2.70 (m, 2H), 2.07 (m, 9H), 1.79-1.60 (m, 8H), 1.56 (m, 2H),

1.31 (m, 10H).^{13}C (100 MHz, CDCl$_3$): δ 170.68, 170.6, 169.3, 121.0, 85.8, 74.7, 72.5,

68.2, 62.7, 61.7, 53.1, 32.7, 29.3, 29.2, 29.1, 29.0, 20.68, 20.63, 20.5. (ESI+) calcd for

C$_{25}$H$_{40}$N$_4$O$_9$ [M+H]$^+$, 541.6 found 541.3.

Compound 11:

The pure compound (11) was obtained as a white solid with 0.114g (81%), m.p. 143.0-

145.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.69(s, 1H), 7.13 (d, 1H, J = 8.5 Hz), 6.08 (d,

1H, J = 9.3 Hz), 5.47 (t, 1H, J = 9.37Hz), 5.25 (t, 1H, J = 9.3 Hz), 4.62 (q, 1H, J = 9.3

Hz), 4.27 (dd, 1H, J = 9.37, 4.68 Hz), 4.12(m, 1H), 4.03(m, 1H), 2.67 (br, s, 2H), 2.33

(br, s, 2H), 2.05 (m, 9H), 1.75 (s, 3H),1.61 (m, 6H), 1.29 (m, 10H). ^{13}C (100 MHz,

CDCl$_3$+CD$_3$OD): δ 189.0, 175.1, 147.8, 174.5, 173.5, 118.2, 89.7, 78.6, 72.0, 65.7, 56.9,

32.1, 28.9, 26.1, 24.4, 24.35, 24.30. (ESI+) calcd for C$_{25}$H$_{38}$N$_4$O$_{10}$ [M+H]$^+$, 555.6 found

555.5.

Compound 12:

The pure compound (12) was obtained as a white solid with 0.104 g (82 %), m.p. 281.0-

283.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 8.15 (s, 1H), 7.83 (d, 2H, J = 7.0 Hz), 7.41(m,

2H), 7.34 (m, 1H), 6.67 (d, 1H, J = 9.3 Hz), 6.15 (d, 1H, J = 10.1 Hz), 5.55 (t, 1H, J =

9.3 Hz), 5.27 (t, 1H, J = 9.3 Hz), 4.68 (q, 1H, J = 9.3 Hz), 4.30 (dd, 1H, J = 4.6, 9.3 Hz),

4.15 (m, 1H), 4.03 (m, 1H), 2.05 (m, 9H), 1.73 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.7,

170.6, 69.3, 129.8, 128.8, 128.5, 125.8, 85.8, 74.9, 72.3, 68.0, 61.6, 53.4, 35.1, 22.7,

20.67, 20.61, 20.5. (ESI+) calcd for C$_{22}$H$_{26}$N$_4$O$_8$ [M+Na]$^+$, 497.1 found 497.1.

Compound 13:

The pure compound (13) was obtained as a white solid with 0.106 g (77%). m.p. 200.0-202.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.63 (s, 1H), 7.28-7.19 (m, 5H), 6.66 (d, 1H, J = 9.3 Hz), 6.06 (d, 1H, J = 10.1 Hz), 5.52 (t, 1H, J = 9.3 Hz), 5.21 (t, 1H, J = 9.3 Hz), 4.60 (q, 1H, J = 9.3 Hz), 4.28 (dd, 1H, J = 4.6, 9.3 Hz), 4.13 (m, 1H), 4.02 (m, 1H), 2.73 (t, 1H, J = 7.8 Hz), 2.65 (t, 1H, J = 7.8 Hz), 2.06 (s, 3H), 2.05 (m, 9H), 1.74 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.6, 170.56, 170.52, 169.3, 128.4, 128.3, 125.8, 85.6, 74.7, 72.3, 68.1, 61.7, 53.2, 35.1, 30.7, 25.0, 22.7, 20.6. (ESI+) calcd for C$_{25}$H$_{32}$N$_4$O$_8$ [M+H]$^+$, 517.5 found 517.2.

Compound 14:

The pure compound (14) was obtained as a white solid with 0.112 g (87 %), m.p. 212.0-214.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.61 (s, 1H), 6.73 (d, 1H, J = 9.3 Hz), 6.07 (d, 1H, J = 10.1 Hz), 5.53 (t, 1H, J = 9.3 Hz), 5.21(t, 1H, J = 9.3 Hz), 4.59 (q, 1H, J = 9.3 Hz), 4.28 (dd, 1H, J = 4.6, 9.3 Hz), 4.12 (m, 1H), 4.03 (m, 1H), 2.73 (t, 1H, J = 7.8 Hz), 2.69 (t, 1H, J = 7.8 Hz), 2.05 (m, 9H), 1.75 (s, 3H),1.64 (m, 2H), 1.29 (m, 6H), 0.86 (t, 3H, J = 7.0 Hz) . ^{13}C (100 MHz, CDCl$_3$): δ 170.6, 170.5, 169.3, 148.7, 120.0, 85.5, 74.7, 72.3, 68.1, 61.7, 53.2, 31.5, 29.0, 28.8, 25.5, 22.7, 22.5, 20.67, 20.62, 20.5, 14.0. (ESI+) calcd for C$_{22}$H$_{26}$N$_2$O$_2$ [M+Na]$^+$, 505.5 found 505.2.

Compound 15:

The pure compound (15) was obtained as a white solid with 0.121 g (84 %), m.p. 174.0-176.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.61 (s, 1H), 6.88 (d, 1H, J = 8.5 Hz), 6.09 (d,

1H, J = 10.1 Hz), 5.54 (t, 1H, J = 9.3 Hz), 5.21 (t, 1H, J = 9.3 Hz), 4.59 (q, 1H, J = 9.3

Hz), 4.28 (dd, 1H, J = 9.3, 4.6 Hz), 4.12 (m, 1H), 4.03 (m, 1H), 2.73 (t, 1H, J = 7.8 Hz),

2.67 (t, 1H, J = 7.8 Hz), 2.05 (m, 9H), 1.74 (s, 3H),1.64 (m, 2H), 1.24 (m, 16H), 0.86 (t,

3H, J = 7.0 Hz). ^{13}C (100 MHz, CDCl$_3$): δ 170.6, 170.5, 169.3, 148.7, 120.0, 85.5, 74.7,

72.3, 68.2, 61.7, 53.2, 31.8, 29.6, 29.57, 29.5, 29.3, 29.2, 29.1, 25.5, 22.6, 14.0. (ESI+)

calcd for C$_{22}$H$_{26}$N$_2$O$_2$ [M+Na]$^+$, 561.6 found 561.2.

Compound 16:

The pure compound (16) was obtained as a white solid with 0.121 g (76 %), m.p. 180.0-

182.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.69 (s, 1H), 5.94 (d, 1H, J = 8.5 Hz), 5.77 (d,

1H, J = 9.3 Hz), 5.41(t, 1H, J = 10.1 Hz), 5.23 (t, 1H, J = 10.1 Hz), 4.59 (q, 1H, J = 10.1

Hz), 4.27 (dd, 1H, J = 9.3, 4.6 Hz), 4.12 (m, 1H), 4.03 (m, 1H), 2.70 (t, 2H, J = 7.8 Hz),

2.05 (m, 9H), 1.75 (s, 3H),1.66 (m, 2H), 1.60 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, J = 7.0

Hz). ^{13}C (100 MHz, CDCl$_3$): δ 170.6, 170.56, 175.0, 169.3, 148.8, 119.9, 85.6, 74.7, 72.3,

68.1, 61.7, 53.2, 31.8, 29.61, 29.6, 29.3, 29.2, 29.1, 25.5, 22.7, 22.6, 20.67, 20.63,14.0.

(ESI+) calcd for C$_{22}$H$_{26}$N$_2$O$_2$ [M+Na]$^+$, 617.7 found 617.3.

Compound 17:

The pure compound (17) was obtained as a white solid with 0.155g (68%), m.p. No

characteristic melting point. At 300.0 °C turn into black char. ^{1}H NMR (400 MHz,

CDCl$_3$+Me$_3$OD): 7.74 (br, s, 2H), 7.65 (d, 2H, J = 8.5 Hz), 5.88 (d, 2H, J = 10.1 Hz),

5.33(t, 2H, J = 9.3 Hz), 5.12 (t, 2H, J = 9.3 Hz), 4.44 (q, 2H, J = 9.3 Hz), 4.20 (dd, 2H, J

= 9.3, 4.6 Hz), 4.05 (m, 2H), 3.94 (m, 2H), 2.65 (m, 4H), 1.97 (m, 18H), 1.63(m, 10H).

^{13}C (100 MHz, CDCl$_3$+Me$_3$OD): δ 171.1, 170.8, 170.6, 169.55, 128.4, 128.3, 126.9, 83.7, 74.6, 72.3, 68.0, 61.7, 52.9, 28.1, 22.1, 20.5, 20.3. (ESI+) calcd for C$_{36}$H$_{50}$N$_8$O$_{16}$ [M+Na]$^+$, 873.8 found 873.2.

Synthesis of sugar azide (20):
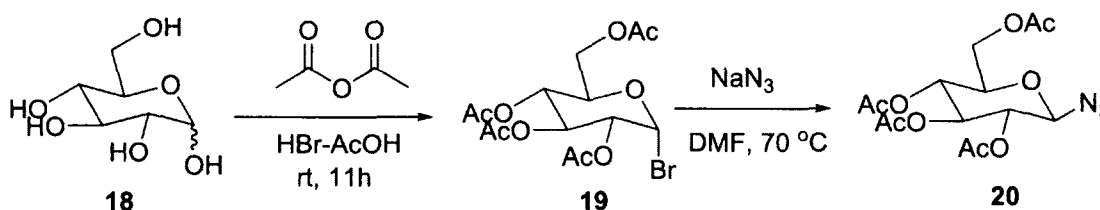
500 mL RBF charged with α-D-Glucose (**18**) (5.0 g, 27.0 mmol) to this 25 mL of Acetic anhydride was added. 5 mL of HBr-AcOH was added to the reaction mixture and stirring continued for for 5 h at rt. After 5 h added additional 25 mL of HBr-AcOH to the reaction mixture and stirring continued for additional 6 h. Then 100 mL of DCM was added to the reaction mixture and poured into ice cold water. DCM layer was separated. Then water layer extracted with DCM (2x20 mL). Combined organic layers were quenched with saturated NaHCO$_3$ and organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. Product was recrystallized from THF-Hexanes 9.8 g product (85.88 %).

To a solution of 2,3,4,6-tetra-O-acetyl-α-D –glucopyranosyl bromide (5 g, 12.15 mmol, 1 equiv) was dissolved in dry DMF (25 mL). To this solution NaN$_3$ (2.37 g, 36.45 mmol, 3 equiv). The reaction mixture was stirred at 70 °C under nitrogen for 4h. Reaction was

monitored using TLC and LC-MS, after completion crude product was washed with water and extracted with ethyl acetate (100 mL). Organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography with Hexane: EtOAc (15:85) to get the desired product 2,3,4,6-tetra-O-acetyl-β- D – glucopyranosyl azide (20) (3.67 g, 81% yield) as white crystals. The pure compound was obtained as a white solid with 3.67 g (81 %), m.p. 124.0-126.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.21 (dd, 1H, J = 9.2, 9.6 Hz), 5.11 (dd, 1H, J = 9.2, 10 Hz), 4.95 (dd, 1H, J = 8.8, 9.6 Hz,), 4.64 (d, 1H, J = 8.8 Hz), 4.27 (dd, , 1H , J = 4.8, 12.4 Hz), 4.16 (dd, 1H, J = 2.4, 12.4 Hz), 3.79 (ddd, 1H, J = 2.4, 4.8, 10 Hz), 2.10 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H,). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 170.5 , 170.0, 169.3, 169.2,169.1, 87.8, 73.9, 72.5, 70.5 , 67.7 , 61.5, 20.5.

General procedure for the synthesis of Triazoles:

To a 50 mL of round bottom flask 100 mg of compound (20) (100 mg, 0.26 mmol) and 10-Undecynoic acid (125 mg, 0.69mmol) were dissolved in tBuOH:THF:Water: 1:1:1(6 mL). To this solution copper (II) sulfate (17 mg, 0.106 mmol) and L-Ascorbic sodium salt (42 mg, 0.212 mmol) were added. Reaction was kept at room temperature for 14h. Reaction was monitored using TLC and LC-MS, shows the conversion by this time. The solvents were evaporated under reduced pressure. The resulting residue was dissolved in chloroform (10 mL), washed with water (2 mL) and the extracted crude product was purified using flash chromatography DCM:MeOH (95:5) to get the desired product (compound 21) as white solid with 0.131 g with 78%.

Compound 21:

The pure compound (**21**) was obtained as a white solid with 0.131g (78%), m.p. 143.0-145.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 (s, 1H), 5.84 (m, 1H), 5.38 (m, 2H), 5.20 (m, 1H), 4.26 (dd, 1H, J = 12.4, 5.4 Hz), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.09 (dd, 1H, J = 12.4, 2.4 Hz), 3.98 (m, 2H), 2.66 (t, 2H, J = 7.8 Hz), 2.29 (t, 2H, J = 7.8 Hz), 2.04 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.82 (s, 3H), 1.59 (m, 2H), 1.27 (m, 8H). ^{13}C (100 MHz, CDCl$_3$): δ 178.7, 170.5, 169.9, 169.4, 168.9, 149.0, 118.8, 85.6, 74.9, 72.6, 70.1, 67.7, 61.5, 33.9, 29.0, 28.97, 28.93, 28.9, 25.4, 24.6, 20.6, 20.0. (ESI+) calcd for C$_{25}$H$_{37}$N$_3$O$_{11}$ [M+H]$^+$, 556.5 found 556.2.

Compound 22:

The pure compound (**22**) was obtained as a white solid with 0.102 g (86 %), m.p. 158.0-160.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66 (s, 1H), 5.84 (d, 1H, J = 9.3 Hz), 5.43 (t, 1H, J = 8.5 Hz), 5.36 (t, 1H, J = 9.3 Hz), 5.23 (t, 1H, J = 9.3 Hz), 4.31 (dd, 1H, J = 12.4, 5.4 Hz), 4.16 (dd, 1H, J = 12.4, 1.5 Hz), 4.00 (m, 1H), 3.92 (m, 2H), 2.96 (m, 2H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.88 (m, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.4, 169.8, 169.3, 169.1, 146.2, 120.23, 85.7, 75.1, 72.4, 70.5, 67.7, 28.7, 20.6, 20.5, 20.4, 20.1. (ESI+) calcd for C$_{18}$H$_{25}$N$_3$O$_{10}$ [M+H]$^+$, 444.4 found 444.1.

Compound 23:

The pure compound (**23**) was obtained as a white solid with 98 mg (85 %), m.p. 153.0-155.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78 (s, 1H), 5.88 (m, 1H), 5.43 (m, 2H), 5.24 (m, 1H), 4.81 (s, 2H), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.15 (dd, 1H, J = 12.4, 5.4 Hz),

4.00 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.89 (m, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.5, 169.9, 169.3, 169.0, 148.5, 120.2, 85.6, 75.0, 72.6, 70.3, 67.6, 61.5, 56.3, 20.6, 20.4, 20.1. (ESI+) calcd for C$_{17}$H$_{23}$N$_3$O$_{10}$ [M+Na]$^+$, 452.3 found 452.1.

Compound 24:

The pure compound (**24**) was obtained as a white solid with 0.127 g (88%), m.p.178.0-180.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70 (s, 1H), 5.86 (m, 1H), 5.41 (m, 2H), 5.24 (m, 1H), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.14 (dd, 1H, J = 12.4, 2.4 Hz), 4.00 (m, H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.95 (m, 2H), 1.85 (m, 2H), 1.74 (m, 2H), 1.56 (m, 2H), 1.37 (m, 1H). ^{13}C (100 MHz, CDCl$_3$): δ 170.4, 169.8, 169.3, 168.8, 156.2, 118.1, 85.6, 75.0, 72.5, 70.2, 69.4, 67.7, 61.5, 37.9, 25.2, 21.8, 20.6, 20.4, 20.0. (ESI+) calcd for C$_{22}$H$_{31}$N$_3$O$_{10}$ [M+H]$^+$, 498.5 found 498.3.

Compound 25:

The pure compound (**25**) was obtained as a white solid with 0.120g (83 %), m.p. 188.0-190.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72 (s, 1H), 6.02 (m, 2H), 5.42 (t, J = 9.37 Hz, 1H), 5.23 (t, J = 9.37 Hz, 1H),4.60 (m, 1H) , 4.29 (dd, J = 9.37,4.68 Hz, 1H), 4.14 (m, 1H), 3.97 (m, 1H), 3.63 (m, 2H), 2.70 (m, 2H), 2.07 (m, 9H), 1.79-1.60 (m, 8H), 1.56 (m, 2H), 1.31 (m, 10H).^{13}C (100 MHz, CDCl$_3$): δ 170.4,169.8, 169.3, 168.8, 149.1, 118.7, 85.5, 75.0, 72.7, 70.1, 67.7, 62.8, 61.5, 32.7, 29.3, 29.2, 29.1, 29.0, 25.6, 25.2, 20.6, 20.1. (ESI+) calcd for C$_{25}$H$_{39}$N$_3$O$_{10}$ [M+H]$^+$, 542.6 found 542.3.

Compound 26:

The pure compound (26) was obtained as a white solid with 0.129 g (81 %), m.p. 180.0-182.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.49 (s, 1H), 5.86 (m, 1H), 5.41 (m, 2H), 5.22 (m, 1H), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.30 (dd, 1H, J = 12.4, 5.4 Hz), 4.14 (dd, 1H, J = 12.4, 2.4 Hz), 3.98 (m, H), 2.70 (t, 2H, J = 7.8 Hz), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.86 (s, 3H), 1.65 (m, 2H), 1.56 (m, 24H), 0.86 (t, 3H, J = 7.8 Hz). ^{13}C (100 MHz, CDCl$_3$): δ 1704, 169.8, 169.3, 168.8, 149.2, 118.6, 85.6, 75.0, 72.7, 70.1, 67.7, 61.5, 31.8, 29.6, 29.5, 29.3, 25.6, 22.6, 20.6, 20.5, 20.1, 14.0. (ESI+) calcd for C$_{22}$H$_{31}$N$_3$O$_{10}$ [M+H]$^+$, 498.5 found 498.3.

Compound 27:

The pure compound (27) was obtained as a white solid with0.170 g (74 %), m.p. 162.0-164.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): 7.54 (br, s, 2H), 5.84 (m, 2H), 5.41 (m, 4H), 5.23 (m, 2H), 4.29 (m, 2H), 4.14(m, 2H), 3.98 (m, 2H), 2.73 (m, 4H), 2.06(m, 12H), 2.02 (m, 6H), 1.86 (m, 6H), 1.73 (m, 4H). ^{13}C (100 MHz, CDCl$_3$): δ 170.4, 169.8, 169.3, 168.9, 148.6, 119.0, 85.5, 74.9, 72.6, 70.1, 67.6, 61.5, 31.1, 28.3, 27.7, 25.2, 20.6, 20.5, 20.1. (ESI+) calcd for C$_{36}$H$_{48}$N$_6$O$_{18}$ [M+H]$^+$, 853.8 found 853.3.

CHAPTER 4

SYNTHESIS AND CHARACTERIZATION OF α-O-BENZYL D-

GLUCOSAMINE DERIVATIVES AS ORGANO/ HYDRO GELATORS

4.1. INTRODUCTION

The study of small molecular gels has developed into a well-recognized field in materials science, pertaining to the general area of soft matter. Low molecular weight organogelators are a new class of materials that can form gels in organic solvents or water.[1-2a-c] The main driving forces for the small molecules to aggregate through supramolecular interactions are such as hydrogen bonds, π–π interactions, coordination bonds and van der Waals interactions. Tuning of these characteristics has been accomplished by using mechanical, thermal, electrochemical and electromagnetic stimuli. Hydrogelators have potential applications in biomedical research as scaffolds for tissue engineering, drug delivery carriers, protein immobilization and separation.[131-136]

Carbohydrates based gelators have drawn a lot of attentions in recent years. We have been working on the design, synthesis and analysis of monosaccharide based, self-assembling systems and the study of their gelation properties.[137-155] We have previously shown that monosaccharide derivatives can form effective low molecular weight gelators for both organic solvents and aqueous mixtures.[23-24] Several classes of monosaccharide derivatives have been found to be excellent hydro/organo gelators. These include various alpha-methoxy4,6-benzylidene acetal protected glucose and glucosamine derivatives.

Among the modifications on the basic skeletons, a series of analogs including esters, carbamates, amides, and urea derivatives have shown to be able to form effective gelators. We have found previously that amides and ureas are more efficient gelators as compare to the corresponding esters and carbamates,[24-25] as it is now clearly understood that having an extra hydrogen bonding group like amide and urea increase the gelation property in certain kind of organic/water mixtures .
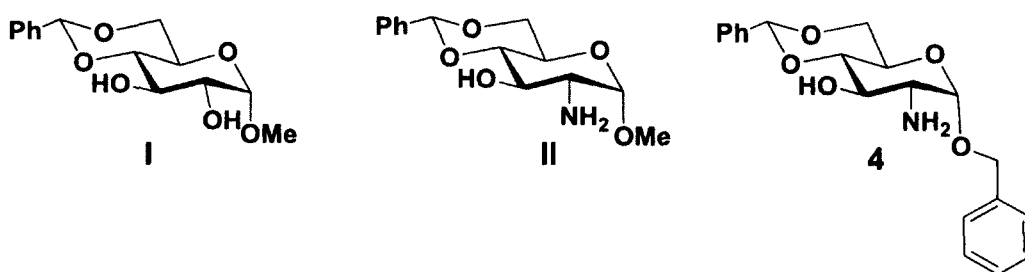
Figure 44. Different head groups of monosaccharides derivatives of sugars.

To further explore and to increase the gelation property of amides and ureas as compared to methoxy group at the anomeric position, we changed the anomeric position with α-O-benzyl glycoside of D-glucosamine to give the compound 4.

4.2. RESULTS AND DISCUSSIONS

In this research, we have studied the gelation capability of a series of glucosamine derivatives using compound 4 as the head group. As shown in Scheme 18, a series of amide and urea derivatives were synthesized and screened for their gelation properties in several solvents. The synthesis and structure and gelation relationship are reported here. In order to find out the effect of the anomeric configuration towards gelation, we

synthesized analogs using the α-O-benzyl glucosamine **4** as the head group, the synthesis

and gelation results are discussed here. The choice of the functional groups is based on

the previous study, so that we may be able to fine tune or modulate the gelation property

by changing anomeric position of the sugar ring.

Scheme 17. Synthesis of α-O-benzyl glycoside of D-glucosamine head group
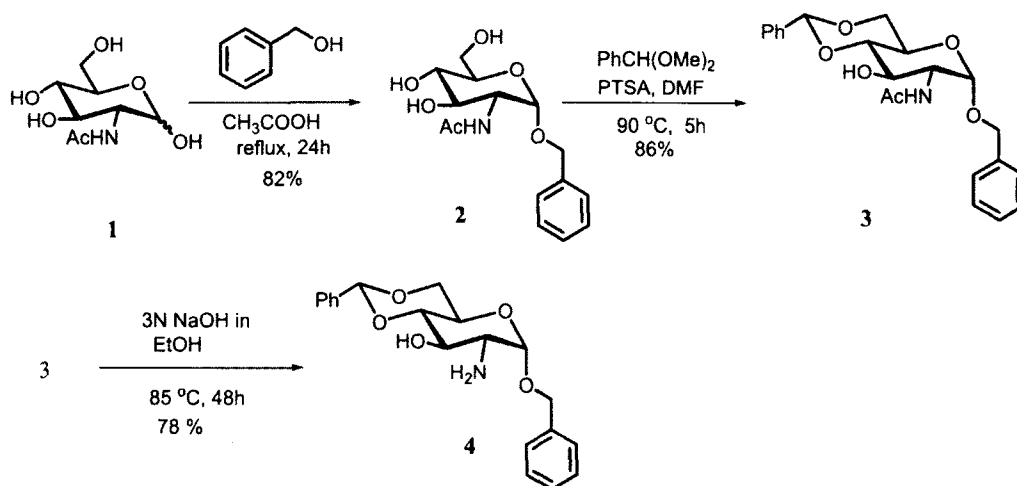
Scheme 18. Preparation of α-*O*-benzyl glycoside of D-glucosamine amides and urea derivatives
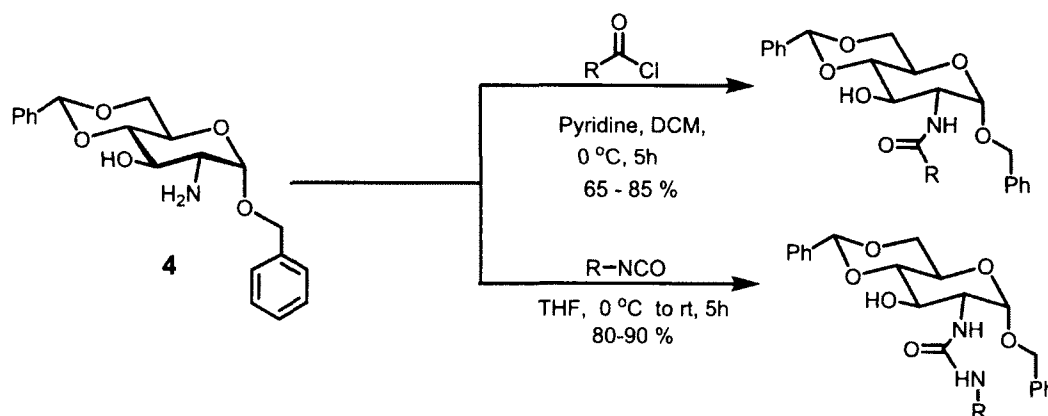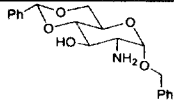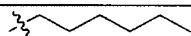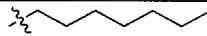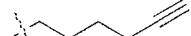
The systematic change will allow us to understand how the benzyl group will affect the assembling process which in turn, affecting the gelation properties. From our previous research, the -OMe group apparently played a positive role in the gelation process. By attaching an O-benzyl group at anomeric position, this will allow us to understand what functional groups will be tolerated on the basic gelator system.

The amide reactions generally proceeded with good yields and ureas were obtained in close to quantitative yields. The product can be purified on silica gel by flash chromatography using a polar solvent. The structures of the amide and urea synthesized and their gelation properties are shown in tables **5** and **6**. The selection of the R groups for ureas and amides are based on our previous research[13] and the availability of starting materials. These include compounds with saturated alkyl chains, cyclohexyl and aromatic group. From the screening of the gelation results of these compounds, we can determine how the structure of the alkyl or aryl groups affects self-assembling. The urea analogs showed gelation tendencies more than the amides, with the alkyl chain derivatives with **5-7** carbons being most versatile gelators for organo/aqueous mixtures.
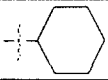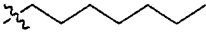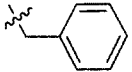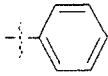
The amide derivatives compound **6-8** formed gels in EtOH/H_2O (1:2) and DMSO/ H_2O (1:2). But the aryl containing compounds are not as effective as compared to the urea derivatives. Compounds **15** and **16** formed organogels in EtOH/water and DMSO/water at concentrations lower than 2 mg/mL as shown in table **6**. A photo of the gel formed by **15** is shown in **figure 45**.

Table 5. Gelation test results of amide compounds

Compound	R =	Hexane	Water	EtOH	Water:DMSO (1:2)	Water:EtOH (1:2)
4		I	I	G 6.6	G 10	G 2.5
3		I	I	G 6.6	G 10.0	G 2.5
6		I	I	G 10.0	G 2.5	G 2.0
7		I	I	G 6.6	G 2.5	G 2.0
8		I	I	G 5.0	G 2.0	G 5.0
9		I	I	G 5.0	G 4.0	P
10		I	I	G 6.6	P	G 6.6
11		I	P	G 6.6	G 5.0	G 20.0
12		I	I	G 6.6	G 2.0	UG 20.0

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg mL; I, insoluble; P, precipitating; S, soluble at ~ 20 mg mL^{-1}; the ratios for mixed solvents are volume : volume ratios.

Table 6. Gelation test results of urea compounds

Compound	R =	Hexane	Water	EtOH	Water:DMSO(1:2)	Water:EtOH (1:2)
13		I	I	G 1.6	G 2.2	G 2.5
14		I	I	G 20.0	G 2.5	G 2.2
15		I	I	G 20.0	G 2.0	G 1.33
16		I	I	G 10.0	G 2.2	G 1.4
17		I	I	G 10.0	G 5.0	G 10.0

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg mL; I, insoluble; P, precipitating; S, soluble at ~ 20 mg mL^{-1}; the ratios for mixed solvents are volume : volume ratios.

Figure 45. A photographs of a gel by compound **15** in EtOH:Water /1:2 in 1.33 mg/ mL.

We analyzed several gels in their gel states using optical microscopy, in an attempt to reveal the supramolecular assembly of the gels with the solvents still trapped inside. The dried xerogels were also studied by optical microscopy. These results are shown in figures **46, 47** and **48**. The gel of **11** in ethanol/water showed bundled fibrous assemblies, as shown in figure **46**. At lower magnification, we can see the long fibers floating in the gel solvent matrix. The optical micrographs of the xerogels gels formed by compounds **6** and **13** are shown in figures **47** and **48**.

Figure 46. Optical micrographs (A. B. C.D) and, gel of compound **11** in EtOH / H_2O (1:2) at 20 mg/mL, at 60x and 100x magnifications.

(A)   (B)

Figure 46 Continued
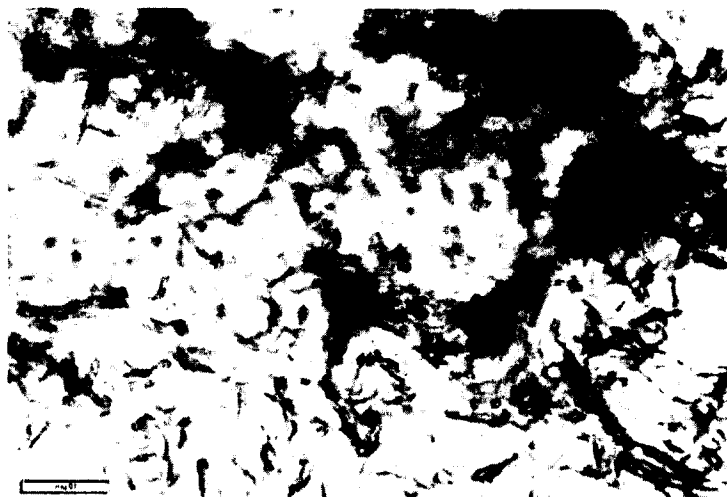
(C)

(D)
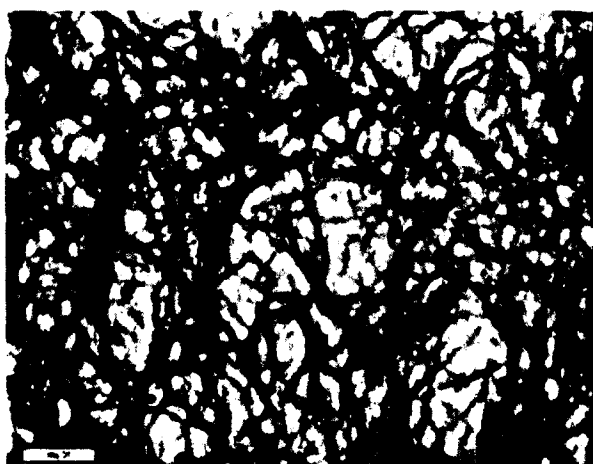
(E)
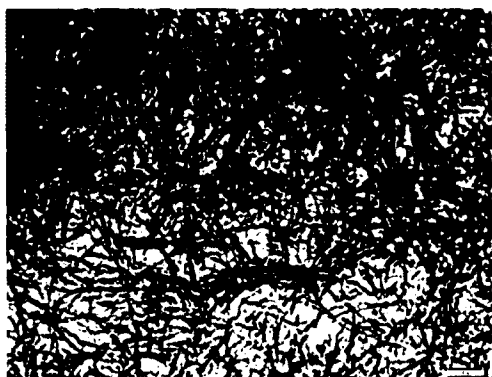
(F)

(G)

Figure 47. Optical micrographs (E. F. G) and. gel of compound **6** in EtOH /H$_2$O (1:2) at

2.5 mg/mL, at 60x and 100x magnifications.

(H)   (I)
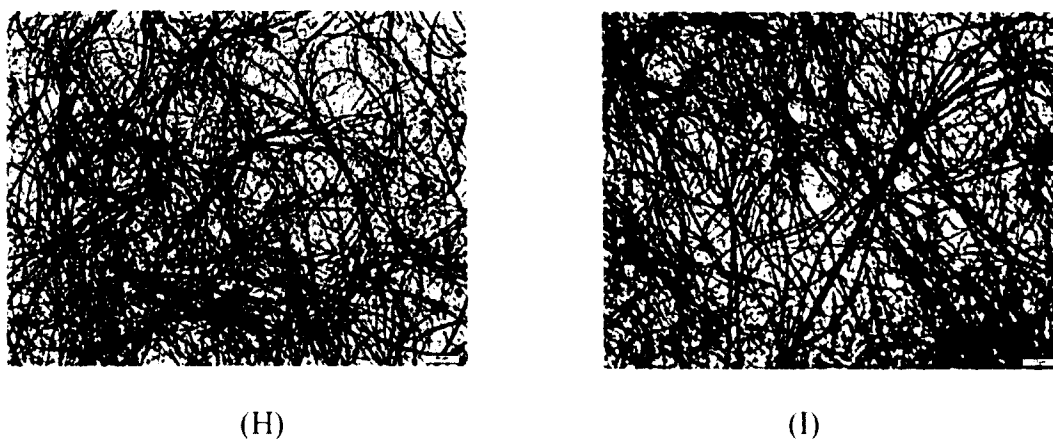
Figure 48. Optical micrographs (H, I,) and, gel of compound **13** in EtOH / H$_2$O (1:2) at

2.5 mg/mL, at 60x magnifications.

The gelation of alkyl chain urea and amide compounds were studied in three different

concentrations. We also studied the minimum gelation concentration of compounds

formed in EtOH/H$_2$O (1:2) solvents. Like others LMOGs, gelators **13** and **14** gelatinized

these solvents through non covalent interactions and thus the thermally reversible gel-to-

sol phase transition is a characteristic feature of the resultant gels. To compare their

thermal properties, studied the gel-sol phase transition temperatures, T$_{gel}$, upon the

gelator concentration of compounds **6, 7, 14** and **15** as shown in **figure 49**. Compared the

stability of hydrogel for amide and urea compounds. Urea derivatives have higher Tgel

compared to the amide derivatives, from this we can assume that the hydrogen bonding

plays an important role in case of urea molecules.
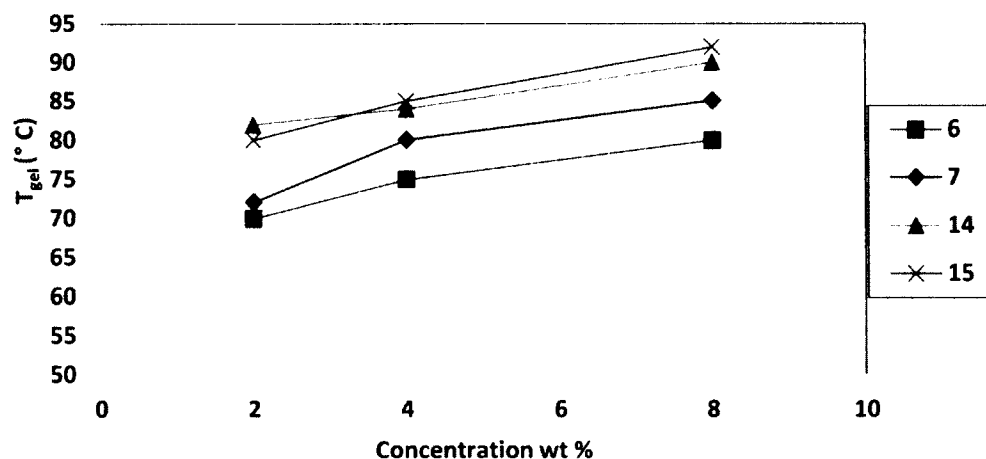
Fig 49. Dependence of the gel-sol phase transition. T$_{gel}$ upon the gelator concentration.

We have studied the dynamic rheology properties of amide derivatives as shown in **figure 50.** the dynamic moduli G' and G" are shown as a function of angular frequency ω at their minimum gelation concentrations for compounds **6. 7, 8** and **9**. As shown in **figure 50.** the storage modulus G' is greater than the Loss modulus G" for all these compounds and these compounds have high shear stress. The fact that G' is greater than G" is an indication that the gels are elastic semisolid.
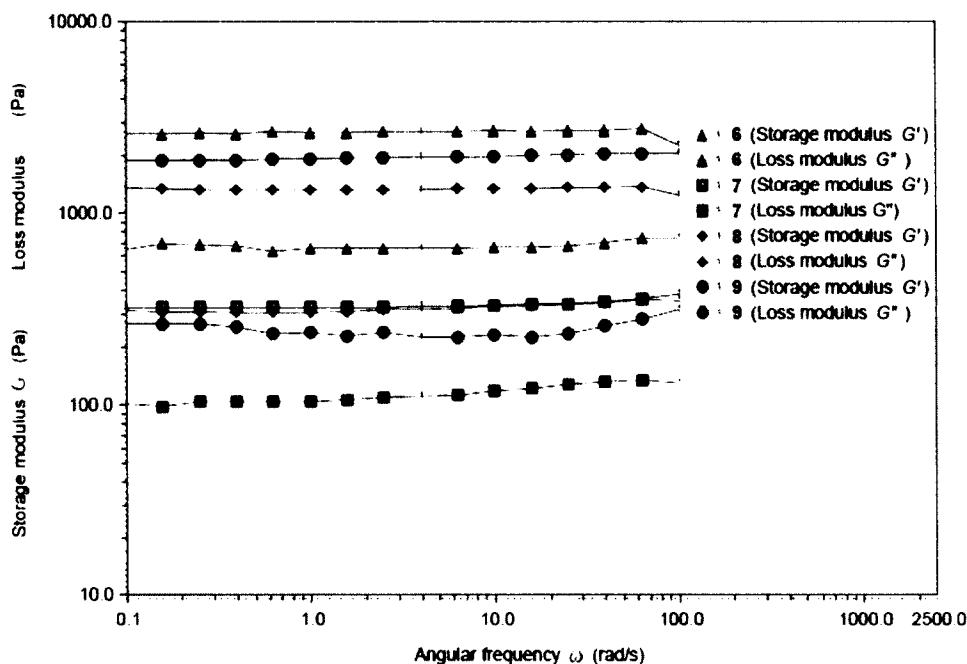
Figure 50. Viscoelastic properties of amides derivatives 1) compound **6** in DMSO:

Water: 1:2 in 2.5 mg/ mL 2) compound **7** in DMSO: Water: 1:2 in 2.5 mg/ mL 3)

compound **8** in DMSO: Water: 1:2 in 2.0 mg/ mL 4) compound **9** in DMSO: Water: 1:2

in 2.0 mg/mL.

We have also studied the dynamic rheology properties of urea derivatives shown in

figure 51. The dynamic moduli G′ and G″ are shown as a function of angular frequency

ω at their minimum gelation concentrations for compounds **13, 16** and **17**. The storage

modulus G′ is greater than the Loss modulus G″ for all these compounds and these

compounds have high shear stress. The fact that G′ is greater than G″ is an indication that

the gels are elastic semisolid. These compounds have higher G′ and G″ value than amide.

From this we can say that these molecules have stronger gelation property than amides.
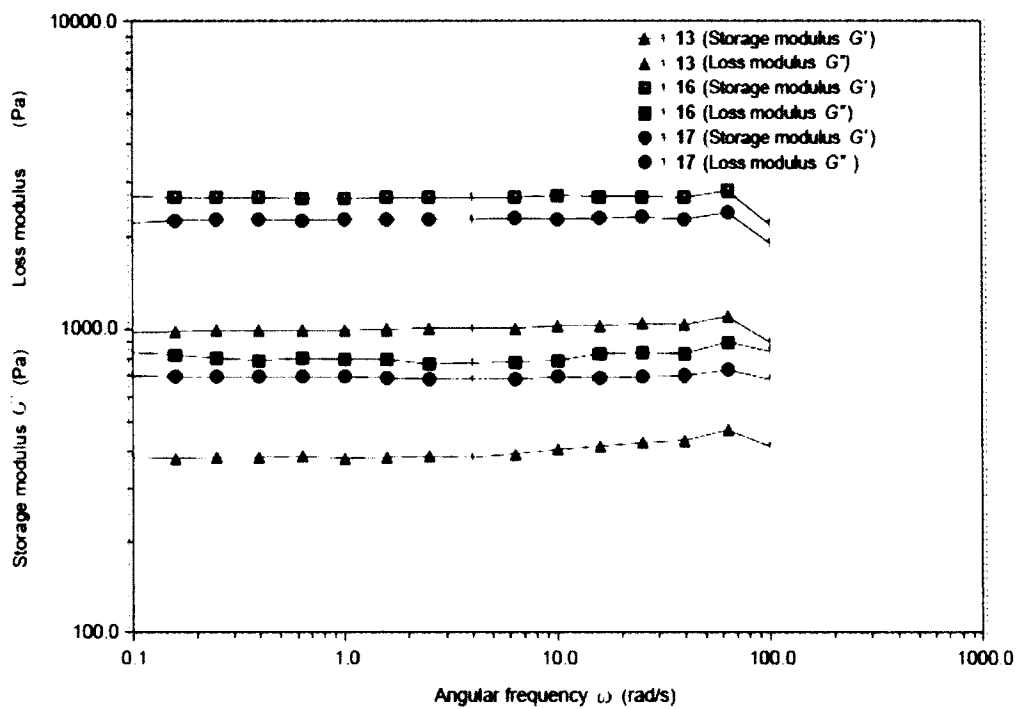
Figure 51. Viscoelastic properties urea derivatives 1) compound **13** in DMSO: Water: 1:2 in 2.2 mg/ mL 2) compound **16** in DMSO: Water: 1:2 in 2.2 mg/ mL 3) compound **17** in DMSO: Water: 1:2 in 5.0 mg/ mL.
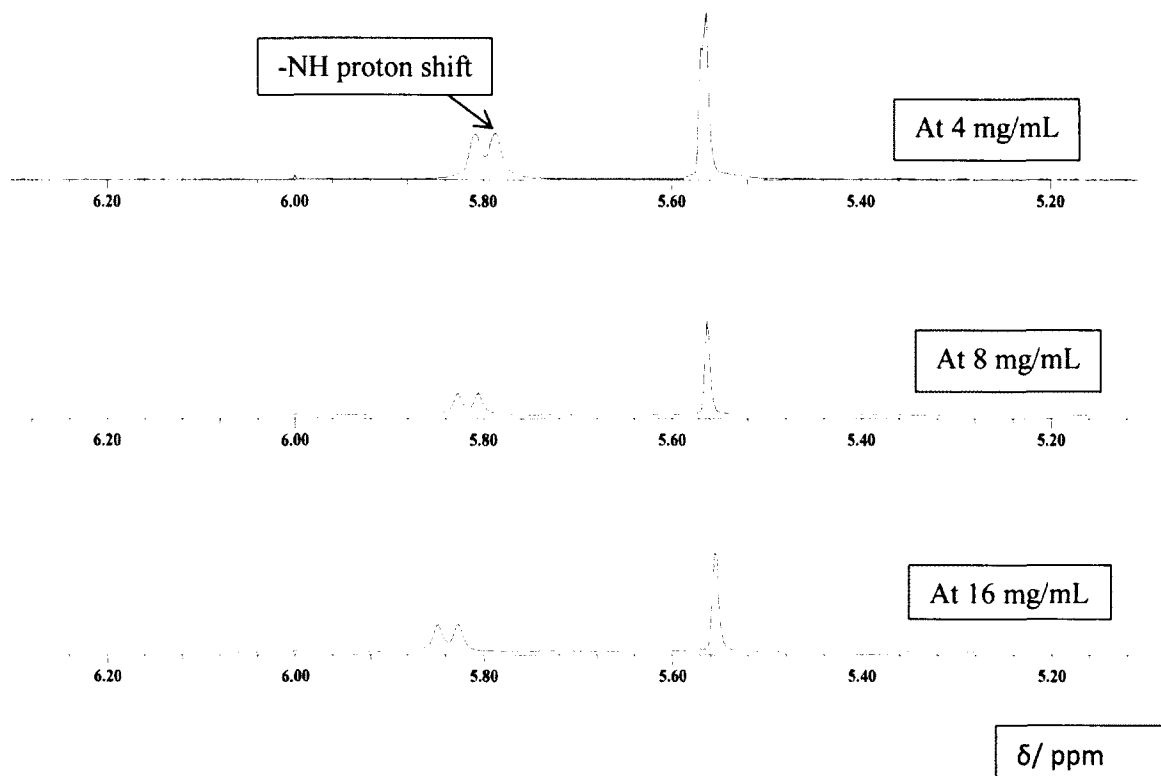
Figure 52. ^{1}H NMR spectra's for compound **6** at different concentration (each spectrum in 0.5 mL of CDCl$_3$).

To study the hydrogen bonding effect for the organo gelation, we have choosen compound **6** for this study. For this study four different concentrations from 4, 8 and 16 mg in 0.5 mL of CDCl$_3$ were studied. All the signal are almost same except at the NH-bond in amide at 5.8 ppm in the NMR signal shifted slighly downfield at 32 mg/mL concentration, as shown in **figure 52**. It shows that at higher concentration the molecules close to geather, and the NH bond shifted to downfiled because of hydrogen boning.
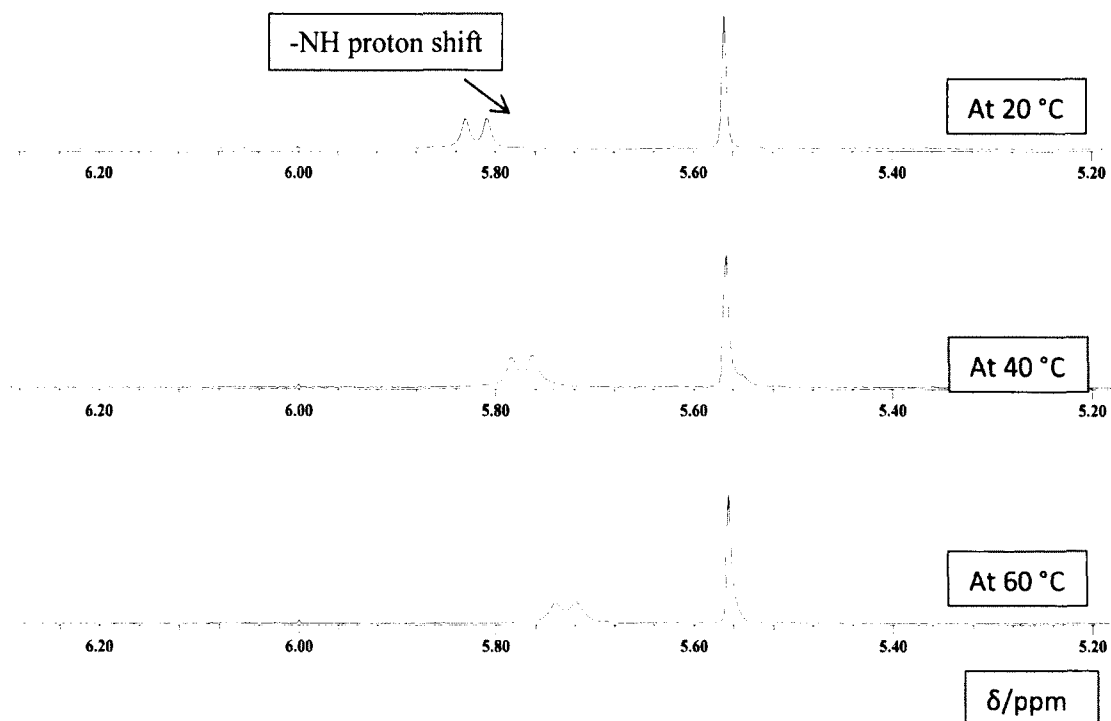
Figure 53. ^{1}H NMR spectra's for compound **8** (8 mg in 0.5 mL CDCl$_3$) at different temperatures.

We have aslo studied the hydrogen bonding effect for the gelation at different temperature. We have choosen one of the amide compound (**8**) for this study. From the **figure 53** shows that there is a slight change of NH absorption when incresing the temperature from 20 °C to 60 °C. All the signals are almost same except at the NH-bond in amide at 5.8ppm in the NMR signal shifted to upfield slightly This indicated that hydrogen bonding will effect the gelation property by varying the concentration and temperature for these amides. Proposed 1D- hydrogen boning for compound **8** shown in **figure 54**.
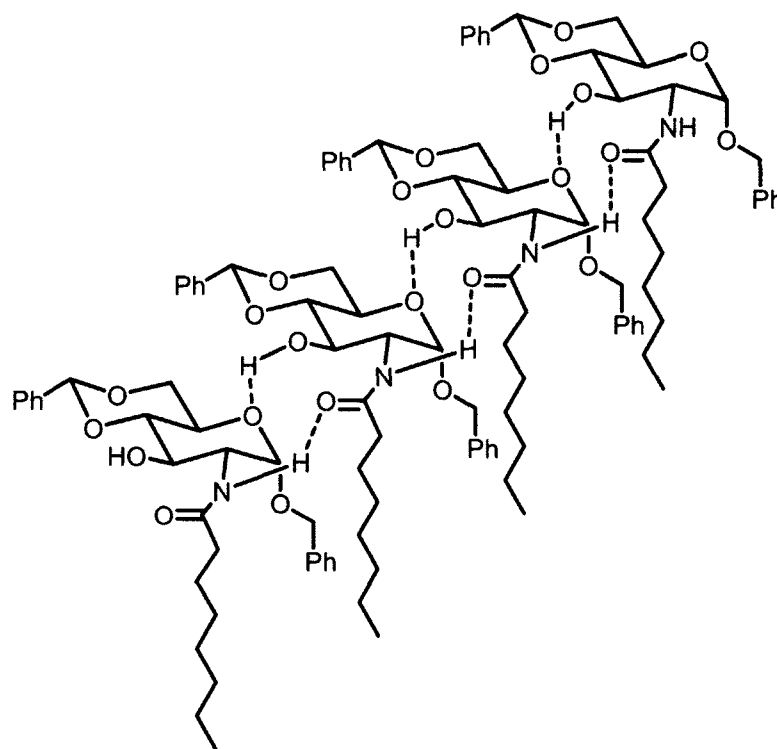
Figure 54. Proposed hydrogen bonding model for compound **8**.

For all these compounds the purity was tested by ^{1}H NMR, ^{13}C NMR spectra and LC-MS. For few compounds spectra's were shown in **figure 54** and **55**. Their chemical shift values were discussed in experimental section.

^{1}H NMR spectra (400 MHz, CDCl$_3$) and ^{13}C NMR spectra (100 MHz, CDCl$_3$):

Compound 4:
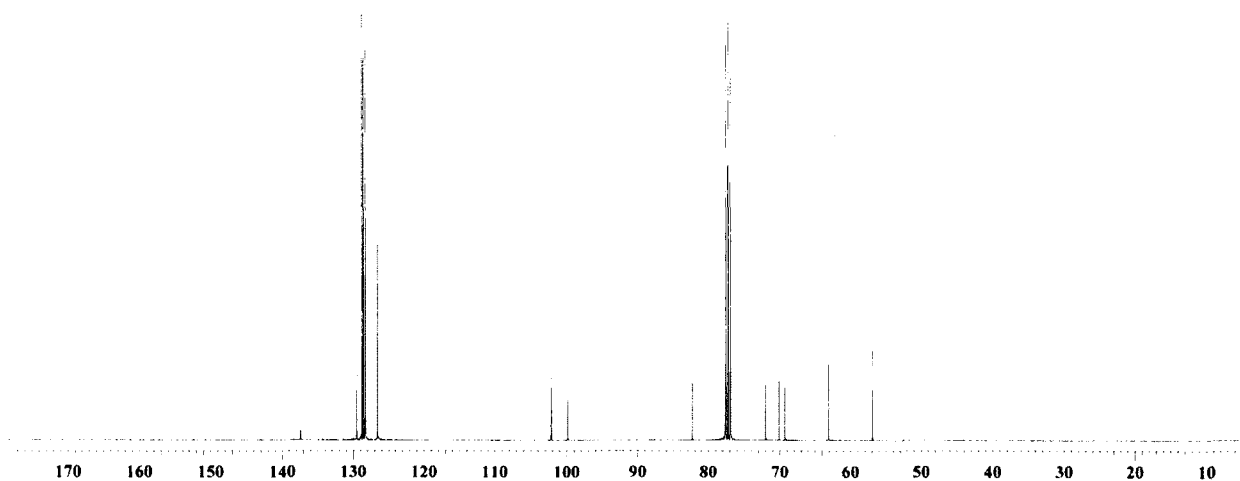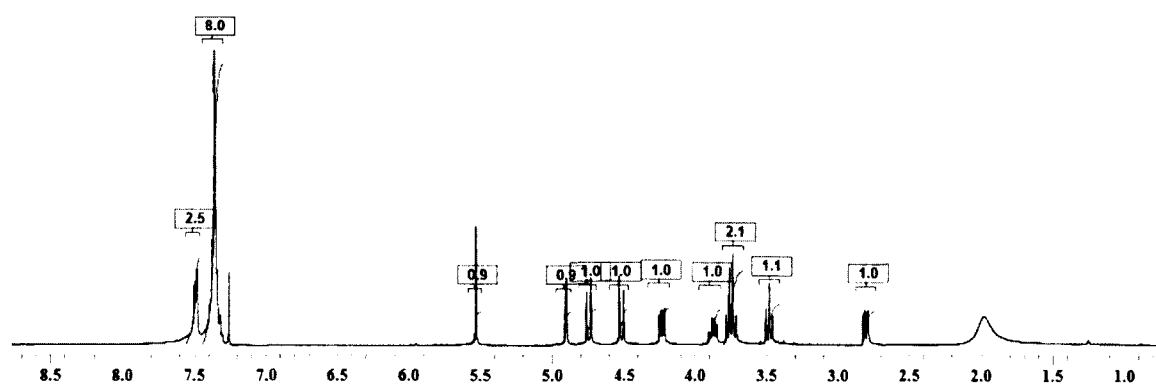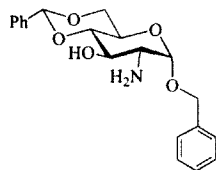
Figure 55. ^{1}H NMR (400MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra for compound **4**.

Compound (6):
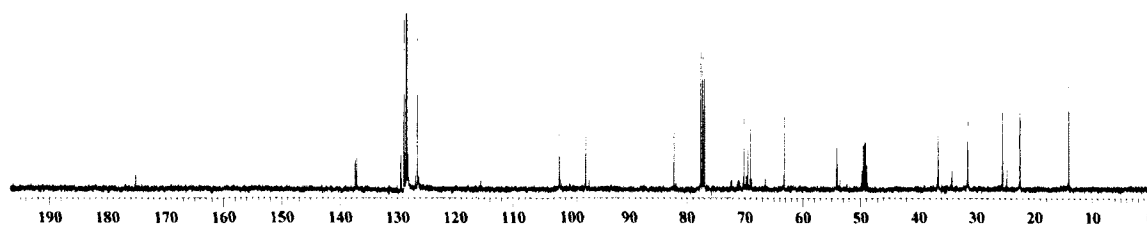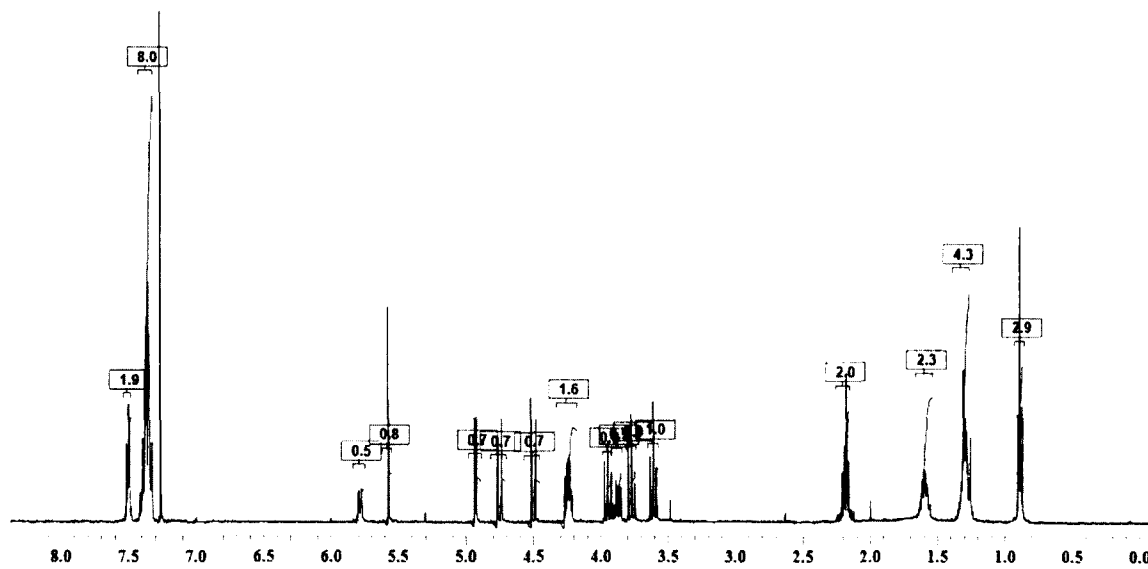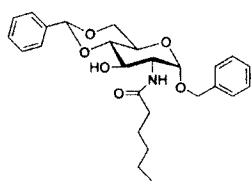
Figure 56. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}CNMR (100 MHz, CDCl$_3$) spectra for compound **6**.

4.3. CONCLUSIONS

In summary, we have designed and synthesized a series of alpha-O-benzyl glycoside of N-acetyl glucosamine analogs and obtained several effective organo/hydrogelators. In general, urea derivatives showed better gelation than amides. We have also studied the hydrogen bonding effect by varying temperature and concentration These organo/hydro gelators found in the current research can be explored for further applications in several systems. Future studies include the exploration of their effectiveness in enzyme immobilization, designing analytical tools to understanding molecular interactions, and as matrix for delivery of biological agents.

4.4. EXPERIMENTAL SECTION

General Methods

All reactions, unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. All the reagents and solvents were obtained from Sigma-Aldrich, VWR, and Fisher. Flash chromatography was carried out using silicycle 230-400 mesh silcagel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates, and visualized using UV light. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with Varian 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. Proton and carbon spectra chemical shifts were reported using TMS and $CDCl_3$ as internal standard at 0 ppm and at 77.00 ppm, respectively. Melting point was measured using fischer scientific instrument.

Gelation Testing: The compounds were tested in a 1 dram vial with a rubber lined screw cap from Kimble. A starting concentration of 20 mg/mL was used (2mg in 0.1mL). The suspension was heated to dissolve the compound (a homogeneous solution) and sonicated, if necessary. The solution was allowed to cool for 15-20 minutes. If a stable gel formed, 0.2-0.3 mL of the same solvent (or solvent mixture) was added and the heating/sonication and cooling was repeated. The process was repeated until the gel was no longer stable and the concentration prior to the unstable gel was recorded as the minimum gelation concentration (MGC).

Optical Microscopy: The slides were prepared after a stable gel has formed. About small amount of the gel was placed on a clean 3 by 1 inch glass slide and dried overnight to several days. The xerogels were observed with an Olympus BX60M optical microscope using a DSP Color Hi-Res EXvision camera and an Olympus U-TV1X lens. The program used to acquire and store the photos was Corel Photo-Paint 7.

Synthesis of b enzyl-4,6-O-benzylidene-2-deoxy-2-amino-α-D-glucopyranoside (4):

N-Acetyl-D-glucosamine 1 (2.0 g, 9.04 mmol) and p-toluene sulfonicacid (0.17 g, 0.9 mmol) were dissolved in 20.0 mL of toluene and 10 mL of benzyl alcohol. The reaction mixture was refluxed in a dean-stark apparatus with water removal by azeotropic mixture. After 12h, the solvent were removed under reduced pressure. Hexane: EtOAc (10:1) (20 mL) was added to the oily residue and stirred vigorously for 3h. The amorphous precipitate was filtered off, washed with hexane and the crude product was

recrystallized from ethanol to yield a colorless solid (2.31 g, 82 % yield). Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (1g, 3.23 mmol) was dissolved in anhydrous 6.0 mL of DMF, followed by benzaldehyde dimethyl acetal (0.6 mL, 3.87 mmol) and p-toluenesulfonic acid (0.055 g, 0.323 mmol) were mixed and heated at 90°C for 5hrs. After 2h and 4h excess methanol produced was removed under reduced pressure. Reaction was completed after 5h, reaction was quenched with NaHCO$_3$ and stirred the solution at room temperature for 30 min. Filtered the salt and DMF was removed under reduced pressure, the crude mixture was purified by recrystallization in isopropanol to get the desired product compound **3** as (1.1 g, 86%) white solid. Compound **3** (1g) was then dissolved in 25 mL of refluxing 3N KOH ethanol for 18 hours. Reaction was diluted with DCM (~30 mL) and water (2x20 mL). After drying the DCM layer over anhydrous sodium sulphate, the crude product was purified by column chromatography using 2% MeOH in DCM to get the desired as white solid with (0.71g, 79%).

The pure compound **4** was obtained as a white solid with 79% yield m.p. 177.0-179.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53-7.46 (m, 2H), 7.42-7.29 (m, 8H), 5.53 (s, 1H), 4.90 (d, 1H, J = 3.7 Hz), 4.74 (d, 1H, J = 11.8 Hz, CH_2Ph,), 4.52 (d, 1H, J = 11.8, CH_2Ph), 4.23 (dd, 1H, J = 4.8, 10.3 Hz), 3.88 (ddd~dt, 1H, J = 4.8, 9.5, 9.9 Hz), 3.76 (*pseudo* t, 1H, J = 9.2 Hz), 3.74 (*pseudo* t, 1H, J = 10.3 Hz), 3.48 (t, 1H, J = 9.2 Hz), 2.81 (dd, 1H, J = 3.7, 9.5 Hz), 1.98 (brs, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 137.2, 137.1, 129.2, 128.5, 128.3, 128.0, 126.3, 101.9, 99.5, 71.7, 69.8, 69.0, 62.9, 56.7.

General procedure for the synthesis of amides

To a 50 mL of round bottom flask 100 mg of compound (4) head group was dissolved in 3 mL of DCM and 3 equivalent of potassium carbonate or pyridine was added into the reaction flask. Cooled the reaction mixture at 0 °C and 1.1 equivalent of the corresponding acid chloride were added drop wise to the solution. The mixture was left stirring for 6-10 hrs, after which the mixture was concentrated under nitrogen. The crude residue was purified by flash chromatography using hexane/EtOAc (20:80). The resulting purified compound was tested for their gelation activity.

General procedure for the synthesis of ureas: The urea library was synthesized by mixing 100 mg of compound compound **4** and the corresponding isocyanate in stoichiometric quantities in anhydrous THF. The solution was stirred at room temperature for 3-5 h. The crude products were purified by flash chromatography on silica gel. DCM/MeOH (5%) gradient solvent system was used for the chromatography separation.

Benzyl-4,6-O-benzylidene-2-deoxy-2-Hexynoylamino-α-D-glucopyranoside (6):

The pure compound was obtained as a white solid with 91 mg (72 % yield), m.p. 178.0-180.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$+MeOD): δ 7.52-7.49 (m, 2H), 7.41-7.32 (m, 8H), 5.79 (d, 1H, J = 8.5), 5.51 (s, 1H), 4.93 (d, 1H, J = 3.9 Hz), 4.75 (d, 1H, J = 11.7 Hz, CH$_2$Ph), 4.50 (d, 1H , J = 11.7 Hz, CH$_2$Ph), 4.24 (m, 1H), 3.95 (t, 1H, J = 9.3 Hz), 3.88 (ddd~dt, 1H, J = 4.8, 9.5, 9.9 Hz), 3.77 (*pseudo* t, 1H, J = 9.1 Hz), 3.61 (*pseudo* t, 1H, J = 9.1 Hz), 3.41 (s, 3H), 2.18 (t, 2H , J = 7.3 Hz), 1.60 (m, 2H), 1.30 (m, 4H), 0.89 (t, 3H,

J = 7.2 Hz). ^{13}C (100 MHz, CDCl₃): δ 175.1, 137.2 , 137.0, 129.3, 128.7, 128.4, 128.3, 128.2, 126.4, 102.0, 97.5, 82.2, 70.1, 69.4, 68.9, 63.1, 54.1, 54.0, 36.5, 31.6, 28.9, 25.4, 22.4, 14.0. HRMS (ESI+) calcd for C₂₆H₃₃NO₆ [M+Na]⁺, 478.2200 found 478.2199.

Benzyl-4,6-O-benzylidene-2-deoxy-2-Heptanoylamino-α-D-glucopyranoside (7):

The pure compound was obtained as a white solid with 98 mg (75 % yield), m.p. 188.0-190.0 °C. ^{1}H NMR (400 MHz, CDCl₃+MeOD): δ 7.52-7.49 (m, 2H), 7.42-7.32 (m, 8H), 5.78 (d, 1H , *J* = 8.7 Hz), 5.57 (s, 1H), 4.75 (d, 1H, *J* = 3.9 Hz), 4.66 (d, 1H, *J* = 11.7 Hz, CH₂Ph), 4.50 (d, 1H, *J* = 11.7 Hz, CH₂Ph, CH₂Ph), 4.24 (m, 2H), 4.06 (t, 1H), 3.81 (m, 2H), 3.52 (t, 1H, *J* = 9.15 Hz), 2.25 (t, 2H, *J* = 7.3 Hz), 1.57 (m, 2H), 1.21 (m, 6H), 0.81 (t, 3H, *J* = 7.2 Hz) . ^{13}C (100 MHz, CDCl₃): δ 175.1,137.2, 137.0, 129.3, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 126.4, 102.0, 97.5, 82.2, 70.1, 68.9, 63.1, 54.1, 54.0, 36.6, 36.5, 34.1, 31.6, 25.4, 24.7, 22.6, 14.0. HRMS (ESI⁺) calcd for C₂₇H₃₃NO₆ [M+Na]⁺, 492.2356 found 492.2347.

Benzyl-4,6-O-benzylidene-2-deoxy-2-Octanoylamino-α-D-glucopyranoside (8):

The pure compound was obtained as a white solid with 0.105 g (78 % yield), m.p. 196.0-198.0 °C. ^{1}H NMR (400 MHz, CDCl₃+MeOD): δ 7.52-7.49 (m, 2H), 7.42-7.32 (m, 8H), 5.78 (d, 1H , *J* = 8.7 Hz), 5.57(s, 1H), 4.75 (d, 1H, *J* = 3.9 Hz), 4.66 (d, 1H, *J* = 11.7 Hz, CH₂Ph), 4.50 (d, 1H, *J* = 11.7 Hz, CH₂Ph, CH₂Ph), 4.24 (m, 2H), 4.06 (t, 1H), 3.81 (m, 2H), 3.52 (t, 1H, *J* = 9.15 Hz), 1.58 (m , 2H), 1.28 (m, 8H), 0.88 (t, 3H, *J* = 7.0 Hz). ^{13}C (100 MHz, CDCl₃ + MeOD): δ 175.0, 137.2, 137.0, 129.3, 128.7, 128.4, 128.3, 126.4,

102.0, 97.5, 82.2, 70.1, 69.5, 69.0, 63.1, 54.0, 36.6, 31.8, 29.3, 29.1, 25.8, 22.7, 14.1.

HRMS (ESI⁺) calcd for $C_{28}H_{37}NO_6$ [M+Na]⁺, 506.2513 found 506.2510.

Benzyl-4,6-O-benzylidene-2-deoxy-2-(5-Hexenoyl)-amino-α-D-glucopyranoside (9):

The pure compound was obtained as a white solid with 90 mg (72 % yield), m.p. 230.0-

232.0 °C. ¹H NMR (400 MHz, CDCl₃+MeOD): δ 7.52-7.45 (m, 2H), 7.40-7.29 (m, 8H),

6.19 (d, 1H, J = 8.7 Hz), 5.55 (s, 1H), 4.90 (d, 1H, J = 4.0 Hz), 4.72 (d, 1H, J = 11.7 Hz,

CH₂Ph), 4.46 (d, 1H, J = 11.7 Hz, CH₂Ph), 4.19 (m, 2H), 3.87 (m, 2H), 3.75 (t, 1H, J =

9.8 Hz), 3.57 (t, 1H, J = 9.5 Hz), 2.31 (m, 2H), 2.22 (m, 2H), 1.95 (t, 1H, J = 2.6 Hz),

1.80 (m, 2H). ¹³C (100 MHz, CDCl₃ + MeOD): δ 174.1, 137.0, 134.7, 129.2, 128.3,

126.3, 101.9, 98.8, 83.4, 82.0, 70.8, 69.3, 68.8, 62.3, 55.3, 53.5, 34.9, 24.2, 24.1, 17.6.

HRMS (ESI⁺) calcd for $C_{26}H_{29}NO_6$ [M+Na]⁺, 474.1887 found 474.1884.

Benzyl-4,6-O-benzylidene-2-deoxy-2-(6-Bromohexanoyl)-amino-α-D-

glucopyranoside (10):

The pure compound was obtained as a white solid with 0.125 g (84 % yield), m.p. 184.0-

186.0 °C. ¹H NMR (400 MHz, CDCl₃+MeOD): δ 7.52-7.45 (m, 2H), 7.40-7.29 (m, 8H),

6.19 (d, 1H, J = 8.7 Hz), 5.55 (s, 1H), 4.90 (d, 1H, J = 4.0 Hz), 4.72 (d, 1H, J = 11.7 Hz,

CH₂Ph), 4.46 (d, 1H, J = 11.7 Hz, CH₂Ph), 4.19 (m, 2H), 3.87 (m, 2H), 3.75 (t, 1H, J =

9.8 Hz), 3.57 (t, 1H, J = 9.5 Hz), 2.12 (m, 2H), 1.75 (m, 2H), 1.51(m, 2H), 1.35 (m,

2H). ¹³C (100 MHz, CDCl₃ + MeOD): δ 174.2, 136.8, 136.6, 129.0, 128.4, 128.0, 127.9,

126.1, 101.7, 97.2, 81.9, 69.8,69.0, 68.6, 62.8, 53.7, 35.8, 33.4, 32.1, 27.3, 24.4. HRMS

(ESI⁺) calcd for $C_{26}H_{32}BrNO_6$ [M+Na]⁺, 556.1305 found 556.1301.

Benzyl-4,6-O-benzylidene-2-deoxy-2-Benzoylamino-α-D-glucopyranoside (11):

The pure compound was obtained as a white solid with 0.102 g (82 % yield), m.p. 195-197 °C. ^{1}H NMR (400 MHz, CDCl$_3$+MeOD): δ 7.69-7.64 (m, 2H), 7.49-7.44 (m, 3H), 7.39-7.34 (m, 3H), 7.36-7.24 (m, 7H), 6.19 (d, 1H, J = 8.7 Hz), 5.53(s, 1H), 5.02 (d, 1H, J = 3.6 Hz), 4.72 (d, 1H, J = 12.0 Hz, CH$_2$Ph), 4.46 (d, 1H, J = 12.0 Hz, CH$_2$Ph), 4.19 (m, 2H), 3.87 (m, 2H), 3.75 (t, 1H, J = 9.8 Hz), 3.62 (t, 1H, J = 9.5 Hz). ^{13}C (100 MHz, CDCl$_3$ + MeOD): δ 168.8, 137.3, 137.0, 132.0, 129.4, 128.85, 128.80, 128.7, 128.5, 127.3, 127.0, 126.3, 126.5, 102.1, 97.6, 82.3, 70.3, 69.6, 69.0, 63.2, 54.7. HRMS (ESI$^+$) calcd for C$_{27}$H$_{27}$NO$_6$ [M+Na]$^+$, 484.4962 found 484.4958.

Benzyl-4,6-O-benzylidene-2-deoxy-2-Naphthoyalamino-α-D-glucopyranoside (12):

The pure compound was obtained as a white solid with 0.114 g (80 % yield), m.p. 236.0-238.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$+MeOD):): δ 7.71-7.67(m, 2H), 7.59-7.49 (m, 3H), 7.45-7.34 (m, 12H), 6.51 (d, 1H, J = 8.7 Hz), 5.59(s, 1H), 5.05 (d, 1H, J = 4.0 Hz), 4.78 (d, 1H, J = 11.7 Hz, CH$_2$Ph), 4.54 (d, 1H, J = 12.0 Hz, CH$_2$Ph), 4.44 (m, 1H), 4.28 (dd, 1H, J = 10.2, 5.1 Hz), 4.08 (t, 1H, J = 9.1 Hz), 3.95 (ddd~dt, 1H, J = 5.1, 9.8, 10.5 Hz), 3.80 (t, 1H, J = 10.2 Hz), 3.68 (t, 1H, J = 9.5 Hz). ^{13}C (100 MHz, CDCl$_3$ + MeOD): δ 170.3, 136.6, 137.0, 136.2,133.1, 130.4, 129.5, 128.7, 128.1, 127.8, 127.7, 126.7, 125.9, 125.8, 124.8, 124.7, 124.2, 101.4, 97.4, 81.7, 69.4, 69.5, 68.8, 68.3, 62.6, 54.1. HRMS (ESI$^+$) calcd for C$_{31}$H$_{29}$NO$_6$ [M+Na]$^+$, 534.1887 found 534.1883.

Compound (13):

The pure compound was obtained as a white solid with 0.125 g (92 % yield), m.p. 248.0-250.0 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.46 -7.41 (m, 2H), 7.39 -7.31 (m, 4H), 7.32 -7.25 (m, 4H), 7.14 (t, 1H, J = 6.2 Hz), 6.73 (d, 1H, J = 8.5 Hz), 5.84 (m, 2H), 5.59 (s, 1H), 5.30 (d, 1H, J = 3.1 Hz), 4.78 (d, 1H, J = 12.4 Hz, CH$_2$Ph), 4.58 (d, 1H, J = 8.0 Hz), 4.50 (d, 1H, J = 12.4 Hz, CH$_2$Ph) 4.22 (dd, 1H, J = 10.6, 3.6 Hz), 3.73 (t, 1H, J = 9.5 Hz), 3.56 (m, 1H), 1.77-1.67 (m, 2H), 1.66-1.57 (m, 2H), 1.54-1.47 (m, 2H), 1.27-1.18 (m, 2H), 1.14-1.00 (m, 2H). ^{13}C (100 MHz, DMSO): δ 157.0, 137.5, 128.4, 127.9, 127.6, 127.2, 126.0, 100.5, 97.5, 81.5, 68.3, 67.8, 62.6, 54.5, 47.4, 33.0, 25.0, 24.0. HRMS (ESI$^+$) calcd for C$_{27}$H$_{34}$N$_2$O$_6$ [M+Na]$^+$, 505.2309 found 505.2305.

Compound (14):

The pure compound was obtained as a white solid with 0.106 g (77 % yield), m.p. 190.0-192.0 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.48 -7.45 (m, 2H), 7.42 -7.30 (m, 8H), 6.13 (t, 1H, J = 5.4 Hz), 5.82 (d, 1H, J = 8.5 Hz), 4.85 (d, 1H, J = 3.1 Hz), 4.72 (d, 1H, J = 12.4 Hz, CH$_2$Ph), 4.50 (d, 1H, J = 12.4 Hz, CH$_2$Ph), 4.16 (dd, 1H, J = 3.8, 9.8 Hz), 3.60 (t, 1H, J = 8.5 Hz), 3.52 (t, 1H, J = 8.5 Hz), 2.99 (m, 2H), 1.37 (m, 2H), 1.27 (m, 6H), 0.83 (t, 3H, J = 7.0 Hz). ^{13}C (100 MHz, DMSO): δ175.1, 137.2 , 137.0, 129.3, 128.7, 128.4, 128.3, 128.2, 126.4, 102.0, 97.5, 82.2, 70.1, 69.4, 68.9, 63.1, 54.1, 54.0, 36.5, 31.6, 28.9, 25.4, 22.4, 14.0. HRMS (ESI$^+$) calcd for C$_{27}$H$_{36}$N$_2$O$_6$ [M+Na]$^+$, 507.2465 found 507.2463.

Compound (15):

The pure compound was obtained as a white solid with 0.116 g (82 % yield), m.p. 196.0-198.0 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.47 -7.41 (m, 2H), 7.39 -7.24 (m, 8H), 6.09 (m, 1H), 5.79 (d, 1H, J = 3.6Hz), 5.62(s, 1H), 5.23 (d, 2H, J = 3.6 Hz), 4.82 (d, 1H, J = 3.6 Hz), 4.70 (d, 1H, J = 9.3 Hz, CH$_2$Ph), 4.47 (d, 1H, J = 9.3 Hz, CH$_2$Ph), 4.13 (m, 1H), 3.71 (m, 3H), 3.52 (m, 2H), 2.96 (m, 2H), 1.34 (m, 2H), 1.22 (m, 8H), 0.83 (m, 3H). ^{13}C (100 MHz, DMSO): δ 175.1,137.2, 137.0, 129.3, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 126.4, 102.0, 97.5, 82.2, 70.1, 68.9, 63.1, 54.1, 54.0, 36.6, 36.5, 34.1, 31.6, 25.4, 24.7, 22.6, 14.0. HRMS (ESI$^+$) calcd for $C_{28}H_{38}N_2O_6$ [M+Na]$^+$, 521.2622 found 521.2619.

Compound (16):

The pure compound was obtained as a white solid with 0.118 g (85 % yield), m.p. 234.0-236.0 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.45-7.41 (m, 2H), 7.39-7.32 (m, 7H), 7.31-7.26 (m, 3H), 7.25-7.20 (m, 2H), 6.60 (t, 1H, J = 5.4 Hz), 5.99 (d, 1H, J = 8.5 Hz), 5.62 (s, 1H), 5.23 (d, 2H, J = 5.4 Hz), 4.72 (d, 1H, J = 11.7 Hz, CH$_2$Ph), 4.50 (d, 1H, J = 11.7 Hz, CH$_2$Ph), 4.23 (m, 2H), 4.16 (m, 1H), 3.75 (m, 3H), 3.61(m, 1H), 3.52 (t, 1H, J = 8.5 Hz). ^{13}C (100 MHz, DMSO): δ 158.1, 140.4, 137.5, 128.7, 128.2, 128.1, 179.9, 127.58, 127.54, 126.9, 126.5, 126.3, 100.8, 97.8, 81.9, 68.8, 68.5, 68.0, 62.9, 54.9, 42.9. HRMS (ESI$^+$) calcd for $C_{28}H_{30}N_2O_6$ [M+Na]$^+$, 513.1996 found 513.1992.

Compound (17):

The pure compound was obtained as a white solid with 0.112 g (83 % yield), m.p. 230.0-232.0 °C. δ 8.72 (s, 1H), 7.47-7.43 (m, 2H), 7.39-7.32 (m, 7H), 7.31-7.26 (m, 3H), 7.23-7.19 (m, 2H), 6.90 (t, 1H, J = 7.0 Hz), 6.25 (d, 1H, J = 8.5 Hz), 5.63(s, 1H), 5.93 (d, 2H, J = 3.1 Hz), 4.74 (d, 1H, J = 12.4 Hz, CH_2Ph), 4.53 (d, 1H, J = 12.4 Hz, CH_2Ph), 4.17 (dd, 1H, J = 8.5, 3.9 Hz), 3.75 (m, 3H), 3.61(m, 1H), 3.52(t, 1H, J = 8.5 Hz). ^{13}C (100 MHz, DMSO): δ 154.8, 140.2, 139.6, 137.5, 128.7, 128.68, 128.61, 127.9, 127.57, 127.51, 126.3, 121.6, 121.0, 118.0, 117.3, 100.7, 97.7, 81.7, 68.6, 68.3, 67.9, 62.9, 54.8, 54.2, 48.3. HRMS (ESI$^+$) calcd for $C_{27}H_{28}N_2O_6$ [M+Na]$^+$, 499.1839 found 499.1836.

CHAPTER 5

EFFICIENT SYNTHESIS OF ENANTIOPURE SULFINAMIDES AND SULFINYL KETIMINES

5.1. INTRODUCTION

Chiral amine containing compounds represent an extremely important class of compounds in pharmaceutical industry. Chiral sulfinamide mediated chemistry has become one of the most active methods for the synthesis of compounds containing chiral amine functionalities.[156-159] These chiral sulfinamide have potential application in the field of chiral ligands for many catalytic asymmetric transformations.[160-162] Although the potential of chiral sulfinamides has long been recognized, only a few methods have been developed for the preparation of enantiomerically pure *tert*-butanesulfinamide. Among the prominent work on chiral sulfinamide reported by different groups, one of the methods is from the Davis et al.[163] For the synthesis of *p*-toluenesulfinamide from Anderson's reagent, another method was reported by Ellman and co-workers[164a] for the synthesis of *tert*-butanesulfinamide from *tert*-butyl *tert*-butanethiosulfinate, and other methods.[164b-166] However, these methods cannot meet the demand for accessing sulfinamides with diverse structures, which are required to fine-tune stereoselectivities in asymmetric synthesis. To meet this need, soon after the report from the group of Ellman, Senanayake and his group designed and developed a versatile cyclic-oxathiozolidinone-based chiral sulfinyl-transfer agent which provides access to a range of sulfinamides with diverse structures (**Scheme 19**).[167]

The accomplishment of this method based on the recognition that the reactivity of the cyclic oxathiozolidinone **2** could be activated by an electron-withdrawing substituent on the nitrogen atom, thus allowing for the facile cleavage of the sulphur-nitrogen bond to provide the desired sulfinate intermediate **3**.[53a] However the reaction conditions required for the cleavage of the sulphur-oxygen bond in **3** to liberate the desired sulfinamides relied heavily on the steric bulkiness of the R substituent.[167] While the sulphur-oxygen bond could be readily cleaved with LHMDS at 0 °C to room temperature to generate some sulfinamides, in the case of hindered substrates, the use of excess NH_2Li/NH_3 (Li/NH_3) was required. Currently, NH_2Li/NH_3 is prepared *in situ* by portion wise addition of a large excess of solid Li metal to anhydrous NH_3 at reaction temperatures of less than -70 °C.[53a,167] These reaction conditions, in addition to the safe handling and disposal of waste generated by using NH_2Li/NH_3, have limited our ability to produce these important sulfinamides on large scale. Therefore, the efficient and practical synthesis of sterically hindered chiral sulfinamides remained an unsolved problem in the field. By knowing that the steric environment provided by the bulky alkyl or aryl substituents of the sulfinamides is critical for obtaining high stereoselectivities,[170-171] it was highly necessary to develop a more practical and cost-effective process for their synthesis by replacing NH_2Li/NH_3 with a safer and greener reagent such as LHMDS for the final sulphur-oxygen bond cleavage.[168] We envisioned that this goal could be achieved by tuning the sulphur-oxygen bond reactivity in our cyclic oxathiozolidinone templates.

Scheme 19. Methods for the synthesis of sulfinamides

$$
\begin{array}{ccccc}
\mathbf{1} & \xrightarrow{SOCl_2} & \mathbf{2} & \xrightarrow{RMgX} & \mathbf{3}
\end{array}
$$

LHMDS

S-O bond

Cleavage

require excess
NH$_2$Li/NH$_3$
no reaction with
LHMDS

R''—S(O)—NH$_2$
R = Me, Ethyl, Phenyl

R''—S(O)—NH$_2$
4
R = t-butyl, Triisopropylphenyl
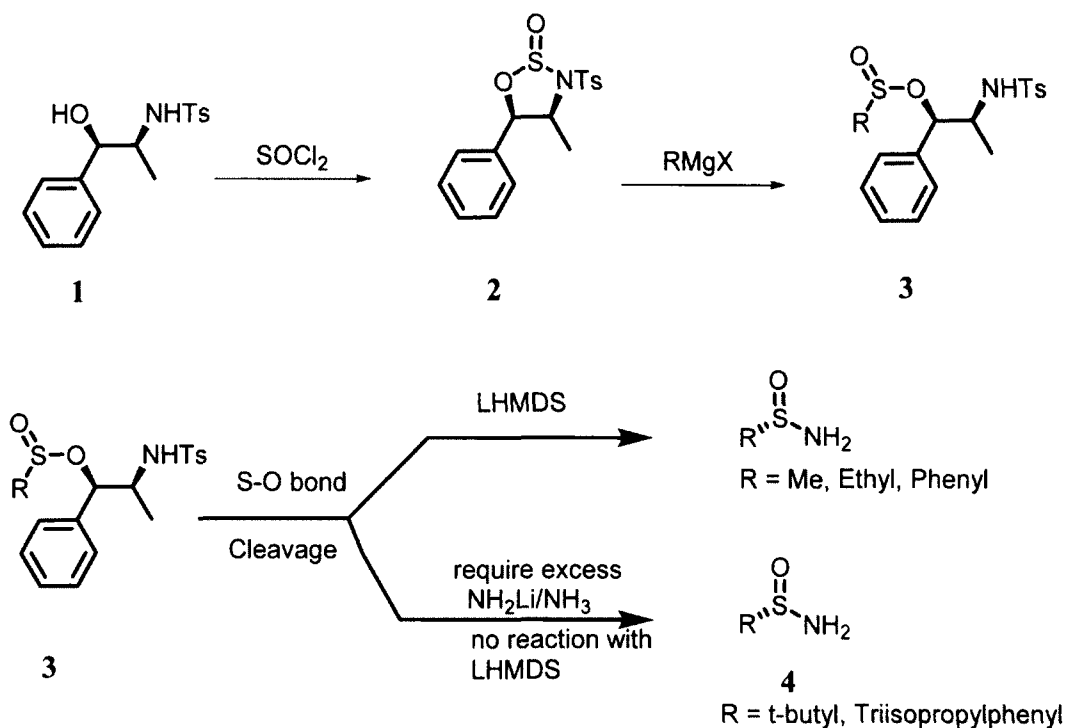
5.2. RESULTS AND DISCUSSIONS

Herein, we report a new chiral sulfinyl-transfer agent containing a more activated sulphur-oxygen bond, from which both sterically hindered enantiopure sulfinamides and sulfinyl ketimines were prepared under mild reaction conditions. To identify a template with a more reactive sulphur-oxygen bond, the presence of an electron-withdrawing substituent on the phenol ring increased the reactivity, whereas the reactivity was attenuated with an electron-donating group. The effect of sterics on the reactivity of the sulphur-oxygen bond was also observed.[172-179]

It was planned that optically pure **6** could be efficiently accessed on large scale from the simple and commercially available chiral aminophenol **5**.[179] After screening several reaction conditions, it was found that slow addition of pyridine to a solution of **5a** and SOCl$_2$ at −40 °C provided the desired product with excellent selectivity. The reaction temperature has negligible effect on the selectivity, with minimal erosion of the d.r. value noted when the reaction temperature was increased from −40 °C to 0 °C. Despite the promising profile of this chiral template, crystallization of **6a** to diastereomerically pure material proved highly challenging. Modification of the sulfonyl group on the nitrogen atom did not improve the crystallinity of **6a**. The *para*-chloro-substituted phenol derivative **5 b** that has been used successfully in the synthesis of p-chiral phosphine oxides[179] was subsequently examined. Analogous reaction conditions afforded **6b** with equally high selectivity. Again, raising the temperature did not adversely affect the selectivity. In contrast to **6a**, **6b** was readily obtained by recrystallization from EtOAc/ heptanes in diastereomerically pure form (>99.5:0.5 d.r) with an *S* configuration at the sulfur center as confirmed by a single-crystal X-ray structure.

Scheme 20. Screening for the synthesis of compound **6**
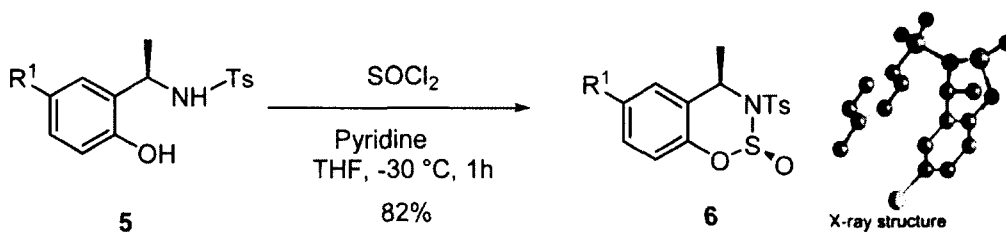
Table 7. Conditions surveyed for the synthesis of **6**

Entry	5	R¹	Base	T [°C]	6	d.r
1	**5a**	H	Pyridine	-40	**6a**	98:2
2	**5a**	H	Pyridine	-15	**6a**	98:2
3	**5a**	H	Pyridine	0	**6a**	97:3
4	**5b**	Cl	Pyridine	-40	**6b**	99:1
5	**5b**	Cl	Pyridine	-10	**6b**	98:2
6	**5b**	Cl	Pyridine	0	**6b**	98:2

With sufficient quantities of the chiral template **6b** in hand, the evaluation of the synthesis of (R)-tBSA (**8a**) by cleavage of the S-N bond with tert-butylmagnesium chloride and subsequent cleavage of the S-O bond upon addition of LHMDS was initiated (**Table 8**). Addition of tBuMgCl to **6** in THF at −30 °C selectively cleaved the sulphur-nitrogen bond, thus providing the diastereomerically pure, stable, and crystalline sulfinate ester **7a** in 91% yield. Then treatment of **7a** with LHMDS in THF at −10 °C to 0 °C cleaved the sulphur-oxygen bond effectively in quantitative conversion. After quenching the reaction with aqueous NH₄Cl solution, enantiopure (R)-tBSA (**8a**) was isolated in 90% yield and 99.7:0.3 e.r. Temperatures from -60 °C to −10 °C for the Grignard addition and 0 °C for the LHMDS addition did not result in any loss of the enantiomeric purity of **8a**.

This efficient and simple method was further demonstrated in the synthesis of other sterically hindered sulfinamides (**Scheme 59, Table 8**). A variety of structurally diverse and sterically hindered alkyl and aryl sulfinamides were readily synthesized in high yields and e.r. values. In the case of **8d** and **8e**, a slight decrease in enantiopurity was observed when the LHMDS addition was performed at higher temperature. An excellent e.r. value (99:1) was obtained if the addition was started at −78 °C or by addition of 0.2 equivalents of MgBr$_2$·OEt$_2$. Additionally, it has been demonstrated that the double nucleophilic substitution can be carried out by a one-pot protocol.[180] But this method is not effective for the synthesis of simple aryl sulfinamides, because after the sulfinate ester was obtained, it reacted immediately with aryl Grignards and mainly sulfoxide byproduct were obtained.

Scheme 21. Synthesis of variety of sulfinmides using new chiral auxiliary
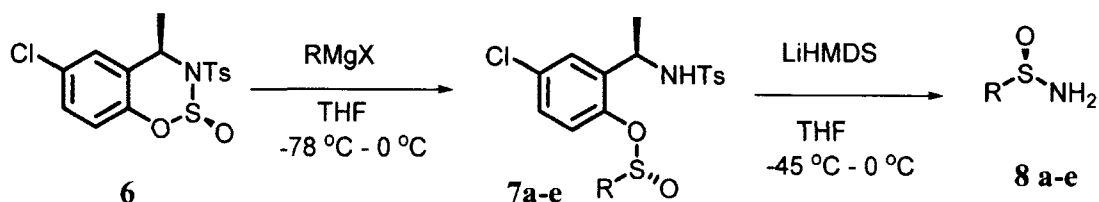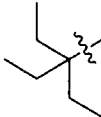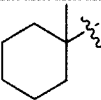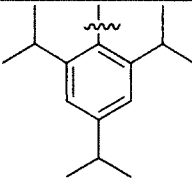
Table 8. Synthesis of variety of sulfinate ester and sulfinmides

Compound	R	Yield (%)	Compound	Yield (%)	enantiomeric ratio (er)
7a		91	**8a**	89	99.7:0.3
7b		85	**8b**	84	98.8:1.2
7c		75	**8c**	82	98.8:1.2
7d		88	**8d**	91	99:1
7e		68	**8e**	48	99.9:0.1

To highlight the utility of this new process, the scope of this chemistry was extended to the direct synthesis of sterically hindered chiral sulfinyl ketimines (**9a-e**). Ketimines can be synthesized by addition of an imine nucleophile to the sulfinate esters **7a-e** (**Table 8**). Sulfinyl ketimines are key intermediates in the synthesis of chiral amine compounds and their synthesis has been carried out by condensation of a ketone with sulfinamide in the presence of a Lewis acid, such as tetra alkoxy titanium. However, when sterically hindered ketones are employed, the yield decreases even under forcing reaction

conditions. Therefore, the synthesis of 9a-e from **7a-e** would allow for an efficient and direct synthesis of sterically hindered sulfinyl ketimines shown in **scheme 22**.
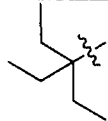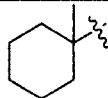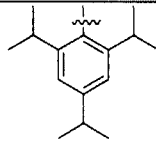
The synthesis of (S)-N-(tert-butyl-phenylmethylidene)-2-tert-butane-2-sulfinamide **9a** was first explored. Addition of tBuLi at −78 °C to benzonitrile in THF generated the lithium imide, which was then slowly added to **8a** in THF at −78 °C. This hindered lithiumimide readily cleaves the sulphur-oxygen bond to yield sulfinyl ketimine **9a** in good yield upon isolation and greater than 99:1 e.r., exclusively as one E/Z isomer (**Table 9**). Increasing the reaction temperature led to decreased enantiopurity 90:10 e.r. for **9a** at −40 °C. Conversely, under the same reaction conditions, the synthesis of **9a** using the sulfinate **3** failed to provide the desired product and no reaction was observed in **scheme 19**. This result clearly demonstrates the higher reactivity of the sulphur-oxygen bond in the phenol backbone.

Scheme 22. Synthesis of variety of ketimines and amines

9 a-e   **10 a-e**
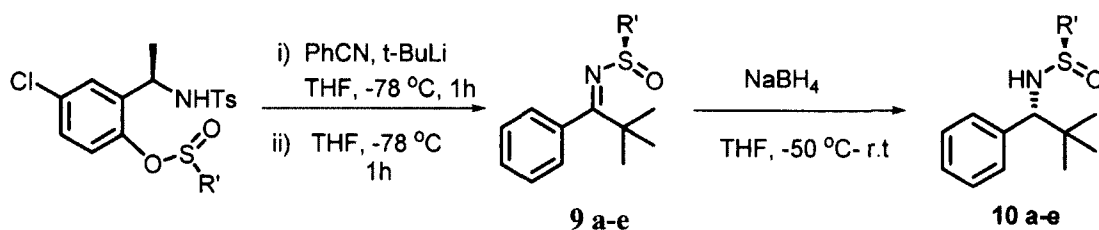
As presented in table **9**, a variety of hindered ketimines were prepared by following this sequence. Ketimines with different alkyl functionalities (**9 a, c, d**) were prepared in good yields and excellent selectivities. The ketamine **9e**, containing a hindered aryl group, was also prepared in good yield and 98:2 e.r.

Table 9. Synthesis of sterically hindered chiral ketimines and amines

Compound	R'	Yield (%)	er	Compound	Yield (%)	dr
9a		85	99:1	**10a**	99	93:7
9c		91	99.5:0.5	**10c**	95	94:6
9d		78	98.3:1.6	**10d**	98	95:5
9e		71	98.4:1.5	**10e**	97	>99:1

For comparison, only 20 % yield was obtained from the condensation reaction between TIPP sulfinamide (TIPPSA) and the ketone. It is worth pointing out that ketimines with different sulfinyl groups would provide an avenue for fine-tuning the stereoselectivity in the synthesis of chiral amines by either reduction or nucleophilic addition. While direct synthesis of nonhindered chiral ketimines using Anderson's reagent was previously reported, our newly developed chiral template allows an efficient and direct synthesis of structurally diverse bulky chiral sulfinyl ketimines by stereoselective substitution of a chiral sulfinate.[181-183]

The reduction of **9** in the synthesis of the chiral amine **10** was initially studied to understand the effect of the alkyl and arylsulfinyl groups on the stereoselectivity. Reduction

of **9a** with different reducing reagents was first examined. We have examined NaBH₄, L-selectride, and 9-BBN, out of these three reducing agents NaBH₄ in THF gave the best selectivity, thus providing **10a** in 93:7 d.r.[184] and almost quantitative yield. The same reaction conditions were then applied to other substrates. Similar selectivities were observed when other alkylsulfinyl groups were used (**10c, d**). However, better selectivity was observed when the triisopropyl sulfinyl group was used, and only one diastereomer of **10e** was observed. The effect of the sulfinyl group on the selectivity is obvious and the application of this method in the synthesis of other chiral amines under different reactions conditions is under further exploration.

For all these compounds the purity was tested by ¹H NMR, ¹³C NMR spectra and LC-MS. For few compounds spectra's were shown in **Figure 57, 58, 59, 60** and **61**. Their chemical shift values were discussed in experimental section.

^{1}H NMR and ^{13}C NMR spectra:

Compound 7c:
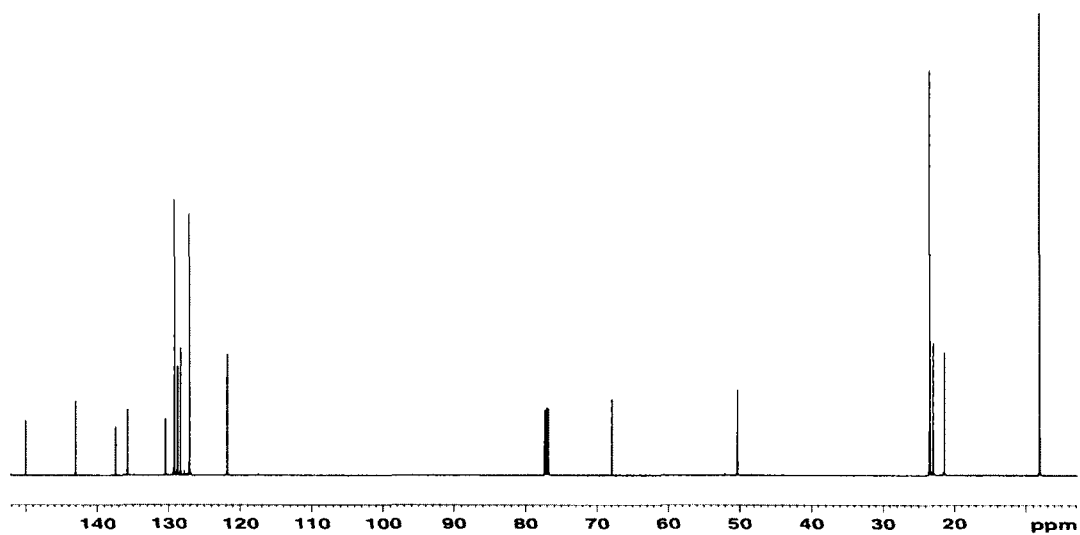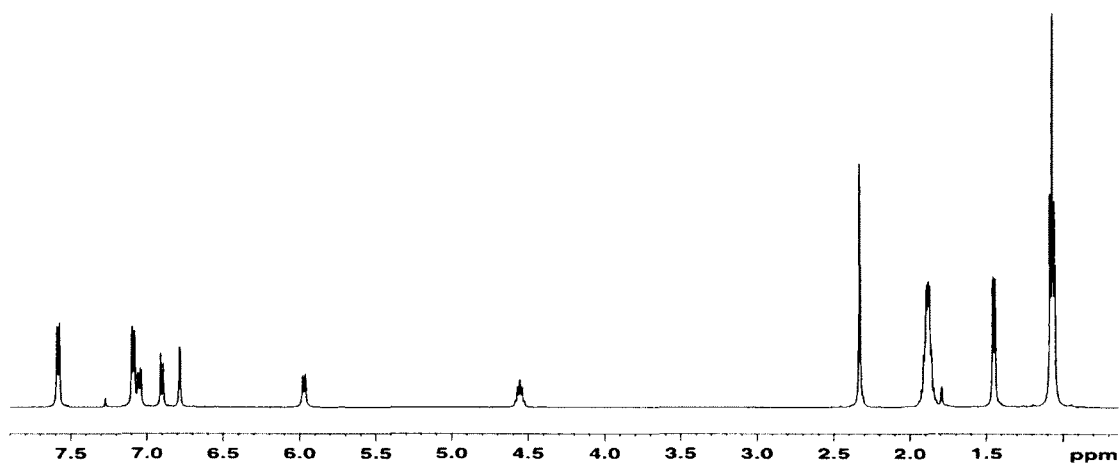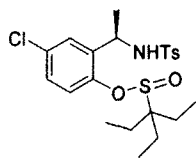
Figure 57. ^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) spectra for compound **7c**.

Compound 8c:
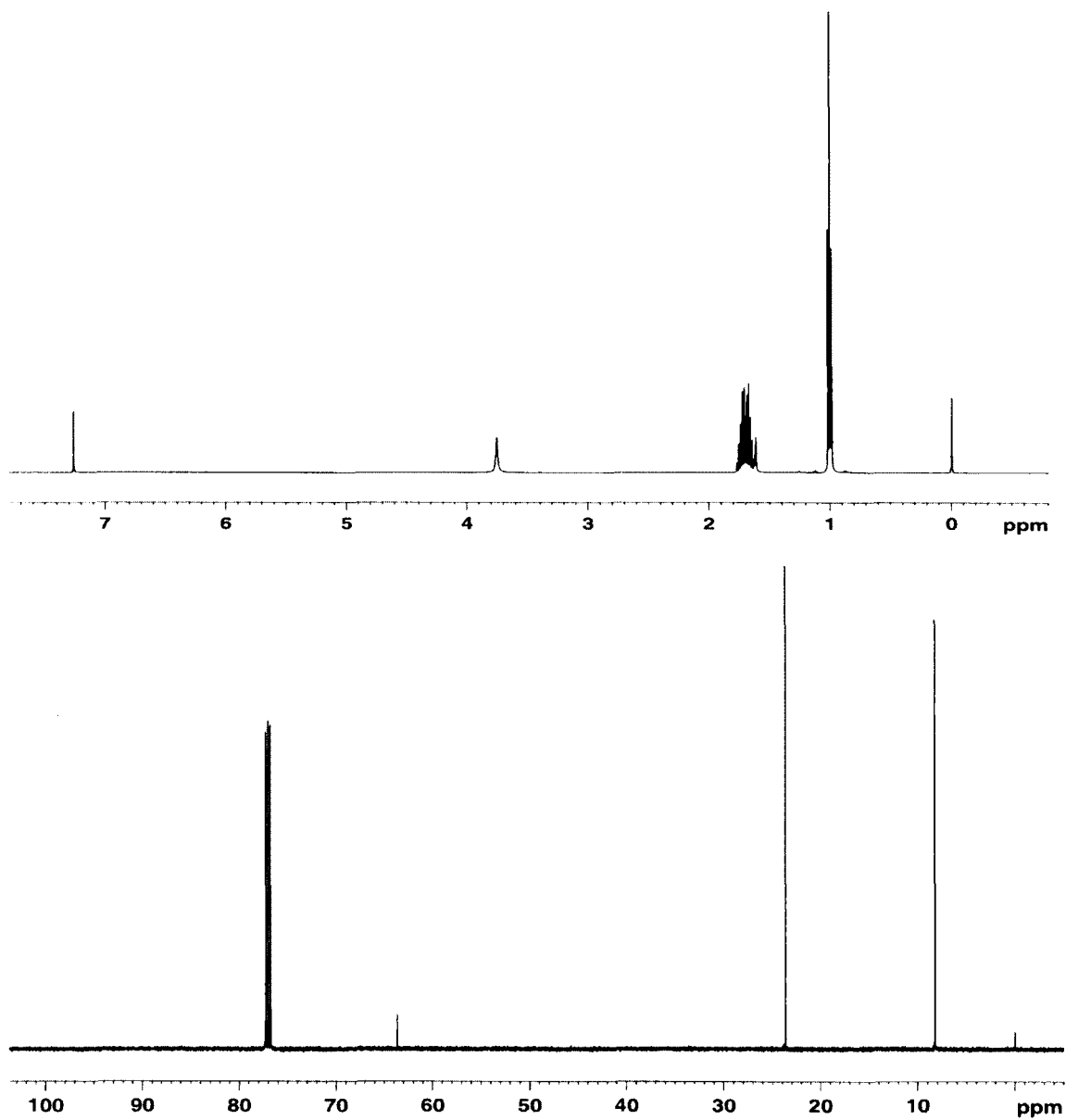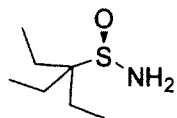
Figure 58. ^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) spectra for compound **8c**.

Compound 9c:
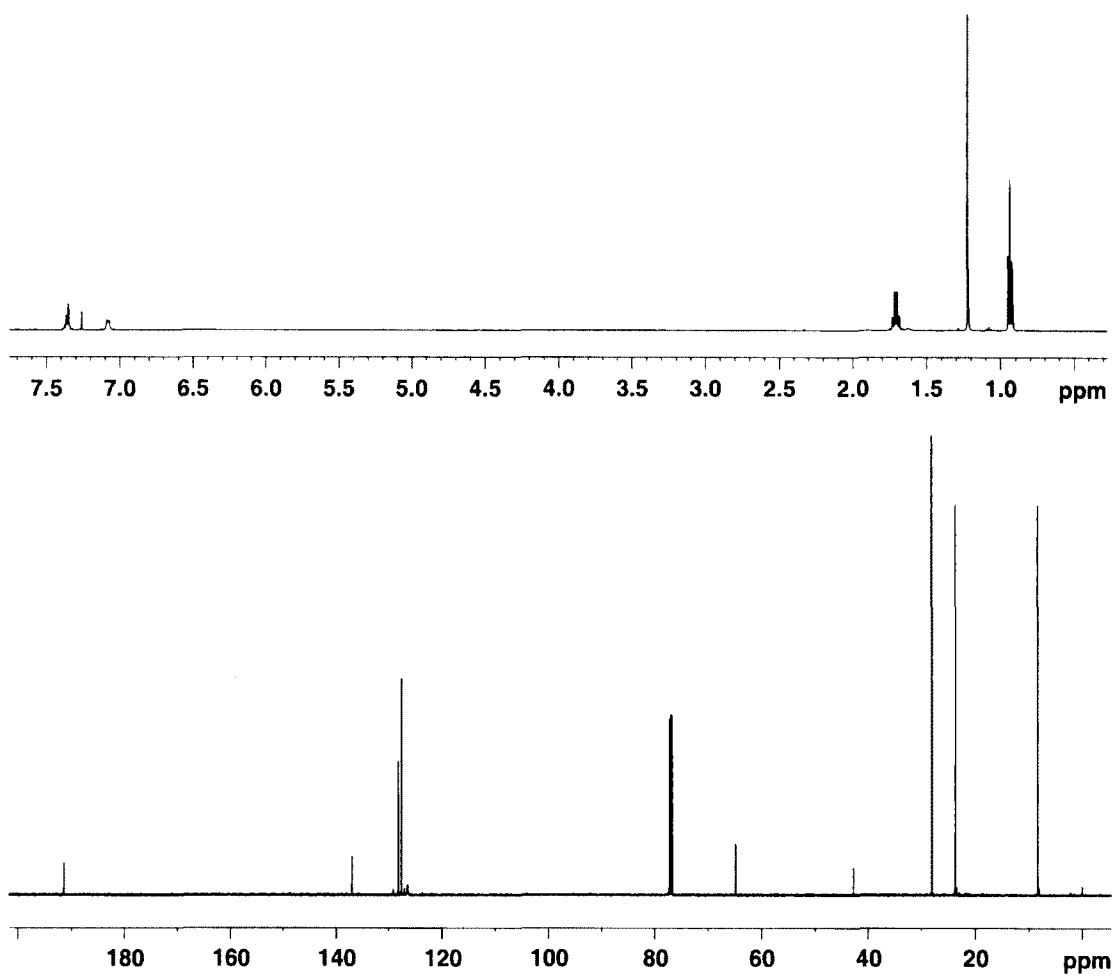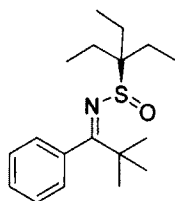
Figure 59. ^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) spectra for compound **9c**.

Compound 10d:
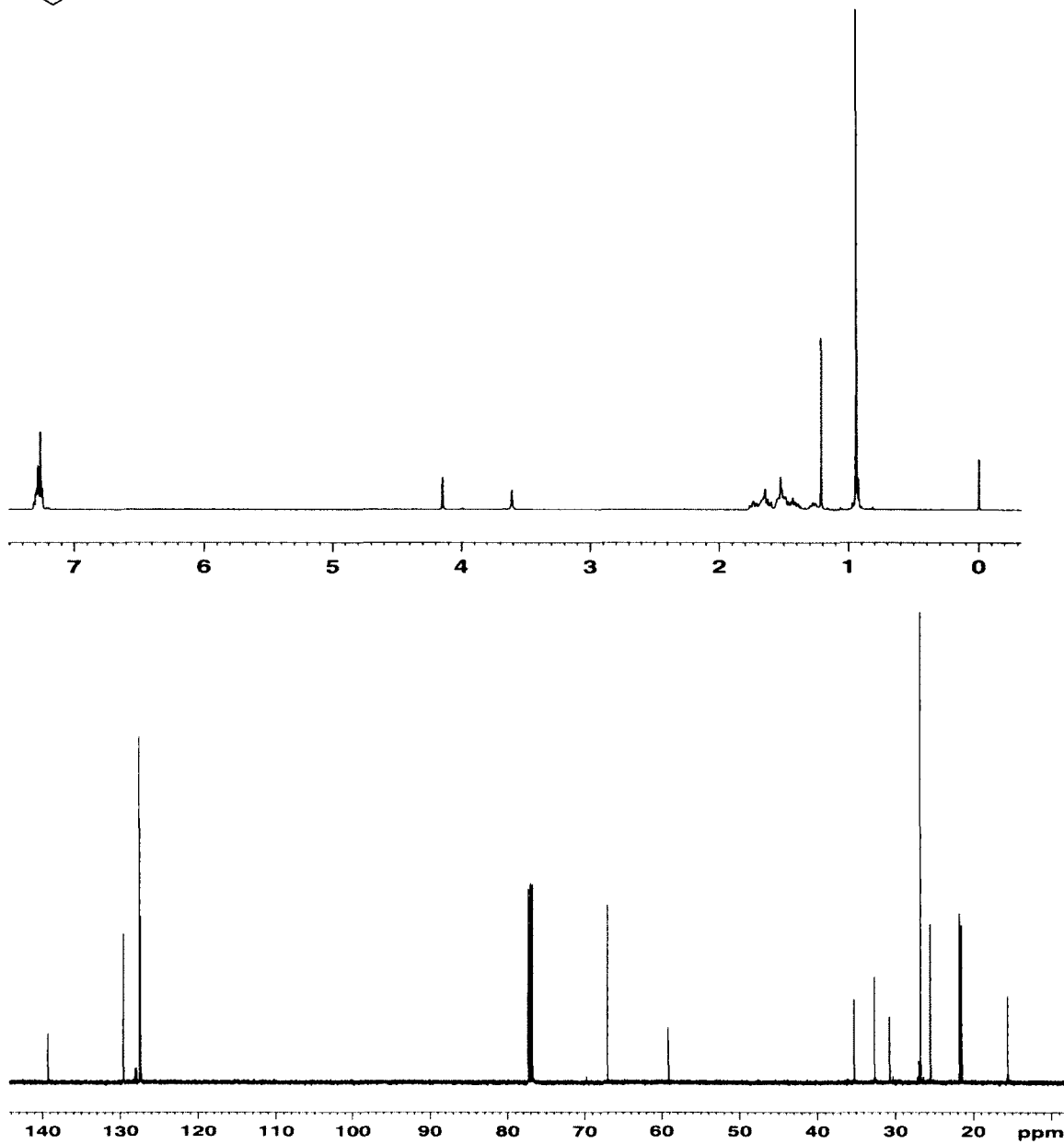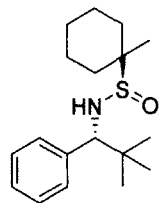
Figure 60. ^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) spectra for compound **10d**.

Chiral HPLC of compound 9c:
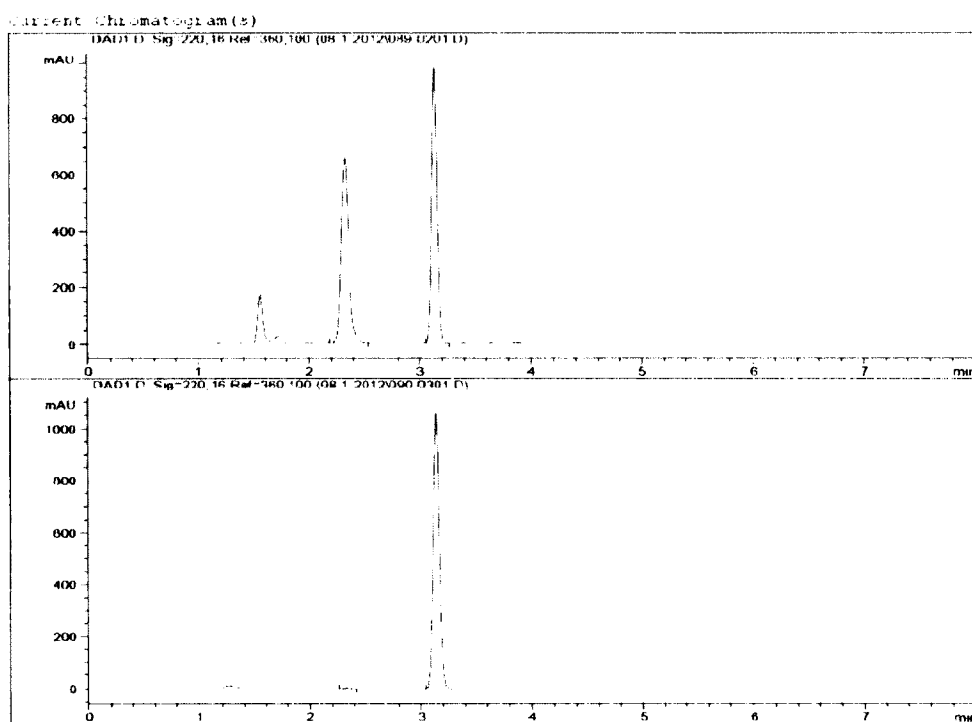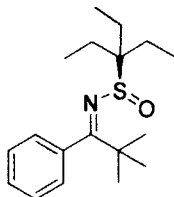
Signal 1: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.331	MM	0.0781	19.40685	4.14342	0.4777
2	3.136	MM	0.0632	4043.54150	1066.16650	99.5223

Totals : 4062.94836 1070.30993

Figure 61. Chiral HPLC condition: Chirapack AD-3 column, 4.6X250 mm, 10μ; 25 % ethanol in heptane, 1.5 mL/min; 222nm; (R)-9c , rt = 3.14 min, (S)-9c, rt = 2.33 min.

5.3. CONCLUSIONS

In summary, an efficient approach to enantioselective synthesis of diverse sulfinamides and imines using a new chiral auxiliary has been achieved. We have developed a chiral amine template based on a phenol backbone **5**, from which the optically pure chiral sulfinyl-transfer agent benzo[1,3]oxathiozin-2-one **6** was prepared effectively. The intermediate **6** contains sulphur-nitrogen and sulphur-oxygen bonds with differentiated reactivities that allow the synthesis of sterically hindered chiral sulfinamides and sulfinyl ketimines under mild reaction conditions. This method is practical, efficient, green, and has the potential to provide an economical commercial process for the synthesis of enantiopure bulky sulfinamides, such as tertiary butyl sulfinamide and triisopropyl sulfinamide.

5.4. EXPERIMENTAL PROCEDURE

General Methods

All reactions were carried out under argon atmosphere, reagents and solvents were obtained from commercial suppliers used directly without any purifications. All the solvents were used for the reaction were purchased from sigma-aldrich. All reactions, unless otherwise noted were carried out in oven dried glassware under argon atmosphere. Combiflash chromatography was carried out using silicycle 230-400 mesh silcagel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254

plates, and visualized using UV light and phosphomolybdic (PMA) staining. LC-MSD was carried on Agilent 1100 series. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with Bruker 400 or 500MHz spectrometers in $CDCl_3$ with TMS as an internal standard. Proton and carbon spectra chemical shifts were reported using TMS and $CDCl_3$ as internal standard at 0 ppm and at 77.23 ppm, respectively. Diastereomeric ratios were determined by ^{1}H NMR spectrum analysis as well as HPLC analysis. Enantiomeric excess were obtained by chiral HPLC analysis using Chiral pack AS, AD and OD ChiralCel columns.

Synthesis of (2S, 4R)-6-chloro-4-methyl-3-[(4-methylphenyl)sulfonyl]-3,4-dihydro-1,2,3-benzoxathiazine2-oxide (6b)

A 3-neck 250 ml round-bottom flask fitted with a stiring bar, and argon inlet, was charged with amine (20 g, 61.2 mmol) and THF (120 ml) cooled to -30 °C . To this solution thionyl chloride (6.08 ml, 85.6 mmol) was added drop wise, followed by pyridine (12 ml, 0.153 mol) was added dropwise over 30 min. Reaction was monitored through TLC and LC-MS. Reaction was completed after 1hr, quenched the reaction mixture with saturated sodium bicarbonate and diluted with ethylacetate. The organic layer was washed with brine and dried over Na_2SO_4. The organic phase was condensed under a rotavap and the residue was recrystallized using EtOAC/Hexane. The product was obtained as white crystalline solid with (18.67 g) 82% yield and 99.6:0.4 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (d, J = 7.2 Hz, 3H), 2.39 (s, 3H), 4.86 (q, J = 7.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 7.16 (dd, J = 8.7 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 23.9,

51.9, 121.4, 126.1, 127.1, 127.3, 129.2, 130.1, 130.1, 135.1, 142.8, 143.3. HRMS: m/z

calculated for $C_{15}H_{14}ClNO_4S_2$ Na (M+Na); 393.9950; found: 393.9952.

Synthesis of 4-chloro-2-((R)-1-(4-methylphenylsulfonamido)ethyl)phenyl 2-methylpropane-2-sulfinate (7a):

A 3-neck, 250 ml round-bottom flask fitted with a magnetic stirring bar, an internal

temperature probe, and an argon inlet was charged with compound (**6**) (5 g, 13.47 mmol,

1.0 equiv) and THF (15 mL). The reaction mixture was cooled to an internal temperature

of -30 °C by using dry ice and water mixture To this solution *t*-BuMgCl (2 M in THF,

7.4 mL, 14.7 mmol, 1.1equiv) was added dropwise over 15 min. The reaction mixture

was maintained at an internal temperature between -30 °C to -20 °C, with monitoring by

TLC and LC-MS. After 1h the reaction was quenched with saturated $NaHCO_3$ (15 mL)

at this temperature, temperature was raised when adding the base and diluted with EtOAc

and the layers were separated. The aqueous fraction was back-extracted with EtOAc (2 x

50 mL) and the layers were separated. The combined organic fractions were washed with

brine and dried over Na_2SO_4. The organic fraction was concentrated under reduced

pressure. Purification by column chromatography (30% EtOAc:hexanes) provided the

desired product as a white solid (5.26 g, 91 %). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.56 (d, *J*

= 8.2 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.03 (dd, *J1=J2*=8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz,

1H), 6.71 (d, *J* = 2.7 Hz, 1H), 5.76 (d, *J* = 8.9 Hz, 1H), 4.51 (q, *J* = 7.2 Hz, 1H), 2.33 (s,

3H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.39 (s, 9H); ^{13}C (125 MHz, CDCl$_3$) δ 21.4, 21.8, 22.8,

50.8, 59.1, 122.0, 127.1, 128.4, 129.1, 129.1, 130.6, 135.6, 137.5, 143.0, 149.9. HRMS:

m/z calculated for $C_{19}H_{25}ClNO_4S_2$ (M+H), 430.0914; found: 430.0908.

Synthesis of 4-chloro-2-((R)-1-(4-methylphenylsulfonamido)ethyl)phenyl 2-methylbutane-2-sulfinate (7b)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (6) (3 g, 8.06 mmol) and THF (10 mL). The reaction mixture was cooled to an internal temperature of -30 °C. To this solution 1,1-dimethyl propyl magnesium chloride solution (1M, 10.5 mL, 10.47 mmol, 1.3 equiv) was added drop wise for 15 min. The reaction mixture was maintained at an internal temperature between -30 °C to -20 °C, with monitoring by TLC and LC-MS. Reaction was completed after 45 min, quenched with saturated $NaHCO_3$ (15 mL) and the organic layer extracted with EtOAc (30 mL). The organic layer was washed with brine and dried over Na_2SO_4. The organic phase was allowed to dryness, and the residue was crystallized from EtOAc/hexanes. The product (7b) was obtained as white solid (2.98 g, 85.14 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.05 (dd, $J1$ =$J2$= 8.4 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 5.78 (d, J = 8.9 Hz, 1H), 4.49 (m, 1H), 2.32 (s, 3H), 1.83 (m, 1H), 1.75 (m, 1H), 1.47 (d, J = 7.5 Hz, 3H), 1.36 (s, 3H), 1.346 (s, 3H), 1.07 (t, J = 7.6 Hz, 3H); ^{13}C (125 MHz , $CDCl_3$) δ 7.8, 18.46, 18.48, 21.4, 22.8, 27.7, 50.9, 62.6, 122.0, 127.1, 128.4, 129.12, 129.18, 130.5, 135.6, 137.5, 143.0, 150.0. HRMS: m/z calculated for $C_{20}H_{27}ClNO_4S_2$ (M+H), 444.1067; found: 444.1064.

Synthesis of 4-chloro-2-((R)-1-(4-methylphenylsulfonamido)ethyl)phenyl 3-ethylpentane-3-sulfinate(7c)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (6) (1g, 2.68 mmol) and THF (6 mL). The reaction mixture was cooled to an internal temperature of -45 °C. To this solution 1,1,1-triethylmethylmagnesiumchloride solution (0.15 M, 19.6 mL, 2.94 mmol, 1.1 equiv) was added drop wise for 15 min. The reaction mixture was maintained at an internal temperature between -45 °C to -30 °C, with monitoring the reaction using TLC and LC-MS. Reaction was completed after 1h, quenched with saturated sodium bicarbonate (10ml) and the organic layer extracted with EtOAc (2 x 15mL). The organic layer was washed with brine and dried over Na_2SO_4 . The organic fraction was concentrated under reduced pressure. Purification by column chromatography (30% EtOAc:hexanes) provided the desired product as a white solid (0.94 g,75 %). ^1H NMR (500 MHz , $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 7.05 (dd, $J_1 = J_2$ = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 5.96 (d, J = 8.8 Hz, 1H), 4.52 (m, 1H), 2.33 (s, 3H), 1.825(m, 6H), 1.44 (d, J = 7.0 Hz, 3H), 1.06 (t, J = 7.4 Hz, 9H).^{13}C (125 MHz, $CDCl_3$) δ 8.1, 22.9, 23.5, 50.3, 67.9, 121.8, 127.0, 128.3, 128.7, 129.2, 130.4, 135.7, 137.4, 143.0, 150.0. HRMS: m/z calculated for $C_{22}H_{31}ClNO_4S_2$ (M+H), 472.1383; found: 472.1381.

Synthesis of 4-chloro-2-((R)-1-(4-methylphenylsulfonamido)ethyl)phenyl 1-methylcyclohexane-1-sulfinate (7d)

To a solution of **6** (8.5 g, 22.9 mmol) in THF (60 mL) cooled to -15 °C , to this solution added 1-methylcyclohexylmagnesium chloride (78 mL, 0.32 M in THF, 24.9 mmol) slowly while keeping the reaction temperature <-12 °C. After addition, the mixture was stirred for 30 min to complete the reaction as monitored by TLC and LC-MS analysis. Saturated aqueous NH$_4$Cl solution (50 mL) was added to quench the reaction and diluted with brine (40 mL) and EtOAc (100 mL). The mixture was warmed to RT and the organic phase was removed. The aqueous phase was extracted once with EtOAc (50 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by chromatography eluted with EtOAc/hexane (5:95 to 20:80, v/v) to yield **7d** (10 g) as a white solid in 90 % yield. ^{1}H NMR (500 MHz, CDCl$_3$) δ , 1.43 (s, 3H), 1.46 (d, J = 7.5 Hz, 3H), 1.51-1.87 (m, 10H), 4.45(m, 1H), 2.33 (s, 3H), 5.84 (d, J = 9.0 Hz , 1H), 6.70 (d, J = 2.6 Hz, 1H); 6.87 (d, J = 8.6 Hz, 1H),7.03 (dd, $J1$ =$J2$ = 2.60, 8.4 Hz, 1H), 7.08 (d, J = 7.9Hz, 2H), 7.57 (d, J = 8.3Hz, 2H), ^{13}C (125 MHz,CDCl3) δ 15.2, 21.3, 21.4, 21.5, 22.8, 25.4, 29.7, 30.8, 50.4, 62.7, 122.0, 127.1, 128.3, 128.8, 129.2, 130.4, 135.7, 137.4, 143.0, 149.9. HRMS: m/z calculated for C$_{22}$H$_{29}$ClNO$_4$S$_2$ (M+H), 470.1227; found: 470.1227.

Synthesis of 4-chloro-2-((R)-1-(4-methylphenylsulfonamido)ethyl)phenyl 2,4,6-triisopropylbenzenesulfinate (7e)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (**6**) (3 g, 8.08 mmol)

and THF (12 mL). The reaction mixture wascooled to an internal temperature of -78 °C.

To this solution 1,3,5-triisolpropylphenylmagnesium bromide solution (0.23 M, 35.5 mL,

8.8 mmol, 1.1 equiv) was added drop wise for 30 min. Reaction was monitored using

TLC and LC-MS, completed after 1h. Reaction was quenched with sat'd NaHCO$_3$

sodium bicarbonate (15 mL) and the organic layer extracted with EtOAc (2 x 25 mL).

The organic layer was washed with brine and dried over Na$_2$SO$_4$. The organic fraction

was concentrated under reduced pressure. Purification by column chromatography (30%

EtOAc:hexanes) provided the desired product as a white solid (3.16g, 68 %). ^{1}H NMR

(500 MHz ,CDCl$_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.18 (s, 2H), 7.09 (d, J = 8.4 Hz, 2H),

7.08 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.83 (br, s, 1H), 5.38 (br, 1H), 4.58

(m, 1H), 4.01 (sep, J = 7.2 Hz, 2H), 2.90 (sep, J = 7.2 Hz, 1H), 2.33 (s, 3H), 1.35 (d, J =

6.8 Hz, 3H), 1.32 (d, J = 6.8 Hz, 12H), 1.28 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz,

CDCl$_3$) δ 21.4, 22.9, 23.6, 23.7, 24.3, 24.5, 28.5, 31.5, 34.5, 49.9, 121.3, 123.2,126.9,

128.3, 128.3, 129.2, 130.3, 135.2, 135.2, 137.1, 137.3, 143.1, 149.3, 150.5, 154.3.

HRMS: m/z calculated for C$_{30}$H$_{39}$ClNO$_4$S$_2$ (M+H), 576.2009; found: 576.2004.

Synthesis of (R)-*tert*-butanesulfinamide (8a).

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal

temperature probe, and an argon inlet was charged with compound (7a) (3 g, 6.9 mmol)

dissolved in THF (10 mL) at 0 °C. To this solution LiHMDS solution (1 M, 5.3 mL, 2.2

equiv) added at 0 °C. Reaction was monitored using TLC and LC-MS, completed after

1h. Reaction was quenched with water (3 mL) and the organic layer was extracted with

EtOAc (2 x 25 mL) and dried over Na$_2$SO$_4$. The organic fraction was concentrated under

reduced pressure. Purification by column chromatography (90% EtOAC: hexanes) provided the desired auxiliary (2.43 g, 94%) and (R)-tert-butanesulfinamide (0.75 g, 89 %) with 99.38 % ee. The enantiomeric excess was analyzed by chiral HPLC analysis.

^{1}H NMR (500 MHz, CDCl$_3$) δ 3.82 (br, 2H), 1.18 (s, 9H).^{13}C NMR (125 MHz, CDCl$_3$) δ 22.1, 55.3. Chiral HPLC condition: Chiralpak AS column, 4.6X250 mm, 10μ; 90:10 hexane ethanol; 1.0ml/min; 222nm; (R) , r$_t$ = 6.6min, (S), r$_t$ = 9.4min.

Synthesis of (R)-2-methyl butane-2-sulfinamide (8b)

A 3-neck 100 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (7b) (3 g, 6.7 mmol) and dissolved in THF (12 mL) at -5 °C to 0 °C. To this solution LiHMDS solution (1M, 14.8 mL, 2.2 equiv) was added at 0 °C. The reaction mixture was maintained at an internal temperature 0 °C, with monitoring by TLC and LC-MS. Reaction was completed after 1h, quenched with water (3 mL) and the organic layer was extracted with EtOAc (50 mL) and dried over Na$_2$SO$_4$. The organic fraction was concentrated under reduced pressure. Purification by column chromatography (90% EtOAC: hexanes) provided the desired product (R)-1,1-dimethyl propylsulfinamide (0.76g, 84 %) with 99.7% ee. The enantiomeric excess was analyzed by chiral HPLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ δ 0.98 (t, J = 7.4 Hz, 3H), 1.16 (d, J = 6.2, 6H), 1.65(ds, J = 4.6 Hz, 7.5 Hz, 2H), 4.2(b, 2H).^{13}C NMR (125 MHz, CDCl$_3$) δ 7.9, 18.5, 18.63, 28.5, 58.7. Chiral HPLC condition: ChiralCelAD-H column, 4.6X250 mm, 10μ; 20% ethanol in heptane; 1.2ml/min; 222nm; (R) , r$_t$ = 9.88 min, (S), r$_t$ = 13.41min.

Synthesis of (R)-2-methyl butane-2-sulfinamide (8c)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (7c) (200 g, 0.423 mmol) and THF (3 mL) at -35 °C. To this solution LiHMDS solution (1M, 1.27 mL, 1.26 mmol, 3 equiv) was added at this temperature, reaction moved slolwly to 0 °C . Reaction was monitored using TLC and LC-MS, to push the reaction added another 1equiv of LIHMDS. The reaction mixture was maintained at an internal temperature 0 °C, with monitoring by TLC and LC-MS. Reaction was completed after 5h, quenched with water (3 mL) and extracted with ethyl acetate and dried over Na_2SO_4. The organic fraction was concentrated under reduced pressure. Purification by column chromatography (90% EtOAC: hexanes) provided the desired product (R)-1,1,1-trimethylpropylsulfinamide (50.5 mg, 73 %) as a white solid with >99:1 er. The enatiomeric ratio was analyzed by chiral HPLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.75 (s, 2H), 1.62-1.77 (m, 6H), 0.98 (t, J = 6.8 Hz, 9H).^{13}C NMR (125 MHz, CDCl$_3$) δ 8.2, 23.6, 63.6. Chiral HPLC condition: Chiralcel OD column, 4.6X250 mm, 10μ; isopropanol in heptanes (15:85. v/v), 35 °C, 1.0ml/min; 222nm;(R)-8c , rt = 8.10 min, (S)-8c, rt = 11.10 min.

Synthesis of (R)- 1-methylcyclohexane-1-sulfinamide (8d)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with amine (7d) (200 mg, 0.42 mmol) and THF (3 mL). The reaction mixture was cooled to an internal temperature of 0 °C. To this solution magnesium bromide diethyl etherate (54.94 mg, 0.21 mmol) was added and cooled down to -40 °C , at this temperature LiHMDS solution (1M, 1.05 mL, 2.5 equiv)

was added slowly. To push the reaction added another 1.5equiv of LiHMDS and moved slowly to 0 °C , reaction was completed after 4h. Reaction was quenched with water (3 mL) and extracted with ethyl acetate(10 mL) and dried over Na₂SO₄ . The organic fraction was concentrated under reduced pressure. Purification by column chromatography (90% EtOAC: hexanes) provided the desired product (R)- 1-methylcyclohexane-1-sulfinamide (61.25 mg, 90 %) as whiter solid with 98.92:1.07 er. The enantiomeric ratio was analyzed by chiral HPLC analysis. ^{1}H NMR (500 MHz, CDCl₃): δ 3.67 (s, 2H), 1.27-1.79 (m, 10H), 1.19 (s, 3H).^{13}C NMR (125 MHz, CDCl₃) δ 14.9, 21.5, 21.7, 25.5, 30.2, 32.1, 58.8. HRMS: m/z calculated for C₇H₁₆NOS (M+H): 162.0953; found: 162.0943. Chiral HPLC condition: ChiralCelAD-H column, 4.6X250 mm, 10μ; heptane/IPA :7:3; 1.0ml/min; 222nm; (R) , r$_t$ = 3.62 min, (S), r$_t$ = 4.41min.

Synthesis of (R)-2,4,6-triisopropylbenzenesulfinamide (8e).

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with (7e) (1 g, 2.69 mmol) and THF (6 mL), the solution was kept at -78 °C. To this solution 1,3,5-Triisopropyl phenyl magnesium bromide solution (0.20 M , 10.38 mL, 3.23 mmol, 1.2 equiv) was added drop wise over 30 min. Reaction was monitored using TLC and LC-MS, observed some double addition product. After 2h, added the LiHMDS (1M, 8.07 mL, 8.07 mmol, 3equiv) solution drop wise over 15 min .The completion of the reaction took for the two steps in 3:30 h. Reaction was quenched with saturated sodium bicarbonate (15 mL) and the organic layer was extracted with EtOAc(2 x 20 mL), organic layer was washed with brine and dried over Na₂SO₄ .The organic fraction was concentrated under reduced

pressure. Purification by column chromatography (50% EtOAC: Hexane) provided the desired product (R) 1,3,5-Triisopropylphenylsulfinamide (0.34 g, 48 %) as white solid with 99.49 % ee. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.08 (s, 2H), 4.45 (s, 2H), 4.00 (sep, J = 7.0 Hz, 2H), 2.84 (sep, J = 7.0 Hz, 1H), 1.32 (d, J = 7.0 Hz, 6H), 1.27 (d, J = 6.7 Hz, 6H), 1.23 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 23.7, 24.1, 24.3, 28.2, 34.3, 123.0, 138.7, 147.3, 151.9. Anal.Calcd. for C$_{15}$H$_{25}$NOS : C, 67.37; H, 9.42; N, 5. 24; O, 5.98; S, 11.99. Chiral HPLC condition: Chiralcel OD-H column, 4.6X250 mm, 10μ; 90:10: Isopropanol/hexane; 1.0ml/min; 222nm; (R) , r$_t$ = 4.18min, (S), r$_t$ = 5.03 min.

Synthesis of (R,E)-N-(2,2-dimethyl-1-phenylpropylidene)-2-methylpropane-2-sulfinamide(9a)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (7a) (1 g, 2.32 mmol) and THF (6 mL). The solution was kept at -78 °C. In another flask, charged with benzonitrile (0.73 mL, 7.16 mmol) and THF (2.5 mL) cooled down to -78 °C. To this solution t-Butyllithium (1.7 M, 6.96 mL, 6.96 mmol) was added drop wise over 30 min. The solution was turned in to light orange red colour , after 1h this solution was added to solution of (7a) . Reaction was monitored using TLC and LC-MS, completed after 1h, quenched with 2M NaOH..The organic layer was extracted with hexane (2 x 20 mL), organic layer was washed with brine and dried over Na$_2$SO$_4$. The organic fraction was concentrated under reduced pressure. Purification by column chromatography (30 % EtOAc: Hexane) provided the desired product (9a) (0.52 g, 85 %) as a white solid with >99 :1 er. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (m, 3H), 7.07 (m, 2H), 1.22 (s, 9H), 1.19

(s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 22.0, 28.0, 42.6, 55.8, 126.5, 127.7, 128.3, 137.0,

192.5. HRMD: m/z calculated for C$_{15}$H$_{24}$NOS (M+H), 266.1579; found, 266.1573. Chiral

HPLC condition: ChiralCel AD-H column, 4.6X250 mm, 10μ; 1.0 % isopropanol in

heptane,1.0ml/min; 222nm; (S)-9a , rt = 2.78 min; (R)-9a, rt = 4.58min.

Synthesis of (R,E)-N-(2,2-dimethyl-1-phenylpropylidene)-3-ethylpentane-3-sulfinamide (9c)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal

temperature probe, and an argon inlet was charged with compound (7c) (200 mg, 0.42

mmol) and THF (3 mL) , the solution was kept at -78 °C. In another flask was charged

with benzonitrile (0.18 mL, 1.76 mmol) and THF (2.5 mL) cooled down to -78 °C. To

this solution t-Butyllithium (1.7M, 0.98 mL, 1.68 mmol) was added drop wise over 30

min. The solution was turned in to light orange red colour , after 1h this solution was

added to solution of (7c) . Reaction was monitored using TLC and LC-MS, completed

after 1h, quenched with 2M NaOH .The organic layer was extracted with hexane (2 x

20 mL), organic layer was washed with brine and dried over Na$_2$SO$_4$. The organic

fraction was concentrated under reduced pressure. Purification by column

chromatography (30 % EtOAc: hexanes) provided the desired product (9c) (119 mg, 91

%) as a white solid with >99 :1 er. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32 (m, 3H), 7.0 (m,

2H), 1.66 (m, 6H), 1.21 (s, 9H), 0.93 (t, J = 7.4 Hz, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ

8.3, 23.7, 28.1, 42.7, 64.8, 127.6, 128.2, 137.0, 191.3. HRMS: m/z calculated for

C$_{18}$H$_{30}$NOS (M+H), 308.2048; found:308.2044. Chiral HPLC condition: Chirapack AD-3

column, 4.6X250 mm, 10μ; 25 % ethanol in heptane, 1.5 mL/min; 222nm; (R)-9c , rt = 3.14 min, (S)-9c, rt = 2.33 min.

Synthesis of (R,E)-N-(2,2-dimethyl-1-phenylpropylidene)-1-methylcyclohexane-1-sulfinamide (9d)

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with compound (7d) (500 mg, 1.06 mmol) and THF (3 mL) , the solution was kept at -78 °C. In another flask was charged with benzonitrile (0.45 mL, 4.45 mmol) and THF (3 mL) and cooled down to -78 °C. To this solution t-Butyllithium (1.7 M, 2.4 mL, 4.24 mmol) was added drop wise over 30 min. The solution was turned in to light orange red colour , after 1h this solution was added to solution of (7d). Reaction was monitored using TLC and LC-MS, completed after 1h, quenched with 2M NaOH. The organic layer was extracted with hexane (2 x 15 mL), organic layer was washed with brine and dried over Na_2SO_4 . The organic fraction was concentrated under reduced pressure. Purification by column chromatography (30% EtOAc: Hexane) to afford the desired product (9d) (0.25 g, 78 %) as a white solid with >98:2 er. ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.22 (s, 9H), 1.24 (s, 3H), 1.35-1.72 (m, 10H), 7.0 (m, 2H) ,7.32(m, 3H); 13C NMR (125 MHz, CDCl3) δ 15.7, 21.5, 21.7, 25.7, 28.1, 30.1, 31.1, 42.6, 59.6, 126.5, 127.7, 128.2, 137.1; HRMS: m/z calculated for $C_{18}H_{28}NOS$ (M+H), 306.1892; found: 306.1885. Chiral HPLC condition: ChiralCel OJ-3 column, 4.6X250 mm, 10μ; 6% isopropanol in heptane, 1.0ml/min; 222nm; (R)-9d , rt = 4.42 min, (S)-9d, rt = 3.62 min.

Synthesis of (R,E)-N-(2,2-dimethyl-1-phenylpropylidene)-2,4,6-triisopropylbenzene sulfinamide.

A 3-neck 50 ml round-bottom flask fitted with a magnetic stirring bar, an internal temperature probe, and an argon inlet was charged with benzonitrile(0.16 mL, 1.56 mmol) and THF (2.5 mL) and cooled down to -78 °C. To this solution t-Butyllithium (1.7 M, 0.87 mL, 1.48 mmol) was added drop wise over 30 min. The solution was turned in to light orange red colour . In another flask compound (7e) (200 mg, 0.37 mmol) was dissolved in THF (3 mL) and the solution was kept at -78 °C.This solution was added to the imine dropwise over few minutes. Reaction was monitored using TLC and LC-MS, completed after 1h, quenched with 2M NaOH. The organic layer was extracted with hexane (2 x 20 mL), organic layer was washed with brine and dried over Na_2SO_4 . The organic fraction was concentrated under reduced pressure. Purification by column chromatography (30 % EtOAc: Hexane) to afford the desired product (9e) (95 mg, 64 %) as a white solid with 98.5:1.5 er. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, J =6.5 Hz, 6H), 1.17 (d, J =6.8 Hz, 6H), 1.19 (s, 9H), 1.23 (d, J = 6.9 Hz, 6H), 2.86 (hept, J=6.90 Hz, 1H), 3.10-4.0 (b, 2H), 6.70-7.0 (m, 4H), 7.27-7.40(m, 3H). ^{13}C NMR(125 MHz, $CDCl_3$) δ 23.65, 23.71, 25.17, 27.88, 28.36, 34.28, 42.15, 122.38, 126.06, 127.92, 128.29, 137.12, 138.13, 149.99, 152.48, 187.73; HRMS: calculate for $C_{26}H_{38}NOS$ (M+H), 412.2674; found: 412.2674. Chiral HPLC condition: Chiralcel OD-H column, 4.6X250 mm, 10μ; 1 % EtOH in heptane, 1.0 ml/min; 222nm; (R)-9e , rt = 5.06 min, (S)-9e, rt = 4.67min.

General procedure for reduction of Imine:

Synthesis of (R)-N-((S)-2,2-dimethyl-1-phenylpropyl)-2-methylpropane-2-sulfinamide (10a)

In a vial compound (**9a**) (50 mg, 0.18 mmol) was dissolved in anhydrous THF (1 mL). This solution was kept at -50 °C, at this temperature sodium borohydride (21.38 mg, 0.56 mmol) was added after 30 min. Reaction was slowly moved to room temperature. Reaction went 100% completion after 90 min. Reaction was quenched with water (1mL) and extracted with EtOAc (10 mL). The crude product was concentrated to get the desired product with (48.3 mg, 98 %) with 93:7 dr. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.24 (m, 5H), 4.12 (br, 1H), 3.57(m, 1H), 1.22 (s, 9H), 0.94 (s, 9H).^{13}C NMR (125 MHz, CDCl$_3$) δ 22.6, 26.7, 35.2, 55.5, 67.1, 127.4, 127.5, 129.5, 139.1. HRMS: m/z calculated for C$_{15}$H$_{26}$NOS (M+H), 268.1735; found: 268.1735.

Synthesis of (R)-N-((S)-2,2-dimethyl-1-phenylpropyl)-3-ethylpentane-3-sulfinamide (10c)

In a vial compound (**9c**) (50 mg, 0.162 mmol) was dissolved in anhydrous THF (1 mL). This solution was kept at -50 °C, at this temperature sodium borohydride (18.4 mg, 0.487 mmol) was added after 30 min reaction was slowly moved to room temperature. Reaction went 100% completion after 90 min. The reaction was quenched with water (1 mL) and extracted with EtOAc (10 mL). The crude product was concentrated to get the desired product with (47.5 mg ,95 %) with 94:6 dr. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.90-0.98 (m, 17H), 1.61-1.74 (m, 7H), 3.81 (s, 1H), 4.14 (d, J = 2.2 Hz, 1H), 7.22-7.29 (m, 5H); ^{13}C

(CDCl$_3$, 100 MHz): δ 8.4, 24.1, 27.0, 35.4, 64.3, 67.7, 127.5, 127.6, 129.7, 139.4. HRMS: m/z calculated for C$_{18}$H$_{32}$NOS (M+H), 310.2205; found: 310.2202.

Synthesis of (R)-N-((S)-2, 2-dimethyl-1-phenylpropyl)-1-methylcyclohexane-1-sulfinamide (10d)

In a vial compound **(9d)** (50 mg, 0.18 mmol) was dissolved in anhydrous THF (1 mL). This solution was kept at -50 °C, at this temperature sodium borohydride (21.38 mg, 0.56 mmol) was added after 30 min reaction was slowly moved to romm temperature. Reaction went 100% completion after 90 min. The reaction was quenched with water (1 mL) and extracted with ethylacetate. The crude product was concentrated to get the desired product with (49.5 mg, 98 %) with 95:5 dr. ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.94 (s, 9H), 1.22 (s, 9H), 1.2-1.77 (m, 10H), 4.15 (br, 1H), 3.60 (m, 1H), 7.24 (m, 5H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 15.5, 21.48, 21.7, 25.5, 26.8, 30.7, 32.6, 35.2, 59.1, 67.0, 127.4, 127.5, 129.5. HRMS: m/z calculated for C$_{18}$H$_{30}$NOS (M+H), 308.2048; found: 308.2045.

Synthesis of (R)-N-((S)-2,2-dimethyl-1-phenylpropyl)-2,4,6-triisopropyl benzene sulfinamide (10e)

In a vial compound **(9e)** (50 mg, 0.18 mmol) was dissolved in anhydrous THF(1 mL). This solution was kept at -50 °C, at this temperature sodium borohydride (21.38 mg, 0.56 mmol) was added after 30 min. Reaction was slowly moved to room temperature. Reaction went 100% completion after 90 min. The reaction was quenched with water (1mL) and extracted with EtOAc (10 mL) The crude product was concentrated to get the desired product with (49mg, 97 %) with >98:2 dr. ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.95

(s, 9H), 1.18-1.28(m, 18H), 2.82-2.90 (m, 1H), 3.72-4.10 (b, 2H), 4.30 (d, J = 2.0 Hz, 1H), 4.75-4.79 (m, 1H), 7.24-7.37(m, 5H).^{13}C NMR (125 MHz, CDCl$_3$) δ 23.7, 23.7, 24.3, 24.3, 26.7, 28.1, 30.3, 34.2, 34.8, 67.2, 122.9, 127.5, 127.6, 129.6, 137.9, 138.7, 147.9,151.7. HRMS: m/z calculated for C$_{26}$H$_{40}$NOS (M+H), 414.2831; found: 414.2835.

CHAPTER 6

CONCLUSION

In summary, we have synthesized and studied several new series of low molecular weight gelators (LMWGs) from D-glucose and D-glucosamine as the starting materials. D-glucosamine is a versatile starting material to make different peptoids and triazoles which were discussed in chapters 2, 3 and 4. We have also synthesized a new class of chiral oxathiozinone and hindered amines from chiral amino phenol as discussed in chapter 5.

From the research results in chapters 2, 3, and 4, we can draw some conclusions regarding the design, synthesis, and properties of several series of gelators from simple carbohydrate based starting materials. **Figure 62** shows the several sugar headgroups (1-3) used in this study. A series of amides, ureas were prepared using compound **1b**. The triazoles of compound **2** and **3** have been compared in self-assembly study. These compounds form stable hydrogels and organogels. The role of triazole and different functional groups in affecting the self-assembly properties was studied. The following are detailed summaries for each of these systems.
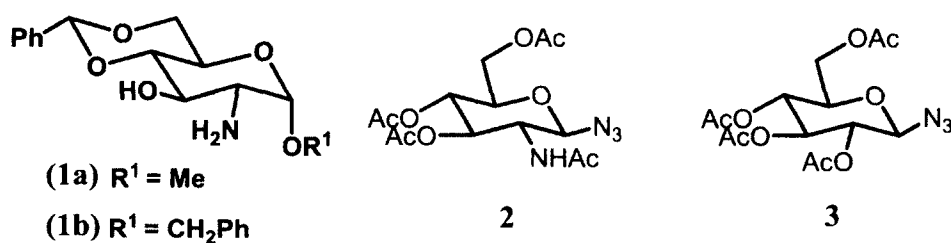
Figure 62. Principal structures of sugar headgroups used for gelation studies.

In chapter 2, we have designed and synthesized a series of low molecular weight tripeptoids by a one-pot Ugi reaction and obtained several effective organo/hydrogelators. These compounds are brand new class of organogelators that have not been reported before. Using MCRs to discover low molecular weight gelators is a novel method that will produce interesting structures with a variety of potential applications. The compounds **4, 5, 6** and **7** formed gels in ethanol, DMSO and water mixtures. Compounds **4, 7** formed in part due to the presence of glycine ester and bromine atom on phenyl group. In case of compound **5** there is no bromine, and the gelation behaviour of this compound is not as great compared to **6**. From this we conclude that not only hydrogen bonding affects gelation but also the electronic effect plays a very important role in these kind of molecules.[126a,185]
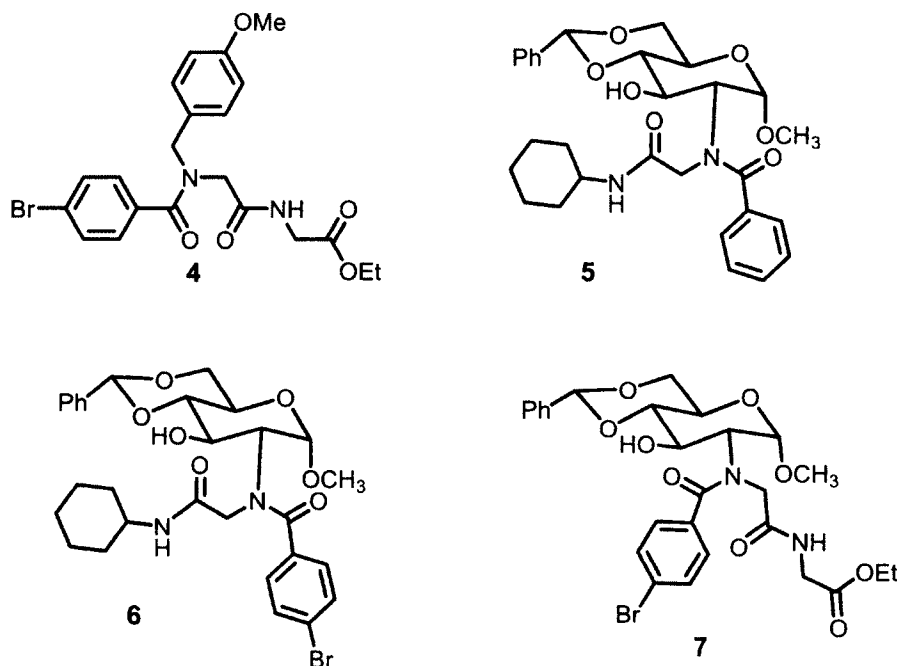
Figure 63. The structures of peptoid derivatives which are effective LMWGs.

Among the different triazole derivatives studied here, the long aliphatic chain

derivatives showed the best gelation results. Several of these compounds are shown in

Figure **63**, the saturated alcohol derivatives **8-10**, one acid derivative **11** and alkyl

derivatives of **12-14**. Compounds **10**, **12** and **14** form gels in pure water and aqueous

mixtures of ethanol or DMSO.[186]
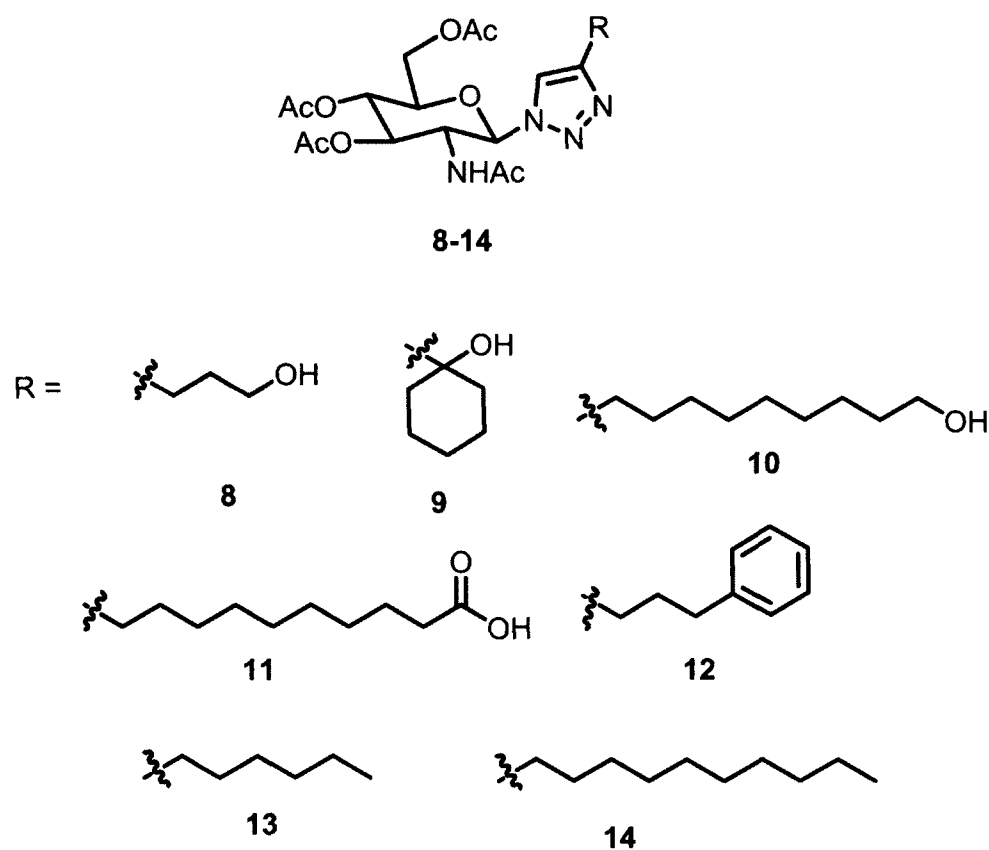
Figure 64. Several different sugar triazole from compound 2.

After synthesizing the N-acetyl glucosamine derivatives we have chosen the D-glucose

for our studies. When compared to compounds **8-14** the compounds **15-21** are not giving

better result. Only compound **18** formed hydrogel and interestingly the dimer of D-glucose triazole formed gels than the N-acetate system. In general the longer chain alkyl derivatives formed more stable gels at lower concentrations. Further studies using IR, small angle x-ray scattering or x-ray powder diffraction will be done in the future to help understand the packing modes of this molecules.[187]
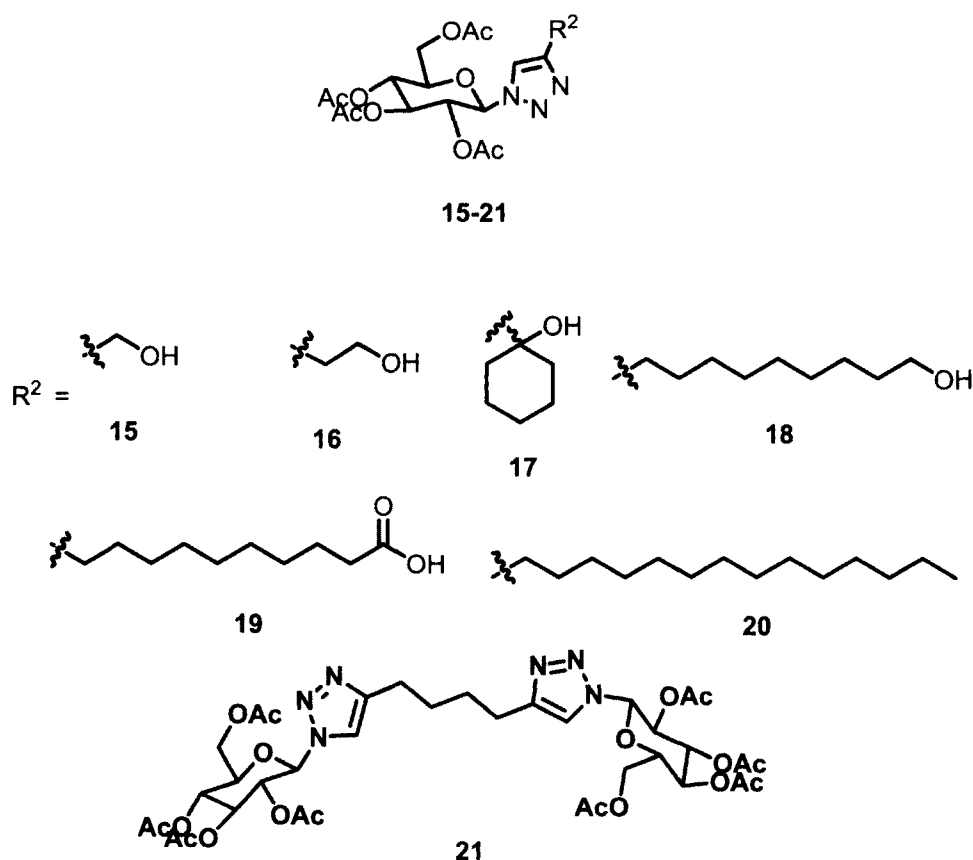
Figure 65. Several different sugar triazole from compound **3**.

The third type of gelators synthesized contains the apha-benzyl substituent at the anomeric position. Among the amide and urea derivatives of compound **1b** that were

synthesized, several of them showed positive gelation results in either DMSO, ethanol, water or mixtures of water and DMSO or ethanol. The structures of these compounds are shown in **Figure 65**. The terminal alkyl derivatives were the more efficient gelators. For the short chain alkyl amides and ureas, we found that **6-7** carbon chain ureas gave the best gelation results.
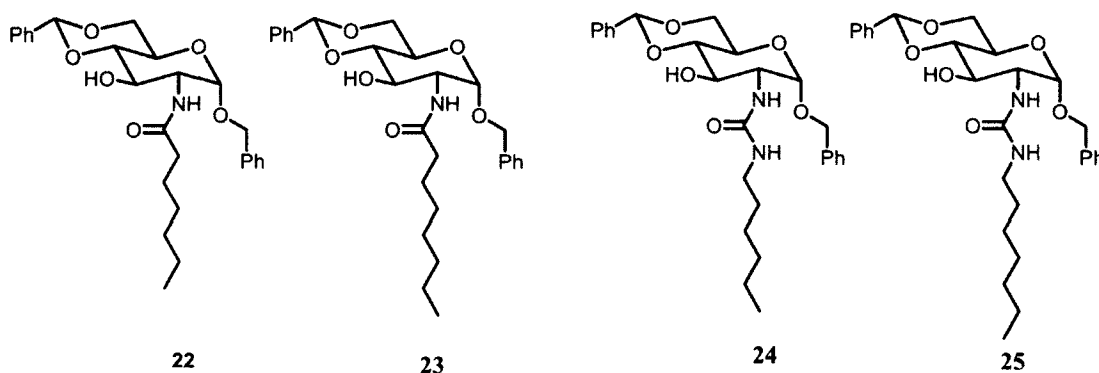
Figure 66. Amide and urea derivatives of compound **1b**.

These results indicated that besides hydrogen bonding, many other non-covalent forces are important in the self-assembly of these compounds. These include van der Waals interactions. The essential requirement is that that the molecules can self-assemble into entangled network therefore entrapping the solvent. The rheology of these analogs indicates that G' and G'' values for ureas were more than the amide. From this we can predict that hydrogen bonding plays an important role in case of both amides and ureas, but ureas can form stronger hydrogen bonding than amides.[188]

In chapters 5, we report a new chiral sulfinyl-transfer agent containing a more activated

S-O bond, from which both sterically hindered enantiopure sulfinamides and sulfinyl

ketimines were prepared under mild reaction conditions. To identify a template with a

more reactive S-O bond, the presence of an electron-withdrawing substituent on the

phenol ring increased the reactivity, whereas the reactivity was attenuated with an

electron-donating group. The effect of sterics on the reactivity of the S-O bond was also

observed.[189]

Scheme 23. Synthesis of chiral auxiliaries compound **27**
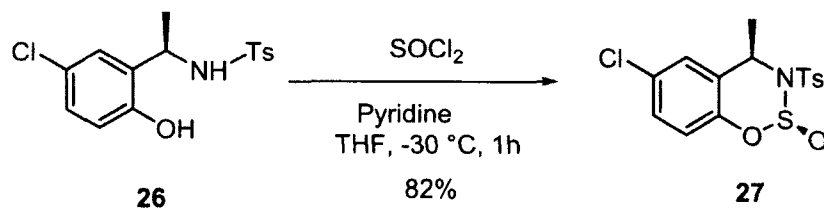
It was envisioned that optically pure **27** could be efficiently accessed on large scale from

the simple and commercially available chiral aminophenol **26**. From compound **26** a

variety of structurally diverse and sterically hindered alkyl and aryl sulfinamides were

readily synthesized in high yields and e.r. values. The scope of this chemistry was

extended to the direct synthesis of sterically hindered chiral sulfinyl ketimines (**29**) (in

Scheme 24) by addition of an imine nucleophile to the sulfinate ester **28**. Sulfinyl

ketimines are key intermediates in the synthesis of chiral amine compound **30**.

Scheme 24. Synthesis of chiral amines from compound **28**
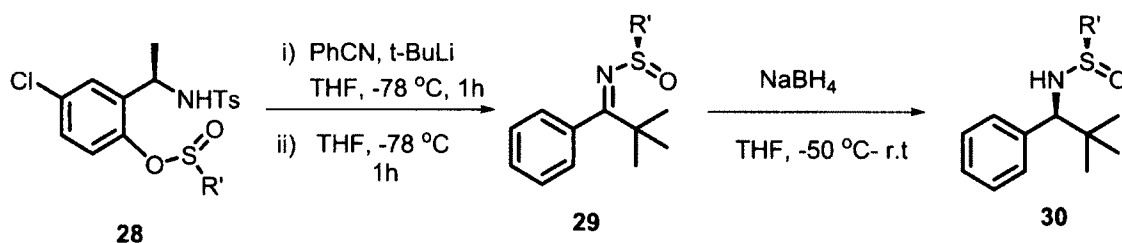
In conclusion, we obtained effective organo/hydrogelators based on D-glucose and D-glucosamine. We have also synthesized a variety of hinderd chiral sulfinmaides from the new chiral auxiliaries.

In the future the good organo/hydro gelators found in the current research can be explored for further applications in several systems: exploration of their effectiveness in enzyme immobilization, designing analytical tools to understand molecular interactions, and as matrix for delivery of biological agents, *etc*. By using the chiral auxiliary **27** the current research can be further explored to synthesize the new class of chiral sulfoxides and can be used many other applications.

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APPENDIX

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List of Publications:

1. **Hari P. R Mangunuru**, Hao, Yang and Guijun Wang. "Synthesis of peptoid based small molecular gelators by a multiple component reaction" *Chem. Comm.* **2013,** *49*, 4489-4491.

2. Guijun Wang and **Hari P. R Mangunuru**."Synthesis of peptoid based small molecular gelators. **US Patent App. 14/242,170, 2014.**

3. Zhengxu S. Han, Melissa A. Herbage, **Hari P. R. Mangunuru**, Yibo Xu, Li Zhang, Jonathan T. Reeves, Joshua D. Sieber, Zhibin Li, Philomen DeCroos, Yongda Zhang, Guisheng Li, Ning Li, Shengli Ma, Nelu Grinberg, Xiaojun Wang, Navneet Goyal, Dhileep Krishnamurthy, Bruce Lu, Jinhua J. Song, Guijun Wang and Chris H. Senanayake. "Design and Synthesis of Chiral Oxathiozinone Scaffolds: Efficient Synthesis of Hindered Enantiopure Sulfinamides and Sulfinyl Ketimines". *Angew. Chem. Int. Ed.* **2013,** *52*, 6713 – 6717.

4. Zhengxu S. Han, Navneet Goyal, Melissa A. Herbage, Joshua D. Sieber, Bo Qu, Yibo Xu, Zhibin, Li, Jonathan T. Reeves, Jean-Nicolas Desrosiers, Shengli Ma, Nelu Grinberg, Heewon Lee, **Hari P. R. Mangunuru**, Yongda Zhang, Dhileep Krishnamurthy, Bruce Z. Lu, Jinhua J. Song, Guijun Wang and Chris H. Senanayake. "Efficient Asymmetric Synthesis of *P*-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-oxide Agents". *J. Am. Chem. Soc.* **2013,** *135*, 2474-2477.