

# Chapter 16

## Surface Modification of Resorcinarene-Based Self-Assembled Solid Lipid Nanoparticles for Drug Targeting



Sanjoy Das and Malay K. Das

**Abstract** Supramolecular chemistry associates the dual concepts of self-arranging and molecular perception to generate novel nanocarrier systems. Nanoparticles have numerous benefits over other drug delivery carriers. Solid lipid nanoparticles (SLNs) have acquired significant attention as a potential substitutive carrier system to usual colloidal carriers like liposomes, emulsion, as well as polymeric nanoparticles. SLNs are the novel fundamental approaches to alter the oral bioavailability problems of the poorly aqueous soluble drug. However, due to the hydrophobicity of SLNs, they are essentially stabilized to prevent aggregation and diminish the liability of clearance by the macrophage system. Therefore, coating the SLNs surface by a highly hydrophilic moiety leads to prevent aggregation and severe interaction with healthy cells. Resorcinarenes are synthetic supramolecular macrocycles with bowl-shaped head and several hydrogen-bonding tails which are capable of developing additional host-guest complexes through the self-associate process. Resorcinarenes are the most frequently studied macrocycles for the buildup of supramolecular SLN systems, because the bowl-shaped head of the resorcinarene molecules can enable them to adhere readily to the SLN surface, permitted them to interact with the substances outside the coating but prevented them from touching each other, leading to meaningful impact on the stability aspects and physical–functional properties of nanoparticles. Significantly, resorcinarenes and its water-soluble components show good biodegradability, biocompatibility, and nontoxicity, which are essential requirements for applications in any type of drug delivery carriers. This chapter highlights the recent development in resorcinarene-based lipid nanocarriers for drug delivery and targeting.

**Keywords** Self-assembled SLNs · Metal nanoparticles · Surface-modified resorcinarene-based SLNs · Surface-modified resorcinarene-based metal nanoparticles · Drug delivery · Drug targeting

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## 1 Introduction

In current years, the meaningful effort has been committed to establishing nanotechnology for drug delivery, since it offers a convenient means of transporting low molecular weight drugs and biomolecules like genes, proteins, and peptides to cells or tissues and protects them against enzymatic deterioration [1–3]. Nanoparticles with their typical features like narrow particle size, broad surface area, and the capability to change their exterior properties have numerous benefits over other drug delivery carriers [4, 5]. Targeted drug delivery to the specific organ is highly attractive for local or systemic treatment or diagnosis of various diseases [6, 7]. Drug targeting indicates for discriminating and efficient localization of therapeutically active ingredient at target tissues or cells, while lowering its connection to nontarget cells or organs, leading to effective treatment at the therapeutically effective doses and minimize the toxic adverse effects [8, 9].

Solid lipid nanoparticles (SLNs) have acquired significant attention as a potential substitutive carrier system to usual colloidal carriers like liposomes, emulsion, as well as polymeric nanoparticles [10, 11]. The SLNs are the attractive contraption that is beneficial because the solid compartment of the lipids provides more flexibility in controlling the release process of the entrapped drug [12, 13]. SLNs are prepared by solid lipid instead of using liquid lipid and are distributed in water or an aqueous surfactant solution, giving particle size in the ranges between 50 and 1000 nm [14, 15]. SLNs are one of the essential approaches to alter the oral bioavailability problems of the low water or aqueous soluble drugs, resulting in protection of entrapped drugs from deterioration, the release of drug in a delayed or controlled manner, and good desirability [16–18]. SLNs are generally prepared using natural solid lipids, water, emulsifiers, and co-solvent [19]. In addition to these natural solid lipids, macrocyclic synthetic supramolecules have been exhibited to be a good candidate to replace these amphiphiles [20].

Supramolecular chemistry associates the dual concepts of self-configuration and molecular perception to generate novel nanocarrier systems [21]. Self-assembles of supramolecular architecture can automatically form nanoparticles and currently used as the development of nanodrug carriers [22]. Method for self-assembling of nanoparticles significantly relies on the nature or character of the particles used and the medium which they are dispersed [23, 24]. The self-assembling technique denoted potential aspect to produce nanomaterials with tunable properties, or a device-like function has triggered a worldwide research attempt to develop bottom-side-up approaches using an extended set of nano-range building blocks [25–27].

Resorcinarene is an organic surfactant, a cyclic oligomer with a bowl-shaped head and several hydrogen-bonding tails based on the condensation reaction between resorcinol and aldehydes [28]. Resorcinarenes and cyclodextrins are the most widely investigated supramolecules for the development of SLNs [29, 30]. The cyclodextrins have been manifested to self-assemble as SLNs when suitably modified, but their intrinsic toxicity limits their application for biomedical purposes [31, 32]. SLNs based on resorcinarenes have been studied, and it has been demonstrated that in addition to their remarkable physicochemical properties, they exhibit no intrinsic toxicity [33, 34].

In addition, they have shown remarkable properties as controlling agents of a widely used UV absorber, which offers a new scope of applications as carriers for sunscreens [35]. Interestingly, resorcinarenes while derived from resorcinol and aldehyde neither show toxic effects nor provoke immune reactions [36]. Such molecules seem to be promising candidates for the expansion of supramolecular SLN systems and show their molecular acceptance properties with respect to biomolecules like carbohydrates, proteins, and amino acids [37, 38].

Precisely, bowl-shaped head of the resorcinarene molecules can enable them to adhere readily to the SLNs surface and permitted them to interreact with the substances outside the coating but restrained them from touching each other [39, 40]. This technique has a meaningful impact on the physical–functional properties and stability aspects of nanoparticles [40]. However, the definite capability of these supramolecular structures to entrapped various active components in both supramolecular cavity and the SLNs compartment might be an interesting substitutive to the conventional SLNs and potential for drug targeting, contrast agents in the biological system, and cosmetic additives. This chapter highlights the recent development in resorcinarene-based lipid nanocarriers for drug delivery and targeting.

## 2 Stereochemistry of Resorcinarenes

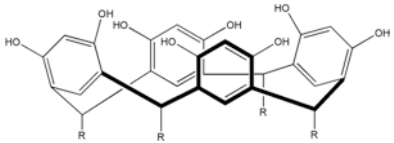
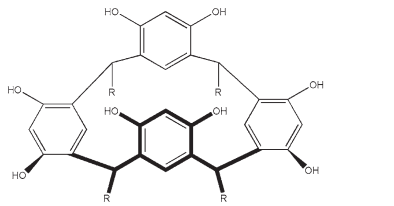
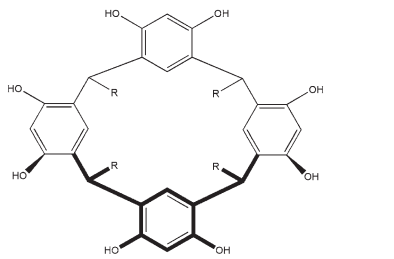
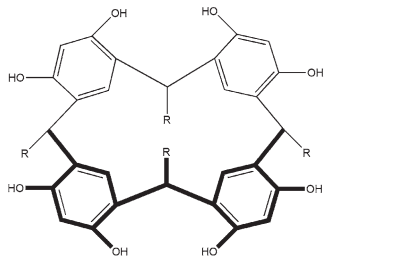
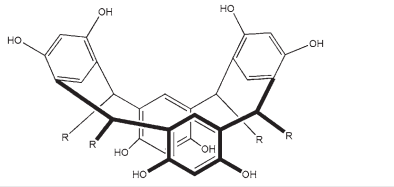
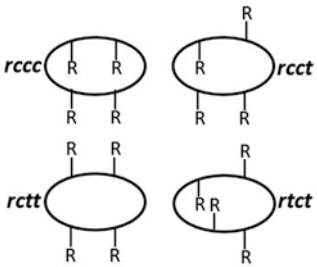
Resorcinarenes are nonpolar, 3D compounds and have generated a number of stereoisomers [41]. The stereochemistry of resorcinarenes is generally explained by a combination of the three subsequent stereochemical criteria [42]. The steric conformation of resorcinarenes is shown in Table 16.1.

The first criterion is the configuration of the macrocyclic ring. The macrocycle can adopt one of five highly symmetrical conformations, viz., Crown ( $C_{4v}$ ), i.e., one macrocycle ring oriented in an upward position as like bowl shape, thus forming the crown conformer; Boat ( $C_{2v}$ ), i.e., two opposite macrocycle rings can occupy an upward position with another two rings lying in perpendicular position to them, thus forming the boat conformer; Chair ( $C_{2h}$ ), i.e., one upward ring oriented with two adjacent rings perpendicularly and the fourth ring in a downward position, thus forming chair isomer; Diamond ( $C_s$ ), i.e., two adjacent rings oriented in upward and another two adjacent rings oriented in downward position; and Saddle ( $D_{2d}$ ), i.e., two opposite rings facing upward and another two rings facing downward [43, 44].

The second criterion denotes the orientation of groups attached to carbon atoms at the benzylic position of resorcinarenes, results in four stereoisomers, viz., *cis* (*rccc*), i.e., all attached groups facing the same direction in a *cis*-relationship to a reference group; *cis–cis–trans* (*rcct*), i.e., one group on opposite orientation to the other three groups; *cis–trans–trans* (*rctt*), i.e., two groups opposite to the pair containing the reference group; and *trans–cis–trans* (*rtct*), i.e., reference group is in a *cis*-relationship with the substituent opposite to it and *trans*-relationship with those adjacent to it [44].

The last criterion is the configuration of individual substituents on the carbon atoms at the benzylic position of the resorcinarene macrocycle which may be either

**Table 16.1** Resorcinarene stereoisomers and its structures

Sl. no.	Conformation	Structure
1	Crown ( $C_{4v}$ )	
2	Boat ( $C_{2v}$ )	
3	Chair ( $C_{2h}$ )	
4	Diamond ( $C_s$ )	
5	Saddle ( $D_{2d}$ )	
6	Configuration at methylene bridges	 <p> <math>rccc</math>      <math>rcct</math>  <math>rctt</math>      <math>rtct</math> </p>

axial or central position of the macrocycle C-symmetry [44]. The combination of all these three criteria results in a wide number of possible stereoisomers with several of which have been reported experimentally.

### 3 Synthesis of Resorcinarene Derivatives

#### 3.1 Acid-Catalyzed Preparation of Resorcinarenes

Resorcinarenes are synthesized by a one-step condensation reaction procedure using an equal amount of resorcinol and aldehyde in the presence of a solvent and an acid catalyst [45, 46]. Methanol or ethanol is the most extensively used solvent in the resorcinarenes preparation [47]. The reaction mixtures are refluxed for a couple of hours, and the products formed are crystallized out from the solution on cooling [48]. An outline of the reaction scheme is shown in Fig. 16.1.

#### 3.2 Novel Preparation of Variant Resorcinarenes

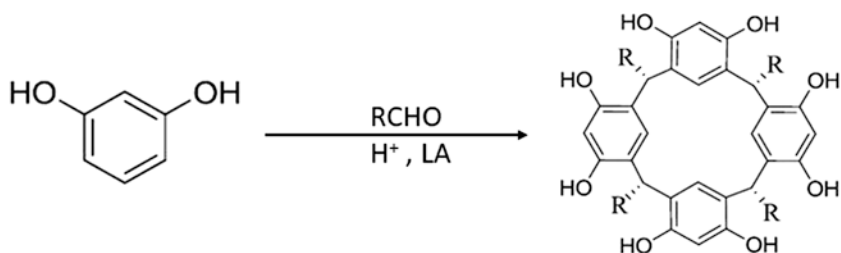
Functionalized or modified resorcinol is used as starting material in the preparation of functionalized resorcinarenes [49]. The resorcinols with electron donating groups at their 2-positions form any resorcinarenes under the acidic conditions, while under the basic conditions resorcinols with electron accepting groups at their 2-positions form novel resorcinarenes derivatives [49]. The synthesis scheme is shown in Fig. 16.1.

#### 3.3 Preparation of Pyridine Derivatives of Resorcinarenes

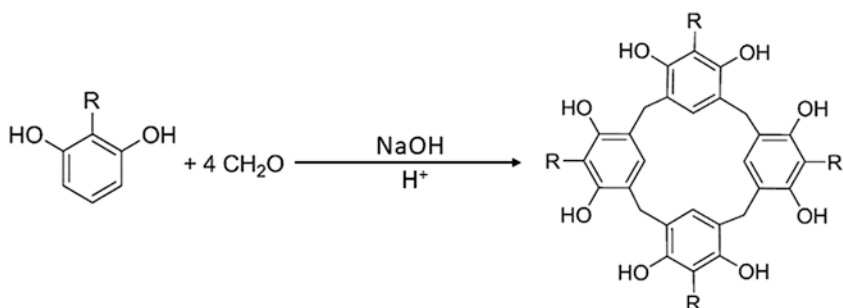
Pyridine derivatives of resorcinarenes, i.e., pyridine[4]arenes, have been prepared by cyclocondensation of 2,6-functionalized pyridines and aldehydes under similar reaction procedure as for the preparation of conventional resorcinarenes [50]. The synthesis scheme is shown in Fig. 16.1.

#### 3.4 Synthesis of Heteroatom Containing Macrocyclic Cyclophanes or Heterocalixaromatics

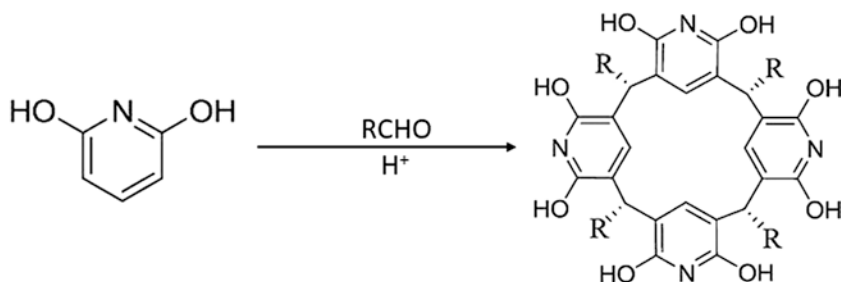
The addition of heteroatom bridges in place of methylene bridges i.e., nitrogen in a place of CH<sub>2</sub> at the benzylic position of the resorcinarenes is an exceptionally interesting modification conferring new class of resorcinarenes derivatives called heterocalixaromatics [51]. For instance, nitrogen can adopt *sp*<sup>3</sup> or *sp*<sup>2</sup> electronic configuration providing different conjugation system between the heteroatoms and



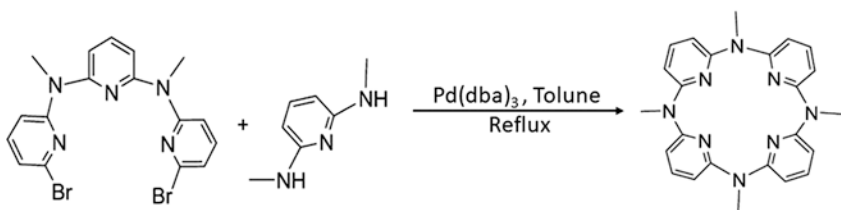
*Scheme 1: Acid-catalyzed Preparation of Resorcinarenes*



*Scheme 2: Novel Preparation of Variant Resorcinarenes*



*Scheme 3: Preparation of Pyridine Derivatives of Resorcinarenes*



*Scheme 4: Synthesis of Heteroatom Containing Macroscopic Cyclophanes*

**Fig. 16.1** Synthesis scheme of resorcinarene derivatives

adjoining aromatic rings [52]. Based on the configuration or conjugation, various  $C-N$  bond length and  $C-N-C$  bond angle are thus formed, and heteroatom linkages significantly affect the electron density of aromatic rings, and the electron features of macrocycle cavities may be regulated by heteroatoms [52]. Therefore, such compounds are synthesized using more complex procedures as compared to the conventional resorcinarenes. The synthesis scheme is shown in Fig. 16.1.

## 4 Functionalization of Resorcinarenes

Several types of methodologies have already been explored to define the functionalization of resorcinarenes over the last few years. These methodologies permit the preparation and modification of resorcinarenes that are mainly performed at the three functionalized positions, i.e., lower rim, upper rim, and  $O$ -alkylation or acylation (Fig. 16.2) [53].

### 4.1 Lower-Rim Functionalization

Functionalization at this position arises from the preferred type of aldehyde used in the preparation of resorcinarenes, since the group attached to the aldehyde functionality ends up composing lower rim [53, 54]. A vast variety of aldehydes including saturated alkyl aldehydes, unsaturated alkyl aldehydes, and phosphorous containing aldehydes are used in the resorcinarenes preparation [55]. These functionalized aldehydes lead to the construction of resorcinarenes bearing several lower-rim functionalities [56].

### 4.2 Upper-Rim Functionalization

Like any other aromatic compound, resorcinarenes can undergo electrophilic substitution reaction, at their upper-rim ortho positions to furnish tetrafunctionalized resorcinarenes under the suitable conditions [57]. The appearance of two

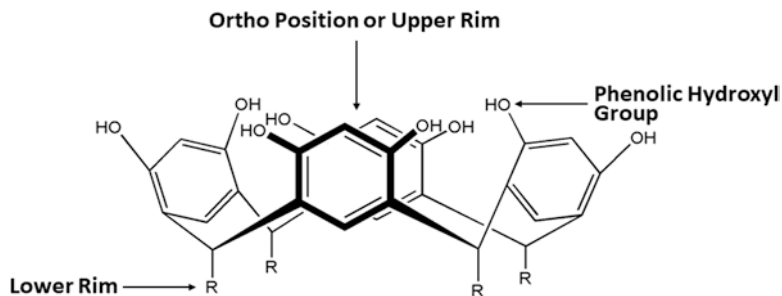


Fig. 16.2 Functionalizable positions of resorcinarenes

electron-donating hydroxy groups in the aromatic rings of the resorcinarenes is mainly susceptible to electrophilic substitution at ortho position [58]. The ortho substituent has the ability to form intramolecular H-bonds with the neighboring hydroxy groups of the resorcinarene units leading to the formation of  $C_4$  spinning symmetry-based chiral derivatives [59].

### 4.3 O-Alkylation

O-Alkylation-based functionalization has been used for the synthesis of octafunctionalized resorcinarenes by reacting alkyl groups [60]. For example, reacting the 3-alkoxy-5-benzylbromidealkoxybenzynes with the phenolic hydroxyl group of resorcinarenes in the presence of potassium carbonate managed to furnish resorcinarene dendrimers via this type of functionalization [61, 62]. The phenolic hydroxyl group plays a major contribution in the equalization of resorcinarene conformation and allows for O-alkylation or acylation reactions which promote resorcinarenes chirality [63].

### 4.4 Selective Functionalization

Apart from the synthesis of functionalized resorcinarenes mentioned above, methodologies for the selective functionality of resorcinarene derivatives have been planned [64]. There are two methodologies, which can be adopted to access distal functionalized resorcinarenes, i.e., *lithium-halogen exchange* mainly generates nucleophilic organolithium intermediates from alkyl halides whose reaction with electrophiles leading to the formation of functionalized organic compounds [65, 66] and *selective acylation* depends mainly on the feature of both solvent and acylating agent leading to selective distal functionalization of resorcinarenes [67, 68]. For example, the reaction between octahydroxy resorcinarenes and *N*-bromosuccinimide resulted in the manufacturing of distally brominated resorcinarenes [69].

## 5 Resorcinarene-Based Self-Assembled SLNs

### 5.1 SLNs of Resorcinol-Dodecanal Cyclotetramer

Resorcinol-dodecanal cyclotetramer (RDC) was prepared by one-step synthesis procedure based on the acid-catalyzed reaction between resorcinol and dodecanal in ethanolic solution [70]. SLNs based on RDC were prepared by solvent displacement method [71]. These types of SLNs can be acquired by without surfactant and



comparison to other substitutive colloidal or nanocarrier system where a surfactant is essential in their formulation was of interest to consider the feasible impact of conjugated surfactant [72]. The result demonstrated that small but significantly larger size of the particle was detected when using Pluronic F68 (2% w/w) in the organic phase leads to the diameter of 180 nm [73]. Above this quantity, when the surfactant concentration is significantly raised up to 20% w/w, the size of the SLNs remained invariant. In general, a higher surfactant concentration lowers the surface tension and promotes the partition of the colloidal particle by decreasing the particle size which is joined to enlarge the superficial area [73]. The main variation in the nature of surfactant toward these SLN systems might be correlated with the response of the HLB value of each supramolecular structure which affects their self-emulsification characteristics [74, 75]. However, the particle size of the RDC-based SLNs remains stable or reliable in the pH range from 4 to 8, while vulnerable stability was noticed at pH range within 2–4. The impact of stirring or rotating speed, microwave irradiation, and ultrasonic and thermal treatment had no detectable impact on the drug stability as well as particle size [76].

## 5.2 *SLNs of Resorcinarene Bis-Crown Ethers*

Resorcinarene bis-crown ethers (*CNBC5*) was prepared by sequence beginning with a reaction between ethylene glycol and several tetramethoxy resorcinarenes [77]. SLNs based on *CNBC5* were prepared by solvent displacement method without surfactant and characterized by using photon correlation spectroscopy (PCS), which shows a hydrodynamic particle diameter of 220–320 nm [71–78]. The impact of alkyl chain length and concentration of *CNBC5* on the size of SLNs has been explored in two different ways, i.e., in the first case, with a fixed molar concentration of *CNBC5*, the size of particles significantly increases when the length of alkyl chain has been increasing, while in another case, the concentration was kept constant and the size of the particle was almost similar than that of the first case [78]. This result demonstrated that change in the *CNBC5* amount within the two cases did not produce any effect on the SLNs properties and the alteration of the particle size depended only on the length of the alkyl chain.

## 5.3 *SLNs of Tetrakis (N-Methylpropyl)Tetraundecylcalix[4] Resorcinarenes (L-RA-Pro)*

Amphiphilic tetrakis (*N*-methylpropyl)tetraundecylcalix[4]resorcinarenes (*L-RA-Pro*) was prepared by a Mannich-type reaction of *L*-proline, resorcinol-dodecanal cyclo-tetramer, and formaldehyde in ethanol [79]. SLNs based on *L-RA-Pro* was prepared by solvent displacement method and characterized by PCS, which shows a

hydrodynamic diameter around  $195 \pm 5$  nm [71–80]. *L-RA-Pro*-based SLNs were chemically stabilized by *N*-hydroxysuccinimide and then reacted with bovine serum albumin (BSA) to obtain proteo-SLNs [80]. These results suggested that when *L-RA-Pro* based SLNs are reacted with BSA, forms a uniform surface monolayer due to a particular interaction between *L-RA-Pro* based SLNs and BSA. Photon correlation spectroscopy (PCS) analysis demonstrated that SLNs showed no indicative changes after the chemical modification in the case of particle size [80].

## 6 Surface Modification of Resorcinarene-Based Self-Assembled SLNs

The surface of the nanoparticle is modified with coupling agents after nanoparticle preparation. The polymer employed for the nanoparticles preparation must have one reactive group, which is observed on the nanoparticles surface for proper conjugation [81]. The coupling agents are dispersed in the external phase of a nanoparticles suspension, which activate the reactive group of the nanoparticles [82, 83]. These activated reactive groups of nanoparticles are then adjoined with targeting or functional material like ligand, drug, organic material, enzymes, etc. [84, 85]. Macrocyclic amphiphiles including cyclodextrins, resorcinarenes, and calixarenes are attractive materials for the nanoparticles preparation because they have outstanding self-organizing properties by forming host–guest complexes within their cavities [86]. Herein, very few information has been investigated regarding the surface modification of resorcinarene-based self-assembled SLNs. In 2007, Stefan Ehrler et al. reported that the synthesis of SLNs based on a prolyl bearing resorcinarene (*L-RA-Pro*) and their chemical modification with bovine serum albumin (BSA) and the interaction with surface-bound anti-albumin antibodies have been studied [80]. The prolyl bearing resorcinarene (*L-RA-Pro*)-based SLNs was prepared by solvent displacement method [71]. The amphiphilic properties of *L-RA-Pro* have been validated by Langmuir balance method, and it was demonstrated that these molecules at their air–water interface form monomolecular layers, with prolyl moieties immersed in the water sub-phase and able to contact with copper and to build up a ternary supramolecular enantioselective complex with phenylalanine [87]. The complex process of self-organization of amphiphiles to form SLNs is driven by amphiphilic self-assembly and it is expected that prolyl moieties of *L-RA-Pro* are partially operative at the SLNs surface [87]. For further modification of SLNs surface, it could be submitted to chemical activation using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) and subsequently reacted with BSA to develop proteo-SLNs [80] as shown in Fig. 16.3.

The evidence of the successful grafting of bovine serum albumin at the surface of the SLNs based on *L-RA-Pro* arises from their capability of interacting with surface-bound polyclonal specific antibodies, which form a fine layer at the surface of the SLNs [88].

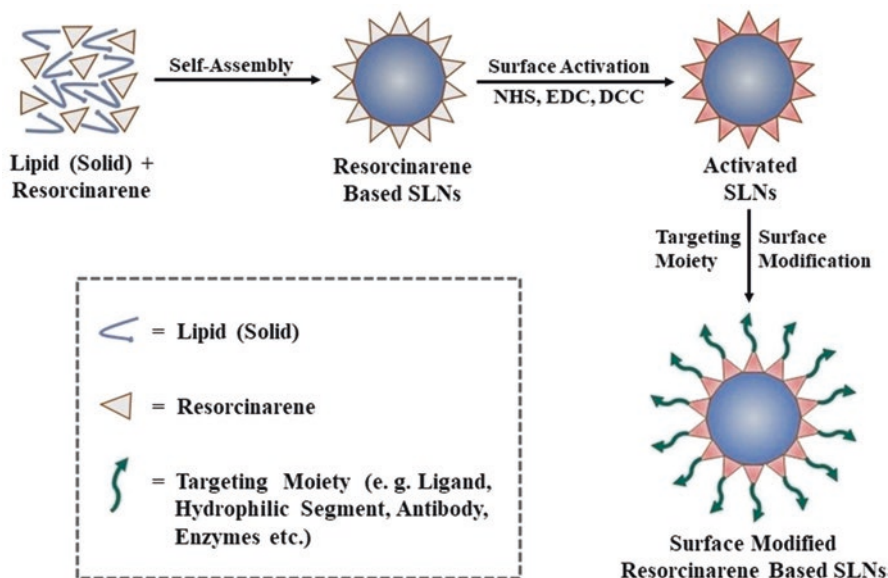


Fig. 16.3 Surface modification scheme of resorcinarene-based SLNs

## 7 Potential of Drug Targeting by Surface-Modified Resorcinarene-Based SLNs

The application of nanotechnology in drug targeting has driven to further advances in the preparation of novel nanoparticles system for diagnosis and treatment of many diseases [89]. As the conventional nanoparticulated system has some limitations, surface modification has enabled further growth and enhanced the capability of such nanoparticles [90, 91]. Generally, the nanoparticle surfaces are covered with the hydrophilic moiety or polymer to provide long circulation and are conjugated with enzymes or targeting ligands for site-specific delivery [92]. Solid lipid nanoparticles (SLNs) have gained attraction because of their outstanding properties such as biocompatibility, biodegradability, stability, superior drug-loading capacity, and ease of modification [93]. However, due to the hydrophobicity of SLNs, they must be stabilized to hinder aggregation and minimize the risk of clearance by the macrophage system [94]. Therefore, coating the SLNs surface by a highly hydrophilic moiety made of molecules such as polyethylene glycol or proteins such as albumin or supramolecules such as resorcinarenes leads to inhibit aggregation and non-specific interaction with healthy tissues or cells as well as minimizing the harmful effects of toxic materials [95].

Supramolecular appeals have been engaged in the drug delivery system and fascinate much attention among the researchers [96]. The enormous research attempt has been assumed to enhance the therapeutic potency and reduce the side

effects of anticancer drugs, because they have demerits of affecting both cancer cells along with the healthy cells, with the concomitant secondary side effects such as cardiotoxicity, neurotoxicity, and cytotoxicity [97, 98].

Different generations of supramolecules or synthetic macrocycles such as resorcinarenes, calixarenes, cyclodextrins, and pillarenes have been hired for the construction of a new drug delivery system [99, 100]. Resorcinarenes are bowl-shaped synthetic supramolecular macrocycles composed of eight –OH groups that can engage in hydrogen bonding and capable of developing additional host-guest complexes through the self-associate process [101, 102]. Significantly, resorcinarenes and its water-soluble components show good biodegradability, biocompatibility, and nontoxicity, which are essential requirements for applications in any drug delivery carriers [103]. Therefore, the use of surface-modified resorcinarene-based SLNs may open new routes for drug targeting.

## 8 Surface Modification of Metal Nanoparticles with Resorcinarenes

Metal nanoparticles are one of the markedly studied nanomaterials with their potential significance for both basic and applied research [104]. Although such nanomaterials have magnificent physical, chemical, optical, or electronic properties, they do not hold compatible surface or interfacial properties for particular applications, so it may be urgent to modify such nanoparticles surface [105, 106]. The surface modification of metal nanoparticles is used to upgrade their stability, biocompatibility, surface energy, and so on [107]. The suitable modification of such nanoparticles surface differs the surface structure, composition, or morphology of materials and may result to controlled assembly or transferring of nanoparticles to the aqueous or organic media [108]. There are numerous ways for modification of the hydrophilicity or hydrophobicity on the surface of metal nanoparticles such as ligand exchange, ligand chemical modification, and/or supplementary layers of polymers that fix the particles in relevant phase [108, 109]. Therefore, modification of metal nanoparticle surfaces by the hydrophilic macrocycles, i.e., resorcinarene derivatives forming inclusion complexes on the surface of nanoparticles, resulted to the efficient delivery of metallic nanoparticles in aqueous or organic-phase count on the scientific demand [110, 111]. The surface modification of various metal nanoparticles by resorcinarenes and its derivatives are summarized in Table 16.2.

## 9 Conclusion and Future Prospects

The amphiphilic properties of macrocycles lead to the good stability of SLNs in an aqueous colloidal solution due to the arrangement of the macrocycles coat on the nanoparticles surface. The macrocycles layers are convenient for the self-associate

**Table 16.2** Metal nanoparticles and surface-coating materials

Sl. no.	Nanoparticles	Surface coating	Particle size (nm)	References
1	Gold nanoparticles	Tetramethoxyresorcinarene tetraaminoamide	6–17	[112]
		Resorcinarenes 1–3 derivatives	3–20	[113]
		Resorcinarene 1, 2, 4–8 derivatives and tetrazaaresorcinarene analog	9–35	[114]
		Tetrabenzylthiol resorcinarene	15–50	[115]
2	Silver nanoparticles	Tetrapentylcalix[4]resorcinarene	4–6	[116]
		Resorcinarene tetrahydrazide	15	[117]
		Ferrocene resorcinarene	60	[118]
3	Cobalt nanoparticles	C-undecylcalix[4]resorcinarene	15–100	[119]
4	Platinum nanoparticles	Amino resorcinarene	2–3	[120]

process leading to the partial association of SLNs in aqueous media while preventing their aggregation and also furnishing the preferences to the supramolecular modification of the SLNs surface through the intermolecular interaction with oppositely charged surfactants and organic molecules. The formation of resorcinarenes layered on the surface of SLNs has reinforced the receptor properties owing to the configuration of diverse aggregates with guest molecules via host-guest interrelation make them a preferred candidate for drug targeting. Although scientists have achieved remarkable success toward resorcinarene-stationed drug delivery system, so far, there are only a few researches that have been accomplished on a cellular level. The suspicious toxicity and the current unavailability of FDA approval to use these macrocycle supramolecules in medicine enable us to expect that such types of nanocarrier system deserve further clinical and preclinical medical testing in near future.

**Declaration** All figures and tables are original and self-made.

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