



Nanoscale Covalent Organic Frameworks in Modern Cancer Therapy

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Abstract

Covalent organic frameworks (COFs) are innovative crystalline porous materials that have garnered significant interest due to their intricate structures and unique characteristics, such as combinability, crystallinity, porosity, stability, flexibility, and biocompatibility. Initially, COFs found utility in industrial sectors, serving functions as adsorbents, separation agents, sensors, and catalysts. However, recent investigations have shifted focus to their potential biomedical applications.

The substantial porosity inherent in COFs facilitates the efficient incorporation of a variety of imaging and therapeutic agents. In some instances, these frameworks can be utilized to deliver therapeutic drugs and functional groups through covalent linkages. Additionally, the organic components of COFs can be altered after synthesis to establish specific interactions with biomarkers. These remarkable properties position COFs as promising nanocarriers for bioimaging and therapeutic uses.

Despite nearly a decade of intensive research aimed at the rational design and synthesis of organic covalent frameworks, their therapeutic applications at the nanoscale remain largely underexplored. This article examines recent progress in the application of drug-containing organic covalent frameworks for cancer treatment, highlighting various strategies such as drug delivery, photodynamic therapy, and photothermal therapy.

Keywords: “Covalent Organic Frameworks, Cancer, Nano Scale, Drug Delivery, Photothermal Therapy, Photodynamic Therapy”



Introduction

Cancer poses a significant risk to human health and contributes to morbidity, highlighting the urgent need for effective treatments. In developing countries, one of the crucial factors leading to cancer-related mortality is delayed diagnosis, often stemming from inadequate access to healthcare facilities. While advancements have been made in cancer therapies such as chemotherapy, surgical procedures, and phototherapy, these approaches frequently present challenges, including high toxicity levels, long-term adverse effects, and the potential for cancer recurrence due to incomplete tumor removal [1,2]. The primary reason for the ineffectiveness of molecular chemotherapy agents is their inability to reach tumor locations in adequate concentrations to trigger apoptosis. Moreover, increasing dosages of these drugs to address this challenge can further raise toxicity levels in healthy tissues [3,4].

Nanoparticles offer a promising avenue for cancer treatment, as they can effectively bypass biological filtration mechanisms and selectively accumulate at tumor sites due to enhanced permeability and retention effects [5]. The initial success of nanoparticles in oncological therapies has spurred extensive research into the design of various nanoparticles, including inorganic types (silica, gold, metal oxides, black phosphorus, quantum dots) as well as organic and biomolecule-based formats (dendrimers, mesoporous polymers, liposomes, micelles) [6,7]. These nanoparticles have demonstrated encouraging outcomes in multiple anticancer applications. Nonetheless, their limited functionality can hinder their effectiveness and biocompatibility in cancer therapy [8]. Additionally, metal-based nanoparticles pose potential long-term toxicity risks, while other biomaterials often face challenges related to reproducibility, uncontrollable morphologies, and variability in nanoparticle sizes [9]. Recent studies on nanoparticles derived from COFs for applications in drug delivery, photodynamic and photothermal therapies have revealed significant therapeutic potential [10,11].

Porous organic polymers represent a newly developed class of multifunctional porous materials that have garnered significant research interest from both academia and industry. These materials are primarily composed of adaptable small organic molecules, which are interconnected through robust covalent bonds [12]. COFs are a specific type of crystalline porous organic polymer, formed from lightweight organic molecules linked by dynamic, strong covalent bonds including imine, imide, azine, hydrazone, and boronate ester [13].

In contrast to other porous amorphous organic polymers, COFs exhibit well-ordered, long-range structures, allowing for precise control over the pore architecture and the incorporation of functional groups [14,15]. Their large surface area, customizable pore geometry, excellent crystallinity, intrinsic compatibility, and high flexibility in both molecular structure and functionality have captivated considerable interest, demonstrating substantial potential for various applications [12,16].

The synthesis of these frameworks typically employs highly reversible dynamic chemicovalency, which facilitates the formation of regular and thermally stable structures [17]. Their compelling properties, coupled with advantages over other porous materials with ordered structures, contribute to their promising applications in medicine. Consequently, the characteristics and performance of COFs are significantly influenced by their pore features, which are regulated by the topological configurations and dimensions of the frameworks.

Cancer treatment strategies

Cancer treatment typically involves several methodologies, including surgical excision of tissues, chemotherapy, and radiotherapy. Surgery is particularly effective for the removal of malignant solid tumors, especially during the early stages of cancer progression. Combined treatment strategies integrate various modalities, such as surgery alongside chemotherapy and radiotherapy [1,18].

Chemotherapy has gained prominence over the years due to its straightforward application and convenience in treating cancer patients. However, its widespread use is marred by significant drawbacks, primarily its indiscriminate cytotoxicity, which can lead to adverse side effects [19]. Chemotherapy often affects rapidly proliferating tissues and cells, such as hair follicles, gastrointestinal cells, and bone marrow, resulting in complications like hair loss and compromised immune function. Furthermore, chemotherapy is associated with the development of multi-drug resistance and interactions with cancer stem cells, which diminishes its overall effectiveness [19,20].

Presently, chemotherapy faces substantial challenges, including non-specificity of drugs, cytotoxic effects, short therapeutic half-lives, poor solubility, and the emergence of multi-drug resistance and stem cell proliferation [21]. In order to address these limitations, various innovative approaches are being explored, such as nanomaterial-based chemotherapy, targeted therapy, molecular therapy, photodynamic therapy, photothermal therapy, chemodynamic therapy [22,23].

The emergence of nanotechnology offers promising solutions that could potentially mitigate the disadvantages associated with traditional chemotherapy [24,25]. Ongoing extensive research is being conducted to develop nanomedicines that enhance cancer treatment efficacy while minimizing harmful effects. In the subsequent sections, the application of COFs in contemporary cancer treatment techniques will be discussed.

Covalent organic frameworks in cancer therapy

COFs possess distinct characteristics, including modularity, functional versatility, intrinsic porosity, conjugated chains, and high crystallinity, which render them highly promising materials for a variety of biomedical applications [14]. These properties allow COFs to perform multiple functions, such as encapsulating guest molecules, enhancing

photoelectric properties, facilitating the release of reactive oxygen species (ROS), promoting heat dissipation, and increasing photocatalytic activity [26].

The high crystallinity of COFs significantly contributes to their thermal and optical stability. These advantages distinguish COFs from other porous crystalline materials, making them appealing candidates for applications in photodynamic and photothermal therapies, bioimaging, biosensing, and cancer biomarker detection [27].

The modularity of COFs, characterized by their framework consisting of linkers and spacers, enables precise morphological control through the selection of appropriate structural components during the initial pore design phase [28]. This adaptability supports the development of a diverse array of COF structures with tailored properties, thereby paving the way for the creation of multi-stimulus responsive COFs [29]. Such advancements expand the potential applications of COFs within the biomedical sector.

COFs exhibit significant versatility in integrating desired functionalities within their structures. This adaptability arises from their chemical tunability, which allows for the introduction of specific interactions between COFs and guest molecules. Such modifications enhance drug loading capacity and controlled release, and can also bestow unique properties like luminescence [30]. Additionally, structural moieties that are functionally modified can impart photoelectric characteristics to COFs, creating functional platforms that effectively combine therapeutic and diagnostic capabilities [31-33].

The intrinsic porosity of COFs is characterized by tunable pore sizes and open channels at the nanoscale. This unique trait results in a large free pore volume, enabling the entrapment of various guest molecules through non-covalent interactions. Consequently, this feature allows for rapid transport, high loading efficiency, and controlled release of encapsulated molecules while preserving their bioactivity. Moreover, the open pore channels facilitate the release of ROS and the dissipation of heat generated from photochemical reactions, enhancing the efficacy of photothermal and photodynamic therapies [34].

The substantial surface area afforded by the porosity of COFs further improves electrostatic charge separation and light-harvesting capabilities, broadening their applications in biosensing and photocatalysis. COFs are characterized by highly ordered crystal structures resulting from π - π stacking interactions, which provide exceptional crystallinity and thermal stability, making them well-suited for photocatalytic purposes [35]. Although achieving high crystallinity can often compromise chemical stability or the extent of π -electron delocalization, COFs have demonstrated an ability to maintain both high crystallinity and optical stability. This remarkable property is attributed to their unique molecular architecture, which promotes efficient charge transfer while safeguarding the conjugated systems against degradation. COFs show remarkable stability in aqueous solutions, which is attributed to strong covalent bonds and unique properties at the nanoscale [36,37]. This stability is crucial for efficient cellular internalization and long-lasting therapeutic effect in in vivo and in vitro studies [38,39]. In addition, the reversible nature of their bonds suggests potential biodegradability, making them more suitable for biomedical applications. Unlike conventional nanomaterials that often contain harmful heavy metals, COFs are composed of only organic structural parts, which significantly increases their biocompatibility and biodegradability [28]. This lack of heavy metals further reduces the risk of toxicity and promotes the natural degradation of COFs in the body, minimizing potential adverse effects.

Covalent organic frameworks in drug release

Initial investigations into COFs primarily targeted applications in gas storage and separation, leveraging their distinctive attributes such as high porosity, customizable structure, and exceptional stability. However, a more recent and promising application for COFs is their use as nanoplatforms for drug delivery. Their intrinsic characteristics render them particularly appealing for this purpose.

The porous channels within COFs create an optimal environment for the incorporation of therapeutic drugs, helping to prevent premature release and enhance drug concentration at tumor sites. This capability has inspired extensive research focused on the design and fabrication of host-guest nanosystems utilizing COFs for drug delivery applications [40].

Although recent studies have highlighted the potential of COFs as drug delivery nanocarriers, challenges such as poor dispersion and limited bioavailability within tumor cells must be addressed to optimize their effectiveness. Researchers propose that employing post-synthesis modification techniques could improve the properties of COFs after their initial formation, enabling the development of more effective COFs for drug delivery applications.

Ji et al. developed nano-sized COFs that feature a hypoxia-responsive azo ligand, which effectively immobilizes both the photosensitizer chlorin e6 and the hypoxia-activated drug tirapazamine within the framework (Figure 1(A)). When exposed to the hypoxic conditions typical of tumor environments, the structure of the covalent organic framework disintegrates, facilitating the release of the encapsulated drugs. Upon irradiation with near-infrared light, the photosensitizer utilizes oxygen to produce cytotoxic reactive oxygen species, resulting in increased levels of hypoxia. Experimental assessments conducted in vitro and in vivo demonstrated that this drug delivery system, activated by a two-step hypoxic mechanism, can effectively destroy cancer cells and significantly suppress tumor growth [41].

Das et al. employed a novel drug carrier known as TRIPTA-COF for targeting triple-negative breast cancer (Figure 1(B)). This biocompatible covalent organic framework was conjugated with cisplatin, a well-established chemotherapeutic agent. The findings from this study demonstrated that the covalent organic framework significantly reduced the proliferation and migration of cancer cells, as well as inhibited the epithelial-mesenchymal transition, an

essential process in cancer development. These results indicate that this covalent organic framework serves as a promising drug carrier for breast cancer treatment, enhancing the efficacy of cisplatin and contributing to improved clinical outcomes in patients diagnosed with this cancer type [42].

Al-Khalifeh et al. presented the C6N6 covalent triazine framework as an effective drug carrier for the anticancer agents fluorouracil and nitrosoureas, with stability achieved through van der Waals interactions. Their analysis revealed significant charge transfer and differences in electron density between the drug and the carrier, as indicated by natural bond order assessments. Notably, the fluorouracil-containing complex exhibited the largest reduction in adsorption energy when examined under acidic conditions, suggesting that the drug can be readily released from the carrier at target sites (Figure 1(C)). This is particularly advantageous given that cancer cells typically exhibit a lower pH relative to normal cells. Consequently, it can be inferred that the covalent triazine framework holds considerable therapeutic promise as a nanocarrier for fluorouracil in cancer therapy [43].

The construction of 3D COFs with large pore sizes presents significant challenges due to the complexities associated with cross-linking frameworks. Wang et al. successfully synthesized and designed a 3D non-interacting covalent organic framework that boasts the largest pore size among all 3D organic covalent frameworks, measuring 47 Å, while maintaining a low density of 0.106 g cm⁻³. This framework features a highly interconnected mesoporous structure that exhibits good stability. Furthermore, it demonstrated effective drug loading and controlled release capabilities for five different therapeutic agents in a simulated body fluid environment, underscoring its potential as a drug nanocarrier [44].

Porous and crystalline organic covalent frameworks, characterized by their specific surface areas and functionalized pore walls, facilitate the adsorption of a variety of bioactive molecules within their porous structures. Bonia et al. developed a perylene-based covalent organic framework that serves as an effective bulk reservoir for the anticancer drug mitoxantrone (Figure 1(D)). This covalent organic framework, when loaded with mitoxantrone, demonstrated the capability for cellular release towards cancer cells. This release can be attributed to the strong interactions between the drug and the perylene-based covalent organic framework [45].

Mokhtari et al. developed a covalent imine-linked organic framework characterized by a hexagonal topology, synthesized under autoclave conditions. These COFs were subsequently utilized as a pH-dependent carrier for the in vitro release of doxorubicin. Their intrinsic properties facilitated a high drug encapsulation efficiency. Furthermore, the release of the drug exhibited pH-dependent behavior at both acidic and physiological pH levels. Cell analysis revealed that the organic covalent frameworks alone did not impact cell proliferation, whereas the drug-loaded frameworks specifically inhibited the proliferation of cancer cells [46]. Table 1 displays the information regarding the application examples of COFs utilized as drug carriers.

Table 1- The case studies about COFs used as drug carriers

COF	Building Block	Size (nm)	Drug	Cancer Cell Type	Reference
TA-COF-P@CT	1,3,5-triformyl-2,4,6-trihydroxybenzene (TP) 4,4'-Azodiaminobenzene (AD)	2	Tirapazamine drug Chlorine sensitizer Ce6	4T1	[41]
TRIPTA-COF	1,3,5-triformyl phloroglucinol (TFP) 1,3,5-tris-(4-aminophenyl)-triazine (TAPT)	10	Cisplatin	MDA-MB-231	[42]
C6N6	Two-dimensional covalent triazine framework	-	Fluorouracil Nitrosourea	-	[43]
TUS-64	Hexakis(4'-formylphenyl)tryptcene (HFPTP), Tetrakis(4-aminophenyl)porphyrin (TAPP)	5	Captopril Ibuprofen Isoniazid 5- Fluorouracil Brimonidine	-	[44]
MXT-PER@PDA COF 1	(2,5,8,11 perylene tetrayl) tetrabenzaldehyde p Phenylenediamine	100-200	Mitoxantrone	4T1	[45]
DOX@APB-COF	1,3,5-tris(4-nitrophenyl)benzene (TNPB) 2,4,6-tris(4-phenoxyformyl)-1,3,5-triazine (TFPT) 1,3,5-tris(4-aminophenyl)benzene (TAPB)	113	Doxorubicin	MDA-MB-231 MCF10	[46]

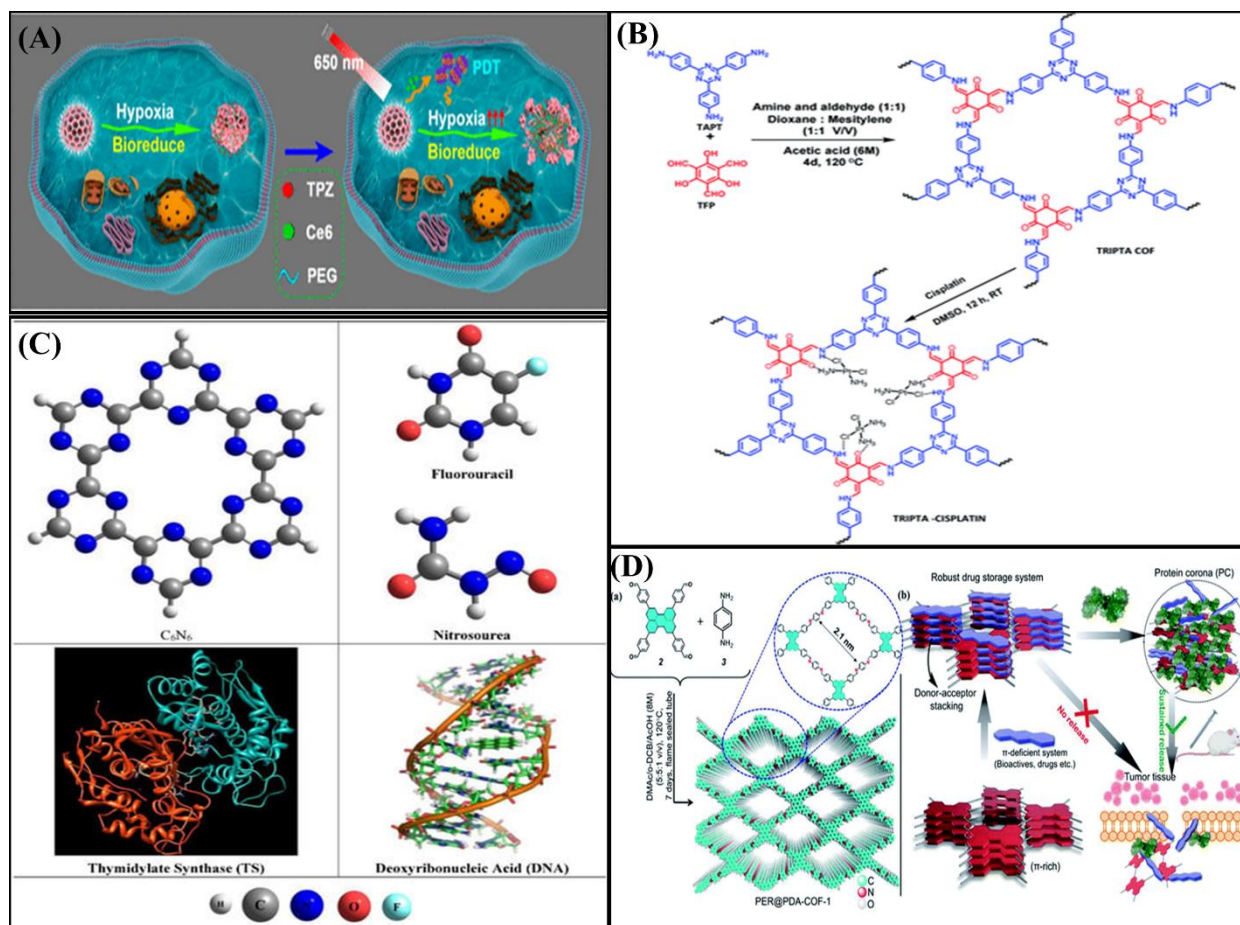


Figure (1): (A) The azo-containing responsive COFs (TA-COF) that were capable of co-loading TPZ and Ce6 were synthesized by the reaction of 1,3,5-triformyl-2,4,6-trihydroxybenzene (TP) and 4,4'-azobis(4-aminobenzene) (AD) [41], (B) Loading of cisplatin onto the 2D crystalline COF material TRIPTA enables targeted drug delivery to metastatic breast cancer cells [42]. (C) A C₆N₆ covalent triazine framework as a drug carrier for the anticancer drugs fluorouracil (FU) and nitrosoureas (NU) [43]. (D) Schematic diagrams of the synthesis of PER@PDA-COF-1, and the donor-acceptor-based strategy for loading bioactives into a crystalline COFs and albumin-stimulated cell release [45]

Covalent organic frameworks in photothermal therapy

Photothermal therapy, which harnesses photothermal agents to generate hyperthermia through light irradiation, effectively promotes the photosensitization of tumor cells and has gained recognition as a viable cancer treatment strategy. Current research is focused on nanomaterials exhibiting high photothermal conversion efficiency, such as conjugated polymers, plasmonic metal nanostructures, semiconductors, and ferromagnetic nanoparticles [47]. Among these, graphene stands out due to its substantial absorption in the near-infrared spectrum and excellent heat generation capacity, making it a strong candidate for use as a photothermal agent [48,49].

COFs, owing to their analogous two-dimensional atomic structures, share similarities with graphene. Additionally, COFs are capable of facilitating rapid heat dissipation through their open pore channels, in contrast to closed porous systems that obstruct heat transfer and contribute to thermal resistance. Hence, COFs demonstrate considerable potential as effective organic hyperthermia agents [50].

Sun et al. developed a nanoscale COF nanoagent designed to inhibit HSP90, thereby improving the efficacy of photothermal therapy for cancer at lower temperatures (Figure 2(A)). This agent effectively elevates the temperature of tumor tissues during laser irradiation, converting laser energy into heat to induce cancer cell death. Gambogic acid served as an inhibitor to counteract the thermal resistance of the tumor, facilitating effective mild-temperature photothermal treatment. In vivo studies indicated that the use of COFs significantly inhibited tumor growth post-treatment. Notably, photothermal therapy conducted at mild temperatures demonstrated a robust anti-tumor response while minimizing unintended thermal damage to surrounding healthy tissues [51].

Nanomaterials exhibiting enzyme-like properties, known as nanoenzymes, have garnered significant interest for their role in catalytic cancer treatment. Nevertheless, creating metal-free nanoenzymes with diverse enzyme-like functions

as versatile therapeutic agents poses ongoing challenges. Wan et al. have systematically developed a carbon-based nanoenzyme derived from a covalent organic framework, aimed at achieving a combination of catalytic therapy and second near-infrared photothermal therapy for cancer. This engineered nanoenzyme possesses various enzyme-like activities, including those resembling oxidase, catalase, and peroxidase, enabling it to generate sufficient ROS for effective cancer cell destruction. Moreover, this nanozyme demonstrates remarkable photothermal conversion capabilities, allowing it to annihilate cancer cells under laser irradiation, attributable to the strong absorption properties of carbon-based materials. Notably, this nanoenzyme exhibits cytotoxic effects specifically targeting tumor tissues [52].

Wang et al. effectively incorporated heteropoly blue, an optimal photothermal cure agent characterized by excellent photothermal conversion efficiency, into COFs using a one-pot method (Figure (2(B))). The resulting construct exhibited commendable biocompatibility, pH-responsive release characteristics, and significant tumor inhibition efficacy, making it suitable for photothermal therapy aimed at effectively suppressing tumor growth [53].

Hu et al. successfully synthesized highly monodisperse COF nanoparticles. These non-porphyrin nanoparticles containing COFs were utilized as novel photosensitizers for photodynamic therapy (PDT), demonstrating impressive photodynamic efficacy upon irradiation with lasers at wavelengths of either 650 nm or 808 nm (Figure (2(C))). Additionally, CuSe nanoparticles, recognized as effective photothermal agents, were effectively conjugated with COFs to create a dual photosensitizer designed for phototherapy. The resulting platform exhibited significant synergistic effects in both photothermal and photodynamic therapy, with in vitro and in vivo studies indicating enhanced therapeutic efficacy in eradicating cancer cells and suppressing tumor growth [54].

Feng et al. presented a magnetic core-shell nanocomposite constructed from a COF, namely $\text{Fe}_3\text{O}_4@\text{COF}$ DhaTph, which serves as a multifunctional nanoagent for cancer theranostics under 660 nm laser irradiation. This composite not only displayed exceptional photothermal and photodynamic capabilities but also facilitated magnetic resonance, photoacoustic, and near-infrared imaging owing to its distinctive magnetic and optical properties. The promising outcomes observed in this study may significantly advance the application of multifunctional nanomaterials based on COFs in cancer diagnosis and treatment [55].

Zhang et al. developed a COF featuring both planar and twisted motifs, designed to serve as an effective dual inducer of pyroptosis and ferroptosis to enhance antitumor immunity (Figure (2(D))). Mechanistic investigations revealed that this framework demonstrated superior near-infrared light absorption, reduced band energy, and extended lifetimes, which collectively promote the generation of ROS and facilitate photothermal conversion, thus triggering pyroptosis. Furthermore, its proficiency in producing ROS modulates intracellular lipid peroxidation, resulting in glutathione depletion and diminished expression of glutathione peroxidase, which in turn stimulates ferroptosis. Additionally, the simultaneous induction of pyroptosis and ferroptosis by this COF significantly hindered tumor metastasis and recurrence [56]. Table 2 displays the information regarding the application examples of COFs utilized as photothermal agents.

Table 2- The case studies about COFs used as photothermal agents

COF	Building Block	Size (nm)	Drug or Photothermal agent	Cancer Cell Type	Reference
COF-GA	3,3',5,5'-Tetramethylbenzidine (TMB) 4,4',4'',4'''-(porphyrin5,10,15,20-tetrayl)tetraaniline (TAPP)		gambogic acid	HSP90	[51]
CN-PEG@IR808	Dihydroethidium (DHE) 3,3',5,5'-Tetramethylbenzidine (TMB), 4,4',4'',4'''-(porphyrin5,10,15,20-tetrayl)tetraaniline (TAPP)	200	Rhodamine IR808	4T1 cells TC-1 cells U87 cells, MCF-7 cells, HL-7702	[52]
HPB@COF	4,4',4'',4'''-(porphyrin5,10,15,20-tetrayl)tetraaniline (TAPP)	100-150	Blue heteropoly	C929	[53]
COF-LZU-1	1,3,5- triformylbenzene (tfb) 1,4-diaminobenzene (dab)	150	CuSe	HeLa cells	[54]
$\text{Fe}_3\text{O}_4@\text{COF}$ -DhaTph $\text{Fe}_3\text{O}_4@\text{COF}$ -TPBDMTP	Tetrakis (4-aminophenyl) porphyrin 2,5-dihydroxyterephthalaldehyde o-dichlorobenzene 1,3,5-tris(4-aminophenyl)benzene 2,5-dimethoxyterephthalaldehyde	200-300	Fe_3O_4	MCF-7	[55]
COF-919 COF-818	5',5'''-bis(4-formylphenyl)-[1,1':3':1'':4'',1'''':3'''',1''''-quinquephenyl]-4,4'''-dicarbaldehyde (M-TPh)	200	glutathione peroxidase 4 (GPX4)	4T1	[56]

	N1,N1'-(1,4-phenylene)bis(N1-(4-aminophenyl)benzene-1,4-diamine) (M-TPA) 4',4''''-(1,4-phenylene)bis(((2,2':6',2''-terpyridine)-5,5''-dicarbaldehyde)) (M-Tpy)			
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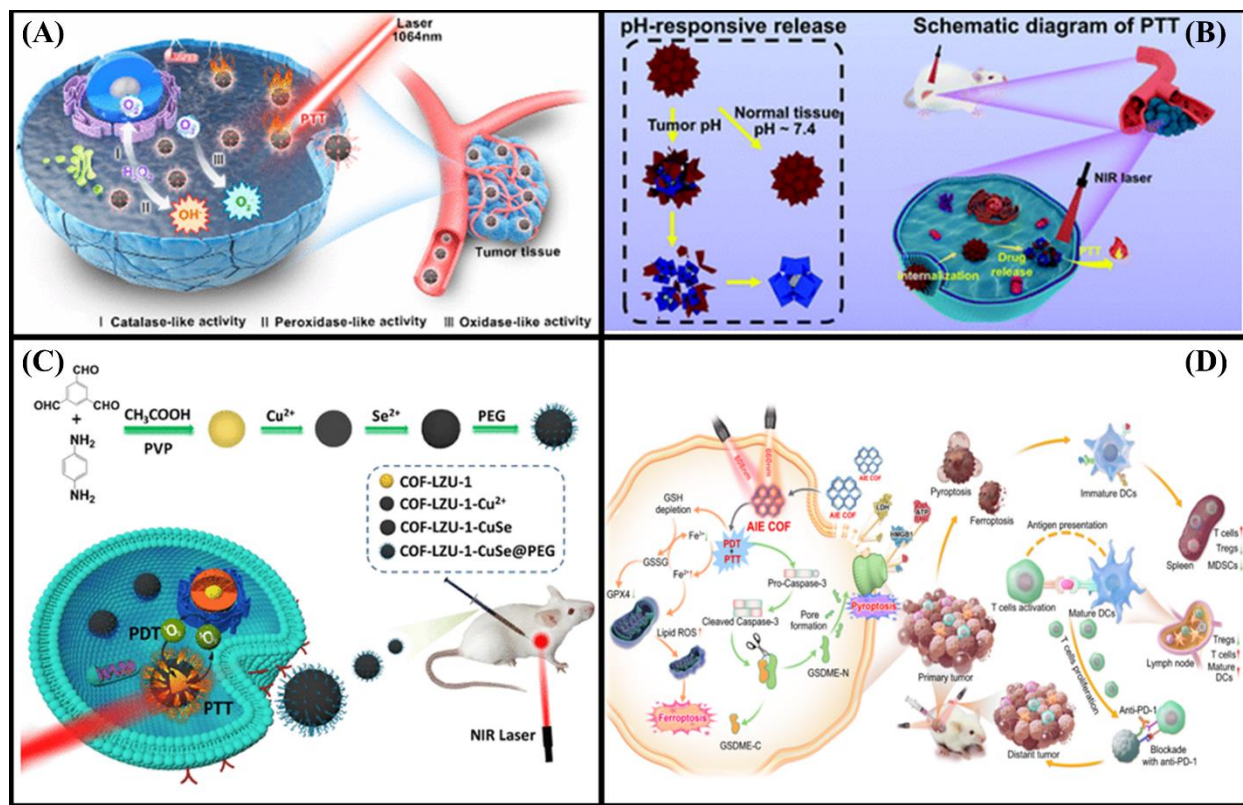


Figure (2): (A) Schematic illustration of a COF-derived carbon-based nanoenzyme to achieve synergistic catalytic and second near-infrared (NIR-II) photothermal therapy for cancer [51]. (B) Schematic diagram of pH-sensitive release of HPB from Polyoxometalate-COFs [53]. (C) Schematic illustration of monodispersed CuSe sensitized COFs photosensitizer with an enhanced photodynamic and photothermal effect for cancer therapy [54]. (D) Schematic diagram of integration of AIEgens into COFs for pyroptosis and ferroptosis primed cancer immunotherapy [56]

Covalent organic frameworks in photodynamic therapy

Photodynamic therapy has garnered significant interest and has been effectively implemented in clinical settings. This therapeutic approach relies on the combined action of photosensitizers, tissue oxygen, and an excitation light source to generate ROS that efficiently eliminate tumor cells upon illumination. Photodynamic therapy is characterized by its noninvasive nature and precision, which can lead to lower recurrence rates, decreased cumulative radiation exposure, and fewer adverse effects [57,58].

The distinctive attributes of COFs, such as high surface area, adjustable pore structures, and π - π stacking interactions, allow them to encapsulate substantial quantities of drugs with minimal leakage [59]. Additionally, their unique photoelectric characteristics position COFs as promising candidates for phototherapy applications. Given that COFs are composed of organic structural components linked by covalent bonds, they may contain non-bonded functional groups within their framework, facilitating the incorporation of various organic photosensitizers [60]. Moreover, COFs can be utilized directly as photosensitizers in photodynamic therapy without the requirement for supplementary additives, enhancing their potential for biomedical applications.

Wang et al. introduced a novel approach to enhance photodynamic therapy for cancer by utilizing an imine-based organic covalent framework to deliver the anti-fibrotic drug pirfenidone directly to the tumor's extracellular matrix (Figure 3(A)). This drug facilitates the degradation of the extracellular matrix by diminishing the synthesis of key components such as hyaluronic acid and collagen. As a result, the solid stress within the tumor is reduced; solid stress refers to the compressive forces exerted by the extracellular matrix and surrounding cells on tumor blood vessels. The alleviation of solid stress allows tumor blood vessels to expand, thereby improving oxygen supply to the tumor. Furthermore, the reduction in extracellular matrix density enhances the uptake of photosensitizing molecules

by the tumor cells. This increase in oxygen delivery and improved absorption of photosensitizing agents subsequently lead to a rise in the generation of ROS within the tumor, thereby augmenting the efficacy of photodynamic therapy [61].

Utilizing catalase to promote in situ oxygen production within tumor tissue significantly alleviates tumor hypoxia. Nevertheless, the acidic environment of tumor microenvironments leads to a marked loss of catalase activity, which diminishes its effectiveness in promoting hypoxia recovery. Van et al. introduced a porphyrin-based three-dimensional COF designed as an enzyme nanoprotector to stabilize catalase while also providing pH protection to preserve its enzymatic activity under acidic conditions. This three-dimensional covalent organic framework offers a high surface area for effective catalase loading. When exposed to laser irradiation, the nanoprotector efficiently generates reactive oxygen species, facilitating the implementation of photodynamic therapy for cancer. Even in the acidic tumor microenvironment, catalase can decompose excess hydrogen peroxide (H_2O_2) to produce oxygen (O_2), significantly enhancing the efficacy of treatment, resulting in considerable tumor suppression by this nanoprotector [62].

Han et al. developed a COF designed to serve as a drug carrier for the photosensitizer indocyanine green and the hypoxia-activating prodrug AQ4N (Figure 3(B)). This framework was modified with hyaluronic acid, resulting in the HA-COF@ICG/AQ4N drug delivery system, which specifically targets tumor cells by recognizing CD44, a receptor overexpressed on the membranes of tumor cells. Upon laser irradiation, indocyanine green generated a synergistic photodynamic and photothermal effect. Concurrently, the photodynamic therapy further intensified the hypoxic conditions of the tumor microenvironment by decreasing intracellular oxygen levels, leading to a synergistic cascade of antitumor actions. The study's findings indicated that this multifunctional nanoplatform, activated by hypoxia, substantially inhibited the growth and metastasis of triple-negative breast cancer [63]. Table 3 provides details on various instances of COFs used as photodynamic agents.

Table 3- The case studies about COFs used as photodynamic agents

COF	Building Block	Size (nm)	Drug or Photodynamic agent	Cancer Cell Type	Reference
PFD@COFTTA DHTA@PLGA PEG	TTA: 4,4',4''-(1,3,5-triazine-2,4,6-triyl)trianiline	60	Pirfenidone fibrotic	CT26	[61]
COF-CAT	1,3,5,7-tetra(4-aminophenyl)-adamantine (TAPA)	100	Catalase		[62]
HA-COF@ICG	1, 4-Benzenedicarboxaldehyde, 2, 5-dimethoxy (DMTP) and 1, 3, 5-Tris (4-aminophenyl) benzene (TPB)	150	indocyanine green (ICG) AQ4N	TNBC cell lines	[63]

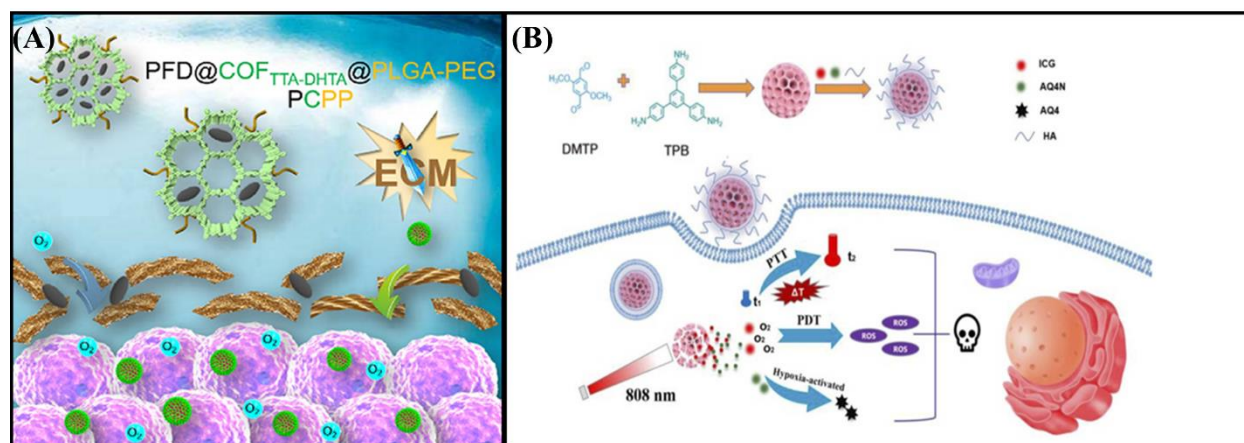


Figure (3): (A) Schematic representation of tumor ECM degradation mediated by PCPP to improve the efficacy of tumor PDT [61]. (B) Schematic of HA-COF@ICG/AQ4N for multimodal antitumor therapy [63]

Conclusion

Cancer nanomedicine represents a promising solution to overcome the limitations associated with traditional chemotherapy and phototherapy techniques, leading to ongoing intensive research into new nanomaterials aimed at enhancing efficacy and immunotherapy. COFs have garnered substantial attention across various research domains due to their low density, well-defined structures, large surface area, customizable pore sizes, and metal ion-free characteristics. Recent interest in nanoscale COFs has facilitated improvements over their bulk counterparts, thereby broadening their applications within biomedicine. These include nanocarriers with exceptional loading capacities for efficient delivery of therapeutic agents and smart theranostic nanoplatforms that exhibit excellent stability, high production of ROS, light-to-heat conversion capabilities, as well as diverse reaction and detection functionalities.

COFs and their associated nanoplateforms, with a wide array of design and performance features, have opened new avenues for innovative opportunities in cancer therapy.

Despite their notable advantages, research into the biomedical applications of COFs remains at a nascent stage. Numerous challenges and limitations must be addressed. Firstly, achieving precise control over drug loading and release profiles from COFs is complicated by their intricate structure and pore configurations. Furthermore, the structural integrity of COFs, particularly their dimensional characteristics, plays a crucial role in determining their performance. Both two-dimensional and three-dimensional COFs offer unique benefits; however, applications involving COFs of various dimensions are infrequently documented. It is anticipated that innovative design strategies and the ability to control the dimensions of COFs will enhance their applicability.

Regarding potential clinical translation, investigating the biocompatibility of various nanoscale COFs, particularly concerning long-term systemic toxicity, should be prioritized. Secondly, the large-scale synthesis of nanoscale COFs remains a significant hurdle, necessitating further exploration into the reproducibility of production batches. The intricate molecular arrangements characteristic of COFs, encompassing varying layer and pore structures, pose substantial difficulties in producing COFs with consistent performance and uniform size distribution across different synthetic methods.

In general, nanoscale COFs present distinct advantages over other porous nanomaterials in the realm of cancer diagnosis and therapy. Unlike the majority of porous nanomaterials that function merely as passive delivery systems requiring post-synthetic modifications for additional capabilities, COFs possess inherent electrical, magnetic, and optical properties that allow for direct therapeutic applications. This intrinsic functionality enables the integration of drug delivery with other therapeutic modalities, such as phototherapy and immunotherapy, within a single nanosystem composed of COFs. Consequently, this multifaceted approach has the potential to address significant challenges in cancer treatment, including the difficulties associated with early diagnosis, treatment resistance, recurrence, and the elimination of metastases.

References

- [1] Rajan, S.S., Chandran, R. and Abrahamse, H., 2024. Overcoming challenges in cancer treatment: Nano-enabled photodynamic therapy as a viable solution. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 16(1), p.e1942.
- [2] Cross, C., Mokua, S., Ngilangwa, R., Santos, C., Ngoma, T. and Mujinja, P.G., 2024. Beyond "Late Presentation": Explaining Delayed Cancer Diagnosis in East Africa. In *Cancer Care in Pandemic Times: Building Inclusive Local Health Security in Africa and India* (pp. 93-111). Cham: Springer International Publishing.
- [3] Bania, R., Borah, P., Deka, S., Dahabiyeh, L.A., Singh, V., Al-Shar'i, N.A., Nair, A.B., Goyal, M., Venugopala, K.N., Tekade, R.K. and Deb, P.K., 2021. Current strategies in targeted anticancer drug delivery systems to brain. In *Advanced Drug Delivery Systems in the Management of Cancer* (pp. 267-280). Academic Press.
- [4] Pérez-Hernández, M., Arias, A., Martínez-García, D., Pérez-Tomás, R., Quesada, R. and Soto-Cerrato, V., 2019. Targeting autophagy for cancer treatment and tumor chemosensitization. *Cancers*, 11(10), p.1599.
- [5] Mundekkad, D. and Cho, W.C., 2022. Nanoparticles in clinical translation for cancer therapy. *International journal of molecular sciences*, 23(3), p.1685.
- [6] Gavass, S., Quazi, S. and Karpiński, T.M., 2021. Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale research letters*, 16(1), p.173.
- [7] Eftekhari, A., Krysch, C., Pamies, D., Gulec, S., Ahmadian, E., Janas, D., Davaran, S. and Khalilov, R., 2023. Natural and synthetic nanovectors for cancer therapy. *Nanotheranostics*, 7(3), p.236.
- [8] Elumalai, K., Srinivasan, S. and Shanmugam, A., 2024. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. *Biomedical Technology*, 5, pp.109-122.
- [9] Rampado, R. and Peer, D., 2023. Design of experiments in the optimization of nanoparticle-based drug delivery systems. *Journal of Controlled Release*, 358, pp.398-419.
- [10] Ghosh, P. and Banerjee, P., 2023. Drug delivery using biocompatible covalent organic frameworks (COFs) towards a therapeutic approach. *Chemical Communications*.
- [11] Liu, J., Liang, X., Kong, L., Cheng, M. and Fu, A., 2024. Design, optimization, and characterization of covalent organic framework-based nanoparticle drug delivery systems. *Materials Letters*, 361, p.136122.
- [12] Shi, Y., Yang, J., Gao, F. and Zhang, Q., 2023. Covalent organic frameworks: recent progress in biomedical applications. *ACS nano*, 17(3), pp.1879-1905.
- [13] Liang, S., Li, M.H., Qi, M., Wang, L. and Yang, Y.W., 2023. Nanoplateforms based on covalent organic frameworks (COFs) for biomedical applications. *Chemistry of Materials*, 35(20), pp.8353-8370.
- [14] Sridhar, V., Yildiz, E., Rodríguez-Camargo, A., Lyu, X., Yao, L., Wrede, P., Aghakhani, A., Akolpoglu, B.M., Podjaski, F., Lotsch, B.V. and Sitti, M., 2023. Designing covalent organic framework-based light-driven microswimmers toward therapeutic applications. *Advanced Materials*, 35(25), p.2301126.
- [15] Kaur, G., Kumar, D., Sundarajan, S., Ramakrishna, S. and Kumar, P., 2022. Recent trends in the design, synthesis and biomedical applications of covalent organic frameworks. *Polymers*, 15(1), p.139.

- [16] Yazdani, H., Shahbazi, M.A. and Varma, R.S., 2021. 2D and 3D covalent organic frameworks: Cutting-edge applications in biomedical sciences. *ACS Applied Bio Materials*, 5(1), pp.40-58.
- [17] Liao, C. and Liu, S., 2021. Tuning the physicochemical properties of reticular covalent organic frameworks (COFs) for biomedical applications. *Journal of Materials Chemistry B*, 9(31), pp.6116-6128.
- [18] Anand, U., Dey, A., Chandel, A.K.S., Sanyal, R., Mishra, A., Pandey, D.K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A. and Dhanjal, J.K., 2023. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases*, 10(4), pp.1367-1401.
- [19] Amjad, M.T., Chidharla, A. and Kasi, A., 2020. Cancer chemotherapy.
- [20] Airley, R., 2009. *Cancer chemotherapy: basic science to the clinic*. John Wiley & Sons.
- [21] Davodabadi, F., Sajjadi, S.F., Sarhadi, M., Mirghasemi, S., Hezaveh, M.N., Khosravi, S., Andani, M.K., Cordani, M., Basiri, M. and Ghavami, S., 2023. Cancer chemotherapy resistance: Mechanisms and recent breakthrough in targeted drug delivery. *European Journal of Pharmacology*, 958, p.176013.
- [22] Kenchegowda, M., Rahamathulla, M., Hani, U., Begum, M.Y., Guruswamy, S., Osmani, R.A.M., Gowrav, M.P., Alshehri, S., Ghoneim, M.M., Alshlowi, A. and Gowda, D.V., 2021. Smart nanocarriers as an emerging platform for cancer therapy: A review. *Molecules*, 27(1), p.146.
- [23] Khan, M.I., Hossain, M.I., Hossain, M.K., Rubel, M.H.K., Hossain, K.M., Mahfuz, A.M.U.B. and Anik, M.I., 2022. Recent progress in nanostructured smart drug delivery systems for cancer therapy: a review. *ACS Applied Bio Materials*, 5(3), pp.971-1012.
- [24] Rajendran, S., Ravi, S.N., Nair, V.M., Sree, R.P., Packirisamy, A.S.B. and Palanivelu, J., 2024. Recent Development and Future Aspects: Nano-Based Drug Delivery System in Cancer Therapy. *Topics in Catalysis*, 67(1), pp.203-217.
- [25] Li, Z., Zhou, Z., Wang, Y., Wang, J., Zhou, L., Cheng, H.B. and Yoon, J., 2023. Activatable nano-photosensitizers for precise photodynamic cancer therapy. *Coordination Chemistry Reviews*, 493, p.215324.
- [26] Fooladi, S., Nematollahi, M.H. and Iravani, S., 2023. Nanophotocatalysts in biomedicine: Cancer therapeutic, tissue engineering, biosensing, and drug delivery applications. *Environmental Research*, 231, p.116287.
- [27] Guan, Q., Zhou, L.L., Li, W.Y., Li, Y.A. and Dong, Y.B., 2020. Covalent organic frameworks (COFs) for cancer therapeutics. *Chemistry—A European Journal*, 26(25), pp.5583-5591.
- [28] Valenzuela, C., Chen, C., Sun, M., Ye, Z. and Zhang, J., 2021. Strategies and applications of covalent organic frameworks as promising nanoplateforms in cancer therapy. *Journal of Materials Chemistry B*, 9(16), pp.3450-3483.
- [29] Yao, S., Liu, Z. and Li, L., 2021. Recent progress in nanoscale covalent organic frameworks for cancer diagnosis and therapy. *Nano-micro letters*, 13(1), p.176.
- [30] He, X., Jiang, Z., Akakuru, O.U., Li, J. and Wu, A., 2021. Nanoscale covalent organic frameworks: from controlled synthesis to cancer therapy. *Chemical Communications*, 57(93), pp.12417-12435.
- [31] Singh, N., Kim, J., Kim, J., Lee, K., Zunbul, Z., Lee, I., Kim, E., Chi, S.G. and Kim, J.S., 2023. Covalent organic framework nanomedicines: Biocompatibility for advanced nanocarriers and cancer theranostics applications. *Bioactive materials*, 21, pp.358-380.
- [32] Zhang, G., 2022. Applications of Covalent Organic Frameworks (COFs) in Oncotherapy. In *Covalent Organic Frameworks*. IntechOpen.
- [33] Wang, J., Zhang, B., Sun, J., Hu, W. and Wang, H., 2021. Recent advances in porous nanostructures for cancer theranostics. *Nano Today*, 38, p.101146.
- [34] Guan, Q., Zhou, L.L., Li, Y.A., Li, W.Y., Wang, S., Song, C. and Dong, Y.B., 2019. Nanoscale covalent organic framework for combinatorial antitumor photodynamic and photothermal therapy. *ACS nano*, 13(11), pp.13304-13316.
- [35] Bagheri, A.R., Li, C., Zhang, X., Zhou, X., Aramesh, N., Zhou, H. and Jia, J., 2021. Recent advances in covalent organic frameworks for cancer diagnosis and therapy. *Biomaterials Science*, 9(17), pp.5745-5761.
- [36] Tang, X., Chen, Z., Xu, Q., Su, Y., Xu, H., Horike, S., Zhang, H., Li, Y. and Gu, C., 2022. Design of photothermal covalent organic frameworks by radical immobilization. *CCS Chemistry*, 4(8), pp.2842-2853.
- [37] Mi, Z., Yang, P., Wang, R., Unruangsri, J., Yang, W., Wang, C. and Guo, J., 2019. Stable radical cation-containing covalent organic frameworks exhibiting remarkable structure-enhanced photothermal conversion. *Journal of the American Chemical Society*, 141(36), pp.14433-14442.
- [38] Li, S., Chen, Z., Tan, L., Wu, Q., Ren, X., Fu, C., Niu, M., Li, H. and Meng, X., 2022. MOF@ COF nanocapsule for the enhanced microwave thermal-dynamic therapy and anti-angiogenesis of colorectal cancer. *Biomaterials*, 283, p.121472.
- [39] Zhang, Y., Zhang, L., Wang, Z., Wang, F., Kang, L., Cao, F., Dong, K., Ren, J. and Qu, X., 2019. Renal-clearable ultrasmall covalent organic framework nanodots as photodynamic agents for effective cancer therapy. *Biomaterials*, 223, p.119462.
- [40] Scicluna, M.C. and Vella-Zarb, L., 2020. Evolution of nanocarrier drug-delivery systems and recent advancements in covalent organic framework–drug systems. *ACS Applied Nano Materials*, 3(4), pp.3097-3115.

- [41] Ge, L., Qiao, C., Tang, Y., Zhang, X. and Jiang, X., 2021. Light-activated hypoxia-sensitive covalent organic framework for tandem-responsive drug delivery. *Nano Letters*, 21(7), pp.3218-3224.
- [42] Das, S.K., Roy, S., Das, A., Chowdhury, A., Chatterjee, N. and Bhaumik, A., 2022. A conjugated 2D covalent organic framework as a drug delivery vehicle towards triple negative breast cancer malignancy. *Nanoscale Advances*, 4(10), pp.2313-2320.
- [43] Alkhalifah, M.A., Yar, M., Bayach, I., Sheikh, N.S. and Ayub, K., 2022. Covalent organic framework (C6N6) as a drug delivery platform for fluorouracil to treat cancerous cells: a DFT study. *Materials*, 15(21), p.7425.
- [44] Wang, S., Pang, Y., Hu, S., Lv, J., Lin, Y. and Li, M., 2023. Copper sulfide engineered covalent organic frameworks for pH-responsive chemo/photothermal/chemodynamic synergistic therapy against cancer. *Chemical Engineering Journal*, 451, p.138864.
- [45] Bhunia, S., Saha, P., Moitra, P., Addicoat, M.A. and Bhattacharya, S., 2022. Efficacious and sustained release of an anticancer drug mitoxantrone from new covalent organic frameworks using protein corona. *Chemical Science*, 13(26), pp.7920-7932.
- [46] Mokhtari, N., Dinari, M. and Khosravi Esmaeilarkhani, F., 2023. Imine-linked covalent organic frameworks: a biocompatible and pH-dependent carrier for in vitro sustained release of doxorubicin. *ACS omega*, 8(28), pp.25565-25573.
- [47] Song, S., Wang, D., Zhao, K., Wu, Y., Zhang, P., Liu, J., Yang, G., Gong, P. and Liu, Z., 2022. Donor-acceptor structured photothermal COFs for enhanced starvation therapy. *Chemical Engineering Journal*, 442, p.135963.
- [48] Xia, R., Li, C., Yuan, X., Wu, Q., Jiang, B. and Xie, Z., 2022. Facile preparation of a thienoisindigo-based nanoscale covalent organic framework with robust photothermal activity for cancer therapy. *ACS Applied Materials & Interfaces*, 14(17), pp.19129-19138.
- [49] Guan, Q., Zhou, L.L., Zhou, L.N., Li, M., Qin, G.X., Li, W.Y., Li, Y.A. and Dong, Y.B., 2020. A carbon nanomaterial derived from a nanoscale covalent organic framework for photothermal therapy in the NIR-II biowindow. *Chemical Communications*, 56(56), pp.7793-7796.
- [50] Feng, J., Yang, S.P., Shao, Y.Q., Sun, Y.Y., He, Z.L., Wang, Y., Zhai, Y.N. and Dong, Y.B., 2023. Covalent Organic Framework-Based Nanomotor for Multimodal Cancer Photo-Theranostics. *Advanced healthcare materials*, 12(30), p.2301645.
- [51] Sun, Q., Tang, K., Song, L., Li, Y., Pan, W., Li, N. and Tang, B., 2021. Covalent organic framework based nanoagent for enhanced mild-temperature photothermal therapy. *Biomaterials Science*, 9(23), pp.7977-7983.
- [52] Wan, X., Ge, Y., Zhang, J., Pan, W., Li, N. and Tang, B., 2023. A covalent organic framework derived N-doped carbon nanozyme as the all-rounder for targeted catalytic therapy and NIR-II photothermal therapy of cancer. *ACS Applied Materials & Interfaces*, 15(38), pp.44763-44772.
- [53] Wang, W., Song, Y., Chen, J., Yang, Y., Wang, J., Song, Y., Ni, J., Tang, M., Zhao, J., Sun, Y. and Sun, T., 2022. Polyoxometalate-covalent organic framework hybrid materials for pH-responsive photothermal tumor therapy. *Journal of Materials Chemistry B*, 10(7), pp.1128-1135.
- [54] Hu, C., Zhang, Z., Liu, S., Liu, X. and Pang, M., 2019. Monodispersed CuSe sensitized covalent organic framework photosensitizer with an enhanced photodynamic and photothermal effect for cancer therapy. *ACS applied materials & interfaces*, 11(26), pp.23072-23082.
- [55] Feng, J., Ren, W.X., Gao, J.L., Li, F., Kong, F., Yao, B.J. and Dong, Y.B., 2021. Core-Shell-Structured Covalent-Organic Framework as a Nanoagent for Single-Laser-Induced Phototherapy. *ACS Applied Materials & Interfaces*, 13(15), pp.17243-17254.
- [56] Zhang, L., Song, A., Yang, Q.C., Li, S.J., Wang, S., Wan, S.C., Sun, J., Kwok, R.T., Lam, J.W., Deng, H. and Tang, B.Z., 2023. Integration of AIEgens into covalent organic frameworks for pyroptosis and ferroptosis primed cancer immunotherapy. *Nature Communications*, 14(1), p.5355.
- [57] Gao, P., Wang, M., Chen, Y., Pan, W., Zhou, P., Wan, X., Li, N. and Tang, B., 2020. A COF-based nanoplatform for highly efficient cancer diagnosis, photodynamic therapy and prognosis. *Chemical Science*, 11(26), pp.6882-6888.
- [58] Zhang, L., Wang, S., Zhou, Y., Wang, C., Zhang, X.Z. and Deng, H., 2019. Covalent organic frameworks as favorable constructs for photodynamic therapy. *Angewandte Chemie International Edition*, 58(40), pp.14213-14218.
- [59] Liu, S., Zhou, Y., Hu, C., Cai, L. and Pang, M., 2020. Covalent organic framework-based nanocomposite for synergetic photo-, chemodynamic-, and immunotherapies. *ACS Applied Materials & Interfaces*, 12(39), pp.43456-43465.
- [60] He, H., Du, L., Xue, H., Wu, J. and Shuai, X., 2022. Programmable therapeutic nanoscale covalent organic framework for photodynamic therapy and hypoxia-activated cascade chemotherapy. *Acta Biomaterialia*, 149, pp.297-306.
- [61] Wang, S.B., Chen, Z.X., Gao, F., Zhang, C., Zou, M.Z., Ye, J.J., Zeng, X. and Zhang, X.Z., 2020. Remodeling extracellular matrix based on functional covalent organic framework to enhance tumor photodynamic therapy. *Biomaterials*, 234, p.119772.



- [62] Wan, X., Zhang, H., Yan, Q., Hu, H., Pan, W., Chai, Y., Gao, Y., Li, N. and Tang, B., 2022. Three-dimensional covalent organic frameworks as enzyme nanoprotector: preserving the activity of catalase in acidic environment for hypoxia cancer therapy. *Materials Today Nano*, 19, p.100236.
- [63] Han, Z., Qian, Y., Gao, X., Yang, D., Cai, Y., Chen, Y., Jin, J. and Yang, Z., 2023. Hypoxia-responsive covalent organic framework by single NIR laser-triggered for multimodal synergistic therapy of triple-negative breast cancer. *Colloids and Surfaces B: Biointerfaces*, 222, p.113094.