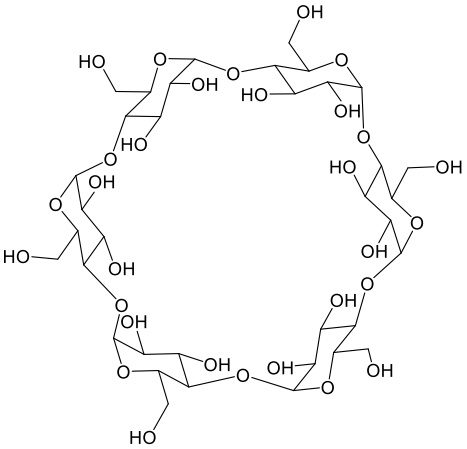
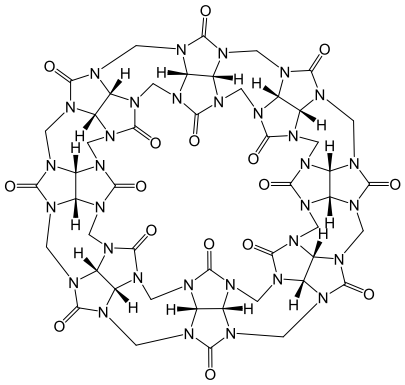
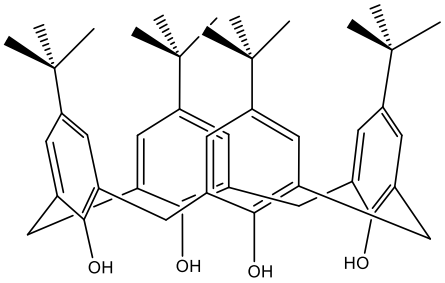
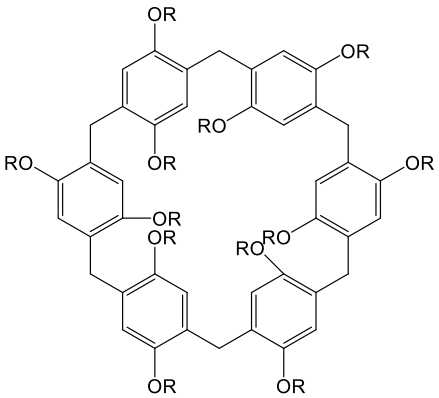
Chapter 1

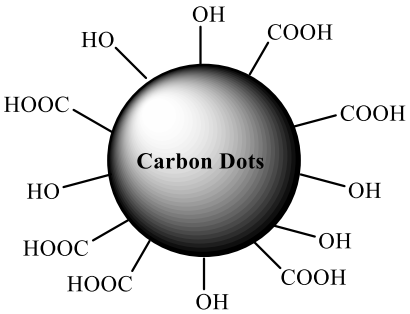
Introduction











1.1. Introduction

1.1.1. Insight into the problem:

Cancer is a disease where control over the cell cycle and apoptosis, DNA damage and defective repair mechanisms is lost[1]. Every year, cancer affects roughly 19–20 million people worldwide[2].

Chemotherapy, usually known as chemo, is a type of cancer therapy that employs drugs to eradicate cancer cells[3]. Chemotherapy attempts to stop tumour growth and cell division in order to prevent invasion and metastasis. Tumour growth can be slowed down at various levels both inside the cell and in its surroundings by chemotherapeutics. By interfering with the production of DNA, RNA, or proteins, traditional chemotherapy drugs largely disrupt the macromolecular synthesis and function of malignant cells. The conventional drugs may need to be taken again and again for apoptosis[4]. Sometimes, chemotherapy is used as the only cancer treatment but more often, patients receive chemotherapy along with surgery, radiation therapy or biological therapy[5]. Chemotherapy can: (a) Make a tumour smaller before surgery or radiation therapy. This is called neo-adjuvant chemotherapy. (b) Destroy cancer cells that may remain after surgery or radiation therapy. This is called adjuvant chemotherapy. (c) Help radiation therapy work more effectively. (d) Destroy cancer cells that come back (recurrent cancer) or spread to other parts in the body (metastatic cancer)[6-8]. On the other hand, because the majority of anticancer drugs, including cis-platin, gemcitabine, and paclitaxel, are intrinsically non-fluorescent or weakly fluorescent, it is difficult to monitor the processes of translocation, activation, and excretion of the drugs in vitro and in vivo[9-12]. Contrary to popular belief, traditional chemotherapy has several downsides. They include poor absorption, large dose requirements, unfavourable side effects, low therapeutic indices, development of multiple drug resistance, and non-specific targeting[13].

1.1.2. Solution of the problem:

In the fight against cancer, several cutting-edge drug delivery techniques are being explored. The process, or technology used to administer and transport an active substance in the body to provide a therapeutic effect is known as drug delivery[14]. By utilising the differences between the normal cells and tumour microenvironments, such as the different temperatures, ions, pH, and enzyme levels that act as stimulants for drug release, supramolecular chemistry offers the

most efficient method of specific release of drugs to the tumour cells[15]. Possibilities of physical, chemical or enzymatic disruptions of the active ingredient are reduced by enclosing the molecules inside a protective shell-like structure. This packaging prevents the drug from degrading and enables it to reach the desired location in the body[16].

Drug delivery methods have made it possible to create a variety of pharmaceutical solutions that enhance therapeutic delivery to the intended site, reduce accumulation off-target, and increase patient compliance. As a result, there is a decrease in unfavourable side effects brought on by systemic dispersion as well as an increase in the bioavailability of the active component[17].

1.1.3. Supramolecular drug delivery system

While designing a new delivery system, one of the key factors to consider is how the carrier and payload interact. Non-covalent interactions are the foundation of supramolecular chemistry, which can link the constituent parts and give them reversible and stimuli-responsive features[18-20]. A fundamental requirement for drug carriers is "smartness," as illnesses always involve local pH changes, free radicals, overexpressed biomarkers, or high concentrations of reactive oxygen species and a good drug carrier should be able to react quickly to one or more of these changes[21,22].

The fundamental forces in living things that support growth and reproduction include electrostatic interactions, cation-cation interactions, stacking interactions, hydrophobic effects, and hydrogen bonding interactions. Supramolecular structures are the best paradigm for replicating biological processes because of these non-covalent interaction. It is relatively simple for these vehicles to achieve disease-related-triggered release of medication payloads, increasing therapeutic specificity[23].

The supramolecular complexes can also easily degenerate under physiological circumstances, which might cause stability issue with unexpected loading exposure. In order to overcome challenges in vitro and in vivo, supramolecular-based delivery carriers must have the essential bio-stability[24]. Supramolecular drug carriers strike a balance between reliability and intelligence that is only possible with thoughtfully designed supramolecular building blocks.

1.2. Supramolecular Chemistry:

The term "chemistry beyond the molecule" refers to supramolecular chemistry. Supramolecular chemistry, which uses particular, directed, adjustable, and reversible molecular recognition motifs, has been shown to be an effective method for creating regulated and organized materials[25].

Supramolecular chemistry is based on intermolecular interactions, or the association of two or more building blocks that are connected by intermolecular bonds, as opposed to molecular chemistry, which is primarily based on the covalent bonding of atoms[26]. The non-covalent interactions are dynamic and reversible, which gives the resulting supramolecular structures exceptional stimuli responsive characteristics and limitless potential. With the introduction of macrocylic hosts into supramolecular systems, host-guest interactions are gaining more and more attention due to their unique characteristics[27-29]. These macrocyclic hosts such as crown ethers, cyclodextrins, calixarenes, pillarenes, and cucurbiturils typically include hydrophobic cavities for embedding guest molecules which includes potent cancer-fighting ingredient[30-33]. The supramolecular macrocyclic host can form multifunctional assemblies by complexing various types of guests using its macrocyclic cavity[34]. When compared to the direct administration of bare chemotherapy drugs, drug encapsulation in a carrier offers a number of benefits, including protection from bloodstream drug breakdown, improved solubility, increased stability, targeted drug delivery, a reduction in toxic side effects, and improved pharmacokinetic and pharmacodynamic properties of a drug[35,36]. Most crucially, the binding affinity of the host-guest linkages can be altered according to the different environments of tumour and normal tissues such as pH, redox and enzymes, it is possible to precisely control the release of the loaded drugs or pro-drugs in the tumour[37-39]. Supramolecular chemotherapy is more adaptable than conventional chemotherapy and nanomedicines that lack stimuli-responsiveness due to the dynamic nature of non-covalent interactions.

1.2.1. Cyclodextrin-based supramolecular chemotherapy:

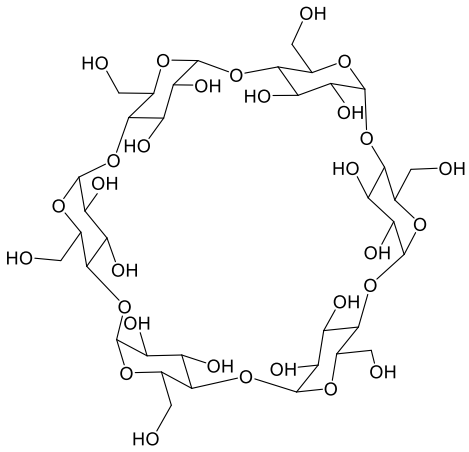


Figure.1.1. Structure of cyclodextrin.

The cyclic oligosaccharide known as cyclodextrin (CD) is made of glucopyranose (figure 1.1). They are known as α, β, and γ-CD depending on 6, 7, and 8 glucopyranose molecules present in it. They are connected by 1, 4-glycosidic linkages. These supramolecular hosts are a desirable class of macrocycles as the cavity's exterior is polar and its interior is non-polar in nature[40-42]. Using glucose monomers as building blocks, cyclic polymerization produces the family of cyclodextrin macrocycles. The technique of drug delivery has long benefited from the use of cyclodextrin. A patent for "Method for manufacture of inclusion compounds of physiologically active organic compounds" was granted in Germany in 1953. It detailed how complexation with various cyclodextrin improved the chemical stability, length of action, and flavour of biologically active chemicals[43-45]. By hydrophobic and van der Waals interactions with guest molecules in aqueous media, CDs are able to trap or enclose suitable sized guest species with a variety of binding affinities. Moreover, it is feasible for CDs to form reversible inclusion complexes with a variety of guest molecules, which facilitates both drug loading and release at the desired site[46,47]. When a poorly soluble drug molecule or a stearically compatible lipophilic functional moiety of the drug is trapped in the lipophilic CD central cavity, inclusion complex formation occurs spontaneously in the aqueous solution. This process is driven by the displacement of energy-rich water molecules. Neither covalent bonds are created nor destroyed during the development of the inclusion complex. Drug/CD complexes are continuously forming and dissociating in this reversible process, which is characterised by dynamic

equilibrium. The inclusion complex can also be prepared in solid state through grinding with mechano-chemical activation[48].

Because the hydrophobic effect serves as its primary driving force, complexation is seen as an entropy-driven process (i.e., the release of water molecules from CDs cavity). Moreover, complimentary interactions such as van der waals forces, hydrogen bonds, electrostatic contacts, and hydrophobic interactions as well as the release of conformational strain all have an impact on complex formation[49,50].

By using an orthogonal host-guest recognition strategy, Dai et. al. have created CD prodrug supramolecular nanoparticles with a reduction-sensitive disulfide bond. They created disulfide-linked permethyl-β-CD-Camptothecin prodrug, water-soluble adamantane-porphyrin photosensitizer and hyaluronic acid grafted by triphenylphosphine and β-CD. The as-designed system could quickly enter the mitochondria of A549 cancer cells, release the active anti-cancer drug there, and release reactive oxygen species (ROS) when exposed to light via its porphyrin component. As a result of their two-step synergistic chemo-photodynamic actions, these nanoassemblies represent an effective strategy against lung cancer [51].

Vaidya et. al., who present an alternative drug delivery method, loaded erlotinib onto β-CD and coated the resultant structures with poly(lactic-co-glycolic acid). By lowering IC50 values, suppressing tumour cells' capacity to form colonies, boosting apoptosis, and inhibiting autophagy, these nanoparticles greatly increased therapeutic efficacy against non-small cell lung cancer (NSCLC) cells[52].

The delivery of metformin to people with type 2 diabetes and lung cancer was the subject of a recent investigation by Lin et. al. The researchers used a carrier system made of folic acid-conjugated β-CD polycaprolactone block copolymers. The stability of drug, controlled release, and targeting capabilities were all enhanced by the delivery platform. To be more specific, the match between folic acid ligands and folate receptors ensured that metformin uptake via endocytosis in A549 lung tumour cells occurred at a pH of 6.4 as opposed to physiological pH. The nanosystem offers promising anti-tumour efficacy with little toxicity towards normal cells as a result of regulated release and active targeting[53].

For the transport of doxorubicin, Hyun and colleagues created a nanocarrier using β-CD, polyethylene glycol, and folic acid. The complexes reduced tumour volume when injected

intravenously into test animals without causing systemic toxicity or cardiotoxicity. In order to distribute doxorubicin in a safe and precise manner, the system is developed to enhance its effectiveness[54].

Farrokhi et. al. suggested a different delivery method for breast cancer. In order to deliver an RNA-cleaving DNAzyme, targeting the c-Myc gene in the MCF-7 cell line, the authors developed a β-CD polymer nanocarrier. According to test results, this delivery method and doxorubicin worked synergistically to limit the proliferation of breast cancer cells more effectively[55].

The inclusion of water-insoluble photosensitizers, such as meso-tetraphenylporphyrin and mesotetra(m-hydroxyphenyl)porphyrin, into permethyl-β-CD was discussed in a recent research by Panagiotakis and colleagues. When the complexes were treated with MCF-7 cells, they demonstrated beneficial characteristics such as photostability, intense intracellular fluorescence, high photokilling efficiency, and minimal dark toxicity[56].

More than 35 clinically approved pharmaceutical formulations utilising cyclodextrin are available, with more than half of these applications involving β-cyclodextrin. Solid, liquid, and suspension dosage forms of cyclodextrins are available. Low permeability of CDs across biological membranes is caused by a combination of factors including high molecular weight, the abundance of hydrogen-bond donors and acceptors within the structure, and prominent hydrophilicity[57].

1.2.2. Cucurbituril- based supramolecular chemotherapy

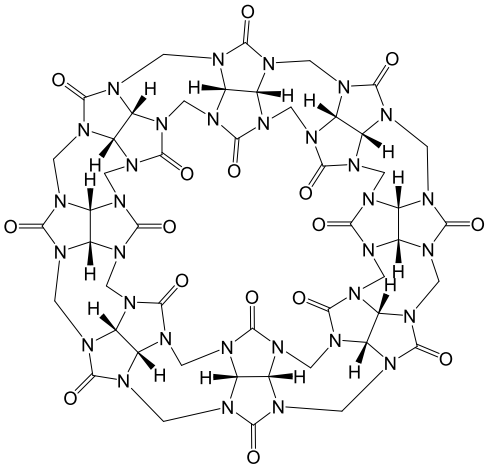


Figure.1.2. Structure of cucurbituril.

In 1905, Behrend and colleagues synthesised the first cucurbituril (CB[n]), and in 1981, Mock and colleagues validated their findings. Glycoluril and formaldehyde were used to generate cucurbit[n]urils (CB[n]s) by condensation method[58,59]. CB[5], CB[6], CB[7], CB[8], and CB[10] make up the majority of the CB[n] family. The highly symmetric, pumpkin-like structure of CB[n]s, with its central hydrophobic cavity and negatively charged carbonyl-lined portals, is what distinguishes them structurally (figure 1.2). By encapsulating various organic and inorganic guest molecules in the hydrophobic cavities of CB[n]s, it has been demonstrated that CB[n]s may form both 1: 1 and 1: 2 host-guest complexes with these molecules. The complexes are held together via ion-dipole interactions, van der Waals forces, and/or hydrogen bonds with the CB[n] portals[60-64].

In terms of cavity sizes, shapes, electropotential surfaces, and hydrophilic or hydrophobic properties, the CB[n] are frequently compared with the cyclodextrins (CD)[65-72]. Even though CD and CB[n] host-guest binding properties seem to be similar, they differ greatly in fact, particularly in terms of binding strength, compatibility with cations, and hydrophobic differences. In general, the CB[n] have greater binding constants, a significantly higher binding ratio, a strong affinity for cations and hydrophobic groups, and the cavity of the CB[n] is accessible from two portals of equal size[73-75].

The CB[n] molecules have substantially stronger structural integrity as well. CB[n] can be substituted at the junction of the two carbons of the cis-fused imidazolone rings of the glycoluril moieties. There are two basic ways to do this: either directly reacting these carbons of a

particular CB[n] or adding a substituted glycoluril to the mix during the synthetic process. The methine carbon was oxidised to produce perhydroxylated CB[n] (R_1 = R_2 = OH), a direct reaction that works best when n = 5–6[76-80]. A range of alkyl derivatives of the OH groups were synthesized. For CB[5] and CB[6] this kind of substitution has proved feasible, and it is likely to be expanded to the higher homologs[80-83]. Several medicines have inadequate bioavailability when used in clinical settings due to instability or hydrophobicity, which is a significant barrier to their usage and development. When CB is employed as a carrier, it can improve the stability and solubility of the molecules as well as offer particular recognition for drug targeting and other capabilities, enabling more effective treatment of diseases including cancer and brain disorders. The most popular CB homologue, CB[7], has also been applied in controlled-release applications. The most popular controlled-release techniques using CB[7] include pH or light stimulation. Most of these techniques follow the same basic idea: after a pharmacologically active substance is encapsulated within CB[7], its pharmacological activity is halted until the complex enters a particular environment, at which point the substance is released, allowing normal pharmacological action[84].

Drugs' stability and activity in their active form can be considerably increased by inclusion within CB[7][85]. Oxaliplatin, a chemotherapeutic drug, can be encapsulated in CB[7] which increases the drug's stability and may lessen its unfavourable side-effects[86,87]. It has also been demonstrated that members of the CB[n] family can bind to a wide variety of other small molecule drugs, including beta blockers, antidiabetics, enzyme inhibitors, anti-neoplastics, and anaesthetics. CB[7] is the most frequently used member of the family due to its relatively high water solubility in comparison to CB[6] or CB[8][88].

It was shown by Pashkina et. al. that CB[7] can combine with nedaplatin to produce a complex. Nedaplatin and CB[7] produced a guest-host complex with a 1:1 stoichiometry. In vitro MTT assay was used to examine the cytotoxicity of free nedaplatin and nedaplatin in a complex with CB[7] using the human cancer cell lines A549, HCT116, and MCF-7. The fact that the nedaplatin-CB[7] complex was more toxic to all tested cell lines than free nedaplatin is remarkable and points to the potential of CB[7] as a drug delivery method[89].

According to Flink et. al., in contrast to cyclodextrins, CB[7] induced apoptosis but not a hemolytic effect on erythrocytes. However, CB[7] showed marked cytotoxic effects on HaCaT keratinocytes and caused apoptotic cell death.

Ding et. al. created the oral colon-targeted drug delivery hydrogel (OCDDH) through the noncovalent cross-linking of phenylalanine (Phe)-modified[90] Konjac glucomannan (KGM) and the loading of berberine (BBR), a naturally occurring anti-inflammatory substance originating from chinese medicine, into the hydrogel matrix. As compared to free BBR, the BBR-loaded KGM-Phe@CB[8] hydrogel showed considerably better therapeutic efficacy in treating colitis without creating any systemic toxicity. This approach might open up new possibilities for the creation of sophisticated supramolecular OCDDH[91].

A unique hybrid nanoparticle was created by Melis et. al. based on the conjugated oligomer (COL) containing gold (COL-Au). This multipurpose hybrid device can perform combination of photodynamic (PDT) and photothermal (PTT) therapies as well as cellular imaging due to its strong photostability and thermal reversibility. An efficient broad-spectrum antimicrobial treatment could be made possible by combining PDT and PTT in a single platform. Additionally, cucurbit[7]uril was used to cap COL-Au nanoparticles in an effort to reduce their dark cytotoxicity towards pathogens and human breast cancer cells while maintaining their light-induced cytotoxic activity when exposed to a 915 nm laser for photothermal therapy (PTT) and white light for photodynamic therapy (PDT), respectively.[92]

1.2.3. Calixarene-based supramolecular chemotherapy

In addition to cyclodextrins, nanotubes, nanoparticles, micelles, and crown ethers, calixarene is a macrocyclic molecule that belongs to the third generation of supramolecular substances[93].

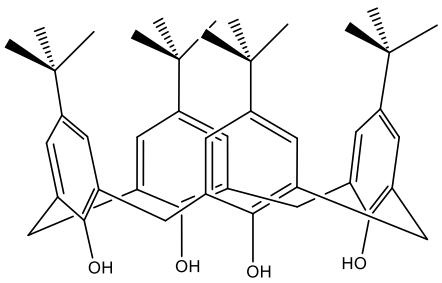


Figure.1.3. Structure of calixarene.

In instance, calixarene is an organic molecule created when para-substituted phenols react with formaldehyde in either an acidic or basic environment. In essence, the calixarenes might be regarded as cyclic polyphenols with certain no. of phenolic units present within their structure[94] (figure 1.3). The name of the compound, calix [n] arene, refers to the quantity of phenolic units it contains in the macrocyclic unit[95]. p-*tert*-Butyl-calyx [n] arene, can undergo chemical

changes at both the lower and upper edges. *Tert*-butyl groups on the upper edge can be easily dealkylated in order to bind various functional groups as required. The four phenolic groups (-OH) on the lower edge can be reacted with a long chain alkyl halide to produce compounds with various characteristics. In order to introduce new functionality, such as esters and ethers, the reactive hydroxyl groups on the lower rim are able to do so. While other processes, such as halogenation, nitration, sulfonation, and others, might alter the upper rim. Due to its adaptability, calixarene can be used for the majority of intended applications with many chemical and physical qualities that are necessary[96]. A hydrophobic cavity formed by this structure can be used to create host-guest inclusion complexes. The functionalization of the calixarene can improve the target's selectivity[97].

According to the quantity of phenolic units included, calix [n] arene have flexible conformational isomers and varying cavity dimensions (generally composed of 4, 5, 6 or 8 phenolic units)[98]. The ability to effectively control the self-assembly process (and resulting structure) gives calixarenes an advantage over crown ethers and cyclodextrins[99-101]. In addition to self-assembling into various ordered molecular aggregates, calixarene molecules can also combine with metal, metal ions, non-metal oxides, and organic molecules to form aggregates with various morphologies. In addition to loading and transporting various pharmacological molecules, these aggregates have been utilised to identify biomolecules such sugars, amino acids, peptides, proteins, and nucleic acids[102-106]. Calixarenes have a strong basis for use in health and pharmaceutical sciences due to their thermal stability, chemical stability, and biocompatibility[107]. The complexation process of guest molecule may involve a number of non-covalent interactions, including hydrogen bonds, π-π stacking, cation-π and CH-π interactions. Furthermore, calixarene conformations can be finely locked in preorganized structures for more specific binding or maintained flexible to take advantage of binding by an induced-fit. In fields such as catalysis, molecular recognition, drug delivery, electrochemistry, sensors, and other gadgets, these macrocycles are being intensively researched[108].

Yilmaz et. al., modified the calix[4]arenes, from both the o-position and the p-position of phenolic units with the L-proline group and employed in cytotoxicity and apoptosis investigations in multiple human cancer cell lines[109].

According to Brito et. al., calix[6]arene reduces the viability and growth of pancreatic cancer cells. Also, they show how calix[6]arene and receptor tyrosine kinase (RTK) work together to

make Panc-1 cells less aggressive. The outcomes demonstrate that calix[6]arene seems to be a candidate drug in individuals with high expression of AXL[110].

A variety of carbonyl amide derivatives based on calix[4]arene were created by An et. al. and they tested its ability to inhibit the proliferation of human cancer cells A549, MCF-7, MDA-MB-231, HT29, and HepG2. The results suggest that bis[N, N-di(2-hydroxyethyl) aminocarbonyl-(2-ethyl)methoxyl] calix[4]arene has the most excellent inhibitory effect against A549 and MDA-MB-231 cells, which were respectively 3.2 times and 6.8 times that of calix[4]arene. At the same time, they demonstrate a potential anti-tumor mechanism of this derivative, including blocking the G0/G1 phase of MD-MB-231 cells by down regulating cyclin D1 and CDK4, inducing apoptosis by up regulating Bax and down regulating Caspase-3, PARP, and Bcl-2, and reducing or halting cell division in this way. This research will significantly advance knowledge on the topic of calixarene-based anticancer drugs[111].

Combining chemotherapy with therapeutic genes is a different treatment approach suggested by Liu et. al. The limitation of this strategy is connected to a potential conflict between medicines and therapeutic genes. The creation of a calixarene nanoparticle that can transport DOX and plasmid DNA targeting miR-21 is demonstrated by a fairly recent in vivo investigation. The complex increases stability and selectivity towards the therapeutic target by lowering drug and gene interference. The calixarene-DOX-DNA plasmid complex-treated mice exhibit a greater anticancer impact[112].

1.2.4. Pillarenes-based supramolecular chemotherapy

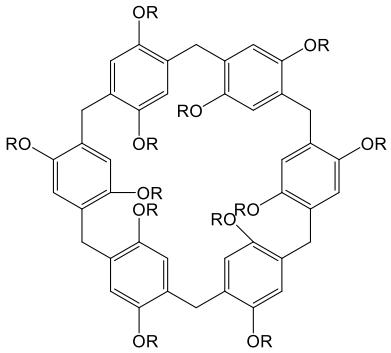


Figure.1.4. Structure of pillarene.

The macrocyclic host compounds known as pillar[n]arenes, or pillarenes for short, have stiff cylindrical structures with several hydroquinone units that are connected by methylene (CH_2)

groups (figure 1.4). Scientists working to develop intelligent materials or functional systems have become very interested in the study of pillarenes as a result of their fascinating characteristics, such as symmetric structures, adaptable functionalization, and distinctive host–guest properties. This interest has grown beyond the boundaries of supramolecular chemistry[113].The water solubility of chemotherapeutic medicines is improved by pillar[n]arenes carrying carboxylate, trimethylammonium or imidazolium units. These pillar[n]arenes can encapsulate various drug molecules in aqueous environments to create supramolecular containers, mostly driven by hydrophobic or electrostatic interactions[114,115].

Pillarenes demonstrate impressive potentials in biomedical science through the development of supramolecular systems for the purpose of drug design, delivery and efficient treatment[116-118]. The use of pillar[n]arenes as carriers for targeted drug delivery systems[119] is of particular interest because different factors for drug activation and release can be used, such as drug release upon chemical reaction with intercellular compounds (thiols, amines, reactive oxygen species (ROS), etc.), drug release in acidic pH medium (low pH), hypoxia, certain types of inflammation etc. depending on the structure of pillar[n]arenes-based carriers, disease type, and nature of the drug[120].For many cancers, the tumour microenvironment is characterised by hypoxia-driven higher levels of ROS, such as hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH•), and singlet oxygen ($^1O_2$), higher pH (7.4)[121,122] and lower pH (pH 5.5-6.0 in endosomes and pH 4.5-5.0 in lysosomes of tumour cells)[123]. The ability to effectively encapsulate drug or pro-drug and release them selectively inside the tumour microenvironment is thus possible through the use of pillar[n]arenes-based transport systems, which can be created through correct synthetic design[124,125].

Pei and co-authors developed nano-drug delivery system where Se-Se-linked dimeric molecules containing pillar[n]arenes (SeSe-(P5)2)) encapsulated mannose-based guests (Man-NH_3^+) and studied its cytotoxic effect on MCF-7 and HepG2 cells.[126]

Shao et al reported a pillar[6]arenes-supported dual prodrug guest system where camptothecin and chlorambucil were coupled via a disulfide linker and combined with a water-soluble pillar[6]arenes-based host to produce a host-guest complex with a ratio of 1:10 and 63.8% drug-loading.[127]

1.2.5. Carbon dots-based supramolecular chemotherapy

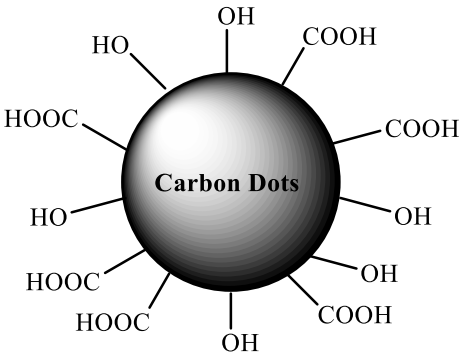


Figure.1.5. Structure of carbon dots (CDs).

A quasi-0D carbon-based material with a size below 10 nm is what is typically referred to as a carbon dot (CD), with characteristic fluorescence is a characteristic that they all share (figure 1.5). The discovery of carbon nanoparticles with fluorescence was made in 2004, which were unintentionally produced during the purification of single-walled CNTs[128]. Sun and co-workers in 2006 synthesized surface passivated nano sized carbon particles in 10% yield by laser ablation of carbon target and named them as carbon dots (CDs)[129]. The production of CDs was constrained by low QY and challenging preparation processes. In 2013, Yang's team used ethylene diamine and citric acid (CA) as precursors to create polymer-like CDs with QY up to 80% using a one-step hydrothermal process[130].

There are two basic ways to synthesise CDs: (i) top-down technique, and (ii) bottom-up approach. Top-down approaches include chemical oxidation, discharge, electrochemical oxidation, and ultrasonic techniques to disassemble larger carbon structures[131]. However, this method has limitations, such as the need for expensive components, difficult reaction conditions, and lengthy reaction times[132]. The bottom-up strategy, in contrast, refers to the transformation of smaller carbon structures into CDs of the appropriate size. In order to create CDs, a bottom-up strategy like solvothermal synthesis, hydrothermal synthesis, ultrasonic treatment, thermal breakdown, pyrolysis, and carbonization are used[133].

Further, compared to their monodispersed particles, the CDs-based aggregates show better desirable photophysical properties[134-138]. Jiang's group discussed mechanism of CD-based

aggregation-induced room-temperature phosphorescence. Li et al constructed a unique form of supra-CDs by the assembly of surface charge-confined CDs through electrostatic interactions and hydrogen bonding. These CDs-based aggregates show a clear modification in spectral characteristics, opening up a novel method for controlling and tuning the spectral characteristics of CDs. The relationship between the characteristics of molecules and their aggregation states has been studied in supramolecular chemistry for a long time[136-140]. Due to their strong fluorescence properties, low toxicity, chemical inertness, and great biocompatibility, CDs were regarded as multipurpose vehicles for drug delivery systems. The loaded medicine can be delivered at specific target by use of CD based drug carriers[141].

Cosme et. al. designed CDs based conjugates and synthesised them by encapsulation of photosensitisers such as protoporphyrin in CDs (PpIX@CD) and their amide cross-linking with CDs (PpIX-CD). They effectively used these CDs based conjugates for photodynamic therapy[142].

A gelatin nanocomposite hydrogel with carbon dot cross-linking was created by Bhattcharya et al. Here, CDs performed a dual function by acting as both a cross-linker and a chromophore, which decreased the use of harmful cross-linkers. The proposed gelatin nanocomposite hydrogel sample performed admirably as a pH sensor in the pH range close to neutral and might be helpful for measuring pH quantitatively. This system exhibits astounding photoluminescence, swelling, and pH-dependent drug release[143].

1.3. Scope of Work

The designing of the novel drug delivery system with low toxicity and high therapeutic efficacy, leads the interest to the traditional gold medicine, turmeric. Turmeric (*Curcuma longa* L.), a nutritional dietary spice from the Zingiberaceae family, has been extensively used for various applications[144]. Basically, its volatile oil and nonvolatile oleoresin consists of bioactive components, which are classified as diphenylheptanoids, diphenylpentanoids (nonvolatile), phenyl propene (cinnamic acid type) derivatives (nonvolatile) and turmeric oil containing terpenoids (volatile)[145]. Major diphenylheptanoids are curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which are collectively called curcuminoids[146].

Numerous studies have demonstrated the therapeutic potential of curcumin, including but not limited to its antioxidant, anticarcinogenic, antibacterial, anti-inflammatory, hypoglycemic, hepato- and neuroprotective properties[147-149]. Researchers are deeply interested in identifying the molecular targets and their encoded mechanisms of action of curcumin, which underlie various biological activities, due to its wide range of therapeutic efficacies[150]. The curcumin molecule has two orthomethoxyphenolic groups joined by a seven-carbon linker chainwith a methylene site between β-diketone moieties. Depending on the context, the presence of the β -diketo group in chemical structure of curcumin undergoes keto-enol tautomerism[151]. According to Liang et al., the presence of a β-diketone moiety causes curcumin to be unstable under physiological conditions, and the deletion/ replacement of β-diketo group may help curcumin to become more stable[152]. Liao et al. elaborated that the β-diketo group is also responsible for poor bioavailability and a quick metabolism of curcumin in vivo[153]. Curcumin is a perfect therapeutic agent due to its cytotoxicity, but its low bioavailability raises serious issues when used in clinical settings[154].

Therefore, the effectiveness of curcumin was noticeably improved when a β-diketo group[155] was replaced with a monoketo group, such as acetone[156-158], cyclohexanone[159,160], cyclopentanone[161] or piperidone[162,163] (Figure 1). Because the ring strain in the cyclopentanone moiety renders bis-hydroxybenzylidene cyclopentanone sterically inappropriate for receptor binding, the bis-hydroxybenzylidene cyclohexanone is known to have a superior efficacy than the cyclopentanone analogues among the cycloalkanone derivatives[164-166].

Being inspired by the research on curcumin over decades which have widely explored the toxicity of curcumin on oncogenic cells, we have designed and synthesized various novel curcuiminoid based drug carriers with the aim to achieve high therapeutic activity.

1.4. Aim and objectives

1. To synthesize and study chiral corand based chemotherapeutic system

2. To synthesize and study cryptand based drug carrier for various anticancer drugs.

3. To synthesize and study Gd-Corate and vesicle based drug carriers.

4. To synthesize and study CDs based supramolecular architectures.

5. To synthesize and study CDs based nanoassembly for pH triggered sustained release of anticancer drug.

1.5. References

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