SYNTHESIS AND STUDY OF NEW GLYCOLURIL DERIVATIVES

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LIST OF ABBREVIATIONS


CBn: Cucurbiturils (n glycoluril units)

CB[5]: Cucurbit[5]uril

CB[6]: Cucurbit[6]uril

CB[7]: Cucurbit[7]uril

CB[8]: Cucurbit[8]uril

CB[10]: Cucurbit[10]uril

DAGU: Diacetyl glycoluril

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

FTIR: Fourier Transform Infrared Spectroscopy

HRMS: High Resolution Electron Impact Mass Spectrometry

IR: Infrared Spectroscopy

MHz: Megahertz

min: Minute(s)

mmol: Millimole

pH: Potential hydrogen

NMR: Nuclear magnetic resonance

ppm: Parts per million
Rf: Retention factor
TAGU: Tetraacetyl glycoluril
TAMGU: Tetraacetoxymethyl glycoluril
TFA: Trifluoroacetic acid
TLC: Thin Layer Chromatography
δ: Chemical shift (ppm)
d: Doublet
dd: Double doublet
J: Coupling constant in Hertz (Hz)
m: Multiplet
s: Singlet
t: Triplet
g: Gram
h: Hour
Hz: Hertz
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1 CHAPITRE 1: INTRODUCTION

The chemistry of heterocycles in recent decades has become one of the most dynamically developing areas of organic chemistry. The role of heterocyclic compounds in various fields of science and technology (chemistry, medicine, biology, electronics, etc.) cannot be overestimated. Therefore, the development of a new strategy for designing heterocyclic structures remains highly relevant.

The most important fundamental task of the modern organic chemistry is to study in-depth the main types of organic reactions in order to expand the boundaries of their application and create new approaches to the production of practically important organic compounds.

Glycoluril [1] is a simple heterobicyclic compound, which was prepared for the first time in the 19th century. Since then, glycoluril and its derivatives were found to be of great importance for pharmaceutical production, biochemistry, technology, agriculture, clinical and experimental medicine. Some glycoluril derivatives occupied an important place as intermediates for the synthesis of detergents and surface active substances. Also noteworthy is the pharmacological significance of compounds of the glycoluril series, which are widely used in medicine as psychotropic, nootropic substances and tranquilizers of a new generation.

The synthesis and properties of glycoluril thio-analogs are still poorly studied, although, both from scientific and applied points of view, these compounds are no less interesting, as confirmed by the PASS program data: the probability of detecting various types of pharmacological activities in mebicar thio-analogs is very high (0.785 - 0.958). It is well known that the replacement of the oxygen atom by sulfur leads to an increase in biological activity or change in the type of activity of compounds (for example, thiopyracetam is more active than pyracetam).
The introduction of new fragments to the nitrogen atoms of glycoluril or sulfur atom of thioglycoluril could lead to the expansion of the spectrum of pharmacological action. In this regard the synthesis of new derivatives of this latter is an important task.

The purpose of this study is to synthesize and study new compounds of the glycoluril and thioglycoluril.

To accomplish this goal, the work is supposed to solve the following main tasks:

1. Based on the literature, to investigate informations about glycoluril derivatives and their applications.
2. Synthesis and study of some glycoluril derivatives.
4. Acetylation of some cyclic amines using TAMGU as new acetylating agent.
6. Prepare some new diphenylthioglycoluril derivatives via alkylation reaction.
7. Investigate the antioxidant activity of the new synthesized diphenylthioglycoluril derivatives.
8. The application of diphenylthioglycoluril as catalyst in the synthesis of betulin 3, 28 di-O-formate.
2 CHAPTER 2: LITERATURE REVIEW

2.1 Glycoluril and its derivatives

Glycoluril and its derivatives are rigid bicyclic molecules, which contain a number of functional sites. They are considered highly interesting molecular scaffolds due to their rigid concave structure [2-4]. Glycoluril 1 (2,4,6,8-tetraazabicyclo [3.3.0.] octane-3,7-dione) (Figure 1) is a concave molecule that composed of two cyclic urea groups joined across the same two-carbon chains.

Because of its functionalization, it was found to be an attractive bicyclic compound for various reactions in order to synthesize and study new aza-heterocycles.

![Figure 1. Structure of glycoluril 1.](image)

Glycolurils have long attracted the attention of organic chemists; the methods for their synthesis are constantly evolving. A wide variety of different structures of glycoluril and its derivatives, with different substitution patterns have been obtained using different synthetic methods. The chemistry of glycolurils is only at the start of its development and has many prospects.

Glycoluril 1 has four groups of donors (NH) and two groups of acceptors (C=O). Chemical properties of glycoluril 1 is a typical N-nucleophile, which can involves in the N-alkylation, N-acylation, N-halogenation, N-nitration,
N-hydroxyalkylation, etc. However, the presence of a bond (NH–C=O) with the electron-withdrawing carbonyl group makes it a less active base. Therefore, glycoluril 1 is hardly protonated, which making its derivatives formed as a result of an electrophilic attack by the nitrogen atom able to decompose. Glycoluril 1 has also a weaker electrophilic site on the carbon of its carbonyl group. This property is explained by the influence of two electron pairs of nitrogen atoms that compensate the electron deficit on the carbon atom of the carbonyl group.

The widespread interest in glycoluril and its derivatives prompted the chemists to study their crystal structures. The X-ray structures of glycoluril 1 have been studied [5]. The O-O distance varies from 5.90 to 6.02 Å and the angle varies from 118 to 125° (Figure 2). In the molecular structure of diphenylglycoluril the distance between the two carbonyl oxygens is 5.76 Å and the angle between the carbonyl groups is 112.59° [6]. These substituents have a significant influence on the convergence of the two carbonyl groups. N-substituents glycoluril generally do not have a significant effect on the arrangement of carbonyl groups [7]. However, the authors [8] have observed some changes when nitrogen atoms 1.6 or 3.4 are connected, for example, by a xylylene group. They have found that the O-O distance is between 5.51 and 5.71 Å, with angles varies from 107 to 110°.

Figure 2. Crystal structure of glycoluril 1.
2.2 Synthesis of glycolurils and related compounds

The first synthesis of glycoluril 1 was prepared by H. Rheineck in 1865 [1a], he used urea and allantoin 2 as a starting material and named the compound glycoluril (Scheme 1). Glycoluril 1 is the ancestor of a wide range of these compounds.

Scheme 1. First synthesis of glycoluril 1 using allantoin.

All reported reactions of ureas or thioureas with diones (glyoxal 4, butane-2,3-dione 10 and benzil 17) proceed via the same diol 3 which results from the addition of one unit of urea or thiourea with the diones (Scheme 2). This diol is isolable for many of these reactions at neutral or slightly alkaline pH [9] and an X-ray crystal structure has been obtained for 3a [10]. The results show this compound to be a trans-diol; presumably the same stereochemistry also applies for intermediates 3b-3i and 3k-3n.
Scheme 2. Synthesis of intermediate diol 3 on the way to glycolurils.

Glycoluril 1 was prepared by the condensation of urea with glyoxal 4 [1b, 11-15] or mesoxal semi aldehydereacts also with urea in similar ways as glyoxal [16] (Scheme 3). All synthetic approaches were carried out under acidic conditions. The method of condensation of glycoluril 1 from urea and glyoxal using sulfuric acid at 65 °C and 200 Mbar is patented as an industrial method [14].


Reaction conditions: a; 1 week, HCl at 23 °C 1b; b; 1h HCl heat 11-13, 15, c; 65°C, 200 Mbar H₂SO₄ 14
1-Methylglycoluril 6 was obtained with yield 77%, by the condensation of urea with methylglyoxal 7 [17] or with its monooxime 8 [18] under acidic conditions but in low yield 23%. To obtain 1,5-dimethylglycoluril 9, two approaches are used: condensation of urea is carried out with butane-2,3-dione 10 [15], or with diacetyl monoxime 11 [18, 19] (Scheme 4).

![Scheme 4. Synthesis of glycolurils 6 and 9.](image)

1-phenylglycoluril 12 [17], was synthesized by the condensation of urea with phenylglyoxal 14. 5-methyl-substituted analog of 1-phenylglycoluril 13 [18] which was synthesized from urea with methylphenyl-glyoxal monoxime 15 was also obtained (Scheme 5).

![Scheme 5. Synthesis of glycolurils 12 and 13.](image)
1,5-diphenylglycoluril 16 was obtained by condensation of benzil 17 with urea in ethanol (method a) [20]. This cyclocondensation reaction was subsequently carried out both using KOH (method b) [21, 22] or in formic acid (method c) [15] (Scheme 6).

![Scheme 6](image)

**Reaction conditions:** a: 175°C, EtOH, 4-5 h, b: EtOH, KOH, heat 2 h (53%) 1.5 h, c: HCOOH, 110°C (84%).

**Scheme 6.** Synthesis of glycoluril 16 using 3 methods.

The proposed mechanism formation of diphenylglycoluril 16 under alkaline conditions was proposed [22]. This mechanism according to the kinetic calculations can proceed in 2 possible ways: through the formation of acyclic intermediate A or through monocyclic intermediate B (Scheme 7).

![Scheme 7](image)

**Scheme 7.** The proposed mechanism of glycoluril 16.
2.2.1 Other methods for producing glycoluril

In addition to the works of the 18th century, glycoluril 1 during this period of time was obtained by the reaction of urea with trichloric lactic acid [23] (Scheme 8).

Scheme 8. Another route for the synthesis of glycoluril 1.

Another method for the synthesis of glycoluril 1 has been achieved in [10] via α-ureidoalkylation of urea with diol 3a. Grillon et al, showed that diol 3a can be obtained from urea and glyoxal 4, which is known from the mechanism of α-ureidoalkylation [24] (Scheme 9).


The reaction of the diols 4,5-diaryl imidazolines 3c and 3j with urea in the presence of Br₂ [25] has been carried out to afford glycolurils 16 and 18 (Scheme 10).
Scheme 10. Synthesis of glycolurils 16 and 18 using diols 3c and 3j.

2.2.2 Synthesis of 2,4-disubstituted glycoluril

The main method for the synthesis of 2,4 disubstituted glycoluril 19a-j is condensation of diol 3a with 1,3-dimethyl (diisopropyl) urea 20a, 20b and 1-methylurea derivatives 20c-j, respectively [12, 10, 26, 27] (Scheme 11).

Scheme 11. Synthesis of 2,4-disubstitued glycolurils 19a-j.
The diol 1,3-Dimethyl-4,5-diphenyl 3h can also react with urea to afford the 2,4-dimethyl-1,5-diphenylglycoluril 21 [28] (Scheme 12).

Scheme 12. Synthesis of 2,4-disubstituted glycoluril 21.

2.2.3 Synthesis of 2,6 and 2,8-disubstituted glycoluril

The synthesis of 2,6 and 2,8-disubstituted glycolurils was carried out by condensation of N-methylurea 25 with 2,3-dicarbonyl compounds; (glyoxal 4, butane-2,3-dione 10 and benzil 17) (Scheme 13).

Scheme 13. Synthesis of the glycolurils from N-methylurea and various dions.

The condensation of N-methylurea 25 with glyoxal 4 leads to the formation of both regioisomers 22a and 22b. The mechanism formation of glycoluril from glyoxal 4 and N-methylurea 25 is still debatable [10, 29, 30].

Under acidic conditions, water is eliminated from diol 3g to afford the intermediate A, which, under acidic conditions reacts with a second molecule of N-methylurea 25 to form the cis-isomer 22a and the trans-isomer 22b. The formation of these two regioisomers 22a and 22b is depending on which urea
moiety \(-\text{NH}_2\) or \(-\text{NHR}\) the intermediate A is attached, which explains why two alternative reaction directions are possible via the intermediates B, B1 and C, C1 (Scheme 14).

Scheme 14. Mechanism formation of glycolurils 22a and 22b.

In 1888, Franchimont [31] reported that the N-methylurea 25 reacts with butane-2,3-dione 10 to give two isomeric compounds cis-isomer 3,4,7,8-tetramethylglycoluril 23a and the trans-isomer 3,6,7,8-tetramethylglycoluril 23b in approximately equal amounts, but in 1981 Butler [32] stated that the cis-isomer 3,4,7,8-tetramethylglycoluril 23a is the main compound of this reaction (Scheme 15).
Scheme 15. Mechanism formation of glycoluril 23a.

The reaction of benzil 17 with N-methylurea 25 is known to give only the cis-isomer 24a, because the tran-isomer is generally not found.

The authors [33] proposed a mechanism for the regioselective formation of 2,8-isomer of glycoluril 24a (Scheme 16). In the first step of the interaction of these reagents, an acyclic intermediate D is formed, which rapidly cyclizes to afford dihydroxyimidazolidin-2-one E. Then, after the removal of the water molecule the intermediate F is formed. A protonation of this latter on the hydroxyl group followed by condensation with a second molecule of N-methylurea 25 results in formation adduct H. Therefore, the cyclization of this intermediate leads to glycoluril 24a.

Reactions of 1,3-dimethylurea 25 with butane-2,3-dione 10 or benzil 17 [33, 34] does not yield glycoluril structures (Scheme 17). However, 1,3-dimethylurea 20a does react with butane-2,3-dione 10 to form a complex product 4,4'-methylenebis-(1,3,5-trimethyl-4-imidazolin-2-one) 26. In contrast, the condensation of 1,3-dimethylurea 20a with benzil 17 leads the hydantoin 27, which is formed from the intermediate 3g by a pinacol rearrangement.

Scheme 17. Condensation of 1,3-dimethylurea with diones 10 and 17.
The above mentioned mechanism (Scheme 14) explains why 1,3-dimethylurea 20a does not give glycoluril products. The diols 3f and 3g can not eliminate water to give a double bond in the ring. Thus, these reactions pathway are blocked and gives other products 26 and 27 as the main products.

2.2.4 Synthesis of 2,4,6,8-tetra-substituted glycoluril

The first reported tetraalkylglycoluril is 2,4,6,8-tetramethylglycoluril 28 which was synthesized in 1888 by the reaction of glyoxal 4 with 1,3-dimethylurea 20a [35] (Scheme 18).

![Scheme 18. Synthesis of glycoluril 28 (Mebicar).](image)

2.3 Synthesis of dithioglycoluril

In 1930, Pauly [38] reported that thiourea and glyoxal 4 react to give the dithioglycoluril 29; however, this has been disputed, since Long et al. reported in 1982 [39] that the compound formed was in fact the diiminodithiadiazabicyclooctan 30 (Scheme 19).
The condensations of thioureas with benzil 17 in both basic [40] and acidic solution have reported by Broan and Butler [41], who have shown that quite different products are obtained. Under acidic conditions, very small amounts of thioglycoluril compounds are formed.

The condensation of 1,3-dimethylthiourea 31 with benzil 17 in acidic solution leads to the unsaturated compound 32 as the main product by the elimination of 2 water molecules from the diol 3m, along with a small trace of monothioglycoluril 33, which is formed by an oxygen-sulfur exchange between thiourea and one of the hydroxyl groups of the diol. These results were confirmed by the reaction of 1,3-dimethylthiourea 31 with diol 3m (Scheme 20).

Scheme 19. Condensation of thiourea and glyoxal.

Scheme 20. Synthesis of glycoluril 33.
Broan and Butler in [41] explained that the reaction of benzil 17 with 1,3-dimethylthiourea 31 results in formation of the diol 3m, which is under acidic reaction conditions generated cation S, that followed by condensation with dimethylthiourea 31 to afford the intermediate T, which decomposes by releasing a molecule of 1,3-dimethylurea 10, this latter reacts with the diol 3m to produce monothioglycoluril 33 (Scheme 21).

**Scheme 21.** Mechanism formation of compound 32 and 33.

On the other hand, the reaction of benzil 17 with N-methylthiourea and thiourea under identical conditions leads to the formation of a disulfide derived
from 32 by oxidation as the major product and small amounts of the analogues of 33.

In contrast, in basic solution, when thiourea condenses with benzil 17 a mixture of thiohydantoin 35 and the desired compound diphenylthioglycoluril 34 was obtained in good yield [40]. A series of 3a,6a diaryldithioglycoluril containing methyl- 34a, chloro- 34b and methoxy- 34c fragments (Scheme 22) have been prepared by Broan et al [44].

\[
\begin{align*}
&\text{S} = \text{NH}_2 \text{NH}_2 \text{S} + \text{O} \text{O} \text{HN} \text{NH} \text{HN} \text{NH} \text{S} \text{O} \text{R}_1 \text{R}_2 \text{R}_3 \\
&\text{a, b, c } R_1= R_2= R_3= \text{H (17, 34, 35); R}_1= R_2= \text{Me, R}_3= \text{H (17a, 34a, 35a); R}_1= R_3= \text{Cl, R}_2= \text{H (17b, 34b, 35b );} \\
&R_1= R_3= \text{OMe, R}_2= \text{H (17c, 34c )}
\end{align*}
\]

Reaction conditions: a: EtOH, 145 °C, 3-4 h [2], b: PhMe, BuOH, NaOH, boil, 2.5 h [40], c: EtOH, KOH, heat, 2h [21].

**Scheme 22.** Condensation of thiourea with benzil and its derivatives.

When substituted thioureas are used, no glycoluril thioanalogue is formed, for example, the condensation of 1,3-dimethylthiourea 31 with benzil 17 in basic solution leads to formation of the diol 3m as the only isolable product. Also the reaction of N-methylthiourea with benzil 17 under identical conditions leads to thiohydantoins as the only products

### 2.3.1 Other method for the synthesis of dithioglycoluril

The action of Lawesson's reagent can be used to obtain both mono- and dithioglycoluril from glycoluril [42] (Scheme 23). The authors found that, with an equimolar amount of reagents, only one oxygen atom in the glycoluril molecule 36
is converted to sulfur atom and a mono-analogue 37a is formed, and at a 3-fold excess of the reagent Lawesson the formation of dithioglycoluril 37b was observed.

Scheme 23. Synthesis of mono and dithioglycolurils using Lawesson’s reagent.

The reaction of [3 + 2] cycloaddition of 1,4-diaza-1,3-dienes 39 and trimethylsilyl isothiocyanate 38a-e results in formation a series of dithioglycoluril 40a-e[43]. The authors have proposed a probable reaction mechanism (Scheme 24).

Scheme 24. Synthesis and mechanism formation of dithioglycolurils 40a-e.

Dithioglycolurils 40a and 40c are also obtained by reacting 1,4-diaza-1,3-dienes 38a and 38c with isothiocyanic acid [44] (Scheme 25).
Scheme 25. Synthesis of dithioglycolurils using isothiocyanic acid.

2.4 Chemistry of glycolurils

A variety of compounds have been prepared from glycoluril 1. Reaction of glycoluril 1 with formaldehyde in presence of NaOH gives the tetramethylolglycoluril 41 [45] (Scheme 26).


Tetramethylglycoluril 42 has been prepared from the condensation of glyoxal 4 with 1,3-dimethylurea 20a [35-37]. An alternative method for the synthesis of this latter has been reported in the work [46]. The alkylation of glycoluril in this case was achieved by iodine alkyls in liquid ammonia under the action of NaNH₂ in the presence of alkali metal halides (Scheme 27).
Scheme 27. Synthesis of glycoluril 28 (Mebicar) from glycoluril 1.

The acylation of glycoluril 1 using acetic anhydride under acidic conditions gives the tetraacetylglycoluril TAGU 42, while the diacetylglycoluril DAGU 43 results in good yield if the anhydride is limited to 2.5 equivalents [47] (Scheme 28).

Scheme 28. Synthesis of TAGU 42 and DAGU 43.

Another general reaction of glycoluril involves addition of HNO₃ to glycoluril 1 at 20-60 °C gives the dinitrocompound 44 [48] which can then be reacted further with HNO₃/N₂O₅ at 15 °C to give the tetrinitro compound 45 (Scheme 29).
Scheme 29. Synthesis of dinitro 44 and tetranitro glycoluril 45.

The halogenation of glycoluril 1 using KBrO$_3$ and HCl leads to tetrachloroglycoluril 46, on the other hand the use of KBr/KBrO$_3$ and H$_2$SO$_4$ affords the tetrabromoglycoluril 47 [49] (Scheme 30).

Scheme 30. Synthesis of tetrachloro 46 and tetrabromo glycoluril 47.

Glycolurils are also versatile progenitors of polycyclic ring systems, an important supramolecular compound was produced when the glycoluril 1 is condensed with formaldehyde under strongly acidic conditions [50] to give hexamer cucurbit[6]uril 48 (Scheme 31).

In the literature some effort has been directed toward modifying the diphenylglycoluril 16. The reaction of formaldehyde with diphenylglycoluril under basic conditions gives tetra (Hydroxymethyl) diphenylglycoluril 49 [51], followed by acid catalyzed dehydration yielding the cyclic ether 50 [4, 52] (Scheme 32).

Scheme 32. Synthesis of compounds 49 and 50.

In addition, the acylation of diphenylglycoluril 16 using acetic anhydride at 100 °C affords compound 51, which can be transformed into the corresponding tetra (chloromethyl) diphenylglycoluril 52 by reaction with thionyl chloride [53] (Scheme 33).
Scheme 33. Synthesis of compounds 51 and 52.

The synthesis of tetrahalogeno-diphenylglycolurils has been reported in [54] by reacting diphenylglycoluril 16 with chlorine and CH$_3$COONa to obtain TCDGU 53 and bromine under basic reaction conditions to obtain TBDGU 54 (Scheme 34).

Scheme 34. Synthesis of compounds 52 and 53.

2.5 Uses of glycolurils

Glycolurils are functional substances that are used in various industries, glycoluril 1 is an effective nitrogen-containing fertilizer of prolonged action [55], and has been found to be a biotin analog [5a]. Glycoluril 1 is a bicyclic, cis-fused ring compound; each ring resembles the ureido ring of biotin. Glycoluril 1 has been shown to bind to streptavidin [56], a tetrametric protein found in Streptomyces avidinii. The noncovalent interaction of streptavidin with biotin is characterized by a formation (affinity) constant of 10$^{-15}$ M [57]; crystal structures of the bound substrates show that the two molecules are bound in a similar manner
Thus, the weaker binding of glycoluril compared with biotin results from the missing valerate group.

Recently, in another study, glycoluril derivatives with a carboxylic acid (Valeric acid) side chain have been synthesized and shown to bind to avidin and streptavidin [58]. Avidin is a glycol protein found in egg white, which have the ability to bind with extremely affinity the vitamin biotin. The avidin-biotin interaction ($K_d = 10^{-15} \text{ M}$) is the strongest known biochemical (non-covalent) bond [59] Glycoluril derivatives with a valerate side chain bound either to a bridge head carbon atom or to a nitrogen atom have a higher binding affinity to Av than to Sav [60]. Glycolurils (2,4,6,8-tetraazabicyclo[3.3.0] octane-3,7-diones) exhibit a broad spectrum of biological activity [61, 62, 7a] in particular, they constitute a new class of neurotropic agents [61].

N-alkyl substituted glycolurils possess a broad spectrum of biological activity; in particular, they show psychotropic activity [62]. One of the compounds of this class 2,4,6,8-tetramethylglycoluril 28 (Mebicar) that was introduced into medical practice as a tranquilizer, which has significant advantages over tranquilizers of other classes [61]. Mebicar 28 exhibits extremely low toxicity, does not cause complications and side effects, does not suppress working ability and can be taken under any conditions by people of all ages. Mebicar 28 is not metabolized and leaves the organism within 24 hours.

Another known representative of the N-alkyl substituted glycoluril derivatives is Albicar (2,6-diethyl-4,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-dione) 55 (Figure 3), also described as psychotropically active and candidate for use as tranquilizer [63].
TAGU 42 has been used as an effective bleaching agent [64, 65] and TCGU 46 was found useful as valuable disinfecting and bleaching agent, bacterial toxicant and detergent [66].

Derivatives of glycoluril 1 have been shown to have many interesting properties as well. Nitro derivatives are very powerful explosives [48]; The chemical, known as cis-1,4-Dinitroglycoluril (cis-DINGU) is an important explosive and it has been of interest to the high energy materials community recently. Cis-DINGU was prepared as early as 1888 by Franchimont and Klobbie [67, 68] Tetranitroglycoluril (also known as sorgyul) is a highly explosive compound which has been developed 30 years ago [69].

Another nitramine explosive 56 [70] has an obviously related structure (Figure 4) and shows remarkable thermal stability.

Some representatives of thioglycolurils have attracted the attention of many chemists and biologists because of their wide range of pharmacological effects antiproliferative activity, antifungal activity [71] and sedative activity [72, 73].
Glycoluril 1 was used as a building block in supramolecular chemistry. Its importance was recognized when the crystal structure of cucurbit[6]uril (CB[6]) was determined [74]. Cucurbit[n]urils (CB[n]); n= 5, 6, 7 8, 10 have been synthesized and used by chemists as an advanced drug delivery system [75].

Cucurbiturils have already been used successfully in catalytic processes in construction of polyrotaxanes and supramolecular switches [74, 76-79].

2.6 Synthesis of supramolecular compounds

2.6.1 Bambusuril

Bambusurils are macrocyclic compounds which synthesized for the first time in 2010. Bambusuril (BU[n]) is a family of macrocyclic compounds consisting of 2,4 N-disubstituted glycoluril units connected through N-methylene bridges (Figure 5).

![Figure 5. Structures of A - BU[4] and B -BU[6].](image)
Two homologues of Bambusuril macrocycles, consisting of four (BU[4]) and six (BU[6]) glycoluril units, have been described so far. The main differences in these macrocycles can be seen in their supramolecular properties. Although BU[6] is an excellent receptor for various inorganic anions, the four-membered bambusuril A does not bind anion due to its small cavity size. Methine protons of glycoluril units within the bambusuril macrocycles are directed inside the cavity.

The shape of the bamboo macrocycle resembles a part of a bamboo rod (Figure 6), with the widest parts of the macrocycle (d₃) defined by a series of methylene bridges at its equator, which is approximately the same diameter as the two circles (d₁) formed by the oxygen atoms of glycoluril units opposite macrocyclic portals. The narrowest parts (d₂) are formed by two circles of protons of the methine fragment inside the macrocycle. The anion-binding site is usually located between these two rows of methine hydrogen atoms.

![Figure 6](image.png)

**Figure 6.** Bambus[6]uril and cross-section of its X-ray structure.

- (d₁) is the outer edge of the oxygen atoms
- (d₂) is the internal portal of carbon
- (d₃) the diameter of the internal cavity, represented by methylene bridges.
The above-mentioned structural features distinguish bambusurils from cucurbit[n]urilis [80, 81], despite the fact that they use the same initial monomers, glycoluril and formaldehyde for their preparation. Bambusurils can be better compared with hemicucurbit[n]uril [82-87], since they have an alternative arrangement of building blocks and just one row of methylene bridges. The building block hemicucurbit[n]uril, imidazolidin-2-one (ethylene urea), can be considered as one half of the glycoluril molecule. This makes bambusuril a member of the hemicucurbit[n]uril family.

The bambusuril was expanded mainly by replacing building blocks on two nitrogen atoms of glycoluril. The type of substituent has a great influence on the solubility of bambusuril. Although (Me) BU [6] is apparently insoluble in any solvent, the replacement of methyl groups with benzil groups results in millimolar bambusuril soluble in chloroform and dimethyl sulfoxide. Water solubility of bambusurils were achieved by incorporating carboxyl functional groups in their structure.

2.6.2 Synthesis of bambusuril

The preparation of bambusurils proceeds by the condensation reaction of a 2,4-substituted glycoluril monomer with Mannich-type paraformaldehyde under acidic conditions (Scheme 35):

The choice of solvent depends on the replacement of glycoluril units and can vary from polar water to non-polar chloroform. Most of the studied reactions lead to the formation of bambusuril of four or six glycoluril units. The nature of the obtained homogen bambusuril can be controlled with a template. A four-membered bambusuril is only a macrocycle obtained in the absence of a template, while mixture of four and six-membered bambusurils has been formed using the template. The selection of template can also control the reaction output.

2.6.3 Cucurbiturils

Cucurbiturils are macrocyclic molecules composed of glycoluril monomers linked by methylene bridges (-CH₂-). Oxygen atoms are located along the edges of the band and tilted inward, forming a partially closed cavity.

Cucurbiturils are usually written as cucurbit[n]uril, where n is the number of glycoluril units. Two common abbreviations have been adopted - CB[n] or just CBn.

These compounds are of particular interest to chemists, since they are suitable hosts for various neutral and cationic compounds. It is considered that the binding mode occurs through hydrophobic interactions, and in the case of cationic guests through cation-dipole interactions. The dimensions of cucurbiturils are usually found on a scale of ~ 10 Å. For example, the cucurbit[6]uril cavity (Figure 7) has a height of ~ 9.1 Å, an external diameter of ~ 5.8 Å and an internal diameter of ~ 3.9 Å [88].
Cucurbiturils were first synthesized in 1905 by Berend by condensation of glycoluril with formaldehyde [50], but their structure was not clarified until 1981 [89]. To date, all known cucurbiturils consisting of 5, 6, 7, 8, 10, and 14 repeating units have been identified [90, 91], and have an internal cavity volume of 82, 164, 279, 479 and 870 Å, respectively. Other common molecular capsules that have a similar molecular form with cucurbiturils are cyclodextrins, calixarenes and stolbarene.

### 2.6.4 Synthesis of cucurbituril

Cucurbiturils were synthesized from urea and dialdehyde (for example, glyoxal 4) by nucleophilic addition to form glycoluril intermediate 1. This intermediate compound is condensed with formaldehyde to give the cucurbit hexamer above 110 °C. Typically, multifunctional monomers, such as 1, undergo stepwise polymerization, which produces product distribution, but because of the favorable deformation and abundance of the hydrogen bond, the hexamer is the only reaction product isolated after precipitation [90] (Scheme 36):
Reducing the reaction temperature from 90 to 75 °C can be used to access other cucurbituril sizes, including CB[5], CB[7], CB[8] and CB[10]. CB[6] is still the main product; other types of cucurbituril are formed with low yields, and their isolation requires fractional crystallization and dissolution. CB[5], CB[6], CB[7] and CB[8] cucurbiturils are all commercially available. Larger sizes are a particularly active area of research, as they can bind larger and more interesting guest molecules, thus expanding their potential applications.

Curcubit[10]uril is particularly difficult to isolate. It was first discovered by Day et al [92], in 2002 as an inclusion complex containing CB[5]. The complex CB[10] • CB[5] is unambiguously identified by single-crystal X-ray diffraction analysis, which showed that the complex resembles to a molecular gyroscope. In this case, the free rotation of CB[5] in the cavity CB[10] simulates independent rotation of the flywheel in the gyroscope frame.

Isolation of pure CB[10] could not be carried out by direct separation methods, since the compound has such a high affinity for CB[5]. Strong binding with affinity for CB[5] can be understood, since it has an additional size and shape in the cavity of CB[10]. Pure CB[10] was isolated by Isaac et al in 2005, introducing a more strictly binding guest melamine diamine, able to crowd out CB[5] [93]. Therefore, the guests from melamine diamine were separated from
CB[10] by reaction with acetic anhydride, which turned the positively charged amino groups into neutral charged amides. Cucurbiturils strongly bind cationic guests, but, by removing the positive charge from the guest melamine diamine, reduces the association constant to such an extent that it can be removed by washing with methanol, DMSO, and water. CB[10] has an unusually large cavity (870 Å³), which is free and able to bind unusually large guests, including cationic calix [4] arenas.

2.7 Conclusion

Analysis of the literature shows some studies of glycoluril and its derivatives synthesis also the obtention of thioglycolurils is presented in separate examples.

The main approaches to the preparation of glycolurils and thioglycolurils are cyclocondensation of ureas and their thioanalogues with diones, or by the participation of some diols.

In general, the chemistry of glycoluril continues to evolve. This is due to the fact that glycoluril and their derivatives are widely used in various industries, "medicine, agriculture", as tailor-made polymers, synthetic receptors, liquid crystals, molecular clips and supramolecular gels.

Being synthons in the synthesis of cucurbiturils, they are components of supramolecular structures, such as self-closed molecules. Based on them; fluorescent chemosensors, polymer stabilizers, chemical recognition and self-organization materials are obtained in cyclization reactions.

Bambus[n]urils new class of macrocyclic compounds have been obtained from 2,4-disubstituted glycolurils, which are anion receptors.

Glycolurils and thio-analogs are of interest as matrices for carrying out Claisen condensation or as building blocks for the synthesis of cucurbit[n]urils and condensed oligomers.
3  CHAPTER 3: RESULTS AND DISCUSSION

3.1  Synthesis and study of glycoluril derivatives

Glycoluril is a bicyclic substrate extremely attractive for further functionalization with the goal of synthesis and investigation of new aza-heterocycles [94].

Alkylated glycolurils exhibit varying degrees of psychotropic behaviour [95]. The type and degree of the pharmacological activity of these alkyl glycolurils depends on the nature and the number of substituents on the glycoluril structure, tetra-N-alkylated compounds are the most active, and activity decreases rapidly with decreases in the number of alkyl substituents.

Etherification reactions are well-known dehydration of an alcohol to form ethers in the presence of an acid catalyzed. Usually etherification is carried out in the presence of excess alcohol to supress competing polymerization reactions, which take place under acidic conditions. When the alcohol is lower boiling compared to water and water miscible, larger excess (1.6 per mole methylol) is required. The reaction mixture is refluxed under the influence of heat. Water of the reaction is removed at specified rate, the distillate is condensed remove water and excess of alcohol.

Complete etherification is carried out, resulting one product. The extent of etherification depends upon pH, reaction temperature and amount of alcohol. Low temperature and excess alcohol favours complete etherification. Usually alcohol for etherification must be the solvent for tetramethylolglycoluril and it should react readily to from methylol ethers.

Tetrahydroxymethylglycoluril 41 has been transformed into the corresponding 57 tetramethoxymethylglycoluril [96] and during this preparation, we fell in case of the formation of sodium hyrdochloride like indesirable salt and to avoid this problem we have thought to use nitric acid instead hydrochloric acid, also to improve the yield of tetramethoxymethylglycoluril from 50 % to 95 %.
Scheme 37. Synthesis of compound 57 in acidic medium.

The structure of compound 57 was indicated by the absence of the characteristic O-H stretching vibration at 3200-3600 cm\(^{-1}\) and the presence CH\(_3\) stretching at 2886 cm\(^{-1}\), in addition the absorption bands of the C-O at 1170 cm\(^{-1}\) and 1218 cm\(^{-1}\).

HPLC chromatogram of 57 (Figure 8) indicates the presence of by-products which are due to the water used as solvent with acetonitrile, which led to the partial hydrolysis of compounds 57 to mono, di and tri-methoxymethylglycoluril. The purity of compound 57 was 86.66 %.

Figure 8. HPLC analysis of compound 57.
The \(^1\)H NMR spectrum of compound 57 displayed a singlet at δ 3.18 ppm attributable to the CH\(_3\) group, two doublets at δ 4.71 ppm assignables to N-CH\(_2\)-O and a singlet at δ 5.52 ppm corresponding to –CH group.

The structure of compound 57 was confirmed by \(^{13}\)C NMR spectrum, which indicates the presence of CH\(_2\)-O peak at 66.85 ppm and CH\(_3\)-O signal at 55.59 ppm which confirms the formation of ether.

We investigated the reaction between the compound 41 and ethanol in the presence of nitric acid (HNO\(_3\)), which was proven useful for the synthesis of the compound 58 (Scheme 38).

![Scheme 38. Synthesis of compound 58.](image)

Its IR spectrum was indicated by the absence OH stretching band and the presence of CH\(_3\) bending absorptions at 1435 cm\(^{-1}\) and 1330 cm\(^{-1}\) besides the absorption of C=O at 1710 cm\(^{-1}\).

The \(^1\)H NMR spectrum of compound 58 showed a triplet at δ 1.10 ppm corresponding to the CH\(_3\) group, a quartet representing a CH\(_2\) group at δ 3.40 ppm, two doublets at δ 4.75 ppm assignable to N-CH\(_2\)-O and a singlet at δ 5.53 ppm corresponding to –CH group.
The structure of compound 58 was proved by the presence of N-CH$_2$-O signal at 66.97 ppm and CH$_3$ signal at 15.19 ppm in $^{13}$C NMR spectrum, which indicates the formation of ether. It was also identified as only product by HPLC with purity of 99 % (Figure 9).

![Figure 9. HPLC analysis of compound 58.](image)

Figure 9. HPLC analysis of compound 58.

The condensation of phenylurea 60 with glyoxal 4 under acidic conditions (Scheme 39) leads to the synthesis of compound 59 [97], which is the nitrogen analog of glycoluril, that was laterally used to synthesize the compound 61, also we improved the yield of compound 59 from 35 % to 47 %.

![Scheme 39. Synthesis of compound 59.](image)

The IR spectrum of compound 59 exhibited NH stretching vibration at 3160 cm\(^{-1}\) which confirmed the formation of the secondary amide, in addition to the formation of C=C absorptions at 1445 cm\(^{-1}\), that confirms the presence of aromatic ring.

The \(^1\)H NMR spectrum of compound 59 showed a singlet at \(\delta\) 5.65 ppm corresponding to the CH group, a multiplet assigned to protons of aromatic ring at \(\delta\) 7.28 ppm and a singlet at \(\delta\) 9.11 ppm corresponding to NH group.

The \(^{13}\)C NMR spectrum of the compound 59 displayed the presence of C=O at 155.98 ppm, the CH of aromatic ring at 118.10-129.32 ppm, in addition, the signal at 77.54 ppm corresponding to CH group.

To synthesize compound 61, we treated compound 59 with formaldehyde in the presence of sodium hydroxide, which led to the synthesis of compound 61 (Scheme 40).

![Scheme 40. Synthesis of compound 61.](image)

The IR spectrum of compound 61 displayed the disappearance of the NH stretching vibration with presence of an OH absorption band at 3300 cm\(^{-1}\), in addition to the presence of C-O stretching vibration at 1148 cm\(^{-1}\).

The \(^1\)H NMR spectrum of compound 61 exhibited a singlet at \(\delta\) 6.68 ppm corresponding to the CH group, a multiplet representing protons of aromatic ring at \(\delta\) 7.30 ppm, also a singlet at 5.64 attributable to OH group, two doublets at \(\delta\) 5.56 ppm assignable to N-CH\(_2\)O and a singlet at \(\delta\) 9.01 ppm corresponding to the proton of NH group.
The $^{13}$C NMR spectrum of the compound 61 displayed the presence of C=O at 157.27 ppm, the CH of aromatic ring at 118.27-129.37 ppm, as well as the signal at 79.32 ppm that corresponding to CH group and the signal of (CH$_2$-O) which appeared at 64.64 ppm. It was evident by using HPLC which confirmed its synthesis with purity of 95 % (Figure 10).

![HPLC analysis of compound 61.](image)

**Figure 10.** HPLC analysis of compound 61.

### 3.2 Tetra N-acetoxyethylglycoluril as an efficient and novel reagent for acylation of amines

N-Acetylation reaction is usually carried out with acetic anhydride or acetyl chloride in the presence of either acidic [98] or basic [99] catalysts in different conditions. However the use of acid anhydride and acyl chloride suffer from some drawbacks since they are toxic and hazardous in nature [100]. Thus, development of novel and green methodologies using simple, mild and effective reagent is still required for its usefulness in synthetic organic chemistry as well as in medicinal chemistry. Having this background, it is felt pertinent to report herein an effective as well as an environmentally benign methodology for N-acetylation of amines.
We found that TAMGU 62 is a new benign and facile to prepare, alone without any catalyst can act as N-acetyling agent for the acetylation of amines.

Since the examples of the O-acylation of the hydroxymethylglycoluril are absent in the literature, TAMGU 62 was synthesized from the reaction of teterahydroxymethylglycoluril 41 with acetic anhydride in the presence of pyridine or triethylamine as base catalyst.

O-Acetylation of teterahydroxymethylglycoluril 41 was carried out using anhydride acetic acid in pyridine at room temperature for 24 hours to give the target molecule TAMGU 62 with excellent yield 95%. On the basis of the $^1$H and $^{13}$C NMR spectroscopic data it was found that all of the hydroxymethyl groups had undergone acetylation (Scheme 41).

![Scheme 41. Synthesis of tetra N-acetoxyethylglycoluril 62.](image)

The structure of compound 62 was indicated by the absence of the characteristic O-H stretching vibration at 3200-3600 cm$^{-1}$ and the formation of C=O absorption band attributable to the acetyl group at 1716 cm$^{-1}$, in addition to
the absorption bands corresponding to C-O at 1184 and 1220 cm$^{-1}$. The $^{13}$C NMR spectrum of the displayed the presence of C=O at 171.09, which affirmed the presence of acetyl group, in addition to the peak of the CH$_3$ at 20.82 ppm.

The $^1$H NMR spectrum of compound 62 showed two doublets at $\delta$ 5.30 ppm and 5.6 ppm, which were attributables to the CH$_2$ group. As well as, a singlet representing methine protons at 5.64 ppm. A singlet at $\delta$ 2.07 ppm assignable to the acetyl group.

The required amount of TAMGU 62 was performed using different amounts of it. It was observed that for 1 eq of amine 2 eq of TAMGU was enough for the complete conversion of the starting material.

A number of primary amines underwent N-acetylation smoothly with TAMGU in dichloromethane at reflux temperature in good yields. The course of the reaction of the compounds 63 (a-e) was monitored every 15 min using TLC on Silufol plates in the system C$_6$H$_6$- EtOH (8:2). At the end of 1 hour the reaction mixture contained virtually no starting TAMGU 62. At the end of 2 hours the picture had not changed, which explained the reaction completion. After complete conversion of the amine, the crude reaction mixture was evaporated and then dried in vacuum.

Mechanochemical synthesis of compounds 64 (a-e) in this report also has been studied by reacting 1 eq of compounds 63 (a-e) with 2 eq of TAMGU in dichloromethane as a solvent at room temperature for 10 min. The reaction completion was checked by using TLC, which has shown the total conversion of amines into amides.

The structures of compounds 64 (a–e) were deduced from their spectral data, the solid state IR spectra of these compounds reveals a sharp carbonyl (C=O) stretching vibrations were seen around 1650–1695 cm$^{-1}$. The presence of N–H of primary amides in the skeletons was confirmed from the stretching frequencies in the region 3225-3334 cm$^{-1}$.

All other peaks in the spectra are in well agreement with the contents of functionalities in the synthesized molecules. The $^1$H NMR data of all compounds
showed a characteristic singlet around 5.92–9.08 ppm, which indicates the presence of N–H of amides in the skeletons. Furthermore, the presence of singlet around 1.88- 2.16 ppm reveals the presence of CH$_3$ of acetyl group. The $^{13}$C NMR spectra of all the isolated amides displayed the presence of CH$_3$ signal in the region 23.03-24.41 ppm that confirmed the presence of acetyl group, in addition to the signals at 169.00-170.20 ppm, which prove the presence of carbonyl group of amides 64 (a–e).

3.3 **Tetra N-acetoxymethylglycoluril as precursor in the preparation of cucurbit[6]uril and New oligomer**

The macrocyclic molecules known as cucurbit[$n$]urils (CB$n$) [101] are prepared by the polycondensation reaction between glycoluril and formaldehyde in mineral acid with the exception of cucurbit[6]uril, which can be readily prepared in conc. H$_2$SO$_4$ and temperatures above 100 °C as the sole macrocyclic product [50].

Along with the synthesis of cucurbituril derivatives, other supramolecular hosts based on glycoluril have been prepared, including anionic receptors bambusurils [102–104] and acyclic glycoluril oligomers [105-107].

In this study, we will discuss the synthesis of new acyclic oligomer and the preparation of cucurbit[6]uril using TAMGU 62 as starting material. When compound 62 was treated with HCl in aqueous medium at 100 °C for 20 hours gave compound 48 in 54% yield. Replacing HCl with HCOOH using the same reaction conditions, the compound 65 was obtained in 61% yield (Scheme 43).
Scheme 43. Synthesis of compounds 48 and 65 from TAMGU 62.

The mechanism of formation of the compounds 48 and 65 starts by the hydrolysis of TAMGU 62 under acidic medium affording the intermediate tetramethylologlycoluril 41 (Scheme 44).

Scheme 44. Hydrolysis mechanism of TAMGU.

The rest of the mechanism formation of these compounds 48 and 65 from the intermediate 41 was described in the reported patent [108].

The structure of compound 48 was characterized with IR, $^1$H NMR and $^{13}$C NMR. Its IR spectrum showed broad peak at 3331 cm$^{-1}$ which can be assigned to OH stretching coming from moisture. The peak at 2922 cm$^{-1}$ showed asymmetric
and symmetric stretching of C-H bond. The peak at 1706 cm\(^{-1}\) indicates the presence of carbonyl group from glycoluril unit.

Although, cucurbit[6]uril has very limited solubility in common solvents, it can be complexed with cations to improve the water solubility. We have established that the mixture of cucurbit[6]uril in 0.2 M of CsNO\(_3\)/D\(_2\)O can be used to identify small amounts of cucurbit[6]uril to show \(^1\)H NMR and \(^{13}\)C NMR spectra.

The two protons on methylene group in \(^1\)H NMR (Figure 11) resonate at different chemical shifts because one of protons Ha points towards the carbonyl group resonates at 8.66 ppm as doublet and the other Hb pointing out of the carbonyl group resonating at 7.97 ppm as doublet. The equatorial proton Hc resonates as singlet at 8.09 ppm. These signals were shifted downfield due the influence of CsNO\(_3\) on cucurbit[6]uril, which forms a complex.

![Figure 11](image)

Figure 11. \(^1\)H NMR spectrum of compound 48.

Its \(^{13}\)C NMR spectrum showed the presence of signal representing N-CH\(_2\) at \(\delta\) 81.70 ppm, and a signal at \(\delta\) 127.38 ppm belonging to the CH group, besides to the C=O characterized signal at \(\delta\) 155.16 ppm.
The CB[6]’s mass spectroscopic result gives a peak at 996.00 and its molecular weight is 996.824 very close to theoretical simulation.

The structure of compound 65 indicates the presence of OH at $\nu$ 3442 cm$^{-1}$ and the formation of C=O absorption band at 1703 cm$^{-1}$, as well as the absorption bands of the C-O at 1161 cm$^{-1}$.

We have found that the compound 65 also had poor solubility in common solvents. Therefore, we used the similar previous method by dissolving small amounts of this compound in 0.2 M CsNO$_3$/D$_2$O, which allowed us to identify $^1$H and $^{13}$C NMR spectra. It’s $^1$H NMR spectrum (Figure 12) showed tow doublets at $\delta$ 5.15 ppm and 5.48 ppm, which was attributable to the protons Ha and Hb of the CH$_2$-OH group. However the protons Hc and Hd of N-CH$_2$ grouping were observed at $\delta$ 5.30 and 5.57 ppm. As well as, a singlet represents the methine proton He at 5.63 ppm.

![Figure 12. $^1$H NMR spectrum of compound 65.](image)

Its $^{13}$C NMR spectrum displayed the presence of signal attributable to the CH$_2$OH at $\delta$ 72.53 ppm, signal at $\delta$ 81.70 ppm assignable to N-CH$_2$-N, and the appearance of a signal at $\delta$ 127.38 ppm belonging to CH group, as well as the presence of signal at $\delta$ 157.49 ppm corresponding to C=O.

Molecular weight analysis using ESMS gave m/z of 593.97, which supported the presence of three glycoluril units and four hydroxymethyl moieties.
3.4 Synthesis of some new thioglycoluril derivatives

Recently, thioglycoluril has attracted a continuing interest of researchers due to diverse biological activity and application antiproliferative activity, antifungal activity [109] and sedative activity [71, 72]. Thioglycolurils have found use as organo-catalysts for the Boc protection of amines [73] or for the a-monobromination of 1, 3-dicarbonyl compounds [110]. Thioglycoluril derivatives have been used in the template-directed crossed-Claisen condensation [111], and as molecular clips [112].

Significantly less attention is paid to the chemical transformation of thioglycoluril. Since, it has active centers that can be modified by some reactions such as alkylation and acetylation to provide compounds of potential biological activity.

Therefore, the synthesis of new heterocyclic compounds incorporating the imidazolidin-2-thione moiety fused with any alkyl group represent a challenging task for organic and medicinal chemistry [113].

Generally, alkylation of thiols is carried out via the treatment of thiols with alkyl halides in the presence of strong bases under reflux condition [114-116]. In this section, the task is based on the alkylation of diphenylthioglycoluril 34 using alkyl halides under basic conditions. As stated in section 2.3, the preparation of diphenylthioglycoluril 34 has been reported by Butler and co-workers [40], which can exhibit tautomerism of the type thione-thiol (Scheme 45).

![Scheme 45. Tautomeric form of compound 34.](image-url)
The synthesis of compounds 66a-f has usually been performed by SN2 displacement of a halide group with a thiol group. Typically, substitutions of this kind need rather harsh reaction conditions (base, hot DMF), and often a stochiometric amount of a base, e.g. NaOH [117], sodium alkoxide [118], or KOH [119], to activate the sulfur nucleophile. The formation of non-toxic sodium halide as a side product was the primary reason to select NaOH as the base.

When compound 34 was treated with alkylating agents such as: ethyl bromide, butyl bromide, isobutyl bromide, and chloroacetic acid using DMF as a solvent in the presence of NaOH, the corresponding S-alkylated derivatives 66a-d were obtained in good to excellent yield (Scheme 46). The structures of compounds 66a-d were confirmed by spectroscopic methods such as IR, 1H NMR, and 13C NMR spectroscopy. The IR spectra of compounds 66a-d showed the presence of the NH bands at 3100-3135 cm\(^{-1}\). The structure of compound 66d was also indicated by the presence of OH absorption at 3377 cm\(^{-1}\) and the presence of strong absorption band at 1716 cm\(^{-1}\) attributed to C=O of carboxylic acid.

The formation of compounds 66a-d was evidenced both by the shielding of NH proton from 9.86 ppm in compound 34 to 8.15-8.48 ppm, and the presence of methylene protons (S-CH\(_2\)) group, which appeared at \(\delta\) 2.99 ppm as quartet and 3.15 ppm as triplet in compounds 66a and 66b, respectively, whereas in compound 66c it resonated at \(\delta\) 2.97–3.01 and 3.09–3.14 ppm as doublet of doublets. On the other hand, the 1H NMR spectrum of compound 66d displayed a singlet at \(\delta\) 3.79 ppm integrating for two protons of the S-CH\(_2\).

Furthermore, the structures of compounds 66a-d were proven by the disappearance of C=S, and the formation of S-CH\(_2\) group which was appeared between \(\delta\) 25.03-41.96 ppm in 13C NMR spectra, and the appearance of C=N signal that was shown between \(\delta\) 161.17-164.58 ppm. In addition, the 13C NMR spectrum of compound 66d indicated the presence of C=O group resonated at \(\delta\) 162.79 ppm.
The alkylation of compound 34 by ethyl, butyl, isobutyl bromide and chloroacetic acid on sulfur atom and not on nitrogen atom can be explained by the difference of nucleophility between sulfur and nitrogen which, may be explicated by their respective electronic structures (nitrogen. 1s² 2s² 2p³ and sulfur, 1s² 2s² 2p⁶ 3s² 3p⁴). The chemical reactivity of sulfur is modified by the distance of the valence electrons from the nucleus, the screening effect of the second shell electrons, and the possibility of expansion of the outer shell by hybridisation using the normally vacant 3d orbitals. These factors contribute to the lower electronegativity of sulfur compared with nitrogen. Also, because the sulfur atom

**Scheme 46.** Synthesis of compounds 66a-d.
is larger than the nitrogen atom, the outer shell is more polarisable: this makes sulfur a stronger nucleophile than nitrogen.

Alkylation of compound 34 with ethylene dibromide and epichlorohydrin in the presence of DMF/NaOH afforded compounds 66e and 66f in moderate to good yield (Scheme 47). In these two reactions an intramolecular cyclization took place.

![Scheme 47. Synthesis of compounds 66e and 66f.](image)

It should be noted that diphenylthioglycoluril 34 contains two nucleophilic sites SH and NH. Under basic reaction conditions the both nucleophilic sites are deprotonated, which increases the electronic condensation on sulfur atom and nitrogen atom (nucleophilic activation). On the other hand, the electrophiles (ethylene dibromide and epichlorohydrin) have two sites of attack. Based on our knowledge the atom of sulfur is stronger nucleophile than nitrogen. Thus, the thiolate anion begins a nucleophilic attack on the electrophile and carries out an efficient SN2 displacement on the alkyl halide to give the intermediate 67e and 67f (Scheme 48), followed by the intramolecular cyclization that caused by the attack of nitrogen anion on the second electrophilic site of ethylene dibromide to generate...
the target compound 66e and on the less substituted end of the epoxide in the case of epichlorhydrin to furnish 66f.

![Scheme 48. Suggested mechanism for the reaction of compounds 66e and 66f.](image)

The structures of compounds 66e and 66f were proven by the disappearance of the NH bands and the presence of OH band at 3312 cm\(^{-1}\) in compound 66f in IR spectrum. As it was evident by the absence of the NH signal in their \(^1\)H NMR.

The \(^1\)H NMR spectrum of the compound 66e revealed the presence of two triplets centred at \(\delta 3.13\) and \(3.71\) ppm integrating for protons of S-CH\(_2\) and N-CH\(_2\). In its \(^{13}\)C NMR spectrum the signals of S-CH\(_2\) and N-CH\(_2\) were observed at \(\delta 33.77\) and \(44.10\) ppm, respectively, as well as the signal characteristic to the C=N was appeared at \(\delta 160.98\) ppm. While in \(^1\)H NMR spectrum of compound 66f, the signals due the diastereotopic protons of N-CH\(_2\) grouping were recorded between at \(\delta 2.77–2.79\) and \(2.91–2.93\) as doublet of doublets. Whereas, the diastereotopic protons of S-CH\(_2\) grouping were observed at \(\delta 3.62–3.66\) and \(3.80–3.84\) ppm as doublet of doublets. Furthermore, the signals of CH-O and OH protons were recorded at \(\delta 2.83\) and \(5.47\) ppm, consecutively. Its \(^{13}\)C NMR spectrum displayed the presence of signals at \(\delta 48.27\) and \(32.35\) ppm corresponding to N-CH\(_2\) and S-CH\(_2\), and the signals at \(\delta 63.68\) and \(160.52\) ppm associated to CH-O and C=N, consecutively.
3.5 The application of diphenylthioglycoluril as organic catalyst in the synthesis of betulin 3, 28 di-O-formate

Triterpenes, such as betulin 68 (the trivial name for lup-20(29)-ene- 3b, 28-diol) are abundantly present in birch bark. Betulin and its derivatives possess many interesting biological activities; therefore, they can be seen as excellent renewable starting materials. [120-123].

The protection of betulin at C-3 and C-28 using formylation method can serves as the raw material for many organic syntheses, and especially conversions involving the isopropenyl group which are relatively unstudied.

It has already been related that by the action of formic acid on betulin a cyclic oxide, allobetulin formate is formed [124]. Since in this reaction the double bond and the primary hydroxyl group of betulin react with each other, it can be assumed that they are situated near one another in space.

Surprisingly, when compound 68 (0.67 mmol) was treated with HCOOH in the presence of diphenylthioglycolurilascatalyst 34 (1.2 mmol) at 70 °C, it provided exclusively betulin diformate 69 after stirring the mixture for only 1.5 hour in 87% yield.

\[
\text{Scheme 49. Synthesis of betulin 3,28 di-O-formate 69.}
\]

The mechanistic role of diphenylthioglycoluril 34 is illustrated in (Scheme 50). Hydrogen bond formation between diphenylthioglycoluril and the carbonyl oxygen atoms of HCOOH leads to ‘electrophilic activation’ making the carbonyl group more susceptible to nucleophilic attack. The sulfur atom of
diphenylthioglycoluril 34 in turn forms a hydrogen bond with the hydrogen atom of the alcohol and increases the electron density at the oxygen atom (nucleophilic activation). Electrostatic attraction between the carbonyl group and the oxygen atom leads to nucleophilic attack by the oxygen atom on the carbonyl carbon followed by elimination of H$_2$O and diphenylthioglycoluril yields the corresponding betulin diformate 69.

Scheme 50. Mechanism formation of betulin 3, 28 di-O-formate 69.

Due to the poor solubility of diphenylthioglycoluril in HCOOH, the catalyst can be separated easily after completion of the reaction and reused without any decrease in its activity.

The formation of the betulin diformate was evidenced both by the appearance of two proton singlets at δ 8.13 and δ 8.15 ppm in its $^1$H NMR spectrum, and the presence of resonances of two carbonyl groups at δ 161.23 and δ 161.62 ppm in its $^{13}$C NMR. As was evident by IR spectrum, which indicated the absence of OH stretching band and the presence of new strong absorption pick at
ν(C=O) 1726.56 cm\(^{-1}\) associated to the carbonyl group, and the stretching vibration of the C–O bond was observed at 1247.35 and 1031.59 cm\(^{-1}\).

In addition, the \(^1\)H NMR spectrum of the betulin diformate showed also two singlets at δ 4.62 and 4.71 ppm associated to the terminal methylene of the olefinic group, as well as a set of singlets representing six methyl groups at δ 0.82, 0.88, 0.89, 1.06, 1.09 and 1.71 ppm. The multiplet at δ 4.61 ppm, which was suggested that attributable to a methine proton in the axial orientation bonded at C-3. Two doublets attributables to two methylene protons at C-28 centered at δ 3.95 and 4.37 ppm, consecutively.

### 3.6 Pharmacology

#### 3.6.1 Voltammetric approach for antioxidant activity assessment

The voltammetric assay for the determination of antioxidant properties was applied in this work. The assay was used previously as effective and cheap method for antioxidant activity assessment of different bioactive products [125, 126]. Briefly, this method uses cathodic potential sweep. The electro-reduction of oxygen (ER O\(_2\)) occurs at the cathode under certain voltage. It includes several consecutive reactions presented below:

\[
\begin{align*}
O_2 + e^- & \rightleftharpoons O_2^- \\
O_2^- + H^+ & \rightleftharpoons HO_2 \\
HO_2^- + H^+ + e^- & \rightleftharpoons H_2O_2 \\
H_2O_2 + 2H^+ + 2e^- & \rightleftharpoons 2H_2O 
\end{align*}
\]

This is a basic process underlying the principles of antioxidant activity assessment.
During the process, one-electron oxygen reduction occurs with the formation of active oxygen radicals (O₂, H₂O₂).

It is assumed that antioxidants react with reactive oxygen species on the surface of the indicator electrode. This leads to a decrease in the cathode current of the ER O₂ on the mercury-film electrode in the potential range from 0.0 to -0.7 V. Obtained differences recalculated into coefficient of antioxidant activity.

The antioxidant activity of the test sample was evaluated by the kinetic criterion of the antioxidant activity \( K (\mu\text{mol} / \text{l min}) \), which reflects the amount of oxygen forms reacted with the sample over time. This criterion is determined by the formula (1):

\[
K = \frac{C^0}{t} \left( 1 - \frac{I}{I_0} \right)
\]

Where \( C^0 [\mu\text{mol} \cdot \text{l}^{-1}] \) is the oxygen concentration in solution, \( I \) is the ER O₂ current with the investigated substance addition in the solution, \( I_0 \) is the limiting ER O₂ current without the substance in the solution, \( t \) (min) is time of the interaction between the reactive oxygen species and an antioxidant at the working electrode.

All samples were examined at a final concentration of 0.0125% (0.125 mg / ml). To carry out the measurement, a sample of test substance with a mass of 0.0100 g dissolute in 1 ml of dimethylformamide and then 3 ml of EtOH (96% ethyl alcohol) were added. Then 0.5 ml aliquot was taken and dissolves in 9.5 ml of buffer solution for voltammetric measurement. Three parallel measurements of voltammograms were made and the mean antioxidant activity coefficient was calculated. The results obtained were subjected to statistical treatment. The mean and standard deviation were calculated.

The results of antioxidant activity of compounds; 34, 66a-f and ascorbic acid, are shown in (Figure 13).
Results based on voltammetric assay indicated that all synthesized compounds including thioglycoluril 34 are significant in their antioxidant properties better than ascorbic acid. We recorded voltammograms of oxygen electroreduction in the presence of tested substances 34, 66a-f. There was a decrease of the cathodic current ER O₂, indicating that display of samples of antioxidant activity against oxygen radicals. In addition, there was a shift in potential cathode current ER O₂ positive potentials. All this presupposes the existence of a mechanism of the EC (electro-chemical stage), which means subsequent chemical reaction of antioxidants with active oxygen radicals.

Compounds 66e and 66b were the most efficient of them with antioxidant activity K = 8.8 and 7.5 µmol/lmin, respectively. Moreover, compounds 66d, 66a and 34 exhibited moderate antioxidant activity in comparison with the derivatives 66e and 66b. Additionally, the lowest antioxidant capacity was found to be derivative 66c and 66f.

The following points were noticed. On comparison between the compounds 66a, 66b and 66c, it was noticed that the positive inductive effect (+I) of CH₃
group has affected the antioxidant activity. The inductive effect decreases while moving away from the CH$_3$ group.

Thus, an increase in the inductive effect (+I) will decrease the antioxidant activity in the order; 66c < 66a < 66b.

It was observed that the presence of electron withdrawing group COOH, which has a negative inductive (–I) in compound 66d has improved the antioxidant activity in comparison with thioglycoluril 34. Surprisingly, conversion of the diphenylthioglycoluril 34 to tetracyclic compound 66e resulted in the best antioxidant activity. Whereas, its conversion to tetracyclic 66f gave the lowest antioxidant activity, which probably interpreted by the presence of hydroxyl group.

Thus, influence of the samples on the process of ER O$_2$ was significant with highest impact of 66e substrate.

### 3.7 Conclusion

- The synthesis of tetraethoxyglycoluril and 1,4 diphenyl 2,3 dimethylol glycoluril have been achieved, as well as the preparation of tetramethoxymethylglycoluril in good yield and high purity.
- For the first time, a new glycoluril derivative tetracetoxyethylglycoluril has been synthesized and applied as acetylation agent for the introduction of acetyl fragments into primary amines.
- A new method for the synthesis of cucurbit[6]uril and new acyclic trimer that contains three glycoluril units has been developed using tetracetoxyethylglycoluril as new precursor.
- A new S-alkylated series of diphenylthioglycoluril has been obtained by applying S-alkylation reaction. The reaction mechanism of these derivatives has been proposed.
- The S-alkylation of diphenyl thioglycoluril yielded a highly antioxidant derivatives that surpass the antioxidant of ascorbic acid.
An efficient method for the synthesis of betulin diformate using diphenylthioglycoluril as catalyst. In addition, allobetulin formate has been synthesized successfully from the reaction of betulin diformate with TFA.
4  CHAPTER 4: EXPERIMENTAL SECTION

4.1  Material and methods

NMR Spectroscopy

The NMR analysis was carried out using an NMR spectrometer Bruker AVANCE 400 III HD (Bruker, Billerica, MA, USA). The one-dimensional spectra were recorded on the nuclei of $^1$H atoms (a frequency was 400 MHz) and $^{13}$C (a frequency was 400 MHz) to confirm the structure. Chemical shifts (d) are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants were expressed in Hz.

Thin-layer chromatography (TLC)

The reactions were monitored by TLC on Sorbfil plates using C$_6$H$_6$:CH$_2$Cl$_2$:CH$_3$OH (5:5:1). Spots were detected using a reagent (1% phosphomolybdic acid-water) followed by heating at 110 ºC for 5 minutes.

FT-IR Spectroscopy

Fourier-transform infrared (FTIR) spectra were obtained directly from the products using the high attenuated total reflectance technique in a Bruker Tensor 27 FTIR Spectrometer. The spectra were recorded in the range of 400 to 4000 cm$^{-1}$ with a resolution of 4 cm$^{-1}$ over 16 scans.

Melting point measurement

Melting points (mp) were determined in open capillaries using Buchi apparatus.

High-performance liquid chromatography HPLC
The HPLC gradient-grade methanol and HPLC gradient-grade acetonitrile were supplied by PanReac AppliChem (Darmstadt, Germany).

Mass spectrum

The MS experiments were performed on an Agilent 6550 iFunnel Q-TOF LC-MS system (Agilent Technologies, Santa Clara, CA, USA) equipped with an electrospray ionization source. An electrospray interface was operated in positive ion mode. The conditions for the acquisition parameters were follows: the gas temperature was 200 °C, the drying gas was 14 ml min⁻¹, the nebulizer pressure was 35 psi, the sheath gas temperature was 350 °C, the sheath gas flow was 11 mL min⁻¹, and the capillary voltage was 3.5 kV. The scan range was 100–500 with a 2 Hz sampling rate.

Voltammetric approach for antioxidant activity assessment

The method was conducted with automated voltammetric analyzer “TA-2” (“Tomanalyt”, Tomsk, Russia). The mercury film electrode (MFE) used as working electrode and chloride-silver reference electrode. Solution 0.1 M NaClO₄ in ethanol (96% ethyl alcohol) was used as the background solution for the study.

4.2 Methods of synthesis

Tetramethoxymethylglycoluril (57)
Method A: using Nitric Acid

Into a suitable reaction vessel equipped with stirrer, thermometer, and condenser were charged (74 g, 2.30 mol) of methanol and 3 ml of 70 % con. nitric acid. To this acidic methanol, (30 g, 0.12 mol) of tetramethylol glycoluril were charged, and the reaction mixture was heated to 55 °C with stirring. In about 1 h, all of the tetramethylolglycoluril went into solution. When the reaction mixture became clear, it was cooled to 22 °C, and 20 % sodium hydroxide solution were added to neutralize the reaction mixture to a pH of 7-8. The neutralized clear solution was heated to 50-55 °C and 50 ml of methanol were removed under slightly reduced pressure. The residue in the flask crystallized on standing for a few hours. The crystalline solids were filtered and washed with a small amount of water. The filtrate was then vacuum stripped at 70-80 °C to remove all the water.

The solid residue was then dissolved in benzene and the undissolved salt was removed by filtration. The benzene solution was mixed with the first crop of solid crystals and dissolved with additional benzene and was filtered again. On removal of benzene, tetramethoxy methyl glycoluril 57 was obtained. The yield was 95 %. It was recrystallized from benzene.

Method B: Using Hydrochloric Acid

Into a suitable reaction vessel equipped with a stirrer, thermometer, and reflux condenser there was introduced (74 g, 2.30 mol) of methanol and 3 ml of concentrated hydrochloric acid. To this mixture, (30 g, 0.12 mol) of tetramethylolglycoluril 41 were added and the reaction mixture was stirred at 55 °C. In about 1 h, all the tetramethylolglycoluril went into solution. After half an hour, the reaction mixture was neutralized with a solution of sodium hydroxide 25 % at 22-23 °C. The pH after neutralization was about 8. The salt was filtered. The filtrate was concentrated at 60 °C under reduced pressure; the white crystalline precipitate was filtered and dried. It was recrystallized from benzene.
Melting point: 116-118 °C
Method A: yield 95%.
Method B: yield 50%.
IR (KBr, v, cm⁻¹): 2886 CH₃ stretching, 1436, 1380 CH₃ bending, 1470 CH₂ bending, 1218, 1170 C-O stretching, 1718 C=O stretching.
¹H NMR (400 MHz, DMSO, δH, ppm): 3.18 (s, 3H, CH₃), 4.71 (2d, 2H, CH₂), 5.52 (s, 1H, CH).
¹³C-NMR (400 MHz, DMSO-d6, δC, ppm): 158.07 (C=O), 74.54 (CH), 66.85 (CH₂-O), 55.59 (CH₃-O).

**Tetraethoxymethylglycoluril (58)**

![Tetraethoxymethylglycoluril](image)

Into a suitable reaction vessel equipped with a stirrer, thermometer, and reflux condenser there was introduced (53 g, 1.15 mol) of ethanol and 1.15 g of concentrated nitric acid. To this mixture was added (15 g, 0.047 mol) of tetramethylol glycoluril and the reaction mixture was stirred at 40 °C for 2 h.

The reaction mixture became a clear solution. It is then distilled at reduced pressure between 45-50 °C to remove the ethanol/water azeotrope mixture. After removing the maximum of the ethanol/water mixture, 13.5 g of ethanol were added to the clear solution at room temperature. The solution was neutralized with 25% caustic to a pH 9-10, followed by removal of more of ethanol/water mixture under reduced pressure. The residue was filtered with a filter aid.
Yield: 95 %.

IR (KBr, v, cm⁻¹): 2944 CH₃ stretching, 1435, 1330 CH₃ bending, 1470 CH₂ bending, 1220, 1170 C-O stretching, 1710 C=O stretching.

¹H NMR (400 MHz, DMSO, δH, ppm): 1.10 (t, 3H, CH₃), 3.40 (q, 2H, CH₂), 4.75 (2d, 2H, CH₂), 5.53 (s, 1H, CH).

¹³C NMR (400 MHz, DMSO-d6, δC, ppm): 157.97 (C=O), 72.82 (CH), 66.97 (N-CH₂-O), 63.25 (CH₂-O), 15.19 (CH₃).

1,4-Diphenylglycoluril (59)

Commercial 30 % glyoxal solution (10 g, 0.05 mol), phenylurea (13.6 g, 0.1 mol), water (100 ml) and 70% concentrated hydrochloric acid (2-3 ml) are maintained at 75 °C for 50 minutes. After cooling, the formation of white cream that contains brown solid as impurities, the cream is filtered and extracted three times with 150 ml portions of boiling ethanol to remove the brown solid.

Melting point: 232 °C.

Yield: 47 %.

IR (KBr, v, cm⁻¹): 3160 N-H stretching, 1710 C=O stretching, 1445 C=C stretching, 1148 C=N stretching.

¹H NMR (400 MHz, DMSO, δH, ppm): 5.65 (s, 1H, CH), 7.28 (m, 10H, Ar-H), 9.11 (s, 1H, NH).
$^{13}$C-NMR (400 MHz, DMSO-d6, δC, ppm): 155.98 (C=O), 118.10-129.32 (CH arom), 77.54 (CH).

1,4-Diphenyl 2,3-Dimethylol Glycoluril (61)

(71 g, 0.5 mol) of 59 was added to a stirred suspension of (66 g, 2.2 mol) of formaldehyde in 150 ml of water. The pH of the suspension was adjusted to between 10 and 12 by the addition of alkali, and the suspension heated slowly to 50-60 °C for 1 h. Without allowing the syrup to cool to a temperature which would induce crystallization, 300 ml of methanol was added, with vigorous stirring. The syrup went into solution and within a few minutes diphenyldimethylolglycoluril separated as white powder these were filtered off, washed with 30 ml of methanol, and dried.

Yield: 53%.

IR (KBr, ν, cm$^{-1}$): 3200-3600 OH stretching, 1695 C=O stretching, 1465 CH$\text{2}$ bending, 1148 O-CH$\text{2}$ stretching.

$^{1}$H NMR (400 MHz, DMSO, δH, ppm): 5.56 (2d, 2H, CH$_{2}$), 5.64 (s, 1H, OH), 6.68 (s, 1H, CH), 7.30 (m, 10H, Ar-H), 9.01(s, 1H, NH).

$^{13}$C-NMR (400 MHz, DMSO-d6, δC, ppm): 157.27 (C=O), 118.27-129.37 (CH arom), 79.32 (CH), 64.64 (CH$_{2}$-O).

Tetra N-acetoxymethylglycoluril (62):
(0.3 g, 0.6 mmol) Acetic anhydride (5 ml) and the 41 (5 mmol) were added to dry pyridine (5 ml) and the product was stirred to complete solution at 20°C and held at this temperature for 24 h. The solvent was distilled off and the residue was triturated with ether of give the precipitated 62, which was filtered off and recrystallized from methanol.

Melting point: 145°C.
Yield: 95%.
Rf: 0.71 (C₆H₆: CH₂Cl₂: CH₃OH / 5:5:1).
IR (KBr, ν, cm⁻¹): 2925 (=C=H), 1727 (C=O), 1250, 1219 (C-O-C).
¹H NMR (400 MHz, CDCl₃, δH, ppm): 5.64 (s, 2H, CH), 5.30 (d, 2H, CH₂), 5.60 (d, 2H, CH₂), 2.07 (s, 3H, CH₃).
¹³C-NMR (400 MHz, CDCl₃, δC, ppm): 171.09 (C=O acetyl), 156.04 (C=O glycoluril), 77.14 (CH), 20.82 (CH₃), 67.25 (CH₂).

**Synthesis of Compounds 64(a-e):**

**Method A:**

Into a suitable reaction vessel equipped with stirrer, thermometer, and condenser were charged (2.2 g, 5 mmol) of TAMGU and 20 ml of dichloromethane. To this solution, (2 ml, 22 mmol) of aniline was added, and the reaction mixture was heated to 55 °C with stirring. In about 1 h, the tetramethylolglycoluril precipitate was formed after reaction completion.
(monitored by TLC), the tetramethylolglycoluril was filtered and the filtrate was concentrated to give the correspondent acetamides.

Method B:

The mixture of aniline (2 ml, 22 mmol) and TAMGU (2.2 g, 5 mmol) were placed in ceramic mortar and grinded with pestle for 5 min at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). Upon completion of reaction the mixture was solved in ethanol and filtered, mother-liquor was evaporated to obtain 1 g of 64 (a, b, c, d, e).

N-phenylacetamide (64a):

\[
\begin{align*}
&\text{Melting point: } 116^\circ\text{C.} \\
&\text{Yield: } 92\%. \\
&\text{Rf: } 0.46 (\text{C}_6\text{H}_6: \text{C}_2\text{H}_5\text{OH} / 80:20). \\
&\text{IR (KBr, } \nu, \text{ cm}^{-1}): 3289 (\text{NH}), (\text{C-H arom}) 3000 \text{ cm}^{-1}, 1657 (\text{C=O}). \\
&\text{^1H NMR (400 MHz, CDCl}_3, \delta\text{H, ppm): } 2.13 (\text{s, 3H, CH}_3), 6.99 (\text{m, 1H, Ar-H}), 7.19 (\text{m, 1H, Ar-H}), 7.43 (\text{m, 1H, Ar-H}), 7.94 (\text{s, 1H, NH}). \\
&\text{^13C-NMR (400 MHz, CDCl}_3, \delta\text{C, ppm): } 120.23-138.47 (\text{CH arom}), 169.11 (\text{C=O}), 24.41 (\text{CH}_3).
\end{align*}
\]

N-benzylacetamide (64b):
Melting point: 61 °C.
Yield: 96%.
Rf: 0.44 (C₆H₆: C₂H₅OH / 80:20).
IR (KBr, ν, cm⁻¹): 3373 (NH), 3027 (CH), 1658 (NH), 1496 (C=C aromatic), 1026 (C–N).
¹H NMR (400 MHz, CDCl₃, δH, ppm): 4.35 (m, 2H, CH₂), 6.54 (s, 1H, NH), 7.01-7.21 (m, 5H, Ar-H), 1.95 (s, 3H, COCH₃).
¹³C-NMR (400 MHz, CDCl₃, δC, ppm): 129.01 (C–1), 128.22 (C–2), 129.604 (C–3), 128.3 (C–4), 130.10 (C–5), 138.6 (C–6), 43.60 (–CH₂NH), 170.22 (C=O), 23.03 (CH₃).

**N-cyclohexylacetamide (64c):**

Melting point: 104 °C.
Yield: 87%.
Rf: 0.5 (C₆H₆: C₂H₅OH / 80:20).
IR (KBr, ν, cm⁻¹): 3276 (NH), 2864-2924 (CH₂), 1606 (NH₂), 1370 and 1450 (CH₂).
¹H NMR (400 MHz, CDCl₃, δH, ppm): 1.83 and 1.62 (m, 4H, CH₂), 1.22 (m, 2H, CH₂), 1.085 (m, 2H, CH₂), 1.88 (s, 3H, CH₃), 3.66(m, 1H, CH), 5.92 (s, 1H, NH).
¹³C-NMR (400 MHz, CDCl₃, δC, ppm): 169.22 (C=O), 48.05 (CH), 33.06 (2CH₂); 25.49 (CH₂); 25.36 (CH₂); 23.36 (CH₃).

**N-Acetyl-4-aminoantipyrine (64d):**
Melting point: 197 °C.
Yield: 90%.
Rf: 0.24 (C₆H₆: C₂H₅OH / 80:20).
IR (KBr, ν, cm⁻¹): 1709 (C=O), 1688 (C=O) amide, 3290 cm⁻¹ (NH), 1384, 1354 and 1295 cm⁻¹ (C-N), 1438 and 1407 cm⁻¹ (C-CH₃).
¹H NMR (400 MHz, DMSO, δH, ppm): 9.08 (s, 1H, NH), 7.30 (m, 3H, arom H), 7.50 (m, 3H, arom H), 3.028 (s, 3H, N-CH₃), 2.09 (s, 3H, C-CH₃), 1.97 (s, 3H, CH₃CO).
¹³C-NMR (400 MHz, DMSO-d₆, δC, ppm): 124- 136 (C aromatic), 162 (C=O), 169.46 (C=O), 154 (C=C-NH₂), 108.25 (C=C), 36.60 (N-CH₃), 11.79 (CH₃), 23.13 (CH₃).

2-acetamido 4- phenylthiazole (64e):

Melting point: 206 °C.
Yield: 88%.
Rf: 0.32 (C₆H₆: C₂H₅OH / 80:20).
IR (KBr, ν, cm⁻¹): 3240 (NH), 1667 (C=O), 1600 (C=C), 1520 (C=N).
$^1$H NMR (400 MHz, DMSO, δH, ppm): 7.31 (m, 1H, aromatic), 7.40 (m, 2H, aromatic), 7.89 (m, 2H, aromatic) (m, 3H, arom H), 7.58 (s, 1H, thiazole-H5), 9.00 (s, 1H, NH), 2.16 (s, 3H, CH$_3$CO).

$^{13}$C NMR (400 MHz, DMSO-d$_6$, δC, ppm): 158.51 (C=N), 169.76 (C=O), 108.41 (C=C), 126.22-134.86 (C arom), 149.26 (C=C-Ph), 24.60 (CH$_3$).

**Cucurbit[6]uril (48)**

![Cucurbit[6]uril](image)

To a mixture of TAMGU (3 g, 7.1 mmol) and 25 ml of water, 10 ml of HCl was added and the mixture was stirred at 100 °C, after 7 h of heating a cristalline precipitate was formed, after 13 h we filtered a precipitate resulted, and washed with water to give compound 48 as colorless crystal.

Melting point: 260 °C.

Yield: 54%.

IR (KBr, ν, cm$^{-1}$): 3331 (OH), 1706 (C=O), 1187 (C-N).

$^1$H NMR (400 MHz, CsNO$_3$/D$_2$O, δH, ppm): 8.66 (Ha, d, 1H, N-CH$_2$), 8.09 (Hc, s, 1H, CH), 7.97 (Hb, d, 1H, N-CH$_2$).

$^{13}$C NMR (400 MHz, CsNO$_3$/D$_2$O, δC, ppm): 155.16 (C=O glycoluril), 127.38 (CH), 81.70 (CH$_2$).

HRMS: calcd for C$_{20}$H$_{26}$N$_{12}$O$_{10}$: 966.00; found 996.824.
Oligomer (65)

To a mixture of TAMGU (3 g, 7.1 mmol) and 25 ml of water and 15 ml of HCOOH, was added and the mixture was stirred at 100 °C, after 20 h of heating, the result solution was poured into 20 ml of acetone and the resultant precipitate collected by filtration, washed with water to afford compound 65 as colorless crystal.

Melting point: 296°C.
Yield: 61%.
IR (KBr, ν, cm⁻¹): 3442 (OH), 1703 (C=O), 1218 (C-N), 1161 (C-O).
¹H NMR (400 MHz, CsNO₃/D₂O, δH, ppm): 5.15 (Ha, dd, 1H, N-CH₂-O), 5.30 (Hc, d, 1H, N-CH₂), 5.48 (Hb, dd, 1H, N-CH₂-O), 5.57 (Hd, d, 1H, N-CH₂), 5.63 (He, s, 1H, CH).
¹³C NMR (400 MHz, CsNO₃/D₂O, δC, ppm): 158.66 (C=O glycoluril), 127.38 (CH), 81.70 (N-CH₂), 72.53 (CH₂-O).
HRMS: calcd for C₂₀H₂₆N₁₂O₁₀: 594; found 593.97.

Synthesis of Compounds 66a-f

To the solution of (1 g, 0.003 mol) of compound 34 and 20 ml of DMF, (2.5 mol) of Alkyl halides was added and the mixture was stirred for 5 min. After
this time (0.5 g, 0.012 mol) of NaOH was added. The solution was stirred at 60 °C for 1-4 h. The DMF was evaporated. The precipitate that deposited was crystallized from water. The solid was filtered washed with cold water 3 times.

2,5-bis(ethylsulfanyl)-3a,6a-diphenyl-1,3a,4,6a-tetrahydroimidazo[4,5-d]imidazole (66a)

![Chemical Structure](image)

Melting point: 236°C.

Yield: 76%.

Rf: 0.72 (C₆H₆:CH₂Cl₂:CH₃OH / 5:5:1).

IR (KBr, ν, cm⁻¹): 3100 (NH), 3067 (CH aromatic), 1549 (C=N), and 693 (C-S).

¹H-NMR (400 MHz, DMSO-d₆, δH, ppm, J/Hz): 1.38 (t, J= 7.2 Hz, 3H, CH₃), 2.99 (q, J= 6.4 Hz, 2H, S-CH₂), 7.00 (m, 10H, Ar-H), 8.18 (s, 1H, NH).

¹³C-NMR (400 MHz, DMSO-d₆, δC, ppm): 15.91 (CH₃), 25.03 (CH₂), 98.76 (C-Ph), 127.14, 127.42, 127.80, 140.62 (Ar-C), 164.58 (C=N).

2,5-bis(butylsulfanyl)-3a,6a-diphenyl-1,3a,4,6a-tetrahydroimidazo[4,5-d]imidazole (66b)
2,5-bis(isobutylsulfanyl)-3a,6a-diphenyl-1,3a,4,6a-tetrahydroimidazo[4,5-d]imidazole (66c)

Melting point: 247 °C.
Yield: 93 %.

Rf: 0.88 (C\textsubscript{6}H\textsubscript{6}:CH\textsubscript{2}Cl\textsubscript{2}:CH\textsubscript{3}OH / 5:5:1).

IR (KBr, ν, cm\textsuperscript{-1}): 3135 (NH), 3064 (CH aromatic), 1550 (C=N), and 694 (C-S).

\textsuperscript{1}H-NMR (400 MHz, DMSO-d6, δH, ppm, J/Hz): 1.01 (d, J= 15.6 Hz, 6H, CH\textsubscript{3}), 2.00 (m, 1H, CH), 2.97-3.01 (dd, J= 13.2, 7.2 Hz, 1H, S-CH\textsubscript{2}), 3.09-3.14 (dd, J= 13.2, 6.8 Hz, 1H, S-CH\textsubscript{2}), 6.97 (m, 10H, Ar-H), 8.15 ppm (s, 1H, NH).

\textsuperscript{13}C-NMR (400 MHz, DMSO-d6, δC, ppm): 22.11 (2CH\textsubscript{3}), 28.91 (CH), 38.91 (CH\textsubscript{2}), 99.00 (C-Ph), 127.14, 127.38, 127.93, 140.67 (Ar-C), 163.56 (C=N).

2,2'-(3a,6a-diphenyl-1,3a,4,6a-tetrahydroimidazo[4,5-d]imidazole-2,5 diyl)disulfanediyl]diacetic acid (66d)

Melting point: 238 °C.

Yield: 81%.

Rf: 0.62 (C\textsubscript{6}H\textsubscript{6}:CH\textsubscript{2}Cl\textsubscript{2}:CH\textsubscript{3}OH / 5:5:1).

IR (KBr, ν, cm\textsuperscript{-1}): 3377 (OH), 3112 (NH), 3033 (CH aromatic), 1587 (C=N), 1716 (C=O), and 702 (C-S).

\textsuperscript{1}H-NMR (400 MHz, DMSO-d6, δH, ppm, J/Hz): 3.79 (s, 2H, S-CH\textsubscript{2}), 7.00 (m, 10H, Ar-H), 8.48 (s, 1H, NH).

\textsuperscript{13}C-NMR (400 MHz, DMSO-d6, δC, ppm): 41.96 (CH\textsubscript{2}), 101 (C-Ph) 127.48, 127.80, 128.22, 138.76 (Ar-C), 161.17 (C=N) and 162.79 (C=O).
2,5-bis[(2-bromoethyl)sulfanyl]-3a,6a-diphenyl-1,3a,4,6a
tetrahydroimidazo[4,5-d]imidazole (66e)

Melting point: 256 °C.
Yield: 60%.
Rf: 0.57 (C₆H₆;CH₂Cl₂;CH₃OH / 5:5:1).
IR (KBr, ν, cm⁻¹): 3063 (CH aromatic), 1576 (C=N), 1591 (C=C), and 691 (C-S).
$^1$H-NMR (400 MHz, DMSO-d6, δH, ppm, J/Hz): 3.13 (t, J = 15.6 Hz, 2H, S-CH₂),
3.71 (t, J= 12.8 Hz, 2H, N-CH₂), 7.1 (m, 10H, Ar-H).
$^{13}$C-NMR (400 MHz, DMSO-d6, δC, ppm): 33.77 (S-CH₂), 44.10 (N-CH₂), 106 (C-Ph) 127.74, 128.26, 128.43, 135.99, (Ar-C), and 160.98 ppm (C=N).

4b,9b-Diphenyl-3,4,4b,8,9,9b-hexahydro-2H,7H-1,6-dithia-4a,5,9a,10-
tetraaza-indeno[2,1-a]indene-3,8-diol (66f)
Melting point: 190 °C.

Yield: 85%.

Rf: 0.5 (C_6H_6:CH_2Cl_2:CH_3OH / 5:5:1).

IR (KBr, ν, cm\(^{-1}\)): 3312 (OH), 3050 (CH aromatic), 1596 (C=C aromatic), 1556 (C=N), and 697 (C-S).

\(^1\)H-NMR (400 MHz, DMSO-d6, δH, ppm, J/Hz): 2.77-2.79 (Ha, dd, J= 4, 2.8 Hz, 1H, S-CH\(_2\)), 2.91-2.93 (Hb, dd, J= 8.4, 4 Hz, 1H, S-CH\(_2\)), 3.62-3.66 (Hc, dd, J=11.6, 4.8 Hz, 1H, N-CH\(_2\)), 3.80-3.84 (Hd, dd, J= 12, 3.2 Hz, 1H, N-CH\(_2\)), 5.47 (s, 1H, OH), 7.08 (m, 10H, Ar-H).

\(^13\)C-NMR (400 MHz, DMSO-d6, δC, ppm): 32.35 (S-CH\(_2\)), 48.27 (N-CH\(_2\)), 63.84 (CH-OH) 99.52 (C-Ph), 127.60, 127.74, 127.82, 137.89 (Ar-C), 160.52 (C=N).

**Synthesis of betulin 3,28 di-O-formate (69)**
To a solution of betulin (0.3 g, 0.67 mmol) in HCOOH 25 ml was added diphenylthioglycoluril 34 (0.4 g, 1.2 mmol) and stirred at 70 °C for 1.5 h. After completion of the reaction (as indicated by TLC), the catalyst was separated by filtration, and the filtrate was collected and evaporated. The white residue was recrystallized from acetone followed by second recrystallization from ethanol to furnish 0.29 g of compound 69.

Melting point: 165 °C.
Yield: 87 %.
Rf: 0.91(C6H6: CH2Cl2: CH3OH / 5:5:1).
IR (KBr, ν, cm⁻¹): 3070 (=C-H), 2924–2855 (-CH3 and -CH2), 1726 (C=O), 1649 (C=C), 1247 and 1031 (C-O-C).

1H NMR spectrum (400.17 MHz, CDCl3, δH, ppm, J/Hz): 0.82 (m, 1H, 5-H), 0.88 (s, 3H, CH3), 0.89 (s, 6H, CH3), 1.06 (s, 3H, CH3), 1.09 (s, 3H, CH3), 1.26–1.95 (m, 10H, CH2); 1.30 (m, 1H, CH), 1.63 (m, 1H, CH), 1.69 (m, 1H, CH); 1.71 (s, 3H, CH3), 8.13 and 8.15 (s, 2H, HCO), 2.47 (m, 1H, 19-H), 3.95 and 4.37 (d, 2H, 28-H, 2J = 11.2 Hz), 4.61 (m, 1H, 3-H), 4.62 and 4.71 (s, 2H, 29-H).

13C NMR spectrum (100.63 MHz, CDCl3, δC, ppm): 14.75, 16.0, 16.15, 16.51 (CH3); 18.17 (-C6), 19.12(C-30), 20.79 (CH2), 23.82 (C-2), 25.12 and 26.95 (CH2), 27.87 (CH3), 29.47 (C-21); 29.61, 34.07, 34.46 (CH2); 37.05, 37.63 (C-13), 37.75, 38.35 (CH2);40.88, 42.7, 46.3, 47.7 (C-19), 48.75 (C-18), 50.25 (C-9), 55.35 (C-5), 62.32 (C-28), 81.08 (C-3), 110.03 (C-29), 149.97 (C-20), 161.23 and 161.62 (C=O).
5 CHAPTER 5: REFERENCES


97. G. G. Parekh, Coating composition containing an alkylated glycoluril, a polymeric non-self-crosslinking compound and an acid catalyst // U.S. patent No. 4,064,191. 1977


Отчет о проверке на заимствования №1

АВТОР: imene_boudebouz@yahoo.ca / ID: 6609229
Проверяющий: imene_boudebouz@yahoo.ca / ID: 6609229
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Длительность загрузки: 00:00:03
Имя исходного файла: Imene Boudebouz Dissertation
Размер текста: 1235 кБ
Тип документа: Кандидатская диссертация
Символов в тексте: 121863
Слова в тексте: 18766
Число предложений: 1849

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Заимствования — доля всех найденных текстовых пересечений, за исключением тех, которые система отнесла к цитированиям, по отношению к общему объему документа.

Цитирования — доля текстовых пересечений, которые не являются авторскими, но система посчитала их использование корректным, по отношению к общему объему документа. Сюда относятся оформленные по ГОСТу цитаты; общепользовательные выражения; фрагменты текста, найденные в источниках из коллекций нормативно-правовой документации.

Текстовое пересечение — фрагмент текста проверяемого документа, совпадающий или почти совпадающий с фрагментом текста источника.

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Заимствования, цитирования и оригинальность являются отдельными показателями и в сумме дают 100%, что соответствует всему тексту проверяемого документа.

Обращаем Ваше внимание, что система находит текстовые пересечения проверяемого документа с проиндексированными в системе текстовыми источниками. При этом система является вспомогательным инструментом, определение корректности и правомерности заимствований или цитирований, а также авторства текстовых фрагментов проверяемого документа остается в компетенции проверяющего.

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