Asian Journal of Chemistry; Vol. 36, No. 4 (2024), 755-765

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2024.31061

REVIEW

Recent Advancements in the Applications of Covalent Organic Frameworks for Cancer Therapeutics: A Review

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Received: 16 December 2023; *Accepted*: 24 February 2024; *Published online*: 30 March 2024; AJC-21572

Covalent organic frameworks (COFs) have gained significant attention in recent years as efficient cancer therapeutics owing to their uniform porosity, biocompatibility, diversified structures and stability in the biological medium. This review aimed to explore different synthetic strategies to obtain COFs for biomedical applications. Several synthetic procedures *viz*. solvothermal synthesis, ionothermal synthesis, microwave synthesis, mechanochemical synthesis, sonochemical synthesis have discussed been in terms of their applications in cancer therapy. The cancer therapeutics involves cancer drug delivery, photodynamic therapy (PDT), photo thermal therapy (PTT) and sonodynamic therapy (SDT). In some instances, single therapeutics treatments appear as inadequate effect and thus necessitate combination therapies for effective cancer termination with minimal side effects. The current study covers all the main synthetic techniques and uses of COFs in various cancer therapeutic treatments.

Keywords: Covalent organic frameworks, Cancer therapy, Drug delivery.

INTRODUCTION

With the rapid advancement of nanoscience and technology, there is a growing interest towards the development of multifunctional therapeutic agents capable of detecting and treating cancer *in vivo*. Cancer remains a significant cause of global mortality, ranking as the second leading cause of death in humans. Conventional treatment methods, such as chemotherapy, exhibit inherent limitations, including severe side effects, drug resistance, uncontrollable release and poor tumor accumulation [1]. Consequently, substantial efforts have been directed towards the creation of nanocarriers to facilitate controlled drug release and enhance the effectiveness of cancer therapy with minimum side effects. To get rid of these detrimental effects, various new drug carriers, such as porous nano-silica, DNA, liposomes, metal nanoparticles, quantum dots, *etc.* were targeted by worldwide scientific communities to fulfill this purpose [2-6]. Although, the limitations owing to their drug loading efficiency, greater toxicity, non-biodegradability and inferior biocompatibility restricts their applications in biomedical field. In addition, the inability of release of drug in controlled manner makes them incompetent as potential therapeutic agents. On the other hand, porous materials, by virtue of their structure, can serve as competent materials in biomedical application, which includes, drug delivery, tissue engineering, immune engineering and fabrication of biomedical devices [7-11]. Particularly in the realm of drug delivery, the drug molecules get entrapped in the pore of the porous materials, favouring the release of drug molecules in controlled and sustained manner over time [9,12].

Commonly employed porous polymeric materials in the biomedical field are typically amorphous, lacking optimized pore levels for the encapsulation of drugs within their matrix. An instance of this is poly(lactide-*co*-glycolide) acid (PLGA), extensively used as a biomaterial in both pre-clinical and clinical studies [13-16]. Nevertheless, these materials are frequently amorphous, lacking well-defined porous structures, which necessitates the optimization of biomaterial synthesis to maximize drug encapsulation. Conversely, high-fidelity crystalline materials exhibit well-defined pore structures, potentially making a substantial impact in various biomedical fields [17-19]. Interestingly, beyond biomedical applications, porous materials have garnered significant attention in the realms of adsorption,

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separation, catalysis and energy storage [20,21]. As an illustration, a category of porous materials known as metal–organic frameworks (MOFs) has had a substantial influence in the field of energy storage [20,22,23]. Nevertheless, these porous materials have not demonstrated a comparable impact in the biomedical field, primarily due to the biological toxicity associated with certain metals present in their structure, particularly in the case of MOFs. As an alternative, covalent organic frameworks (COFs), possessing a similar level of porosity, have been developed in the past decade. These COFs offer the added advantage of thermal and chemical stability [24-27]. Furthermore, a greater proportion of COFs may demonstrate better biocompatibility in comparison to MOFs, attributed to the absence of metals in their structures. COFs represent a promising category of porous materials synthesized through covalent bonds. Notably, their 2D or 3D porous crystalline structure, with a specific spatial organization of subunits, imparts them with sought-after properties. These properties encompass structural diversity, low density, porous architecture, high surface area, the absence of heavy metal ions and tunable pore sizes [24,28,29]. Furthermore, covalent bonds like B–O and C–N, commonly found in the construction of COFs, contribute to their chemical and temperature stability. Notably, the internal structured order of COFs sets them apart from other types of covalent polymers, where organic molecules connected *via* covalent bonds tend to exhibit a tendency toward short-range structured order, resulting in amorphous or semi-crystalline materials. Interestingly, the growth of this short-range structured order through slow and reversible reactions between organic ligands or building blocks leads to the development of long-range structure and consequently, the formation of COFs. Additionally, features such as rigidity play a role in shaping the regular structure of COFs [24,28,29]. These criteria necessitate a few fundamental prerequisites for the synthesis of the regular structure of COFs, including the careful selection of reactions and rigid building units. The molecular length and types of building units significantly impact the pore size and porous structure of COFs. In light of these considerations, the reversible reactions have generally been embraced as the preferred synthetic route for producing COFs [30].

Since their inaugural identification in 2005 by Yaghi *et al.* [18], considerable efforts have been devoted in advancing the understanding of linkages for covalent organic framework (COF) formation, refining synthetic methodologies, devising strategies for loading therapeutic agents, functionalizing COFs for targeted delivery to tumors. In addition, profound attention has been directed in modern therapeutic treatments, like photodynamic therapy (PDT), photothermal therapy (PTT), sonodynamic therapy (SDT) utilizing COFs as responsive material. COFs can typically be synthesized by covalently connecting diverse organic monomers through various synthetic techniques, including solvothermal synthesis, sonochemical synthesis, ionothermal synthesis, mechanochemical synthesis and light-promoted synthesis. The present review article highlights the advantages of COFs compared to MOFs and explores various synthetic pathways for producing COFs, as well as their prospective use in cancer treatments. The delivery of cancer therapeutic drugs into the precised tumor site has always remained as challenge to the scientific communities involved in the cancer therapy research. The self-assembly of COFs can provide suitable pores for carrying drug and facilitate sustained release. In addition to chemotherapy, other therapeutic treatments like PDT, PTT, SDT and the combination between different therapies in treating cancer can be found in the present review.

Advantages of COFs: COFs provide several advantages, making themselves competent in various biomedical applications including cancer therapies (Fig. 1). For example, (i) the composition and structure of COFs are entirely determined by the reactive functional groups and geometry of the organic monomers. The judicious selection of functional monomers can predict and control their chemical composition, topological structure, pore size and functionality [31] (ii) COFs exhibit high crystallinity, in contrast to amorphous materials as revealed by PXRD patterns, a more efficient alternative to single-crystal analysis. The highly crystalline nature of COFs provides long-range order and definite crystal structures, making themselves efficient in different therapeutic applications (iii) COFs inherently possess pores and high specific surface areas, facilitating the loading of guest therapeutic drugs. Thus, COFs can appear as excellent nanocarrier for delivering drug to the infected site (iv) COFs appear as robust consisting of covalent bonds with excellent thermal and chemical stability. The structural integrity of the COFs is maintained irrespective of the medium. This type of stability is essential for biomedical application as the materials are transported to the biological medium (v) COFs contain organic moiety devoid of any metal in its structure. Thus, the toxicological effects associated with metal gets eliminated in using COFs in biomedical field. In addition, the organic nature of the material enhances biocompatibility making themselves competent as therapeutic carrier in various medical applications; and (vi) due to the diversity of organic reactions, COFs are highly versatile in terms of functionalization. Beyond various functionalized monomers, covalent-bonding-driven COFs can

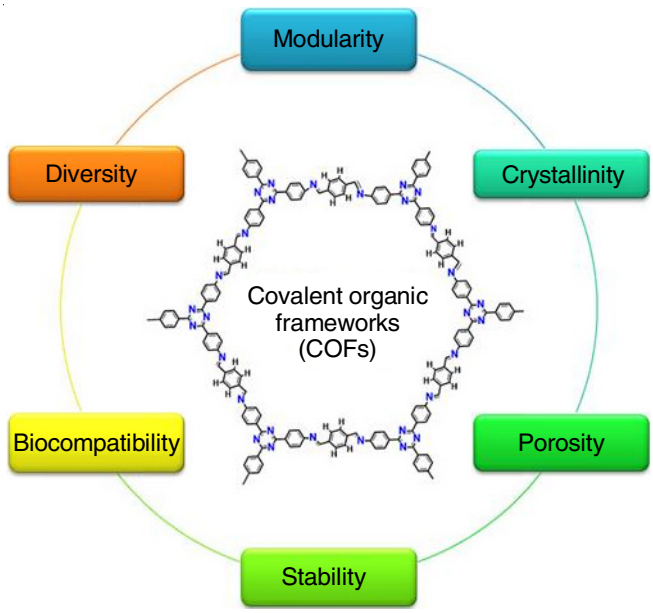

Fig. 1. Diagram displaying advantages of COFs

tolerate a wide range of organic transformations. Post-synthetic modification (PSM) further enhances the versatility, allowing the introduction of a variety of functional organic molecules into the COF framework.

Current status of research in covalent organic frameworks in cancer therapy: Fig. 2 represents the global research executed during the last ten years (2014-2023) on covalent organic frameworks in cancer therapy. Total 328 articles were published during the time span. As indicated from Fig. 2a, the number of publications increased yearly, proving an increased interest of global scientists towards applications of COFs in cancer therapy. However, in 2023 the decreased publications might be associated with the consideration of incomplete year during the analysis. The most active 10 countries publishing articles on the said topics during this period has been plotted in Fig. 2b. As can be seen, P.R. China published highest number of articles followed by USA, India and Iran. Whereas Fig. 2c represents the most active subject areas publishing articles on COFs in cancer therapy.

Synthetic strategies of COFs: To achieve a well-organized and crystalline COFs, two key criteria must be met in the design of its building blocks: firstly, the COF formation reaction should be reversible, demanding the inclusion of reactive groups that facilitate dynamic covalent bond formation. This necessitates the absence of irreversible side reactions and ensures that the reaction system comprises only interchangeable monomers, oligomers and polymers under thermodynamic control. Secondly, the building blocks should exhibit conformational rigidity and the direction of bond formation must be discrete to preserve the geometry of the building blocks within the COF [32,33].

The production of crystals in COFs has been accomplished through various approaches that establish the optimal balance between the thermal reversibility of the linking processes and the dynamics of the corresponding crystals [34]. The main components that make up their spine are composed completely of light elements, including oxygen, silicon, hydrogen, boron, carbon and nitrogen, among others. As a result, COFs have evolved to comprise organic units joined by robust connections, such as -B-N, -B-O-Si-, -B-O-, -C-N- and so on [35,36].

The reticular chemistry involves strong bonding to join molecular basic components to form crystalline open structures. It has greatly extended the range of chemical compounds and materials such as organometallic compounds, MOFs, COFs and so on. The linking processes in COFs and MOFs had to be developed to solve the crystallization challenge, resulting in crystalline products whose structure could be determined unequivocally using X-ray and electron diffraction analysis tools.

In recent years, different approaches for creating regular materials by relying on reversible processes have sparked a great deal of attention [37-39]. Highly potent methods to regulate covalently linked substances produce superior crystallinity and sustainability in COFs while tolerating chemical functionalities with reversible reactions. The methods for obtaining crystalline COFs may be divided into three categories, *i.e.* (i) based on

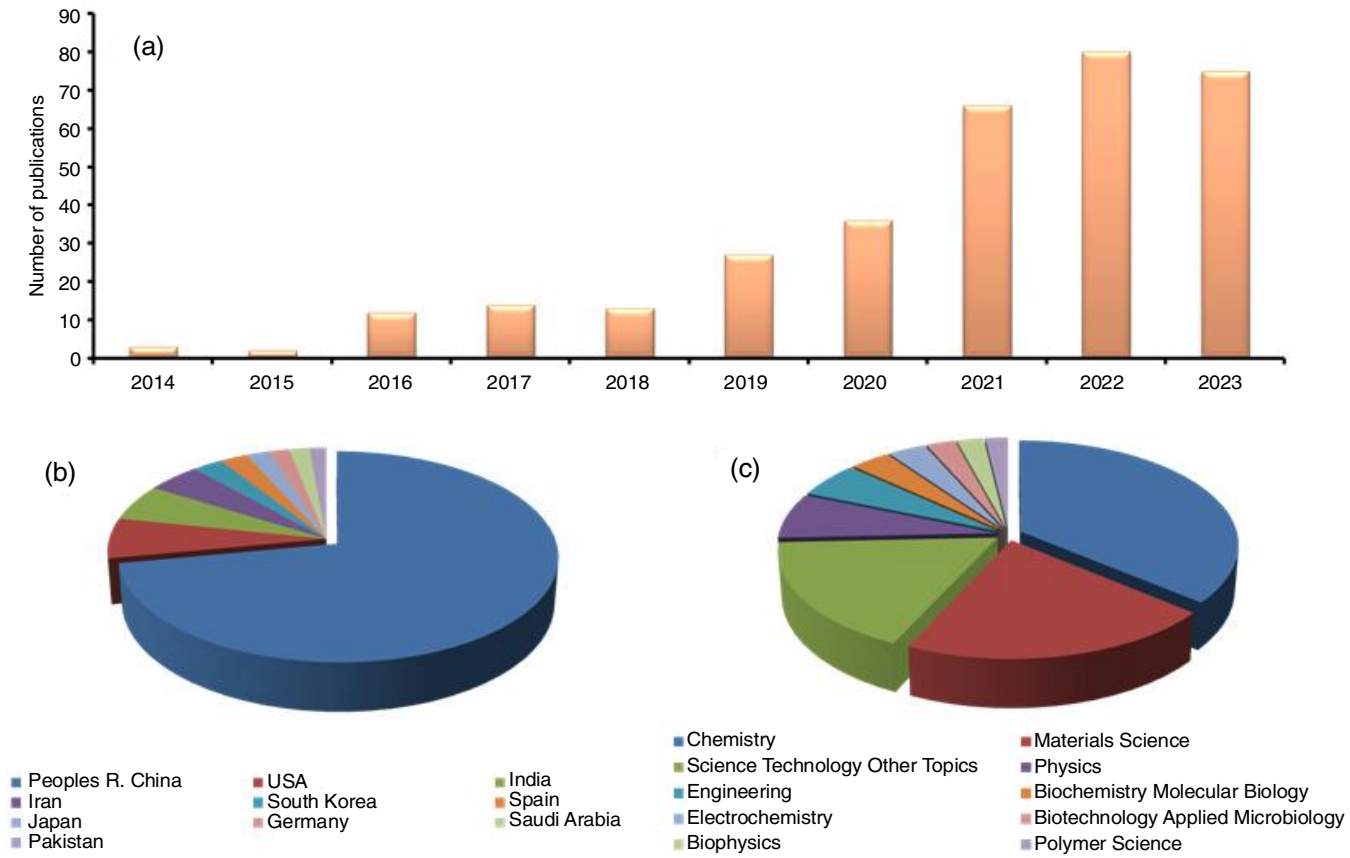

Fig. 2. (a) Year-wise growth of covalent organic frameworks in cancer therapy research in the last ten years (2014-2023), (b) Most productive ten countries doing research in covalent organic frameworks for cancer therapy, (c) Top ten areas publishing articles on covalent organic frameworks for cancer therapy

the reversible reactions, (ii) based on pre-orientation of construction materials and (iii) based on a single step synthesis route [37-39].

In recent years, the most popular approach to achieve crystalline COFs is to crystallize them *via* reversible covalent bond formation. Essentially, reversible reaction allows continual bond creation and breaking and furthermore, defect correction during the construction of the building blocks. Therefore, the system can eventually reach the thermodynamic equilibrium conditions for the final product, whereas in pre-orienting the construction components, the initial or primary step is isolated from the development of strong covalent bonds [40]. Weak connections are employed to align the building blocks, allowing for simple crystallization and reversibility of the ordering process. In a subsequent phase, stronger bonds are used to link the building components. Basic components are usually aligned through utilizing strong connectivity to other basic units and order is accomplished *via* a small number of structural degrees of freedom [41]. This technique has also been used to improve the crystallinity of COFs through reversible reactions *via* decreasing the number of potential conformers [40,41].

To date, numerous synthetic approaches have been identified, including solvothermal, ionothermal, mechanochemical, microwave-assisted and ultrasonication processes. The key to achieve highly ordered covalent networks lies in regulating the thermodynamic equilibrium during covalent bond formation. Specifically, factors such as reaction media and conditions (temperature, pressure and the presence or absence of templates) play crucial roles in the formation of thermodynamically stable polymeric crystalline architectures. In the realm of reaction media, mixed solvent systems and molten metal salts have been devised to create solvothermal and ionothermal conditions, respectively, for COF synthesis. The microwave reactions conducted under solvothermal conditions offer a rapid route for COF synthesis. In contrast to these bulkier methods, the exploration of COF monolayers or films involves reactions on substrates like metal surfaces and graphene sheets.

Solvothermal synthesis technique: In solvothermal method, a Pyrex tube is employed to contain monomers and mixed solvents. The system undergoes degassing through multiple freeze-pump-thaw cycles. Following this, the tube is sealed and subjected to a specific temperature for a defined duration, typically spanning 3-7 days. Preserving porosity in the structure hinges on carefully controlling the reaction pressure. It is equally crucial to manage various factors such as solubility, reaction rate, crystal formation, self-healing and the rate of crystal growth to ensure the successful formation of crystalline covalent organic frameworks (COFs) [42].

Achieving highly crystalline covalent organic frameworks (COFs) involves a delicate balance between framework formation and crystallization, with solvent combinations and ratios playing pivotal roles. For boronate ester and boroxine-linked COFs, various solvent combinations including dioxane-mesitylene [43], DMAc-*o*-dichlorobenzene [44] and THF-methanol [45], have proven effective. Additionally, a dioxane-toluene mixture has been utilized for the synthesis of borosilicate COFs. In case of imine-linked COFs, dioxane–aqueous acetic acid serves as solvent [46], while mesitylene–dioxane–aqueous acetic acid has demonstrated effectiveness for hydrazone linked COFs [47]. Regardless of the specific solvent system, maintaining an appropriate concentration of building blocks is crucial for the reaction to proceed under thermodynamic control. The suitability of building blocks, whether fully soluble or completely insoluble, for COF synthesis requires further experimental investigation [44,48]. Also, to ensure the reversibility of the crystal formation, it is essential to maintain a suitable temperature. In general, COFs have been found to be prepared at temperatures in the range 85-120 ºC. This choice is dictated by the chemical reactivity of the building blocks. To allow the water molecules to be present in the structure, a closed reaction environment is required because that could initialize the reverse reaction in the system.

Microwave synthesis: Boronate ester linked COFs like COF-5, COF-102, 2D COF-5, 3D COF-102, *etc.* have been produced successfully by Cooper *et al.* [49] and Dogru *et al.* [50], who used a microwave reactor for dynamic covalent reactions. The advantages of microwave synthesis over solvothermal methods are noteworthy. For example, (i) microwave synthesis is a fast process of preparation of COFs, thus favouring a large scale synthesis whereas solvothermal synthesis requires almost 72 h, the microwave process takes approximately 20 min, which is evidently significantly faster; (ii) a sealed vessel is not required for the microwave synthesis; (iii) the impurities and residues entrapped in the framework structure can be easily removed by the microwave solvent extraction more efficiently, which will undoubtedly enhance porosity. Furthermore, microwave heating has been shown to improve the properties of COFs, such as the surface area, *e.g.* BET surface area as high as 2019 $m^2 g^{-1}$ was reported in case of microwave synthesis technique, which is found to be somewhat higher than that observed for the solvothermal synthesis procedure. Also, factors such as removing copolymers from COFs more efficiently, producing COFs with high permeability are other advantages of microwave solvent extraction techniques [51]. The microwave protocol could be an intriguing replacement for the solvothermal method.

Ionothermal synthesis: COFs like CTF-1, CTF-2 (CTF stands for covalent triazine framework) have been prepared by using ionic liquid/molten salt like $ZnCl_2$ in ionothermal process. A thick-walled tube, like Pyrex tube, heat (400 ºC) and pressure are the necessary ionothermal conditions for COFs synthesis. In this process, they serve both as solvent as well as an accelerator. After being cooled to room temperature, the resultant mass is crushed and then thoroughly cleaned with water [42,52,53]. The procedure begins by agitating the powder in diluted HCl for 15 h to eliminate $ZnCl_2$ followed by filtration, washing with water and THF and ultimately drying under vacuum. Additionally, the use of an ionic liquid as solvent provides a convenient, moderate and environmentally friendly approach for synthesizing 3D COFs. For instance, the formation of 3D-IL-COF-1 can be achieved in just 3 min, demonstrating a rapid reaction process facilitated by the ionic liquid. This method has successfully yielded a series of 3D COFs incorporating ionic liquid. Furthermore, the ionic liquid was found to be reusable, with acceptable activity loss of crystalline materials. This

research not only introduces an innovative synthesis method for COFs but also opens avenues for environmentally friendly large-scale COF production in the industry [51].

Mechanochemical synthesis: Mechanochemical synthesis route can ease the difficult procedures used in both microwave and solvothermal processes (*e.g.* reaction in a sealed Pyrex tube, inert environment, appropriate solutions, pressure and temperatures for crystallization, *etc.*). This process is a straightforward synthetic route for COF synthesis. In mechanochemical synthesis, the monomers are taken in a mortar and crushed with a pestle at ambient temperature. A small amount of catalyst solution was also transferred to the mortar during crushing the subunits to improve the effectiveness of the reagent. Also ketoenamine, imine and hydrazine COFs are synthesized using mechanochemical synthesis [42,54]. It has been reported that crushing the diamine molecules along with *p*-toluenesulfonic acid and a little amount of water and then adding 1,3,5-triformylphloroglucinol under 170 ºC for 1 min produces excellent quality COFs with high surface area. Straightforward, cost-effective and environmentally friendly approaches are major remarkable advantages of the mechanochemical COF synthesis. Inspite of being quick and simple, mechanical grinding of COF precursor reactants results in either amorphous or weakly crystalline structures [54].

Sonochemical method: The sonochemical method presents an alternative strategy to overcome the constraints associated with solvothermal synthesis. Clouds are formed and the solution goes through cavitation, a process where bubbles are formed and then collapsed, by exposing it to ultrasound. This cavitation leads to exceptionally high temperature and pressure within the solution, thereby accelerating the chemical reaction [42,51]. For example, the reactions involving COF-1 and COF-5 can be scaled up to a 0.5 L batch size with a reduced reaction time of 0.5-2 h, resulting in a significant increase in BET surface area, reaching up to 2122 $m^2 g^{-1}$ [42,55,56].

Vapour assisted synthesis: Recently, the vapour assisted COF synthesis method has also been applied to produce thin COF films. For example, COF precursors were mixed in appropriate solvent mixture (acetone and ethanol). This mixture was then drop-casted on a substrate and then subsequently placed in a desiccator containing a 1:1 ratio of mesitylene and dioxane which was used as a reservoir mixture. After 72 h, a smooth and homogenous COF film was produced at ambient temperature. As a result, the solvent reservoir strongly influences the crystallinity of the products. The thin film growth was proved on a variety of surfaces, with a variety of COFs and with the ability to adjust the depth of layer by altering the quantity of water [42,54].

Light promoted synthesis: Harnessing solar light/energy has emerged as a cutting-edge approach for the synthesis of covalent organic frameworks (COFs). Remarkably, within 3 h of reaction time, light serves as a catalyst, promoting the formation of highly covalently linked and crystalline COF materials. As an illustrative example, the synthesis of COF (hcc-COF) involved the combination of hexaketocyclohexane octahydrate and 1,2,4,5-benzenetetramine tetrahydrochloride in various solvents, conducted within a quartz tube under simulated visible light with a wavelength range of 200-2500 nm in an air atmosphere. To facilitate effective imine condensation, a small quantity of water and acetic acid were introduced as co-catalysts. Under the luminous conditions, the presence of COF was confirmed. The resulting hcc-COF exhibited outstanding electrical properties, boasting a conductivity of 2.22×10^{-3} Sm^{-1}, attributed to its extended conjugated framework that facilitates electron transport [42,57].

Synthesis of monolayers on metal surfaces: In contrast to the intricate synthesis process outlined earlier for COFs, the condensation of building blocks on a metal surface leads to the formation of monolayers of COF-1 and COF-5 [58]. The creation of covalently bound SCOF-1 and SCOF-2 (surface covalent organic framework) nano-architectures involves sublimating the building blocks from heated molybdenum crucible evaporators onto a pristine Ag (111) surface in an ultrahigh vacuum environment. Examination of surface texture through scanning tunneling microscopy (STM) reveals the presence of hexagonal pores accompanied by a limited number of irregular five-, seven- and eight-membered pores. Achieving defect free monolayers on a metal surface may necessitate meticulous adjustment of reaction conditions, enhancement of building block purity and the use of a suitable single-crystal metal substrate interface to guide the alignment of the building blocks.

Synthesis of monolayers on a highly ordered pyrolytic graphite (HOPG) surface: In this experimental setup, a highly ordered pyrolytic graphite (HOPG) surface was employed instead of a metal surface for the fabrication of monolayer COFs [59]. Biphenyldiboronic acid (BPDA), 1,4-benzene diboronic acid (BDBA) and 9,9-dihexylfluorene-2,7-diboronic acid were deposited onto the HOPG surface from their tetrahydrofuran (THF) solutions. Subsequently, the HOPG samples were subjected to heating in a sealed autoclave at 150 ºC for 1 h to yield COF monolayers. The innovative part of the process is using $CuSO_4 \cdot 5H_2O$ acting as a water reservoir that regulates chemical equilibrium, which is crucial for making quality monolayers.

In absence of $CuSO_4 \cdot 5H_2O$, the coverage of HOPG surface by the monolayer was only around 7%. This coverage significantly increased to 98% in the presence of $CuSO_4 \cdot 5H_2O$. The water molecules released from $CuSO_4 \cdot 5H_2O$ during the heating process serve as agents for manipulating equilibrium, pushing the dehydration reaction backward. This promotes the defect remedy process, resulting in the formation of a highly ordered COF network. During the cooling process, these water molecules can be reabsorbed by $CuSO_4$, preventing the decomposition of the SCOFs.

Synthesis of oriented thin films on graphene surfaces: COFs produced through the mentioned techniques typically exist in the form of either insoluble powders or monolayers, posing challenges for reliable interfacing with electrodes or integration into practical devices. Consequently, the development of COF thin films on a substrate holds significant scientific interest and technological relevance. Dichtel and collaborators [60-62] have documented the synthesis and characterization of oriented 2D COF films on single-layer graphene (SLG on SiO_2) surfaces. In the solvothermal reaction systems involving SLG/SiO_2, well-oriented COF thin films emerge on the SLG

surface. Diverse COF films, including COF-5, TP-COF, NiPc-COF, HHTP-DPB-COF and ZnPc-PPE-COF, have been successfully prepared on graphene, with the thicknesses adjustable based on the reaction time. Grazing incidence X-ray diffraction measurements indicate that these thin films exhibit high crystallinity and the layers within them are aligned in a vertical orientation.

Application of COFs in cancer therapy

Drug delivery: Conventionally used chemotherapy drugs, like doxorubicin (DOX), paclitaxel, cisplatin appear as inferior in targeting tumor site as well as enhanced side effects [63]. However, the delivery of these drugs through nanocarriers might help to overcome the difficulties associated with the conventional drug delivery procedure. The nanodimensional drug preferentially gets accumulated at the tumor site associated with enhanced permeability and retention (EPR) effect [64]. The side effects, as a consequence, get minimized with significant improvement in the activity of the therapeutic drugs. In recent years, COFs have proved themselves as very promising nanoplatforms in delivering cancer therapeutics, owing to their attractive properties, such as high porosity, low toxicity and metal free identity. The channels formed by the organization of the organic molecules create suitable pocket for accommodation of the drug molecule restricting impulsive leakage of the molecule and thus favouring the accumulation of drug at the desired tumor site. Thus, drug delivery host-guest systems utilizing COFs has well been explored by worldwide scientific communities to have novel systems for cancer therapeutics. Zhang *et al.* [65] reported water dispersible polyethylene glycol (PEG) modified curcumin and amine functionalized COFs for efficient *in vitro* as well as *in vivo* drug delivery systems. The particle size was optimized below 200 nm, making itself as potential candidate for cellular uptake. The nanocomposites PEG-CCM @APTES-COF-1) appeared as biocompatible favouring controlled release of drug due to the formation of micellar array of the COFs. The self-assembly of the curcumin regenerated using PEG and amine modified COF-1 results in the formation of micellar structure for efficient drug delivery. In another study, Liu *et al.* [66] synthesized a COF based DOX delivery system *via* room temperature condensation reaction of 1,3,5-*tris*(4-aminophenyl)benzene (TAPB) and 2,5-dimethoxyterephthaldehyde (DMTP). The UV-Vis analysis revealed a loading of 32.1% DOX with respect to the COF. In addition, the release of drug was found to be pH dependent. Only 40% of loaded drug was found to be released at pH 7.4 during the first 2 h, whereas, almost complete unloading was done during this period at pH 5 or 6.5. At lower pH, the destruction of the COF structure is well evident from this investigation. Liu *et al.* [67] prepared redox active nanodimensional PEGylated COFs for efficient delivery of DOX molecule. The COFs were formed from the reaction between benzene 1,3,5-tricarbaldehyde and 4,40-dithiodianiline. The self-assembly of the disulfide containing COFs (SS-COF) and Pluronic F68 resulted in the formation of nanocarrier, F68@SSCOF. At pH 5, DOX was released from the redox active system when 10 mM GSH was added to PBS, while non-responsive COFs did not show any significant release. The same results were followed in HepG2 cells with both the responsive and non-responsive DOX loaded COFs. Wang *et al.* [68] focused on the covalent organic polymers for pH responsive drug delivery. A biodegradable polymer was synthesized from the condensation between 4,40-trimethylene dipiperidine with acryloyl *meso*-tetra(phydroxyphenyl)porphine, resulting in the formation of β-amino esters. A shell like scaffold was prepared using PEG shell; a spherical morphology results with average diameter of 30-40 nm. The release of DOX drug in PBS medium was found to be enhanced at lower pH 6 compared to 7.4, signifying the destruction of β-amino esters scaffold in the lower pH of medium. The drug delivery system was fabricated from tri(4-formylphenyl)amines with benzidine. The as-prepared COFs was found to display photoluminescence with emission of bright blue light. The π-π interaction between DOX and COF resulted in the formation of photoluminescence. The efficient unloading of DOX molecule (85%) occurred at pH 5 compared to the neutral medium at a span of 72 h. In MTT assay, although, the COF itself appeared as non-toxic towards cancer cells, the DOX loaded COF was found to damage severely. A new class of COFs, named nuclic acid-gated COF nanosystem was investigated by Gao *et al.* [69] for cancer cell imaging and drug delivery. For this purpose, porphyrin COF nanoparticles were utilized for DOX delivery. The absorption of the single stranded DNA occurs at the DOX containing COF surface, which can be easily monitored by fluorescence and release drug for chemotherapeutic treatment. The drug loaded COF were compared for both the normal cells (MCF-10A) and cancer cells (MCF-7). As observed high fluorescence signals were obtained for drug loaded MCF-7 cells, but for MCF-10A no detectable signal was found.

Photodynamic therapy (PDT): Conventional chemotherapeutic treatments for cancer suffers from several shortcomings, such as, inferior activity, high cost and various side effects. On the contrary, the phototherapy offers a high efficacy, minimal side effects, at an affordable cost. In photodynamic therapy, a photo-sensitizer generates reactive oxygen species (ROS), on irradiation with photon of suitable wavelength. This ROS species have potential to destruct the infected cell [70]. The use of COFs, in photodynamic therapy is very much advantageous associated with the large pore size of the channels for favourable encapsulation of large sized molecules like, porphyrins, phthalonitriles. In addition, the metal free structure of COFs offers good biocompatibility, which is quite difficult to achieve with MOF, due to possible toxicity of the metal [71].

Several COFs were synthesized for PDT to overcome the shortcomings of photosensitizers alone such as inherent hydrophobicity and easy agglomeration. Lin *et al.* [72] reported a 3D porphyrin based COF system to serve as potential species for photodynamic therapy. The porphyrin based system appears as efficient in ROS generation with retention of the original 3D structure throughout the procedure. In another work, a new N-containing COF was investigated for PDT by Bhanja *et al.* [73]. The efficacy of the material was studied by comparing the ROS generation in various cancer cell lines at varying pH. Guan *et al.* [38] obtained boron-dipyrromethane (BODIPY) based COFs from the condensation reaction between amino containing BODIPY and –CHO containing NCOF LZU-1 with

a uniform size of 110 nm. The as prepared COFs were found to possess high efficacy in $^1O_2$ generation, proving itself as potential agent in PDT as revealed by *in vitro* analysis. In addition, properties like cellular uptake, cell apoptosis pathway and subcellular localizations were also investigated. The processes were found to be energy dependent and the requisite energy was gained from the aerobic glycolysis of the tumor cells. The *in vivo* investigation showed high efficacy of photodynamic therapy with minimal damage observed in the infected organ. During the PDT, near infrared light was utilized, as it offers significantly lower toxicity with high penetration into the tissue. Zhang *et al.* [74] reported origination of COF nanodots from simple exfoliation of a two dimensional porphyrin based COF. *In vitro* experiments with HeLa cells proved high efficacy of the PEG coated COF nanodots in PDT. The COF nanodots also displayed excellent stability and high efficiency in killing cancer cells during *in vivo* experiments with mice bearing H22 tumor. In addition, the nanodimensional size of the PEG-COF favoured its release through urination without associated *in vivo* toxicity. This study revealed stabilization of 2D COF through conversion into nanodots of efficient PDT material. A novel multifunctional COF was reported by Tao *et al.* [75] to serve in PDT as well as oxygenation of tumor. This fluorinated COF was synthesized from *meso*-5,10,15,20-tetra(4-hydroxylphenyl) porphyrin (THPP), PEG and perfluorosebacic acid (PFSEA). As PFSEA contained significant amount of perfluoro-15-crown-5-ether (PFCE), the resulting PFCE@THPPpf-PEG significantly enhanced the oxygenation of tumor with associated PDT effect.

While studing on employing COFs for PDT is still in its nascent stages, the remarkable photodynamic and sensitization performance exhibited by these frameworks has garnered significant attention. The PDT efficacy can be tailored by modifying the dimensions, composition and structure of COFs. To fully harness the potential of COFs for PDT in both design and fabrication, two crucial aspects must be thoroughly considered. Firstly, the limited lifespan of nanomaterials due to poor stability before executing their intended task may pose challenges *in vivo*. Therefore, it is imperative to address and enhance the stability of COFs during the material design and fabrication processes. Secondly, the impact of photoquenching arising from π-π stacking between COF layers can influence the effectiveness of PDT. For optimal PDT efficiency, it is highly recommended to focus on the development of COF materials that possess both high electron-transmission efficiency and a high electron-hole utilization rate [76].

Photothermal therapy (PTT): Photothermal therapy represents a contemporary approach to antitumor treatment, wherein focused radiation stimulates a photosensitizer molecule, leading to the photoablation of tumor cells and subsequent cell death. This method appears as very promising in the treatment of tumors owing to their perceived biocompatibility and efficiency as phototransforming agents [77-79]. Various nanomaterials currently under investigation exhibit high photothermal conversion efficiency, including conjugated polymers, plasmonic metal nanostructures, semiconductors and ferromagnetic nanoparticles. Graphene, with its notable absorption in the near-infrared (NIR) region and high heat generation capability, is also considered a potential photothermal agent [80-82]. Additionally, covalent organic frameworks (COFs) emerge as promising candidates due to their unique 2D atomic structures, bearing resemblance to graphene. Unlike closed porous systems that limit heat flow and create thermal resistance, COFs facilitate the rapid transport of generated heat to the surroundings through open pore channels. This distinctive feature makes the use of COFs an attractive approach for the development of organic hyperthermia agents. The use of COFs as delivery vehicles for photothermal conversion agents (PTAs) provides several advantages. This includes the potential for enhanced photothermal conversion efficiency and improved accumulation of PTAs in the tumor microenvironment. This targeted delivery can contribute to minimizing side effects associated with the treatment.

Certain COFs have been intentionally designed for use in photothermal therapy. Tan *et al*. [83] utilized a self-sacrificial template to fabricate a COF incorporating an integrated Fe_3O_4 core with efficient photoconversion capabilities. This design facilitated the rapid elimination of HeLa cells *in vitro*. The researchers successfully controlled the shell thickness and sphere cavity size of the COF, which exhibited low inherent cytotoxicity. In a subsequent study by same researchers [84], the first reported demonstration of an imine-based COF with photoconversion ability was achieved, again utilizing a Fe_3O_4 core. This capability was attributed in part to the COF's layered π-π stacking. While the COF shell enhanced light absorption and exhibited a substantial and rapid temperature change, several challenges were encountered. In another investigation, Liu *et al.* [85] synthesized a pH-responsive porphyrin-based system, termed MnO_2/ZnCOF @Au&BSA, employing MnO_2 nanosheets as a template to mediate the preparation of zinc COF (ZnCOF). This nanoplatform exhibited an "off–on" fluorescence imaging property, with no significant fluorescence signal detectable under physiological conditions due to the aggregation-caused quenching effect through π-π stacking interaction, effectively overcoming signal interference by background noise. Upon the pH-responsive decomposition of ZnCOF in cancer cells with a pH 5.5, the luminescence signal of the scattered fluorescence dye could be activated. *In vivo* studies demonstrated effective anticancer efficacy, with a tumor growth suppression rate of 79.5% and no apparent toxicity to normal cells. Guo *et al.* [86] reported a cationic radical-containing COF named Py-BPy$^{+\bullet}$-COF/PEG, with a layered structure through *in situ* chemical reaction followed by quaternization and one-electron reduction of 2,2′-bipyridine-based COF (Py-BPy-COF). This radical containing COF exhibited good stability and significant absorption in the near-infrared (NIR) region. *In vitro* and *in vivo* cytotoxicity studies suggested that Py-BPy$^{+\bullet}$-COF/PEG could effectively inhibit tumor cells through photoacoustic imaging guided PTT.

Sonodynamic therapy (SDT): Sonodynamic therapy (SDT) is a promising non-invasive modality that relies on ultrasound (US) irradiation, offering the advantage of high tissue penetrating depth compared to light-triggered therapies [87]. Under ultrasound, reactive oxygen species (ROS), including singlet oxygen ($^1O_2$) and hydroxyl radicals (OH$^\bullet$), can be gene-

rated, leading to cancer cell death. In recent study, COF nanobowls with a unique on-off design were developed using a hard template method. The resulting RB@COFs-MnOx-PEG (RCMP) nanobowls exhibited high crystallinity and ordered porous structures, efficiently loading the nanosensitizer Rose Bengal (RB) [88]. Modification with manganese oxide (MnOx) and polyethylene glycol (PEG) resulted in the suppression of SDT under normal physiological conditions. The high concentration of glutathione (GSH) in the tumor microenvironment (TME) caused the degradation of surface MnOx, leading to the conversion of RCMP from the 'off-state' to the activatable 'on-state.' The catalytic nature of MnOx enhanced SDT therapy efficacy by facilitating intracellular oxygen generation and GSH depletion, promoting ferroptosis in cancer cells through the accumulation of lipid peroxidation (LPO) and inactivation of GSH peroxidase 4 (GPX_4). The unique spherical design of nanobowls facilitated cellular uptake and tumor accumulation efficiency, synergistically enhancing RCMP performance in killing tumor cells and preventing osteosarcoma progression. *In vivo* evaluation demonstrated that, under ultrasonic irradiation, RCMP resulted in ferroptosis-augmented SDT in an osteosarcoma model, achieving a high degree of tumor inhibition (74% *versus* 30% in the RCMP group without ultrasonic irradiation). Additionally, another study showed that ultrasonic irradiation of porphyrin-incorporated COFs (TAPB-DMTB-COF) resulted in a significantly higher reduction in tumor weight and volume compared to various control groups, indicating the promising anti-tumor efficacy of COF-based SDT [89].

Combination cancer therapy: A sole therapeutic approach sometimes appeared as inadequate therapeutic effects, as certain tumor cells exhibits resistance towards single therapeutic module. This resistance results in unsuccessful eradication and tumor recurrence. Consequently, the combinatorial cancer therapies, consisting of two different therapeutic modules appear as promising in treating cancer effectively. This approach involves integrating various therapeutic agents and anticancer mechanisms to create a multimodal synergistic therapy, thereby leveraging the strengths of different modalities and mitigating the shortcomings of each.

In the realm of nanomedicine, combining chemotherapy with PTT as a modality for delivering chemotherapy drugs and photothermal agents (PTAs) into the tumor proves to yield superior therapeutic outcomes. This is attributed to the heat generation induced by PTAs, which, upon local infrared light irradiation, aids in the destruction of cancer cells. Wang *et al.* [90] were the first to introduce the utilization of cyanine-assisted aqueous exfoliation to improve the dispersibility and aqueous stability of covalent organic frameworks (COFs). As cyanines are recognized as potential theranostic agents, the water dispersible nanocomposites (COF@IR783) resulting from the combination of cyanines and porphyrin-based COFs (TP-Por) exhibit enhanced absorption in the NIR-I region (at 808 nm), significant light-to-heat conversion efficiency (15.5%) and proficient photoacoustic imaging capability. Furthermore, these nanocomposites serve as effective drug-delivery carriers, accommodating the loading of the anticancer prodrug *cis*-aconityl-doxorubicin (CAD) (referred as COF@IR783@CAD). This combined formulation synergistically induces cancer cell death *in vitro*. The efficacy of chemotherapy is significantly compromised by the diversity and complexity of tumors. However, exploiting the inherent characteristics of covalent organic frameworks (COFs) allows them to integrate stimulus-triggered drug delivery and combination therapies within the challenging tumor microenvironment (TME). In a ground-breaking approach, Liu *et al.* [89] reported pH-responsive porphyrin-based COFs through a two-step Michael-addition reaction, employing a one-pot process for combination therapy. The inclusion of cross-linked biodegradable α-amino ester (BAE) groups imparts pH-responsiveness to the nanosystem, while THPP linker units ensure stability in neutral environments and enable light-triggered reactive oxygen species (ROS) generation. Consequently, the THPP–BAE–PEG/DOX nanoplatform exhibits intelligent disintegration in response to the acidic TME, facilitating the release of doxorubicin (DOX). Moreover, under 660 nm LED irradiation (5 mW cm^{-2}, 30 min), the dissociated THPP contributes to cancer cell death, resulting in significant synergistic antitumor effects compared to mono-chemotherapy or mono-photodynamic therapy (PDT). In pursuit of efficient tumor accumulation, the same research group designed a novel class of COFs with redox-responsive properties. These COFs serve as therapeutic nanoagents by cross-linking two therapeutic functional molecules, THPP and succinic acid-derived cisplatin antitumor prodrug *cis*-Pt(IV)SA, *via* a two-step esterification strategy. The resulting THPP-Pt-PEG COFs exhibit efficient tumor passive homing and function as a glutathione (GSH)-responsive nanoplatform, undergoing cleavage in a reductive environment to effectively alleviate tumor hypoxia. This facilitates subsequent drug release and PDT (660 nm LED light, 5 mW cm^{-2} for 45 min at 24 h post intravenous injection), yielding a remarkable *in vivo* synergistic therapeutic effect that inhibits tumor growth.

The photothermal effect at tumor sites has been shown to induce hypoxic relief within the tumor. The combination of PDT and PTT has proved itself very much promising in combination therapy as oxygen is not mandatory for localized hyperthermia. Wang *et al.* [91] successfully synthesized porphyrin based covalent organic frameworks (COF-366 NPs), serving as phototherapeutic agents in their own right. They achieved this by precisely controlling the spatial arrangement of hydrophobic and π-π interactions in photoactive building units, thereby significantly altering the photophysical properties. This innovative strategy ensures the well-dispersed nature of COF-366 nanoparticles, minimizing self-aggregation and quenching of porphyrin compounds. As a result, COF-366 nanoparticles not only exhibit a greater capacity for producing reactive oxygen species (ROS) compared to porphyrin aqueous solutions but also effectively elevate the temperature when exposed to a single wavelength light source at 635 nm (1.5 W cm^{-2} for 5 min). Moreover, this nanoplatform completely inhibits tumor growth and maintains therapeutic efficacy, even in larger tumors. In another work, Hu *et al.* [92] adapted room temperature cation exchange procedure, exchanging Ag^+ and Cu^{2+} to obtain COF-Ag_2Se nanomaterial. The utilization of COFs as template favoured the optimization of size of CuSe or Ag_2Se, which

appeared as potential photosensitizer in PDT. The high efficacy of the COF-Ag_2Se nanomaterials in killing malignant cells was well evident from both the *in vitro* and *in vivo* studies. In recent developments aimed at enhancing the combination of PDT and PTT using a single-wavelength light source, a homogeneous porphyrin-based COF material (COF-B) was created through protein-assisted synthesis. The inclusion of TAPP as a building block imparts both PTT and PDT activities to the nanocomposites under the excitation of a single laser, while BSA protein helps in the preparation of these nanocomposites, enhancing their dispersibility and stability in aqueous media. The high absorbance at 685 nm in COF-B not only improves its photodynamic activity but also enhances its photothermal conversion efficiency (25.6%), all while maintaining excellent photostability.

Challenges and future scope

This review summarizes the key considerations of various therapeutic approaches and their mechanisms. Despite the promising outcomes, the limited number of studies in this field suggests that these organic materials are still in their early stages, with numerous challenges hindering desired clinical translation in cancer nanomedicine. Firstly, the low dispersibility of COFs in solution has been overcome by surface modification with polymer compounds and transforming into nanodimension. However, challenges arise in isolating mixtures of nanoscale COFs (NCOFs) with different sizes and morphologies, impacting bioavailability and stability. Achieving the optimal dispersibility and particle size, along with suitable surface modification by polymers, is crucial for intravenous injection, a key aspect for *in vivo* applications.

Secondly, While NCOFs exhibit remarkable drug loading capacity, achieving molecular dispersion is critical when encapsulating therapeutic agents to prevent self-aggregation and self-quenching. The challenge lies in maintaining high loading capacity while enhancing ROS production and hyperthermia induction. Controlled drug release remains uncertain, requiring in-depth investigation of interactions, mechanisms and kinetics for sustained drug release. Thirdly, despite therapeutic potential, many NCOFs are passively targeted by the EPR effect. Active targeting is preferable, necessitating further exploration of COF inherent characteristics. Future nanoparticles should consider shape, size, surface characteristics and responsiveness to stimuli, with the introduction of new entities and agents, such as siRNA, mRNA and gene editing. Surface nano-engineering can aid in developing multistage delivery systems with locally activated size-shrinkage structures. In summary, a comprehensive understanding of the complex interactions of NCOFs in the cancer biological milieu and active mechanisms of therapeutic agents is crucial for overcoming challenges and advancing COF-based nanoplatforms in cancer nanomedicine.

Conclusion

This review has extensively investigated the significant progress in utilizing covalent organic frameworks (COFs) for cancer therapy. Properties such as biocompatibility, highly porous structure, inherent stability makes COFs as efficient material for cancer therapeutics. The synthetic procedures including solvothermal synthesis, microwave synthesis, ionothermal synthesis, sonochemical synthesis, mechanochemical synthesis have been found to be effective in the creation of COFs. Technologically advanced procedures like microwave synthesis appears advantageous compared to the conventional solvothermal synthesis, owing to the requirement of less time, production of highly porous structure, easy removal of impurities, *etc.* The modern techniques like vapour assisted synthesis, light assisted synthesis have proved themselves promising in generating COFs with uniform porosity. The uniform, porous, metal free structure makes COFs as excellent candidate for biomedical applications. Doxorubicin, an efficient chemotherapeutic agent, can be transported into tumor site with its controlled release by utilizing COFs as nanocarrier. Several self-assembled structures have been utilized by different groups for delivering doxorubicin depending on pH of the medium. In addition, surface modifications have been done to inhibit agglomeration and increase the efficacy in transporting different drug molecules. COFs can also be utilized in photodynamic therapy (PDT) and photothermal therapy (PTT). In PDT, the reactive oxygen species (ROS) generated on irradiation can cause damage in cancer cell, whereas, in PTT the cancer cells get killed with the raise in temperature from the irradiation. Some COFs are also utilized in sonodynamic therapy (SDT), which involves destruction of malignant cells by non-invasive ultrasound. The individual cancer treatments sometimes appeared as inefficient in treating tumor and thus combination therapies are sometimes recommended, owing to their greater efficacy and least damage in normal cells. Finally, to have maximum efficacy with minimum side effects, the mechanisms of the chemotherapeutic agents in the biological medium must be taken into consideration. More extensive investigations are thus required to have more potent COFs in the field of cancer therapeutics.

ACKNOWLEDGEMENTS

The authors are very much thankful to Swami Kamalasthananda, Principal, Ramakrishna Mission Vivekananda Centenary College, Rahara, Kolkata for providing requisite facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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