Garland, Flower, and Petals via a Hierarchical Self-Assembly of Ursane-Type Triterpenoid Uvaol

Subrata Ghorai and Braja Gopal Bag*

ABSTRACT: Uvaol, a 6-6-6-6-6 pentacyclic dihydroxy ursane-type triterpenoid, is isolable from different parts of plants Plumeria rubra, Olea europaea, Nerium oleander, Lavandula pedunculta, and Malus domestica. It is also obtained by a one-step reduction of naturally occurring triterpenoid ursolic acid. Herein, we report the first self-assembly properties of uvaol in different neat organic liquids and aqueous organic binary liquid mixtures. Spontaneous self-assembly of uvaol in different neat liquids and binary liquid mixtures yielded garland, flower, and petal-like porous superstructures of nano- to micrometer dimensions. Utilization of self-assemblies has been demonstrated in generation of anticancer drug conjugates and the removal of carcinogenic and toxic chemicals.

1. INTRODUCTION

Over the last three decades, one of the most exciting developments in chemistry is the construction of nano- to microstructured objects or materials via spontaneous self-assembly of smaller building units.1−6 A variety of supramolecular architectures has been created by the self-assembly of building amphiphiles via noncovalent interactions, such as van der Waals, electrostatic, aromatic−aromatic, hydrogen bonding, solvophobic interactions, etc. Self-assembled materials with diversities in structures and functionalities have found interesting applications in drug delivery,7,8 pollutant capture,9 tissue engineering,10 templating nanomaterials, etc. The study of the self-assembly of different functional building blocks in aqueous and aqueous binary liquid mixtures helps us in a better understanding of the structure- and self-assembly−property relationships. The nature of self-assembly from different organic compounds, such as proteins and peptides,11−13 sophorolipids,14,15 fatty acids,16−18 sugars,19,20 steroids,21 etc., and also their properties have been reported. Among various natural products, triterpenoids are non-nitrogenous plant metabolites containing 30 carbons. These molecules exist either combined with sugar moieties or in the free state. Most terpenoids being renewable in nature, investigations utilizing terpenoids help in the development of a sustainable society. The functional group interconversions of the molecules provide easy access to different derivatives, thereby providing a window for studying the structure−property relationships.22 A thorough literature survey reveals that the self-assembly of ursane-type triterpenoids is rare. The self-assembly of naturally occurring triterpenoids, such as arjunolic acid, maslinic acid, corosolic acid, betulinic acid, ursolic acid, oleanolic acid, glycyrhretinic acid, α-onocerin, and betulin in different aqueous and aqueous binary liquids has been reported recently by our group.23−29 From these investigations, it was observed that small structural variations in the hydrophobic triterpenoid backbone, the nature of the functional groups, and their position lead to a substantial change in the morphologies of the self-assemblies. These observations inspired us to study the self-assembly of a ursane-type dihydroxy triterpenoid, uvaol (Figure 1), in different liquids. Uvaol is a nanosized (1.41 nm, Figures 1 and 2) amphiphile for the study of its self-assembly properties in several neat liquids and aqueous organic binary liquids. Uvaol 1 containing two hydroxyl groups at the two ends of the molecule along with a 6-6-6-6-6 pentacyclic ursane-type hydrophobic backbone makes it a unique unsymmetrical bola amphiphile for the study of its self-assembly properties in several neat organic liquids and aqueous organic binary liquids. The self-assemblies and flowerlike porous superstructure from metal oxide nanocomposite and inorganic substances in different media have been reported.30−34 But the self-assembly of garland and flowerlike porous architectures from triterpene-
based amphiphiles and synthesized organic compounds is not common.\textsuperscript{6,41,42} Herein, we report the first self-assembly of uvaol in different neat liquids and aqueous binary liquid mixtures yielding supramolecular garland and flowerlike porous superstructures of nano- to micrometer dimensions. Different electron and atomic microscopic techniques, as well as X-ray diffraction studies, indicated that the porous architecture was similar to a garland of petals or flowers having nano- to micrometer dimensions. The flowerlike self-assemblies of 1 having porous surfaces were capable of adsorbing fluorophore molecules. This adsorption property of the self-assemblies was further applied for the removal of toxic dyes such as crystal violet (CV), rhodamine 6G (Rho-6G), rhodamine B (Rho-B), and methylene blue (MB) from their corresponding aqueous solutions. Conjugates of self-assembled uvaol with anticancer drug doxorubicin and curcumin have been generated via noncovalent interactions making it useful for targeted drug delivery.

2. RESULTS AND DISCUSSION

2.1. Isolation of Ursolic Acid and Its Reduction to Uvaol. Ursolic acid, a ursane-type dihydroxy triterpenoid, is present in various plants such as \emph{Plumeria rubra},\textsuperscript{43} \emph{Olea europaea},\textsuperscript{44} \emph{Nerium oleander},\textsuperscript{45} \emph{Lavandula pedunculata},\textsuperscript{46} and \emph{Malus domestica}.\textsuperscript{47} One-step conversion of ursolic acid, a 6-6-6-6-6 pentacyclic triterpenic acid having an identical triterpenoid backbone, to uvaol has also been reported.\textsuperscript{35,48} We have isolated ursolic acid from the leaves of \emph{P. rubra} following an optimized procedure developed in our laboratory.\textsuperscript{45} Reduction of isolated ursolic acid using lithium aluminium hydride in dry tetrahydrofuran as a solvent yielded uvaol as a white solid in 80% yield.

2.2. Study of Self-Assembly Properties. Self-assembly studies of uvaol 1 were carried out in several neat organic liquids, as well as binary aqueous liquids (Table 1). Powdered solid of 1 (generally 1–10 mg) was weighed in a dry vial and then dissolved in a solvent by heating with magnetic stirring. The hot solution obtained was allowed to cool at room temperature and observed visually after 4–5 h. For studying the self-assembly in binary aqueous solvent mixtures, the powdered solid of 1 was first solubilized in the neat organic liquid by heating and then water was added gradually until

| entry | medium (v/v) | conc. (mM) | state\textsuperscript{a} |
|-------|-------------|-----------|-----------------|
| 1     | o-xylene    | 4.52      | Cs              |
| 2     | m-xylene    | 4.52      | cs              |
| 3     | p-xylene    | 4.52      | cs              |
| 4     | mesitylene  | 4.52      | cs              |
| 5     | o-dichlorobenzene | 4.52 | cs |
| 6     | DMSO–water (1:1) | 2.26 | cs |
| 7     | DMF–water (1:1) | 2.26 | cs |
| 8     | DMSO       | 8.6       | s               |
| 9     | water      | 8.6       | I               |

\textsuperscript{a}CS = colloidal suspension, S = soluble, and I = insoluble.
cloudiness appeared. The resultant mixture was heated with magnetic stirring to obtain a clear solution, and then the solution was allowed to cool at room temperature and observed. Interestingly, colloidal solutions were obtained in neat organic liquids (4.52 mM), such as mesitylene and o-, m-, and p-xlenes, and aqueous binary solvents (2.26 mM), such as dimethylformamide (DMF)−water (1:1) and dimethylsulfoxide (DMSO)−water (1:1).

2.3. Characterization of the Morphology of the Self-Assemblies. Morphologies of the self-assembled uvaol were studied using optical microscopy (OM), scanning electron microscopy (SEM), field emission scanning electron microscopy (FESEM), high-resolution transmission electron microscopy (HRTEM), atomic force microscopy (AFM), X-ray diffraction (XRD), and Fourier transform infrared (FTIR) spectroscopy.

2.3.1. Optical Microscopy Study. To visualize the morphology of the self-assemblies of 1 obtained from dilute colloidal solutions of o-, m-, and p-xlenes (4.52 mM); mesitylene; and o-dichlorobenzene and in aqueous binary solvent mixtures, such as DMSO−water (1:1, 2.26 mM) and DMF−water (1:1, 2.26 mM), in their native state, optical microscopy studies were carried out. Flowerlike spherical objects of micrometer size were observed in all of the liquids studied (Figures 3, S4, and S5). Flowerlike superstructures were observed in o-, m-, and p-xlenes with an average diameter of 3.7 μm. In the aqueous binary medium, DMSO−water (1:1, 2.26 mM), spherical objects composed of crystal sheet-like assemblies were observed (Figure S4). These observations have good concurrence with the observations from AFM and FESEM experiments.

2.3.2. SEM Studies. The self-assemblies of 1 in o-, m-, and p-xlenes (2.26 mM) were dried at room temperature and observed using a scanning electron microscope. Flowerlike porous superstructures of 15−20 μm diameter were observed (Figure 4) in the dried self-assemblies prepared from o- and m-xlenes (2.26 mM). Comparatively larger size flowers (80−100 μM diameter) were observed in the dried self-assemblies of 1 prepared from p-xylene (2.26 mM) with the width of the petals being 340 nm. Thorough investigations revealed that the flowerlike superstructures were composed of petals (two-dimensional (2D) sheet) attached with each other via a

Figure 3. OPM images of self-assemblies of 1 in (a) p-xylene (4.52 mM) and (b) m-xylene (4.52 mM) under normal light.

Figure 4. SEM images of dried self-assemblies of uvaol (a−d) in p-xylene (2.26 mM), (e, f, i) m-xylene (2.26 mM), and (g, h) o-xylene.
common center, and these flowerlike objects with micrometer dimensions were obtained in \( p-, m-, \) and \( o- \) xylene (2.26 mM). The shape and the alignment of the petals are rather different from each other (Figures 4−7) probably due to the difference in solvent−solute interactions. Garlandlike assemblies were also observed in \( o-xylene \) (Figure 4g,h), indicating higher-order self-assembly.

2.3. AFM Studies. The interesting flowerlike objects observed using SEM inspired us to investigate the morphology of the self-assemblies of \( 1 \) with high-resolution three-dimensional (3D) topological images from atomic force microscopy. The flowerlike porous superstructures of the dried self-assemblies of \( 1 \) in \( p-xylene \) (0.52 mM) were observed with an average diameter of 2−2.5 \( \mu m \) (Figure 5). This observation indicated that the flowerlike structures were composed of petals of 50−350 nm diameter.

3.4. HRTEM Studies. To obtain further information about the morphology of the dried self-assemblies, HRTEM analysis was carried out. Flower-shaped superstructures with micrometer dimensions from the dried self-assemblies prepared from a dilute colloidal solution of \( 1 \) in \( p-xylene \) (0.45 mM) were visualized using HRTEM (Figure 6). HRTEM images clearly indicated the presence of petals having a thickness of 80−250 nm in the flowerlike superstructure. Thus, the results from HRTEM analysis were consistent with the results obtained from FESEM, AFM, and OPM (discussed earlier).

2.3.5. XRD Studies. We performed XRD analysis in the range of 2θ = 5−50°. The diffraction patterns of dried self-assemblies of uvaol in \( p-xylene \) and the neat powder sample were compared. Sharp peaks in the XRD patterns of the dried self-assemblies were observed as compared to those of the neat powder sample, indicating that the molecules have a more organized arrangement in the dried self-assemblies (Figure S6). Three peaks at 1.41, 0.705, and 0.352 nm were observed in the dried self-assemblies of \( 1 \), which were in the ratio of 1:1/2:1/3. The length of the molecule determined by density functional theory (DFT) calculation was 1.41 nm. Thus, a lamellar type of self-assembly may be proposed.\(^{31}\)

2.3.6. Molecular Modeling and FTIR Studies. The self-assembly of \( 1 \) might be due to H-bonding involving the primary and the secondary −OH groups at the two ends of uvaol along with dispersive interactions by the hydrophobic triterpenoid skeleton. A H-bonded dimer of uvaol obtained by DFT calculation is shown in Figure 2. Each O−H group can act as two H-bond acceptors and one H-bond donor (Figures 2 and 7). The H-bonded dimer of uvaol can form H-bonds with neighboring molecules forming higher-order assemblies. To obtain evidence for the role of H-bonding in the dried self-assemblies of \( 1 \), FTIR spectra were recorded. The shift of the −OH stretching frequency (3355 cm\(^{-1}\)) in the neat powder to a lower frequency (3274 cm\(^{-1}\)) in the dried self-assemblies of uvaol \( 1 \) indicated that the molecules undergo stronger intermolecular H-bonding leading to higher-order superstructures (Figures 2 and S7).\(^{49}\)

2.4. Proposed Model for the Self-Assembly of Uvaol. A model for the self-assembly of uvaol has been proposed as shown in Figure 7. Based on the evidence obtained from DFT calculations and FTIR studies, formation of the H-bonded dimer of uvaol from the nanosized triterpenoid uvaol (1.41 nm) having −OH groups at the two extreme ends of the molecule is supported. They can form higher-order supramolecular assemblies via H-bonding sites present at the two ends of the dimer of uvaol (Figures 2 and 7) and dispersion interactions from the lipophilic surface. Evidence for a lamellar arrangement of molecules during self-assembly was obtained from X-ray diffraction studies (Section 2.3.5). Evidence for flowers having petals of a thickness of 70−290 nm via AFM, SEM, and TEM studies (Figures 4−6) from 1.41 nm long molecules indicates hierarchical self-assembly of molecules. The petals form flowers or garlands via hierarchical self-assembly as evident from electron and atomic force microscopies.

2.5. Utilization of Self-Assemblies. 3D flower-shaped organized structures consist of 2D nanosheets along with a porous surface as observed from AFM and FESEM analysis of the self-assemblies of \( 1 \) in different liquids. These hierarchical porous materials with their exposed sites and highly accessible surface area are highly active in adsorbing ions/electrolytes on the surfaces and therefore accelerate adsorption of electrical charge.\(^{30,54}\)

2.5.1. Adsorption of Carcinogenic Toxic Dye. Our aim was to adsorb a carcinogenic toxic dye, rhodamine B (Rho-B), as a model compound used in the paint and printing industries. For this study, compound \( 1 \) (1.1 mg) was taken in a clean vial and
solubilized in isopropanol (0.70 mL) under a heating condition with magnetic stirring, and then Rho-B solution in isopropanol (0.021 mL, 1.16 mM) was added dropwise and heated for a minute with simultaneous magnetic stirring. Then, the mixture was kept at room temperature for 6 h. An aliquot of a Rho-B-loaded colored solution (10 μM) was placed on a clean dried glass plate and covered with a coverslip and observed under an epi-fluorescence microscope. The bright images under the blue and green fluorescence light compared with images under the normal microscopic light clearly indicated that Rho-B was adsorbed on the surface of the flower-shaped superstructure of 1 (Figure 8). An identical experiment was carried out in a DMSO–water (1:1) binary liquid mixture. Thus, self-assembled uvaol 1 with a porous structure facilitated the adsorption of toxic dye. These studies prompted us to use the self-assemblies to remove toxic and carcinogenic dyes from contaminated water.52,53

2.5.2. Dye Removal Study. The dye removal capability of the self-assemblies of 1 obtained from o-dichlorobenzene was studied. For this purpose, a certain amount of 1 (5 mg) was taken in a clean and dry vial and solubilized in o-dichlorobenzene (1 mL) under a heating condition with 1 (Figure 8). An identical experiment was carried out in a DMSO–water (1:1) binary liquid mixture. Thus, self-assembled uvaol 1 with a porous structure facilitated the adsorption of toxic dye. These studies prompted us to use the self-assemblies to remove toxic and carcinogenic dyes from contaminated water.52,53

Figure 6. HRTEM image of dried self-assemblies of uvaol (a–c) in p-xylene (0.45 mM).

Figure 7. Proposed model of self-assemblies of uvaol yielding flower and garlandlike architectures.

Figure 8. Epifluorescence micrographs of self-assembled uvaol (3.4 mM) in isopropanol loaded with rhodamine B (0.034 mM): (a, c) under green and blue fluorescence light, respectively, and (b) under normal light.
magnetic stirring and allowed to cool at room temperature. After 5 h, an aqueous solution of a dye (1 mL, 0.15 mM) was added carefully on the surface of the viscous solution of uvaol in \textit{o}-dichlorobenzene. UV–visible spectroscopy measurements were carried out in a certain interval of time by taking the aqueous solution of dyes from the upper portion of self-assemblies in a quartz cuvette with a 2 mm path length. The experiment was monitored for up to 50 h. The removal of toxic dyes such as Rho-B, MB, CV, and Rho-6G has been demonstrated by the porous flowerlike superstructures from self-assembled uvaol. The intensities of absorbance of dye solutions reduced with time (Figure 9). From the absorbance values, the percentage of dye removed from their aqueous solutions was calculated. Briefly, 98% of Rho-6G, 97% of CV, 95% of Rho-B, and 95% of MB were removed in 5, 30, 30, and 50 h from their respective aqueous solutions, whereas control experiments with \textit{o}-dichlorobenzene alone did not show a detectable removal of the dyes, indicating adsorption of the dyes by the self-assemblies of uvaol. The anticancer activity of triterpenoid uvaol, its self-assembly properties in aqueous medium, and success in the removal of toxic chemicals encouraged us to study whether anticancer drug molecules can also be conjugated with the assembled uvaol via noncovalent interactions. This enables the desired concentration of the drug molecules at the target site without many side effects. Moreover, no chemical transformation is required once the drug molecules reach the target site. Additionally, the anticancer activity of uvaol itself is combined with the drug. Keeping this concept in mind, we designed two experiments for the conjugation of anticancer drugs doxorubicin (Dox) and curcumin, with self-assembled uvaol in \textit{d}-dichlorobenzene–water (1:1, 2.26 mM) and ethanol–water (1:1, 2.26 mM), respectively. A solution of Dox (0.02 mM) in \textit{d}-dichlorobenzene–water (1:1 v/v, 2.26 mM) was heated and the mixture was allowed to cool at room temperature. The bright fluorescence observed under an epifluorescence microscope indicated drug conjugation with self-assemblies of uvaol. Future studies will be carried out to determine the state of the drug molecules: whether they adsorb onto the uvaol aggregates or they incorporate into the self-assembled structure. To determine the effect of the fluorescence emission intensity due to adsorption of Dox by self-assemblies of uvaol, the emission intensity of Dox was measured in the above condition both in the free state and in conjugation with self-assemblies. A gradual decrease in the emission intensity of doxorubicin was observed (Figure 10c) compared to the emission intensity of free doxorubicin. In an identical experiment with the hydrophobic anticancer drug curcumin (0.02 mM), a gradual decrease in the emission intensity of curcumin was observed (Figure 10d) compared to the emission intensity of free.

2.5.3. Anticancer Drug Conjugation with Self-Assemblies. Targeted delivery of drugs in physiology has been one of the most challenging areas of research in recent years. Various approaches to targeted delivery, including formation of self-assembled drug conjugates by covalent modification of drug or the co-assembly of drug–metal nanoparticle conjugates, are reported in the literature. Roy and co-workers reported the co-assembly of betulinic acid with folic acid. Lepeltier and co-workers reported the self-assembly of drug conjugates with covalent modification. Jana and co-workers reported drug conjugation with nanoparticles for targeted drug delivery.
curcumin. Control time-dependent fluorescence intensity of drug molecules under similar conditions without uvaol did not show a significant change (Figure S8). The success in the conjugation of Dox and curcumin with self-assembled uvaol makes it useful in targeted delivery.

3. CONCLUSIONS
In conclusion, the first spontaneous formation of garland and flowerlike superstructures via the self-assembly of ursane-type 6-6-6-6-6 pentacyclic dihydroxy triterpenoid uvaol in liquids has been reported. Such hierarchical self-assembly of uvaol was observed in a range of organic liquids such as o-, m-, and p-xylene; mesitylene; and o-dichlorobenzene and in aqueous binary solvent mixtures such as DMSO–water (1:1) and DMF–water (1:1). Application of self-assembled uvaol for the adsorption and removal of toxic dyes such as Rho-B, MB, CV, and Rho-6G has been demonstrated. Generation of self-assembled uvaol–anticancer drug conjugates has also been demonstrated, making it useful in targeted drug delivery applications.

4. EXPERIMENTAL SECTION
4.1. Anticancer Drug Conjugation with Self-Assemblies. Uvaol 1 (5 mg) was taken in a vial and dissolved in distilled DMSO (1 mL) under heating conditions, and then an aqueous solution of doxorubicin (1.12 mM, 1 mL) was added and the mixture was allowed to cool at room temperature for 4 h. Anticancer drug curcumin conjugated with self-assemblies of 1 was also prepared by following a similar method. The colloidal suspension thus obtained was examined under an epifluorescence microscope and the fluorescence emission intensity was measured in 1, 3, 5 h time intervals. Fluorescence emission spectra of Dox were recorded at $\lambda_{\text{max}}$(ex.) 480 nm, and the fluorescence emission spectra of curcumin were recorded at $\lambda_{\text{max}}$(ex.) 450 nm.

■ ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02630.

Energy minimized structure of uvaol; reduction of ursolic acid to uvaol; method of sample preparation; FTIR spectra of dried self-assemblies of 1; X-ray diffraction study; and NMR and HRMS spectra (PDF)

■ AUTHOR INFORMATION
Corresponding Author
Braja Gopal Bag — Department of Chemistry and Chemical Technology, Vidyasagar University, Midnapore 721102 West Bengal, India; orcid.org/0000-0002-0058-7900; Email: brajagb@gmail.com

Author
Subrata Ghorai — Department of Chemistry and Chemical Technology, Vidyasagar University, Midnapore 721102 West Bengal, India

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c02630

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS
SERB (EMR/2017/000069), Indo-Srilanka project (DST/INT/SL/P25/2016), UGC-SAP, and DST-FIST, Vidyasagar University, are gratefully acknowledged for providing financial support and infrastructural facilities. S.G. thanks CSIR for providing research fellowships.

■ REFERENCES
(1) Carretti, E.; Bonini, M.; Dei, L.; Berrie, B. H.; Angelova, L. V.; Baglioni, P.; Weiss, R. G. New Frontiers in Materials Science for Art Conservation: Responsive Gels and Beyond. Acc. Chem. Res. 2010, 43, 751–760.
(2) Suzuki, M.; Hanabusa, K. l-Lysine-based low-molecular-weight gelators. Chem. Soc. Rev. 2009, 38, 967–975.
(3) Weiss, R. G.; Terech, P. Materials with Self-Assembled Fibrillar Networks, Molecular Gels; Springer: Dordrecht, 2006; pp 1–3.
(4) Bag, B. G.; Majumdar, R. Self-assembly of Renewable Nano-sized Triterpenoids. Chem. Rev. 2017, 1, 841–874.
(5) Bhattacharyya, S.; Samanta, S. K. Soft-Nanocomposites of Nanoparticles and Nanocarbons with Supramolecular and Polymers and Their Applications. Chem. Rev. 2016, 116, 11967–12028.
(6) Bag, B. G.; Barai, A. C.; Sk N, H.; Panja, S. K.; Ghori, S.; Patra, S. Terpenoids, nano-entities and molecular self-assembly. Pure Appl. Chem. 2020, 92, 567–577.
(7) Barnard, A.; Posocco, P.; Pricl, S.; Calderon, M.; Haag, R.; Hwang, M. E.; Shum, V. W. T.; Pack, D. W.; Smith, D. K. Degradable Self-Assembling Dendrons for Gene Delivery: Experimental and Theoretical Insights into the Barriers to Cellular Uptake. J. Am. Chem. Soc. 2011, 133, 20288–20300.
(8) Jadhav, S. R.; Chiou, B. S.; Wood, D. F.; Hoffman, G. D.; Glenn, G. M. John, G. Molecular gels-based controlled release devices for pheromones. Soft Matter 2011, 7, 864–867.
(9) Jadhav, S. R.; Vemula, P. K.; Kumar, R.; Raghavan, S. R.; John, G. Sugar-derived phase-selective molecular gelators as model solidifiers for oil spills. Angew. Chem., Int. Ed. 2010, 49, 7695–7698.
Anti-inflammatory properties of uvaol on DSS-induced colitis and LPS-stimulated macrophages. Chin Med. 2020, 15, 1–13.

(32) Trumbull, E. R.; Bianchi, E.; Eckert, D. J.; Wiedhop, R. M. Tumor inhibitory agents from Vauquelinia corymbosa (Rosaceae). J. Pharm. Sci. 1976, 65, 1407–1408.

(33) Carro, J.; Araújo, P. C.; Silva, J.; Ferro, J.; Correia, A. C.; Lagente, V.; Barreto, E. Uvaol Improves the Functioning of Fibroblasts and Endothelial Cells and Accelerates the Healing of Cutaneous Wounds in Mice. Molecules 2020, 25, 4982–4998.

(34) Ghorai, S. Medicinal properties of a naturally occurring pentacyclic dihydroxy triterpenoid uvaol. Prayogik Rasayan 2020, 4, 11–15.

(35) Wang, H.; Rogach, A. L. Hierarchical SmO Nanoarchitectures: Recent Advances in Design, Synthesis, and Applications. Chem. Mater. 2014, 26, 123–133.

(36) Zhang, H.; Wu, R.; Chen, Z.; Liu, G.; Zhang, Z.; Jiao, Z. Self-assembly fabrication of 3D flower-like ZnO hierarchical nanostructures and their gas sensing properties. CrystEngComm 2012, 14, 1775–1782.

(37) Wu, H.; Gao, Y.; Li, H. Controlled synthesis of nickel phosphate hexahedral and flower-like architectures via a simple template-free hydrothermal route. CrystEngComm 2010, 12, 3601–3611.

(38) Tian, G.; Chen, Y.; Zhou, W.; Pan, K.; Tian, C.; Huang, X.; Fu, H. 3D hierarchical flower-like TiO2 nanostructure: morphology control and its photocatalytic property. CrystEngComm 2011, 13, 2994–3000.

(39) Dai, W.; Yu, J.; Xu, H.; Hu, X.; Luo, X.; Yang, L.; Tu X. Synthesis of hierarchical flower-like Bi2MoO6 microspheres as efficient photocatalyst for photoreduction of CO2 into solar fuels under visible light. CrystEngComm 2016, 18, 3472–3480.

(40) Wang, Y.; Zhu, L.; Yang, X.; Shao, E.; Deng, X.; Liu, N.; Wu, M. Facile synthesis of three-dimensional Mn3O4 hierarchical microstructures and their application in the degradation of methylene blue. J. Mater. Chem. A 2015, 3, 2934–2941.

(41) Saiddharan, S.; Shyni, P. C.; Chaudhary, N.; Ramakrishnan, V. Single Crystal Organic Nanoflowers. Sci. Rep. 2017, 7, No. 17335.

(42) Zhao, H.; Guo, X.; He, S.; Zeng, X.; Zhou, X.; Zhang, C.; Hu, J.; Wu, X.; Xing, Z.; Chu, L.; He, Y.; Chen, Q. Complex self-assembly of pyrimido[4,5-d]pyrimidine nucleoside supramolecular structures. CrystEngComm 2014, 16, No. 3108.

(43) Hassan, E. M.; Shahat, A. A.; Ibrahim, N. A.; Vlitechin, A. J.; Apers, S.; Pieters, L. A new monoterpenoid alkaloid and other constituents of Plumeria acutifolia. Planta Med. 2008, 74, 1749–1750.

(44) Fiad, S.; Hamidi, M. E. Six Pentacyclic Triterpenes In Mature Olive Fruits ‘Pical’. Am. J. Food Technol. 2015, 1, 1–13.

(45) Siddiqui, B. S.; Khatoon, N.; Begum, S.; Durran, S. A. Two new triterpenoid isomers from Nerium oleander leaves. Nat. Prod. Res. 2009, 23, 1603–1609.

(46) von Carstenn-Lichtefelder, C.; Rodriguez, B.; Valverde, S. Triterpenes and fatty acids from Nepeta aragonensis. Phytochemistry 1973, 12, 3002–3003.

(47) Young, R.; Trojan, H.; Kopp, T.; Laszczyn, M. N.; Scheffler, A. Pentacyclic Triterpene Distribution in Various Plants – Rich Sources for a New Group of Multi-Potent Plant Extracts. Molecules 2009, 14, 2016–2031.

(48) Wu, B. Y. T.; Park, L. M. The toxicology of the polyethylene glycols. J. Am. Pharm. Assoc., Sci. Ed. 1950, 39, 475–476.

(49) Boiani, M.; Baschieri, A.; Cesari, C.; Mazzoni, R.; Stagni, S.; Zacchini, S.; Sambri, L. A new tetraarylcyclopentadienone based low molecular weight gelator: synthesis, self-assembly properties and anion recognition. New J. Chem. 2012, 36, 1469–1478.

(50) Liang, J.; Chen, S.; Xie, M.; Wang, Y.; Guo, X.; Guo, X.; Ding, W. Expedient fabrication of flower-like hierarchical mesoporous carbon superstructures as supercapacitor electrode materials. J. Mater. Chem. A 2014, 2, 16884–16891.

(51) Chen, S.; Koshy, D. M.; Tsao, Y.; Pfattner, R.; Yan, X.; Feng, D.; Bao, Z. Highly Tunable and Facile Synthesis of Uniform Carbon Flower Particles. J. Am. Chem. Soc. 2018, 140, 10297–10304.
(52) Namasivayam, C.; Radhika, R.; Suba, S. Uptake of Dyes by a Promising Locally Available Agricultural Solid Waste: Coir Pith. *Waste Manage.* **2001**, *21*, 381−387.

(53) Mittal, A.; Mittal, J.; Malviya, A.; Kaur, D.; Gupta, V. K. Adsorption of hazardous dye crystal violet from wastewater by waste materials. *J. Colloid Interface Sci.* **2010**, *343*, 463−473.

(54) Dash, S. K.; Dashb, S. S.; Chattopadhyaya, S.; Ghosh, T.; Tripathy, S.; Mahapatrad, S. K.; Bag, B. G.; Das, D.; Roy, S. Folate decorated delivery of self-assembled betulinic acid nano fibers: a biocompatible anti-leukemic therapy. *RSC Adv.* **2015**, *5*, 24144−24157.

(55) Baroud, M.; Lepeltier, E.; Thepot, S.; El-Makhoure, Y.; Duval, O. The evolution of nucleosidic analogues: self-assembly of prodrugs into nanoparticles for cancer drug delivery. *Nanoscale Adv.* **2021**, *3*, 2157−2179.

(56) Sinha, A.; Chakraborty, A.; Jana, N. R. β-Cyclodextrin Functionalized Magnetic Mesoporous Silica Colloid for Cholesterol Separation. *ACS Appl. Mater. Interfaces* **2014**, *6*, 22183−22191.