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UiO-68
A promising Drug Delivery Platform for Podophyllotoxin

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Abstract

In pursuit of development of a drug carrying platform for delivery of Podophillotoxin, an anti-cancer drug, a porous metal–organic frameworks (MOFs), UIO-68, was synthesized and used. The unique structure of UIO-68which are built of inorganic nodes and organic ligands lead to successful encapsulation of different ions and molecules.Following our recent study, UIO-68was prepared and characterized using variety of analytical methods containing FTIR, FESEM, and EDS. The loading and releasing profile of Podophyllotoxin in the synthesized platform UIO-66 were evaluated. The in vitro cytotoxicity results revealed UIO-68-Podophyllotoxin was able to increase cytotoxicity compared to that of Podophyllotoxin on HT-29 cancerous cells indicating the remarkable role of this drug delivery system.

Keywords: UIO-68, MOF, drug delivery, Podophyllotoxin, Cytotoxicity

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1. Introduction

Heavy metal pollution is a global environmental problem, especially in the developing countries, which is caused by increasing industrial and agricultural activities as well as the improper release of metal ions from wastewater and domestic effluents (Boix et al., 2020, Li et al., 2018). These toxic metal ions including Cd (II), As (III and V), Cr (III and VI), Cu (II), Pb (II), and Hg (II) are bioaccumulated readily in humans and animals and believed to be serious threats to the ecological environment and human health (Ma et al., 2019, Zhao et al., 2019). For this purpose, it is much important to effectively remove these toxic pollutants from domestic or industrial wastewater. Many common techniques such as coagulation (Ma et al., 2008), chemical precipitation (Calo et al., 2013), solvent extraction (Cole and Brown, 1959), ion exchange (Crist et al., 1996, Khan et al., 2014), membrane filtration (Fang et al., 2017), electrochemical treatment (Lu et al., 2019) and flotation (Huang et al., 1995) have been used to treat the sewage, while most of them are costly along with having complex operation processes, and these approaches may cause secondary pollution, thus limiting their application (Cai et al., 2017, Ge and Li, 2018). In recent years, adsorption strategies provide a powerful method and have been widely used for the construction of simple and inexpensive platforms to realize high-efficiency removal of heavy metal ions from wastewaters (Sharma and Kumar, 2018, Zhang et al., 2020a, Zhang et al., 2020b, Zhao et al., 2019). In this interesting approach, depending on the strength of the interaction during the adsorption process, it allows an efficient transfer of analytes to the sorbent material. The sorbent is dispersed into the sample solution by magnetic stirring, eddy current or ultrasonic wave, thus increasing the contact area of analyte-sorbent. Therefore, it has become a trend to search for novel materials that can be used not only for adsorption but also for green analysis.

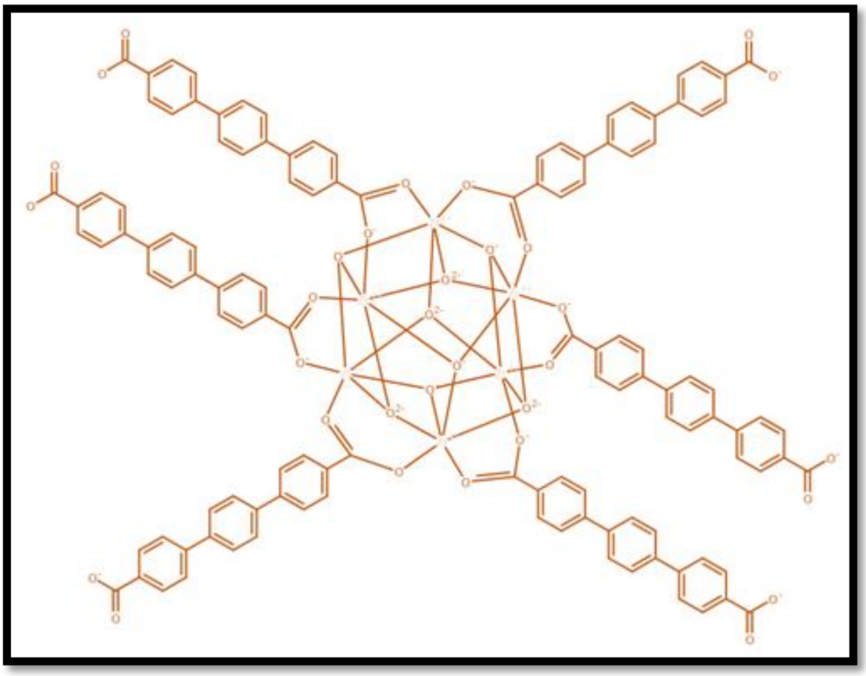

Fig1. UiO-68 Structure

In recent decades, metal-organic frameworks (MOFs) as novel organic-inorganic hybrid materials have been an increasing utilization in analytical chemistry. These novel substances are composed of metal ions (clusters or secondary building units (SBUs)) and organic ligands (linkers) through coordination bonds, have attracted wide attention because of their extraordinary properties (high ordered porosity, large surface area, uniform structural cavities, and thermal/chemical stability) (Kumar et al., 2017). Moreover, these properties have emerged in the research of ZIF, MOF, MIL, HKUST, PCN, and UiO, each of which fits the definition of prototype MOFs, implying that various metal and organic ligands can be combined satisfactorily (Winarta et al., 2020). Due to these fascinating properties, the adsorption of target molecules on the surface of MOFs can be effectively promoted. However, most MOFs have relatively lower hydrothermal and chemical stability, and their structures are easy to collapse under high temperatures, high pressure, or acid/alkaline environment. Besides, the structural stability of MOFs decreases as the length of the organic ligand increases, which inhibits the applications of MOFs. Fortunately, the three-dimensional porous nanocomposites constructed from Zr4+ and carboxylic acids of UiO-MOFs (featuring UiO-66, UiO-67, UiO-68, and UiO-69) have a relatively uniform, large pore size, specific surface area, strong stability as well as active Zr–O clusters, which has been widely studied and used in post-modification and application.

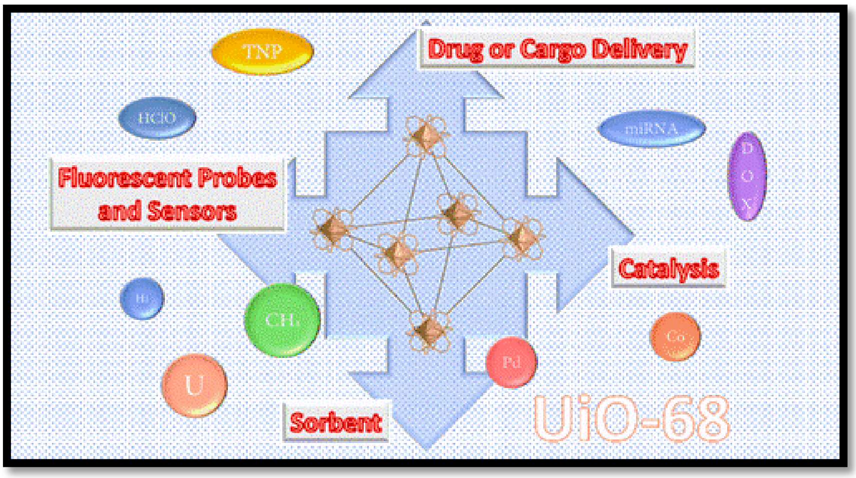

Fig2. UiO-68 and its applications

Furthermore, UiO-MOFs have many attractive active binding sites in the organic ligands compared with other MOFs. According to the hard-soft-acid-base (HSAB) theory, some metal ions can be preferred to specific functional ligands (amino, hydroxyl, sulfhydryl, phosphorous, etc.) by ion exchange, electrostatic interaction, or chelation. The specific functional ligands are Lewis bases and have a lone pair of electrons, which can be formed coordination bonds with heavy metal ions (Lewis acids). Therefore, the post-modification of UiO-MOF with specific functional groups to increase the active site for the adsorption of heavy metal ions is a hot topic as one of the promising adsorbents, which is considered as a reliable and advanced solid sorbent in the field of environment.

The purpose of this review was to focus on the potential of UiO series MOFs as the emerging MOFs material for the effective adsorption and separation of heavy metal ions from environmental samples. UiO-MOFs or functionalized UiO-MOFs composites have been widely applied as an efficient and selective adsorbent due to its structural diversity, excellent water stability, good biocompatibility, and other excellent properties (Mukhopadhyay et al., 2019, Yu et al., 2019, Zhao et al., 2019). Moreover, a comprehensive study about UiO-MOFs and their composites including the synthetic methods and the applications in the removal of heavy metal ions were presented in detail. Finally, the adsorption characteristics and mechanism of UiO-MOFs as solid sorbents for heavy metal ions were discussed, including adsorption isotherms equation, adsorption thermodynamics, and kinetics. Scheme 1 was a schematic illustration of the synthesis, characteristics, and application of UiO-MOFs in the environment.

Synthetic methods of UiO-MOFs

The premise for the synthesis of MOFs is experimental property research and practical application. UiO-MOFs are three-dimensional porous materials and constructed by Zr^{4+} and dicarboxylic acid ligands. Although the ligands of UiO-MOFs have different lengths, UiO-64, UiO-66, UiO-67, UiO-68, UiO-69, and various derivatives have the same reticular structure, the change of the ligand does not affect the thermal stability of UiO-MOFs. Zr(IV)-based MOFs is formed a similar cubic close-packed (CCP) structure with enlarged versions (Cavka et al., 2008, Nguyen et al., 2014), including ($Zr_6O_4(OH)_4(BDC)_6$ for UiO-66; $Zr_6O_4(OH)_4(BPDC)_6$ for UiO-67; $Zr_6O_4(OH)_4(TPDC)_6$ for UiO-68, and $Zr_6O_4(OH)_4(2,6\text{-}NDC)_6$ for UiO-69 (Xu et al., 2019, Kutzscher et al., 2016). As can be seen, $Zr_6O_4(OH)_4$ (as SBU) are coordinated with twelve bridge ligands separately to form a three-dimensional structure, which is consists of one octahedral center hole cage and eight tetrahedral corner cages. The theoretical values of pore volumes of UiO-MOFs (UiO-66, UiO-67, UiO-68) are 0.45, 1.05, and 1.82 cm^3g^{-1}, and the theoretical values of specific surface area are 1087, 3000, and 4170 m^2g^{-1} (Cavka et al., 2008), respectively. Therefore, due to the strong binding ability of Zr–O bond, the synthesis of UiO-MOFs is gradually concentrated on functionalization or changes in ligand length in order to control the physical/chemical properties, pore size, and morphology of UiO-MOFs. UiO-MOFs and functional UiO-MOFs composites are synthesized based on the node and connector approach and can maintain their topology structures and crystallinity when the organic ligands or the inorganic SBUs are enlarged, replaced, or functionalized. This may depend on the interaction forces such as coordination bond, hydrogen bond, π–π interaction, metal bond, and so on. The original pore characteristics of UiO-MOFs are determined by the properties of metal ions and linkers (Qiu and Zhu, 2009). The main structural characterizations can be influenced by the solvent, pH, reaction temperature, and so on. So far, some different synthesis strategies have been reported for UiO-MOFs such as solvent-thermal, microwave, volatilization, diffusion, template synthesis, ultrasonic, and mechanical stirring.

Podophyllotoxin

Podophyllotoxin

Podophyllotoxin (PPT) is the active ingredient in Podofilox, which is a medical cream that is used to treat genital warts and molluscumcontagiosum. It is not recommended in HPV infections without external warts. It can be applied either by a healthcare provider or the person themselves. It is a non-alkaloid toxin lignin extracted from the roots and rhizomes of Podophyllum species. A less refined form known as podophyllum resin is also available, but has greater side effects.

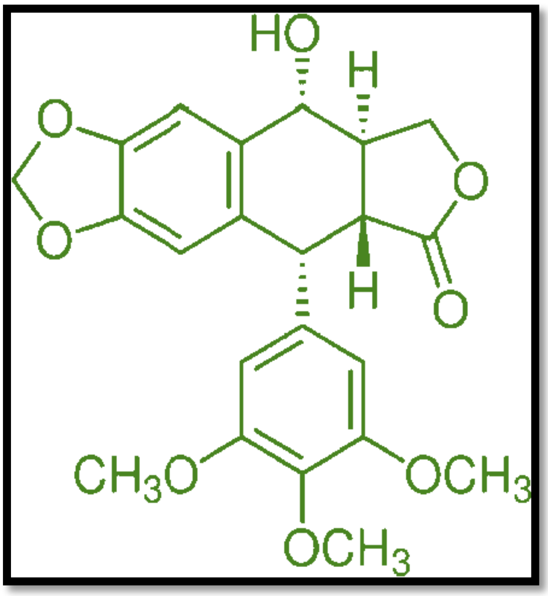

Fig3. Podophyllotoxin structure

Medical uses

Podophyllotoxin possesses a large number of medical applications, as it is able to stop replication of both cellular and viral DNA by binding necessary enzymes. It can additionally destabilize microtubules and prevent cell division. Because of these interactions it is considered an antimitotic drug. Podophyllotoxin and its derivatives are used as cathartic, purgative, antiviral agent, vesicant, antihelminthic, and antitumor agents. Podophyllotoxin derived antitumor agents include etoposide and teniposide. These drugs have been successfully used in therapy against numerous cancers including testicular, breast, pancreatic, lung, stomach, and ovarian cancers.

Podophyllotoxin cream is commonly prescribed as a potent topical antiviral. It is used for the treatment of HPV infections with external warts as well as molluscumcontagisum infections. 0.5% PPT cream is prescribed for twice daily applications for 3 days followed by 4 days with no application, this weekly cycle is repeated for 4 weeks. It can also be prescribed as a gel, as opposed to cream. PPT is also sold under the names condyline and warticon.

Adverse effects

The most common side effects of podophyllotoxin cream are typically limited to irritation of tissue surrounding the application site, including burning, redness, pain, itching, and swelling. Application can be immediately followed by burning or itching. Small sores, itching and peeling skin can also follow, for these reasons it is recommended that application be done in a way that limits contact with surrounding, uninfected tissue

Neither podophyllin resin nor podophyllotoxin lotions nor gels are used during pregnancy because these medications have been shown to be embroytoxic in both mice and rats. Additionally, antimitotic agents are not typically recommended during pregnancy. Additionally, it has not been determined if podophyllotoxin can pass into breast milk from topical applications and therefore it is not recommended for breastfeeding women.

Podophyllotoxin cream is safe for topical use; however, it can cause CNS depression as well as enteritis if ingested. The podophyllum resin from which podophyllotoxin is derived has the same effect.

Mechanism of action

Podophyllotoxin destabilizes microtubules by binding tubulin and thus preventing cell division. In contrast, some of its derivatives display binding activity to the enzyme topoisomerase II (Topo II) during the late S and early G2 stage. For instance, etoposide binds and stabilizes the temporary DNA break caused by the enzyme, disrupts the reparation of the break through which the double-stranded DNA passes, and consequently stops DNA unwinding and replication. Mutants resistant to either podophyllotoxin, or to its topoisomerase II inhibitory derivatives such as etoposide (VP-16), have been described in Chinese hamster cells. The mutually exclusive cross-resistance patterns of these mutants provide a highly specific means to distinguish the two kinds of podophyllotoxin derivatives. Mutant Chinese hamster cells resistant to podophyllotoxin are affected in a protein P1 that was later identified as the mammalian HSP60 or chaperonin protein. Furthermore, podophyllotoxin is classified as an arytetralinlignan for its ability to bind and deactivate DNA. It and its derivates bind Topo II and prevent its ability to catalyze rejoining of DNA that has been broken for replication. Lastly, experimental evidence has shown that these arytetralinlignans can interact with cellular factors to create chemical DNA adducts, thus further deactivating DNA.

Chemistry

Structural characteristic

The structure of podophyllotoxin was first elucidated in the 1930s. Podophyllotoxin bears four consecutive chiral centers, labelled C-1 through C-4 in the following image. The molecule also contains four almost planar fused rings. The podophyllotoxin molecule includes a number of oxygen containing functional groups: an alcohol, a lactone, three methoxy groups, and an acetal.

Biosynthesis

The biosynthetic route of podophyllotoxin was not completely eludicidated for many years; however, in September 2015, the identity of the six missing enzymes in podophyllotoxin biosynthesis were reported for the first time. Several prior studies have suggested a common pathway starting from coniferyl alcohol being converted to (+)-pinoresinol in the presence of a one-electron oxidant through dimerization of stereospecific radical intermediate. Pinoresinol is subsequently reduced in the presence of co-factor NADPH to first lariciresinol, and ultimately secoisolariciresinol. Lactonization on secoisolariciresinol gives rise to matairesinol.

A sequence of enzymes involved has been reported to be dirigent protein (DIR), to convert coniferyl alcohol to (+)-pinocresol, which is converted by pinocresol-lariciresinolreductase (PLR) to (-)-secoisolariciresinol, which is converted by sericoisolariciresinol dehydrogenase (SDH) to (-)-matairesinol, which is converted by CYP719A23 to (-)-pluviatolide, which is likely converted by Phex13114 (OMT1) to (-)-yatein, which is converted by Phex30848 (2-ODD) to (-)-deoxypodophyllotoxin. Though not proceeding through the last step of producing podophyllotoxin itself, a combination of six genes from the mayapple enabled production of the etoposideaglycone in tobacco plants.

Chemical synthesis

Podophyllotoxin has been successfully synthesized in a laboratory; however, synthesis mechanisms require many steps, resulting resulted in low overall yield. It therefore remains more efficient to obtain podophyllotoxin from natural sources.

Four routes have been used to synthesize podophyllotoxin with varying success: an oxo ester route, lactonization of a dihydroxy acid, cyclization of a conjugate addition product, and a Diels-Alder reaction.

Natural abundance

Podophyllotoxin is present at concentrations of 0.3% to 1.0% by mass in the rhizome of the American mayapple (Podophyllumpeltatum). Another common source is the rhizome of Sinopodophyllumhexandrum Royle (Berberidaceae).

It is biosynthesized from two molecules of coniferyl alcohol by phenolic oxidative coupling and a series of oxidations, reductions and methylations.

2. Results And Discussion

Characterization

The chemical structure of the Uio-68 was characterized with different analytical methods such as XRD, SEM & TEM.

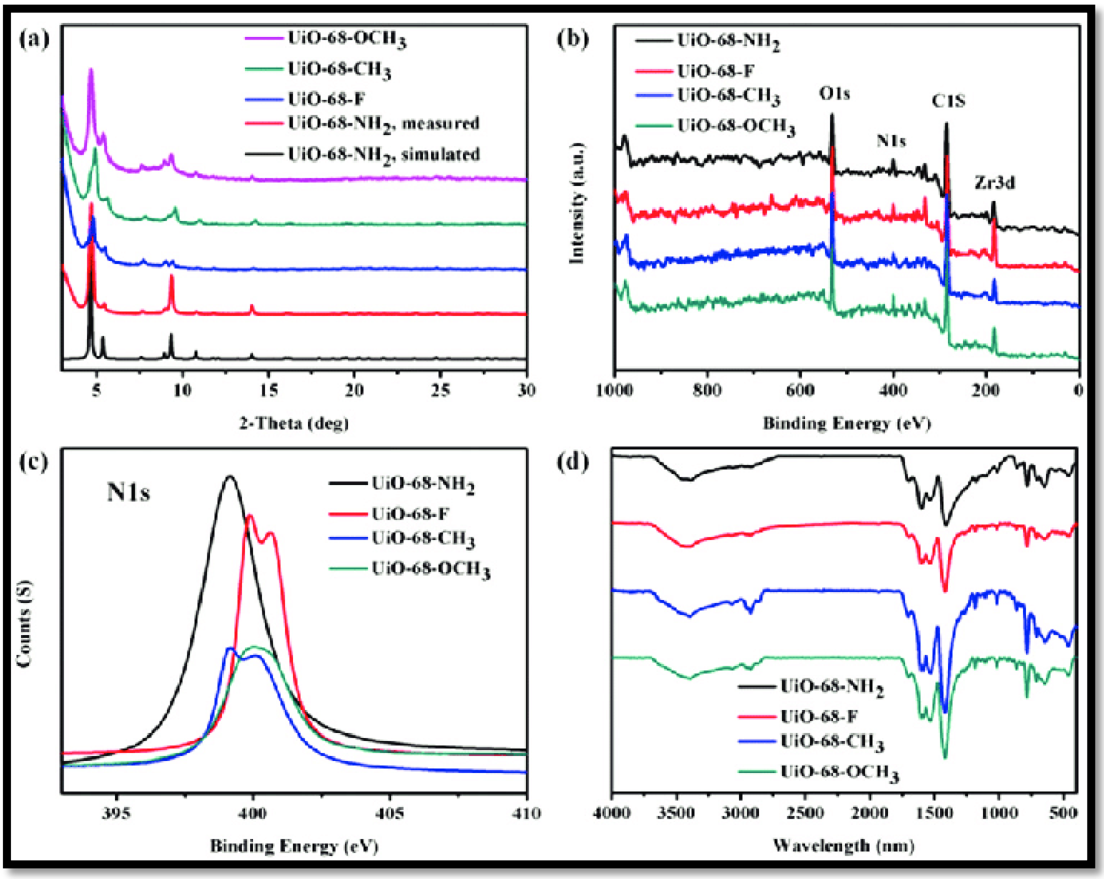

Fig4. (a) PXRD patterns of simulated and measured UiO-68-NH 2 , UiO-68-F, UiO-68-CH 3 and UiO-68-OCH 3 . (b) XPS, (c) XPS of N 1s and (d) IR spectra of UiO-68-NH 2 , UiO-68-F, UiO-68-CH 3 and UiO-68-OCH 3 [36]

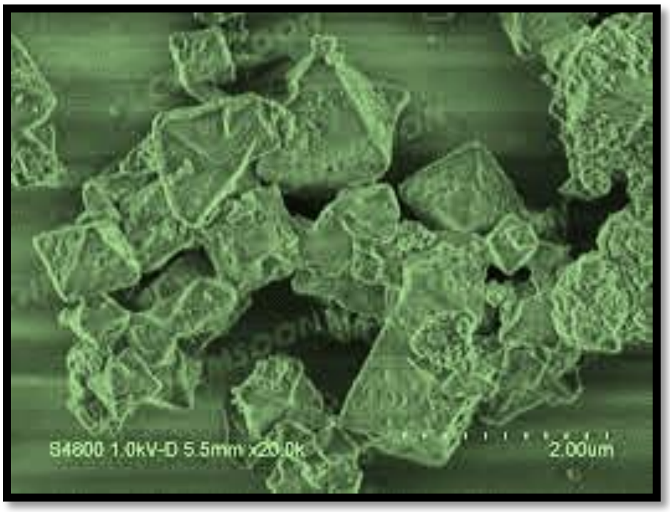

Fig5. TEM of UiO-68

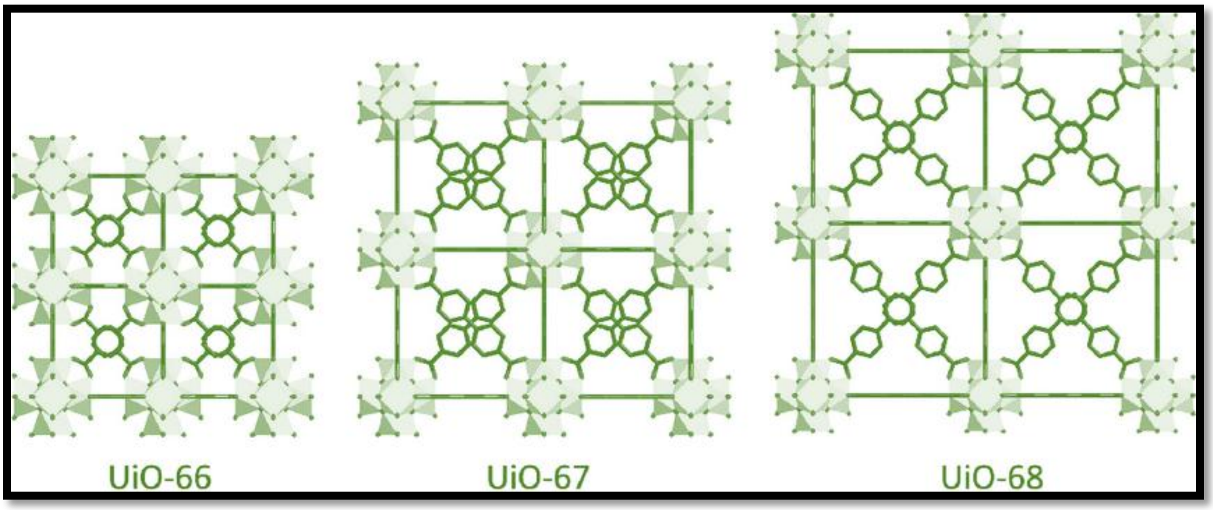

Fig6. Structures of UiO-66, 67, and 68[37]

Conclusions and perspective

In this study, UIO-68 as a drug carrier was applied for delivery of Podophyllotoxin. The obtained nanostructure poses spherical morphology with an average diameter of 39-52 nm. The results showed the high loading capacity (73%) and sustained drug release behavior for Podophyllotoxin after 48h. In addition, upon exposure by UIO-66-Podophyllotoxin, the growth inhibition was increased compared to those for UIO-68 and Podophyllotoxin drug against HT-29 cells. Collectively, UIO-68 may could be used as a promising drug delivery system for Podophyllotoxin.

Outlook for MOFs

The numerous advantages of MOFs, foremost their high surface area and modular composition, place them at a multidisciplinary crossroads. For good reason, MOFs are one of the most active research fields today, with aspects of their fundamental and applied properties permeating into disciplines as varied as electronics, chemical engineering, and optics. Whereas this Outlook does not attempt to delineate the developments and potential in all these areas, we have introduced some of the exciting prospects related to continued synthetic advances in the field. We further elaborated on three applied areas where MOFs are primed to excel: in challenging gas separations, as porous electrical conductors, and in heterogeneous catalysis. These examples are not exhaustive, but present subtleties that are applicable and relevant to many other applications of MOFs. The challenges and opportunities in these select applications, which span both the traditional and the modern aspects of the field, are illustrative of the continually expanding interest and bright future for MOF chemistry.

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