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Covalent Organic Framework (COFs) in Targeted Drug Delivery and Therapeutics: A Critical Review

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Abstract

Covalent organic frameworks (COFs) are an emerging type of crystalline, porous polymers which are formed through covalent bonds using designed organic building blocks. Their high pore structuring, high surface area, and modular chemistry make them attractive platforms for targeted drug delivery and multimodal therapeutics. This is a critical review of the developments in the field of foundational COF chemistry to the most recent biomedical applications, especially with regard to drug encapsulation mechanisms (physical adsorption, covalent conjugation, and host-guest interactions), stimulus-responsive release strategies (pH, redox, enzyme, light), and targeting of the host (passive EPR accumulation and active ligand directed delivery). It focuses on discussion around nanoscale COF fabrication and functionalization approaches that permit controlled loading, colloidal stability, and receptor-mediated uptake, and multifunctional and theranostic COF systems that combine photodynamic/photothermal therapy, catalytic nanozyme activity, gene delivery, and multimodal imaging. In the literature, COFs have shown excellent drug loading capabilities and preclinical efficacy potentials. However, translation is a bottleneck due to several factors, including reproducibility, hydrolytic stability of linkages, full pharmacokinetics/toxicology, and scalable GMO-compatible synthesis. It reported methodological heterogeneities with loading/release assays and advocates standardized reporting (DLC, EE, release conditions, pre-/and post-structural characterization) and intensive in vivo PK/PD and immunotoxicity investigations. Lastly, strategic priorities were outlined in the field, which include rational linkage selection of biodegradability, orthogonal post-synthetic modification protocols, integration of computational design tools, and specific translational work to fast-track clinical translation of COF-based nanomedicines. Taken together, this review evaluates the potential and practical challenges of the COFs as next-generation targeted delivery and therapeutic vehicles.

Keywords: covalent organic frameworks, targeted drug delivery, biomedical applications, nanoscale COF fabrication.

1. Introduction

The development of therapeutic agents has improved a lot. Nonetheless, their therapeutic efficacies are usually influenced by the degree at which they may be conveyed to the specific site of action successfully. Therefore, drug delivery is a serious issue in contemporary medicine. The historic methods of drug delivery to the body have tended to cause systemic toxicity and decreased therapeutic efficacy, primarily due to the lack of solubility of the drugs, their rapid breakdown in the body fluids, and their indiscriminate distribution [1, 2]. Examples include the effect of transporting Doxorubicin or Paclitaxel freely in the body; they can be devastating to the body's healthy cells when they are not confined to just the body tumor they are meant to treat as anti-cancerous therapies, but rather as full body therapies [3]. These problems are demanding new drug carriers that are protective in transit, capable of selectively delivering to diseased cells, and can do so with even some smarts [4].

Over the past three decades, materials from nanotechnology tailored to overcome these delivery barriers have been given provisional attention. Liposomes, polymeric micelles, dendrimers, and metal organic frameworks (MOFs) are examples of nanocarriers that have provided various intelligent additions, such as improved drug loading, prolonged time of circulation in the body fluid, and enhanced tumor accumulation, delivering more drugs to their exact targeted site of action due to their enhanced permeability and retention (EPR) features. However, while some of these systems, Liposomal-based medicines, for instance, have reached clinical use [5], most nanocarriers are currently still found with varying persisting shortcomings, such as burst drug release [6], lack of structural versatility, low survival under physiological situations, and large-scale production. The next-generation search for carriers with higher design flexibility, robustness, and functionality, therefore, is an urgent concern for researchers.

The recent entry is the Covalent Organic Frameworks (COFs) as a potential platform in that regard. COFs were first reported in 2005 [9], and are crystalline, porous polymers formed by the combination of organic building blocks through strong covalent bonds. Their structural diversity enables the creation of two-dimensional (2D) layered structures or three-dimensional (3D) networks with permanent porosity and a very high surface area. Unlike amorphous polymers, COFs possess long-range order, and this enables them to be modified to different pore sizes, topologies, and chemical environments. More specifically, the COFs are fabricated with light elements, such as carbon, oxygen, nitrogen, and boron, which also opens the opportunity to metal-free, biocompatible drug carriers [8].

A few features make COFs particularly appropriate to biomedical use. Through their tunable pore structure, they are able to entrap small drug, peptide, or nucleic acid molecules [9]. Functional groups or biomolecules can be attached to their surface in such a way that they can be specifically targeted to individual cells [10]. Furthermore, the COFs can be adapted to respond to physiological or externally relevant conditions such as pH, redox conditions, enzymes, or light, to enable the release of drugs in a disease-specific microenvironment to be controlled [11, 12]. The combination of structural precision and stability of both covalent bonds is what makes the COFs in comparison to MOFs and mesoporous silica a balance between strength and versatility that other materials do not have.

In recent years, the biomedical research community has increasingly considered the COFs as multifunctional drug delivery systems and, therefore, alternative therapeutic delivery systems. These COF-based systems are photodynamic therapy (PDT) and photothermal therapy (PTT) systems, COF-based gene delivery systems, and COF hybrids incorporating therapeutic and diagnostic (theranostic) capabilities [13-15]. These advances indicate that COFs have the ability to transform the field of targeted delivery of drugs and take steps in a new direction in nanomedicine [16], but they have a narrow clinical translation. Long-term toxicology, biodegradability, and scale-up reproducibility are also under critical scrutiny, and there are few systematic comparisons with the FDA-approved carriers currently available.

The purpose of the review is to provide a general outlook of the current studies on COFs in terms of targeted drug delivery and therapeutics. Starting with an explanation of the fundamental, structural, and synthetic peculiarities of COFs, it is essential to identify their unique advantages over other porous materials. Then, the authors deal with the COF as a design of drug delivery, its encapsulation, stimuli-induced release, and targeting. Along with the delivery of drugs, the application of COFs in modern therapeutic methods, such as phototherapy, gene delivery, and theranostics, was also addressed. Finally, the biocompatibility, stability, and toxicity of COFs were raised, and finally, the significant problems, gaps in knowledge, and future prospects of clinical use have been identified. The review brings together up-to-date developments, subjectively assessing the challenges and potential of COFs in biomedical science, and offers insights into how COFs may be used in the coming generation of precision medicine.

2. Fundamentals of Covalent Organic Frameworks (COFs)

Covalent Organic Frameworks (COFs) are crystalline porous polymers, prepared via the use of organic building blocks that are joined together through strong covalent bonds. In reticular chemistry, the identification of COFs in 2005 by Cote *et al*. was an important development since it could now predictably assemble organic monomers to form unlimited periodic structures with long-lived porosity [7]. This is enabled through light elements, such as carbon, boron, oxygen, and nitrogen, which are light in density; and their highly ordered pore structure give them better surface area, tunability, and crystallinity [17, 18]. The following properties have made COFs stand out compared to amorphous porous polymers and other hybrid materials: they are the focus of an extensive range of applications in energy storage [19], catalysis [8, 20], biosensing, and separation [21] and are more recently being studied in biomedical applications such as targeted drug delivery and therapies [9, 22, 23].

2.1. Structural characteristics: 2D vs 3D COFs

COFs are structurally classified into two broad groups: two-dimensional (2D) layered frameworks and three-dimensional (3D) interconnected frameworks. In 2D COFs, building blocks create planar sheets which are stacked together by interactions of π-π and produce channels which are 1D perpendicular to the sheets [24, 25]. It is a layered architecture, which usually has a large surface area and supports interactions between the guests and the hosts; thus, 2D COFs are suitable for drug loading and release [10]. In comparison, 3D COFs build covalent connectivity in all three directions, which makes frameworks rigid with isotropic channels and improved mechanical stability. The interpenetrated networks that they form frequently produce higher pore volumes,

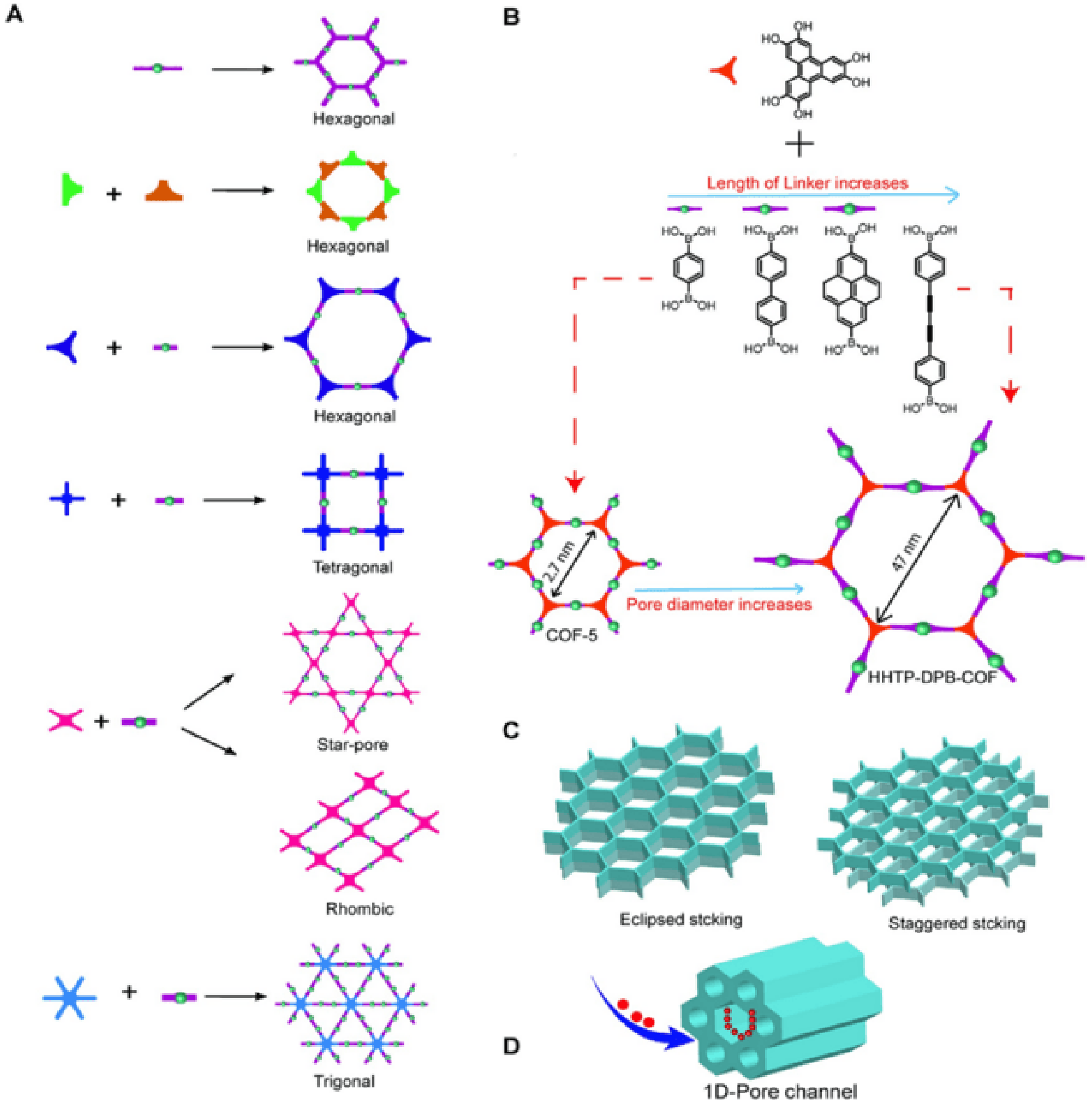

Figure 1. Modular nature of 2D COFs. The porosity of 2D COFs can be modulated by tuning pore geometry, pore size, layer stacking, and pore orientation, which are dictated by the choice of molecular building blocks. (A) Commonly observed pore geometries, (B) Linker length-dependent tuning of pore size. (C) Layer stacking modes: eclipsed vs staggered. (D) One-dimensional pore channels that facilitate guest transport. Adapted from [25].

enhanced accessibility, and strength in aqueous environments than their 2D counterparts [4, 22, 25]. Although this has these benefits, systematic comparisons between the biomedical performances of 2D and 3D COFs are scarce, and it is possible to explore them further.

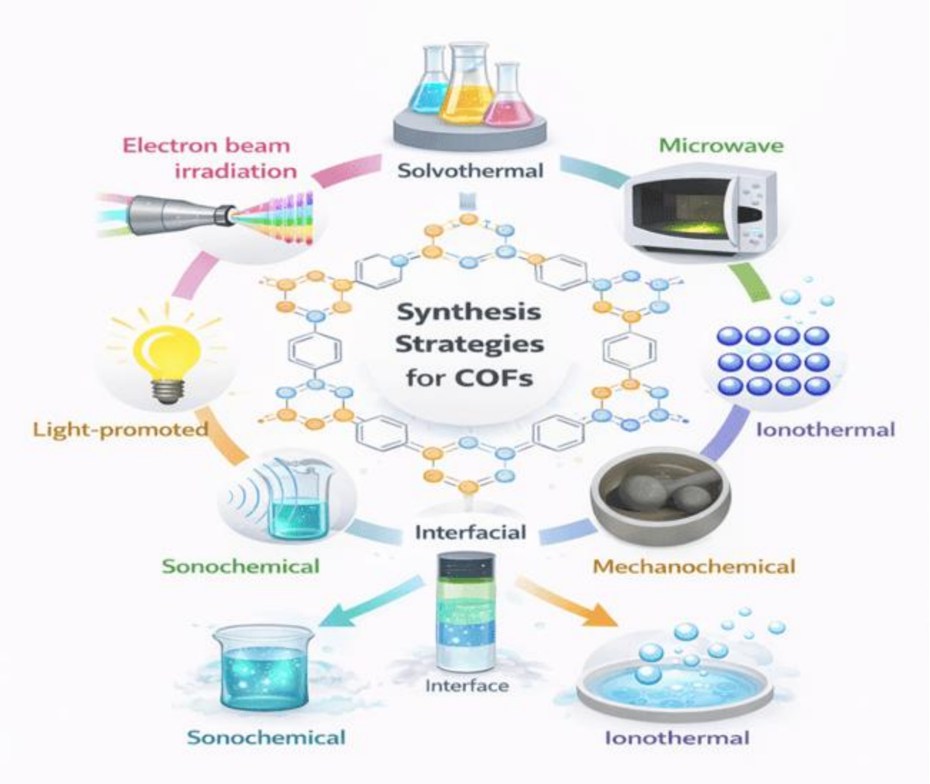

Figure 2. Overview of synthesis strategies for covalent organic frameworks (COFs). ***Figure 2.*** *Overview of synthesis strategies for covalent organic frameworks (COFs). Schematic representation summarizing the principal synthetic routes employed for the preparation of two- and three-dimensional COFs. The strategies are broadly classified based on reaction environment and energy input, encompassing solvent-mediated thermal methods, energy-assisted approaches, and interface- or mechanically driven processes. These diverse pathways enable controlled framework formation under a wide range of experimental conditions. Adapted from [22].*

2.2. Synthesis strategies

Synthesis of COFs has also developed very significantly as compared to the initial solvothermal preparations as described in Fig. 2, 3 and 4. The traditional method is solvothermal synthesis, which requires hours of incubation of monomers in closed tubes at autogenous pressure in the presence of pure crystallinity but with little scalability [9]. In a bid to overcome these shortcomings, the idea of microwave-assisted synthesis has been proposed, wherein reaction times have been shortened to hours, while in most instances the crystallinity can be enhanced [26]. Due to ionothermal synthesis, which relies on ionic liquid or molten salt solvents, high-temperature stability and new topologies can be achieved [27]. Simultaneously, mechanochemical synthesis has caught the interest of the environmentally friendly, solvent-free, and scaled-up process, but crystallinity is occasionally diminished [28]. Alternatively, more recently, interest has centered on a range of alternate methods such as interfacial, sonochemical, and light-assisted protocols, and these methods have enabled a wide range of COF production under mild conditions to be achieved [22]. Notably, synthetic factors including the concentration of monomers, the type of catalysts, and modulators can be adjusted to regulate nucleation/growth to, in turn, tailor particle size and morphology, which is an essential factor in the production of nanoscale COFs (nCOFs) that can be used biologically.

2.3. Methodologies of functionalization

Functionalization is necessary to enable COFs to be transformed into crystalline materials into functional biomedical platforms. It is dominated by two complementary strategies: bottom-up functionalization and post-synthetic modification (PSM). In bottom-up design, functional groups are integrated into monomers to create functional groups that are uniformly distributed in the framework and maintain crystallinity. Intrinsic incorporation of recognition sites or hydrophilic moieties can be done using this strategy. However, this can make synthesis and crystallization more difficult due to steric hindrance. In comparison, post-synthetic modification is done by grafting new functionalities onto existing COFs, covalently. Application to biomedical applications PSM has found extensive application in biomedical applications by providing the opportunity to attach polyethylene glycol (PEG) chains to enable biocompatible use, ligands or antibodies to enable active targeting, and stimulus-responsive linkers to enable controlled drug release [22] [29]. All these methods allow a flexible approach of COFs to drug encapsulation, stability in physiological conditions, and selective therapeutic activity.

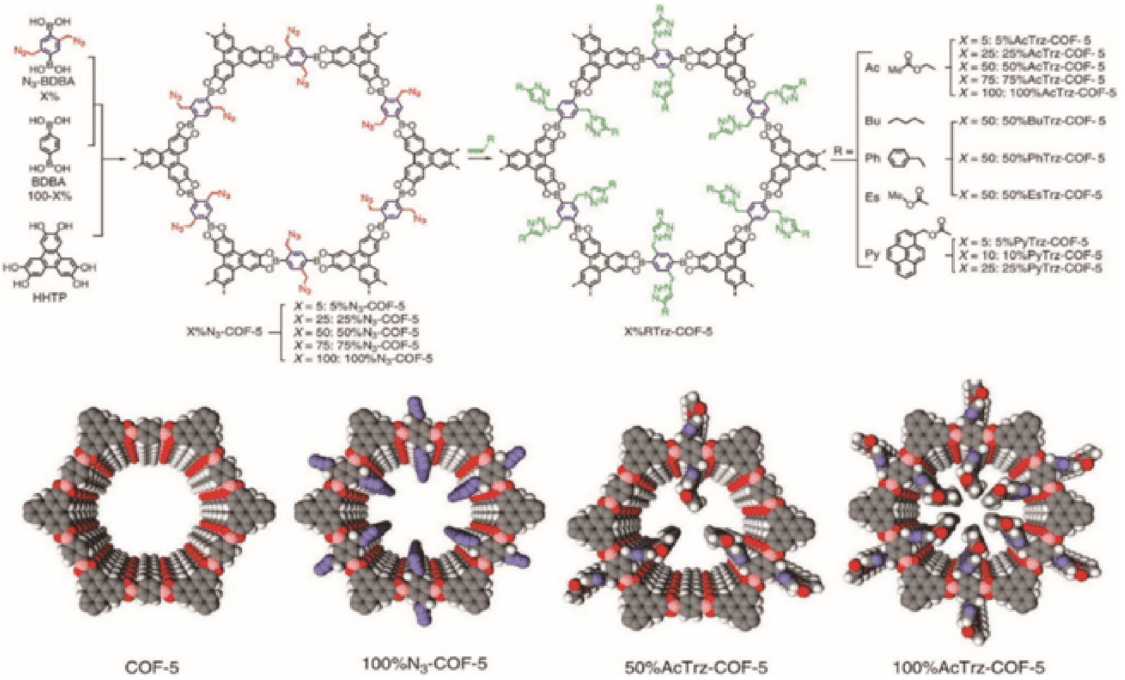

Figure 3. Inner pore space engineering of 2D COFs to achieve different functionality. Azide groups were introduced into the pore walls of a boronic acid-based COF by co-condensing azide-substituted benzene diboronic acid with HHTP in varying ratios. The azide groups were subsequently functionalized through click chemistry to incorporate diverse functionalities, enabling function-led 2D COF platforms. Adapted from [37].

2.4. Comparison with porous materials

COFs have similar features to other porous materials, but have some distinctive biomedical advantages. COFs are metal-free compared to metal–organic frameworks and do not contain any metal ions, thereby eliminating the potential effects of metal ion toxicity and providing more opportunities for functionalization [11, 32, 33]. Moreover, the covalent backbone of COFs is more stable than the coordination bond of MOFs, which increases the stability of the frameworks under physiological conditions [34, 35]. In comparison to mesoporous silica nanoparticles, COFs give a greater level of structural control, with pore size and topology controlled in detail in the synthesis process, and are not limited to templating approaches [35]. Lastly, COFs have a better predictability of pore structures and reproducible host-guest interactions than amorphous porous polymers, which enhances their usefulness in controlled drug delivery. However, issues of hydrolytic stability of some COF linkages and reproducibility of nanoscale synthesis are still being pursued [22, 37].

3. COFs in Drug Delivery

As described in Fig. 5, COFs have been of particular interest as drug-delivery vehicles due to the enabling aspects of the crystalline and porous structure, which allow the pore diameter, chemical composition, and topology properties to be chosen with deliberate control over drug loading, retention, and release [7, 29]. Over the past decade, researchers have investigated the application of COFs as a delivery system for small-molecule chemotherapeutics, photosensitizers, antibiotics, and nucleic acids. They have also integrated COFs with photothermal/photodynamic targets and imaging labels to form multifunctional theranostic systems. The critical review in this section includes; COFs encapsulation mechanisms, COFs stimuli-based release methods, COFs loading capacity and release kinetics, COFs targeting strategies (active and passive), and multifunctional/theranostic COF designs. When feasible, the review identifies reproducible results of independent studies and indicates frequent methodological constraints that need to be mitigated so as to be clinically applicable in medical settings

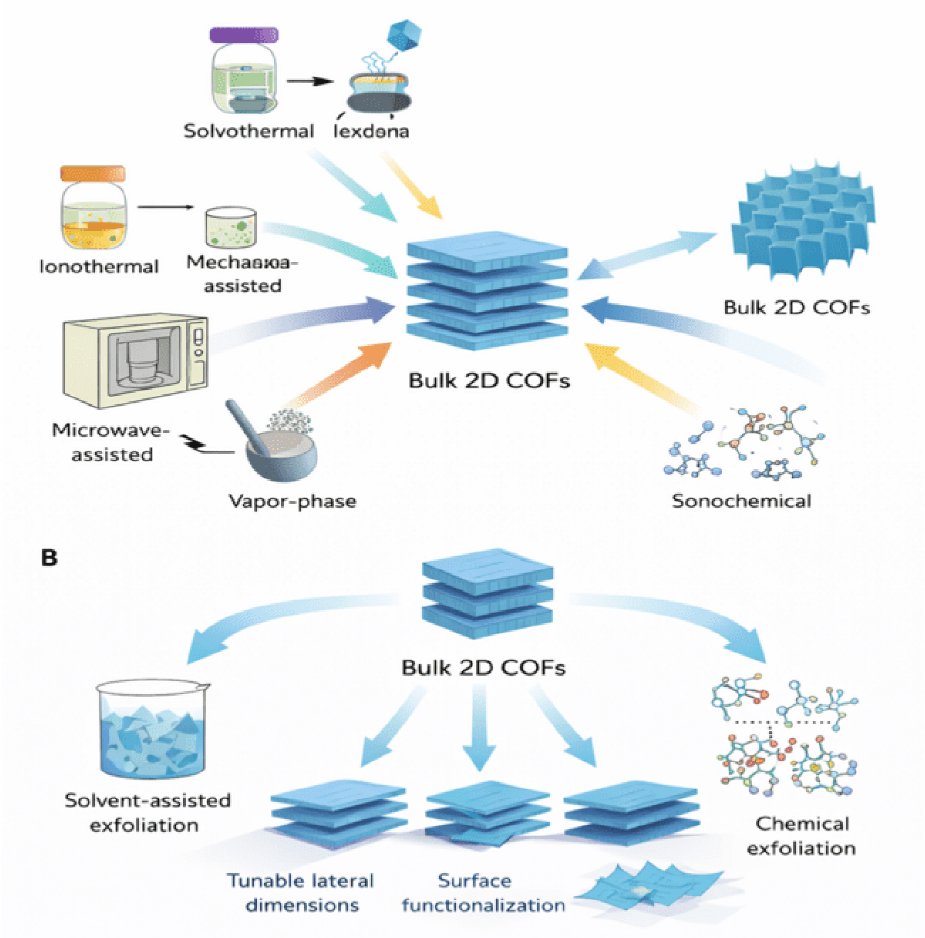

Figure 4. Synthetic strategies for bulk two-dimensional covalent organic frameworks (2D COFs) and their exfoliation into nanosheets. (A) Representative bulk synthesis routes, including solvothermal, ionothermal, mechanochemical, microwave-assisted, vapor-phase, and sonochemical methods, leading to the formation of bulk 2D COFs, (B) Exfoliation approaches such as solvent-assisted, mechanical, and chemical exfoliation that convert bulk 2D COFs into nanosheets with tunable lateral dimensions and surface functionalities. Adapted from [10].

3.1. Encapsulation mechanisms

The existing studies indicate that there are three key ways through which therapeutics can be incorporated into the COF platform (a) physical adsorption onto ordered pores or interlayer galleries, (b) covalent conjugation (pro-drug strategies) using cleavable linkers, and (c) supramolecular host-guest interactions (π-π stacking, hydrogen bonding, and electrostatic attraction). Each method has various benefits and limitations that authors in various COF chemistries have reported. The most common route reported has been physical adsorption since it is synthetically straightforward and does not block the porosity of the framework.

The drugs are normally loaded by incubating the pre-prepared COF powders or colloids into drug-containing solutions, then solvent exchange and drying [20, 22]. COFs with high surface area as well as tunable pore apertures (e.g., imine-linked, 2-2-ketoenamine-linked) can load a large variety of loads, ranging from small hydrophobic chemotherapeutics to planar photosensitizers [29]. Nevertheless, studies indicate that there is a broad disparity in the efficiency of COFs in loading and unloading drugs, primarily because of the differing pore chemistry, particle size, and the loading method administered.

This presents the necessity to standardize loading assays in order to make results across studies more reliable. Stronger control of stoichiometry and less premature release is provided by covalent conjugation (pro-drug strategies). In this method, pharmaceutical moieties are either built in as a part of the monomer (bottom-up) or attached post-synthetically using cleavage bonds, including but not limited to hydrazone, imine, ester, or disulfide bonds [38, 39].

Some have shown that covalent modification can significantly mitigate burst release and allow release in response to a defined stimulus (e.g., acidic pH or reductive intracellular conditions). The disadvantage, though, is synthetic complexity: forming covalent drug-COF linkages and retaining crystallinity and accessibility to pores can frequently demand customized synthetic procedures and raise the regulatory complexity of the resultant item [14].

Table 1. COFs Synthesis Strategies, typical conditions, advantages, limitations, and biomedical relevance.

Method	Typical conditions	Advantages	Limitations	Biomedical relevance	Ref
Solvothermal	Closed vessel, organic solvent, 100–200 °C, several days	High crystallinity, diverse topologies	Long reaction times; poor scalability; high solvent use	Benchmark method; used for many biomedically tested COFs	[9,29]
Microwave-assisted	Microwave irradiation, minutes–hours, lower temperature	Rapid synthesis; reproducible; higher yield; often smaller particles	Specialized equipment; some linkages less stable	Favours nano-COFs, better dispersibility for drug delivery	[26, 30]
Sonochemical / Light-assisted	Ultrasound irradiation or light-driven polycondensation	Mild conditions; faster reaction; can produce nanosheets/nanoparticles	Limited scalability; need optimization for crystallinity	Enables dispersible nCOFs and stimuli-responsive designs	[8]
Mechanochemical (ball milling, LAG)	Solvent-free or minimal solvent, ambient temperature	Green, scalable; very rapid (minutes); solvent-minimizing	Lower crystallinity in some systems; defect control needed	Attractive for scale-up and eco-friendly drug carriers	[8, 28]
Ionothermal / Molten salt	Ionic liquids or molten salts, high temperature (200–400 °C)	High thermal stability; access to unusual topologies	Ionic solvent residues; purification challenges	Limited biomedical use (toxicity, biocompatibility issues)	[27, 29]
Interfacial synthesis	Two immiscible solvents, reaction at interface	Produces thin films, nanosheets; controlled thickness	Small yields; requires delicate control	2D CONs with improved cellular uptake	[8, 29]
Room-temperature synthesis	Ambient conditions, days–hours, catalyst-assisted	Green, simple, cost-effective; avoids harsh solvents	Sometimes poor crystallinity; slower than energy-assisted	Biocompatibility improved by milder conditions	[15]
Continuous-flow / scalable processes	Flow reactors, controlled residence time, often with microwave or mechanochemical input	Scalable; reproducible; compatible with PAT (process analytical technologies)	Still under development; requires industrial demonstration	Critical for translation to pharma-grade nCOFs	[8, 31]
Post-synthetic activation & work-up	Solvent exchange, supercritical CO_2 drying, thermal evacuation	Necessary to reveal porosity, remove trapped solvents	Sensitive step: collapse of fragile COFs possible	Directly affects drug loading and reproducibility in vivo	[31]

Host-guest supramolecular loading takes advantage of complementary interactions between the drug and the pore walls (e.g., π-conjugated COFs such as porphyrin-containing frameworks) and the planar aromatic drug and photosensitizer co-delivered [40, 41]. Experimental results are supported by computational and molecular-dynamics studies that binding energy, orientation, and residence time of guest molecules are sensitive to pore chemistry (hydrophobic versus polar), the location of functional groups, and the diameter of pores.

It has been shown that the strongest effects are obtained by combinations of these modalities: e.g., a COF that physically entraps a drug and has cleavable surface tethers to control release, or a host-guest loaded COF that has post-synthetic PEGylation to allow colloidal stability. The intention of such hybrid strategies is to trade off load capacity with controlled release and in vivo stability [14, 42, 43, 44].

As an illustration from Fig 5, Vyas *et al.,* [45] constructed an imine-based TTI-COF with the nitrogen lone pairs of imines in which quercetin could be irreversibly anchored to allow its delivery to stay within the cell. Though the efficiency of drug loading was challenging to measure because of the unstable nature of quercetin, the experiment depicted that COFs can be applied to more than just chemotherapeutics in the sense of using a natural product.

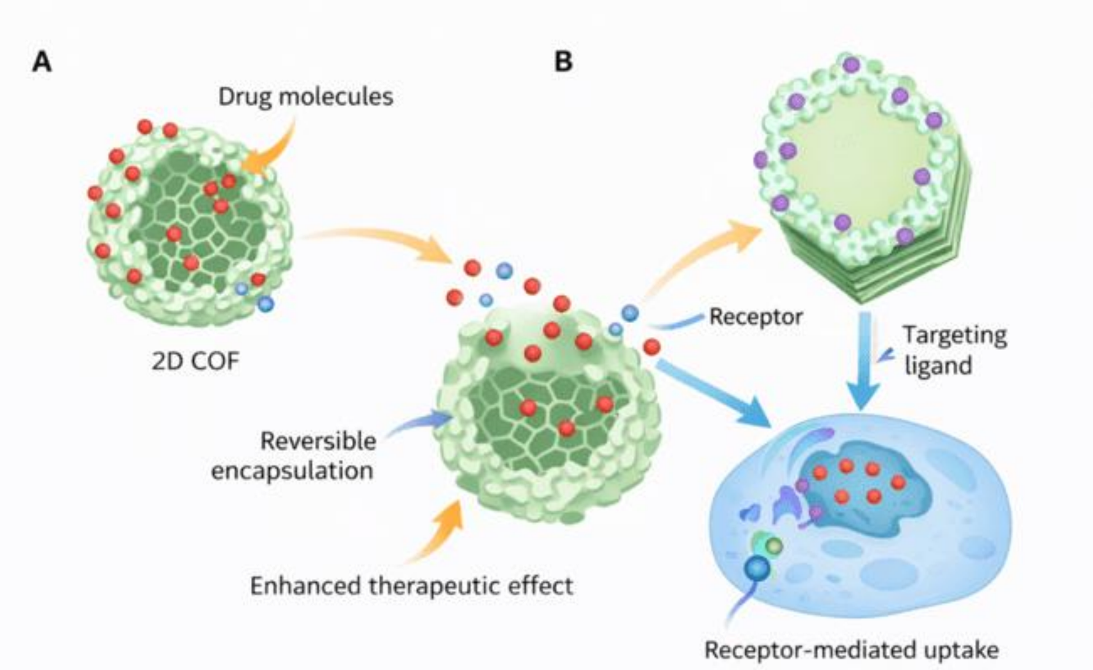

Figure 5. COFs in drug delivery applications. (A) Schematic illustration of drug loading into two-dimensional covalent organic frameworks (2D COFs). Drug molecules are encapsulated within the porous channels of the COF through reversible interactions, enabling controlled retention and release, which collectively enhance the therapeutic effect, (B) Conceptual representation of targeted drug delivery using surface-functionalized COFs. Targeting ligands attached to the COF surface facilitate receptor-mediated cellular uptake, leading to intracellular delivery of the encapsulated drug payload. Adapted from [63].

3.2. Stimuli-responsible drug release

The simplicity with which stimulus-responsive chemistries can be incorporated within the framework backbone or as surface decorations is one of the most significant appeals of COF-based systems. Across existing research, stimulus-responsive strategies can be categorized as endogenous (tumor acidity, redox potential, enzymes) and exogenous (light, heat, ultrasound).

pH-Responsive Release: The microenvironment of tumors, as well as the endo/lysosomal compartments, is more acidic when compared to the blood, and the imine/hydrazone bonds linked with COFs are sensitive to hydrolysis by acids [46]. Hence, a range of publications have taken advantage of these acid-sensitive linkages in COFs modification or acid-cleavable caps to be able to cause a responsive release in areas with acidic pH of 5-6 [22]. There is a consistent report of higher cumulative release at acidic pH than at neutral pH, with some studies indicating more cell-targeted effects on cell sites [47, 49]. However, caution is necessary since most studies have used only in vitro pH buffers that fail to replicate the dynamic and heterogeneous pH gradients found in vivo, and few of them have used COF structural integrity measurements under the same conditions.

Redox-responsive release: Reduced glutathione (GSH) is enriched in the intracellular environment, particularly in tumor cells. COF-associated linkers and surface tethers have also been engineered with disulfide and diselenide bonds in a manner that disulfide cleavage in high-GSH environments causes release of intracellular cargo [50, 53]. A number of porphyrinic COF designs and COF-polymer hybrid systems demonstrate persuasive in vitro GSHactivated release and better therapeutic action in cell-based tests [29, 54, 55]. Notably, redox-responsive delivery can frequently generate fragments sufficiently small to be cleared by the kidneys, which overcomes the issue of biodegradability; although extensive in vivo studies on the effect of safe and full clearance are comparatively few

Endogenous triggers, enzyme-responsive, and others: COF particles have also been covered with enzyme-sensitive coatings (e.g., hyaluronic acid degradable by hyaluronidase) as a shedding mechanism whereby the underlying targeting ligands are revealed or drug load is released [22, 56, 57, 58]. More direct incorporation of enzyme-cleavable bonds in COF backbones is less prevalent, not commonly seen across research, likely because of synthetic complications; the field is in need of more such efforts that integrate enzymology and reticular chemistry design.

Exogenous strategies (light- and heat-triggered strategies): Applying conjugated COFs, especially those that commonly possess porphyrin or other photoactive units, can serve as in-built photosensitizers, useful in photodynamic therapy (PDT) and acting as photothermal agents (PTT) in the presence of near-infrared (NIR) absorbing cores. Some reports showed how COFs can generate reactive oxygen species (ROS) upon illumination and release chemotherapeutics, which attains synergistic chemo-photo therapy in vitro and in small-animal models [40, 41, 55, 59]. However, this has significant drawbacks of light penetration in tissues and possible off-target phototoxicity, which are shortcomings of photoactive nanomedicines in general and not specific to COFs.

Multi-stimuli systems: COFs that combine multiple triggers (e.g., pH + redox, or pH + light) are being designed with increased control: retention in circulation, partial opening in the tumor interstices, and full release intracellularly [17, 60, 61, 62]. Such architecturally complicated designs promise to optimize selectivity but impose a greater task on the mechanistic validation: the researchers would have to prove orthogonal responsiveness and disprove premature activation. The literature across the stimulus classes has come to a consensus on two practical issues: first, the chemistry of the linkage or coating should be adjusted to physiologically relevant trigger magnitudes (e.g. 0.5 -1.0 unit pH differences or intracellular GSH concentrations), and second, mechanism-oriented experiments (PXRD, TEM before/after stimulus, quantitative release assays) are required to attribute the observed release to the intended trigger and not to incidental COF degradation or dissolution.

Besides pH- and redox-sensitive designs, there are also COFs that exhibit targeting capacity by receptor-mediated uptake. As an example, Mitra and colleagues [63] prepared a 5-FU-targeting folate receptor TpASH-FA postsynthetically that was functionalized with folic acid. Even though the loading efficiency of the drug was relatively small (at around 12 percent), it represents the first successful example of functionalized COFs adhering to the receptor-mediated endocytosis pathway, which highlights the versatility of COFs in targeted therapies.

3.3. Loading capacity and release kinetics

The capacity of covalent organic frameworks (COFs) to act as smart drug carriers relies not only on their ability to accommodate therapeutic cargo, but also on their ability to release the cargo under biological conditions. Drug-loading capacity has been reported to range widely among single-digit numbers all the way to a load of more than 30 wt%, with the final result being highly dependent on the framework structure, surface chemistry, and the physicochemical properties of the drug [8, 64, 65]. The most commonly investigated model drug is doxorubicin (DOX); however, studies have also been conducted with 5-fluorouracil and paclitaxel, as well as various antibiotics, indicating that it can be used more widely [66].

One of the general themes across literature is the significance of pore architecture as a great determinant of COFs' drug loading capacity. Microporous COFs are highly fitting for housing small molecules due to their narrow channels, whereas the use of mesoporous or hierarchical structures is often found for housing larger drugs or co-loading approaches. In other recent investigations, a well-designed pore-interface engineering (triazine motifs, thiol or pyridyl decorations) has been demonstrated to boost performance by orders of magnitude; one triazine-based COF delivered more than 30 wt% DOX loadings onto its pore-wall, despite a relatively small total BET surface area, highlighting that pore-wall chemistry can be a better capacity determinant than overall BET surface area [65]. Likewise, imine-linked and 2-ketoenamine COFs containing open mesopores always have a higher encapsulation ability compared to pure microporous networks [64].

Surface chemistry is also important besides architecture. Polarized groups like hydroxyls and carboxylates facilitate hydrogen bonding of hydrophilic drugs, whereas planar aromatic molecules are stabilized by aromatic π-conjugated pore walls [41]. This is why porphyrinic COFs have an unusually high affinity to aromatic drugs, and in certain instances, provide the opportunity to co-deliver chemotherapeutics and photosensitizers. Computational simulations also prove that the energies of drug and pore interactions and orientations are the key determinants of loading capacity and release profiles [66]. COFs also depend on the performance of the particle size and their morphology. Particles down to the nanoscale (50-200 nm) are better dispersed in aqueous solutions, and cells internalize them better, and with shorter diffusion distances, drugs release faster. PEGylated surfaces or surface functionalization techniques increase colloidal stability with possible steric hindrance to loading capacity [8].

In spite of the fact that much attention is usually paid to COF design, loading protocols alone produce a significant influence on reported results. The extent of loading and encapsulation efficiency of drugs (how much drug a COF can carry and retain) is dependent on various factors, including the solvent it is using, the chemical form of the drug (salt or free base), the time it is incubated, and how it is washed. The use of doxorubicin hydrochloride (DOX ·HCl) as an example is frequently transformed into the hydrophobic form of the drug, so it can react with the COF structure more effectively. However, variability is thus brought across studies by this practice, as prepared formulation seems different in labs [67]. Such a methodological heterogeneity complicates the comparison between studies and demands standardized protocols.

The inclusion of drugs is followed by release kinetics, determining therapeutic value. The pattern of release in most COFs is often two-phase: a burst release (when drugs are loosely gated to the surface) and a slower and more gradual release (when drugs are trapped within the pores). Qiu *et al*., [68] indicate that release is typically increased in the presence of biologically relevant stimuli, including acidic pH or high glutathione (GSH) levels. In another experiment, imine bond hydrolysis caused DOX@COF, loaded with a concentration of approximately 32 wt%, to release the drug faster at acidic pH than when neutral conditions were used [64]. This same PEGylated redox-responsive COFs maintained the drug under physiological redox conditions but released it effectively in GSH-rich intracellular conditions [8].

In order to model these behaviors, Higuchi, Korsmeyer-Peppas, or first-order equations are often used. Nonetheless, the strictest work is pushed even further with the incorporation of kinetic modeling and structural characterization prior to and following the release (PXRD, BET, TEM). An example of such studies was Mokhtari *et al*., [69], who established that pH-dependent release was correlated with partial hydrolysis of the bond and with the loss of crystallinity, which suggests that the chemical cleavage process, rather than mere diffusion, took place. More recently, more realistic models of COF disassembly under physiological stimuli have been suggested using mechanistic models inspired by polymer carriers, which combine diffusion and erosion of the matrix [70].

Although this has been advanced, reproducibility is still a problem. Experimental protocol variability, ratio of drug to carrier, release media, dialysis membrane, and agitation still do not allow meta-analysis and generalizable design principles [67].

To conclude, COFs show a promising potential of delivering drugs with high capacity and stimulus responses; however, there is a requirement for more purposeful structural design, surface chemistry, particle size, and loading protocols to produce effective outcomes. Standardization of reporting of drug loading content (wt%), encapsulation efficiency, release conditions, and coupled structural analyses will also be needed. This rigor will facilitate effective cross-study comparisons and accelerate the rational design of clinically relevant COF-based drug carriers.

3.4 Targeting strategies

One of the aims of any drug-delivery platform is to achieve optimal therapeutic concentration in disease sites with a minimum of off-target exposure. Covalent organic frameworks (COFs) have embraced the major targeting approaches taken in nanoparticle therapeutics (1), passive accumulation through the enhanced permeability and retention (EPR) effect (2), active ligand-directed targeting, and 3) externally guided or image-guided approaches, and their modular chemistry is well poised to coordinate these approaches [29]. However, the literature also highlights significant limitations and trade-offs that should be considered to obtain clinical translation.

Passive targeting is the easiest and most common route that is used in COF research. COFs, when prepared in the form of nanoparticles (nCOFs, typically, 50-200 nm), can take advantage of the EPR effect to accumulate in tumor interstitia, and numerous studies in rodents have shown that COFs have improved tumor accumulation and indices as compared to free drug [8, 71]. The practical design options that can be used to maximize passive accumulation are rigorous regulation of the particle size and polydispersity, surface passivation (e.g., PEGylation or albumin coating) to increase the half-life of the particle during circulation, or neutralization of surface charges to reduce opsonization [53, 67]. Nevertheless, dependence on EPR is more and more regarded as inadequate: human tumors are not homogenous in their vascular permeability and extracellular matrix structure, and the EPR effect in murine models does not always prognostically transfer to clinical settings [1, 72]. Modern COF designs have therefore been typically integrated with passive techniques to enhance robustness in biological environments by employing other targeting techniques.

Ligand-mediated targeting is an active process that seeks to enhance cellular selectivity over and above that of EPR. Since COFs can be functionalized with various ligands, such as small molecules (folate), peptides (RGD), polysaccharides (hyaluronic acid), aptamers, and antibody fragments, a wide variety of target cell receptors can be engaged [63, 73]. These functionalizations can typically augment target-mediated endocytosis and in vitro cytotoxicity in target-expressing cell lines, and some animal models can be translated into improved tumor inhibition [63, 73]. COFs have orthogonal post-synthetic modification (PSM), which allows the addition of ligands without collapsing the crystallinity and porosity of their frameworks [74]. However, significant pragmatic trade-offs are reported: large biological ligands or entire antibodies can change biodistribution, become more immunogenic, and clear faster, but smaller ligands (folate, peptides, aptamers) tend to maintaining stealth characteristics and achieve selectivity [74]. One of the most common limitations in reports is the fact that most of the active-targeting studies reported provide in vitro uptake and efficacy of small-animal models, but they do not include systematic in vivo comparisons of targeted versus untargeted formulations that entail full biodistribution, pharmacokinetics (PK), and immune profiling, which are necessary to assess the translational value [76].

The targeting ability can be extended using hybrid and externally directed strategies that combine COFs with magnetic cores, radiolabels, or imaging moieties. Core@shells (e.g., Fe3O4) designs (e.g., Fe3O4) allow magnetic imaging and active targeting, combined with MRI contrasting; the design of core@shells still maintains COF porosity to load drugs; core@shell designs have been shown to generate active targeting and chemo-photothermal effects in preclinical models [53, 78]. Imaging techniques such as radiolabels, photoacoustic tags, or magnetic guidance can be used to monitor the location of COFs in the body and ensure that the drug is getting to the correct location. It is a real-time monitoring that comes in handy when you need to modify doses and ensure delivery. Even though such hybrid systems might hold potential, they also come with their own safety concerns, such as the possibility of inorganic material or radiotracer buildup in the long term that will necessitate cautious testing to be administered to patients [75].

In general, effective targeting using COFs involves a combination of strategies: Preparing particles that are sufficiently small and stealthy enough to accumulate passively in diseased tissues, incorporating small targeting ligands to enhance uptake by particular cells, and tracing the particles using imaging or magnetic techniques for precision monitoring. Thus, to get to the next level, beyond initial laboratory investigations, investigators will be required to undertake standard measures of the principal characteristics (such as size, surface charge, and density of the ligands), to directly compare targeted versus untargeted systems in various models of disease, and to perform comprehensive safety and pharmacology studies. These are steps that would be necessary to take the COF-based targeting towards clinical use.

3.5. Multifunctional and theranostic COFs

The ordered porosity of COFs and their tunable chemistry, and the inherent modular structure of these nanosystems are of particular interest to multifunctional and theranostic applications where delivery, therapy, and monitoring are combined into one nanosystem. Researchers have taken advantage of these properties in the last ten years to combine drug delivery with phototherapy, catalysis (nanozyme activity), gene delivery, and imaging; the resultant platforms often exhibit synergistic therapeutic outcomes in the preclinical environment. However, the combination of various functions is associated with design trade-offs and translational issues, which are worth consideration.

COFs are naturally photosensitised or photothermal by porphyrin-, phthalocyanine-, and other π-conjugated linkers. Nanoscale porphyrinic COFs or exfoliated COF nanosheets have been developed to co-deliver chemotherapeutics (e.g., doxorubicin) and produce singlet oxygen (PDT) or heat (PTT) under light irradiation, which have better tumor suppression compared to any monotherapy in murine models [71, 77]. One important material benefit is the ordered structure: porosity spatially isolates photosensitizer units, which decreases aggregation-induced quenching and maintains photoactivity. However, the application of PDT is inherently limited in the extent of light penetration and oxygen reliance, which is why some current approaches propose the inclusion of oxygen-generative or catalase-mimetic components (nanozymes) to overcome the hypoxia and enhance the production of ROS in tumors [73]. These self-strengthening photocatalytic platforms are an example of how the COF modularity can be used to overcome biological bottlenecks in phototherapy.

Table 2. COFs in drug delivery applications. (A) Schematic illustration of drug loading into two-dimensional covalent organic frameworks. These tabled examples highlight how COFs have developed into complex nanoplatforms that combine chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), and imaging. Drug loading efficiency, morphology, therapeutic outcomes, and tested biological models are reported properties.

Year	COF System	Linkage Chemistry	Morphology/ Size	Therapeutics/ Photosensitizers	Distinctive Features	Biological Activity	Ref
2016	PI-3-COF, PI-2-COF	Imine	Nanoparticles (~50 nm)	5-FU, captopril, ibuprofen	Achieved up to 30% loading (notably with 5-FU); good aqueous dispersibility and biocompatibility	Enhanced cytotoxicity in MCF-7 cells	[86]
2016	TTI-COF	Imine	Elongated rods	Quercetin	Improved anticancer potency of quercetin when COF-loaded versus free drug	Tested in MDA-MB-231 breast cancer cells	[45]
2016	COFABA	Boroxine	Surface-layer morphology	Copper phthalocyanine	First example of a photoresponsive boroxine COF; UV-driven framework switching	–	[4]
2017	TpASH-FA	β-ketoenamine	Nanosheets	5-FU	Postsynthetic folic-acid functionalization enabled receptor-mediated targeted drug delivery	MDA-MB-231 breast cancer cells	63]
2018	TrzCOF	Imine	Nanorods (40–50 nm)	– (inherent anticancer COF)	COF itself showed intrinsic cytotoxicity via ROS generation	HCT-116 colon cancer cells	[87]
2018	PEG-CCM@APTES-COF-1	Boroxine	Nanodisks (120–150 nm)	Doxorubicin, curcumin	COF–polymer nanocomposite enabled dual-drug delivery with fluorescence tracking	HeLa cells & xenografted mice	[88]
2019	LZU-1-BODIPY-2I	Imine	Nanoparticles (~100 nm)	BODIPY dye (PDT)	Conjugation of dye to COF scaffold increased uptake, ROS, and PDT efficiency	HeLa & MCF-7 cells; xenograft models	[77]
2019	ICG@COF-1@PDA	Boroxine	Nanosheets (170 nm × 5.4 nm)	Indocyanine green (NIR PDT)	Suppressed dye aggregation and quenching; improved photodynamic effect	Mouse colorectal cancer models	[77]

Table 2. Continued.

Year	COF System	Linkage Chemistry	Morphology/ Size	Therapeutics/ Photosensitizers	Distinctive Features	Biological Activity	Ref
2019	COF-909	Imine	Nanoparticles (120–150 nm)	Intrinsic COF photosensitizer	Framework itself produced ROS under 630 nm light, enabling PDT without external dye	CT-26 colorectal tumor model	[88]
2019	COF nanodots–PEG	Imine (porphyrinic)	Nanodots (~4 nm)	Porphyrinic COF nanodots (PDT)	PEGylated nanodots showed strong photodynamic activity under 638 nm irradiation	HeLa cells; mouse tumor models	[88]
2019	Py-BPy•-COF/PEG	Imine (pyrene-based)	Nanoparticles (~164 nm)	Photothermal agent (808/1064 nm NIR)	Radical-stabilized COF enabled both photothermal therapy and photoacoustic imaging	A549 xenografted tumors in mice	[89]
2019	COF@IR783@CAD	Boroxine	Nanoparticles (~250 nm)	Cyanine dye (PTT) + Dox prodrug	Synergistic chemo-photothermal platform with strong in vivo tumor inhibition	4T1 breast cancer models	[89]
2019	VONc@COF-Por(3)	Imine	Nanoparticles (~140 nm)	Porphyrin + naphthalocyanine	Dual-mode PDT and PTT agent within one COF scaffold	MCF-7 cells and xenografts	[88]
2019	PEGylated COF–LZU-1–CuSe	Imine	Nanoparticles (~150 nm)	CuSe (photothermal)	Enabled combined PDT/PTT using CuSe with COF scaffold	HeLa tumor models	[90]
2019	HA-functionalized COF–LZU-1–Ag2Se	Imine	Nanoparticles (~150 nm)	Ag2Se (photothermal)	Hyaluronic acid surface gave targeting ability; enabled combined PDT/PTT	HeLa tumor models	[90]
2019	COF-366	Imine (porphyrinic)	Nanoparticles (~100 nm)	Porphyrinic photosensitizer	Allowed photoacoustic imaging with PDT/PTT dual therapeutic mode	4T1 cells & tumor xenografts	[77]

In addition to oxygen modulation, COFs have been designed to accommodate catalytic centers (metal or metal oxide sites) to catalyze in situ chemical reactions: Fenton-like reactions to generate hydroxyl radicals, peroxidase-like reactions to convert H_2O_2 to cytotoxic species, or catalase-like reactions to increase the local O2 [73, 78, 79]. These catalytic functions, in combination with chemotherapy or PDT, have the potential to increase local damage in the tumor microenvironment (TME) in a selective way. Nevertheless, the addition of metal centers brings two issues: (1) the destabilization of the framework, or blockage of the pores, with the consequential reduction of drug loading, and (2) the retention of metal in the long term and systemic toxicity. These will need to be countered by careful placement (e.g., after synthetic-metalation in well-defined locations) and extensive biodistribution/clearance studies.

Although MOFs and lipid-based nanoparticles have taken over the nucleic-acid delivery, new COF platforms have potential in the delivery of siRNA and DNA [80]. Nucleic acids may be electrostatically bound by cationic or iminium-linked COFs, thereby preventing the degradation of nucleic acids by nucleases. Zhou *et al*., [81] reported an iminium-linked COF that delivered SLC7A11 siRNA, along with a metabolic inhibitor, causing a synergy between ferroptosis and apoptosis in fibrosarcoma models. COF-polymer hybrids have the potential to enhance cellular uptake and endosomal escape through the incorporation of membrane-disruptive or pH-responsive moieties [82 – 83]. Future issues involve the need to enhance efficient endosomal escape, altering release kinetics in order to fit into therapeutic windows, and the need to achieve reproducible transfection efficiencies that are equivalent to established vectors.

The major advantage of COFs is their capability to load various payloads in an independent microenvironment within the same system (e.g., hydrophobic chemoagents in π-rich walls and hydrophilic cargo in polar pockets) and to develop sequential or stimulus-controlled release (pH, redox, light). These are DOX co-delivered with photosensitizers to make chemo-PDT and COFs, which release a primary drug within the TME, and a secondary payload intracellularly after cleavage by GSH. This time control finds great utility in combination therapies in which the order of action is dictated by time, yet controlled sequential release would have to be demonstrated through kinetic studies and with mechanistic validation (PXRD, TEM, HPLC quantification) under biologically relevant conditions.

COFs have also been conjugated with imaging reporters, Fe3O4 cores in MRI, fluorescent dyes to track them optically, photoacoustic reporters, or PET reporters, which allow using MRI or optical imaging to direct therapy and trace biodistribution in vivo. In core at shell (imaging core at COF shell) designs, the imaging and therapeutic compartments are decoupled; the core has contrast and the COF shell has porosity through which drugs can be loaded [78]. Imaging-enabling COFs improve confidence in delivery and are able to allow longitudinal evaluation of therapeutic response, but are more complex to synthesize and regulate.

Any additional functionality threatens to undermine other desirable properties (porosity, crystallinity, colloidal stability). Best practices to maintain performance are: (1) assembly of the COF scaffold initially under conditions maximizing crystallinity and porosity; (2) orthogonal, mild post-synthetic modifications (click chemistries, mild metalation) to add additional functionality; and (3) assessment of structure and functionality before and after modification (PXRD, BET, TEM, drug loading/release assays). The dual-ligand-assisted encapsulation approach and staged core@shell growth are viable strategies that generate multifunctional COFs, maintaining framework integrity [78].

Most multifunctional COF systems are still in the proof-of-concept phase despite their strong supporting preclinical results. Limitations include the limited size of cohort studies, insufficient PK/BD profiling, the absence of scalability pathways, and minimal available long-term exposure/toxicity and biodegradation. The complexity of manufacturing and regulatory requirements associated with mixed organic-inorganic composites is also a major challenge. To focus on clinical translation, the field must have simpler, high-impact, multifunctional combinations (e.g., chemo + PDT with oxygen-generating ability), high-quality PK/PD and toxicity testing in larger animal models, and the creation of scalable and solvent-efficient syntheses that can be used in GMP settings.

Multifunctional COFs offer a platform for next-generation functional theranostics [84, 85]. With an emphasis on mechanistically rational combinations, staged chemistries that maintain framework integrity, and a dedication to full preclinical development (PK/BD, repeated-dose toxicity, and identification of metabolites), the field can shift its emphasis to innovative demonstrations of clinically relevant nanomedicines.

4. COFs in Beyond Delivery Therapeutics.

Initially designed to perform gas sorption and catalysis, covalent organic frameworks (COFs) have quickly become popular in mediating therapeutic modalities beyond mere drug delivery with their predictable chemistry and easy functionalization, enabling them to serve as ordered porous systems in photodynamic/photothermal therapy (PDT/PTT), nucleic-acid delivery, combined (multi-modal) therapies and image-guided theranostics. Here, we discuss the recent progress, describe the examples of the most

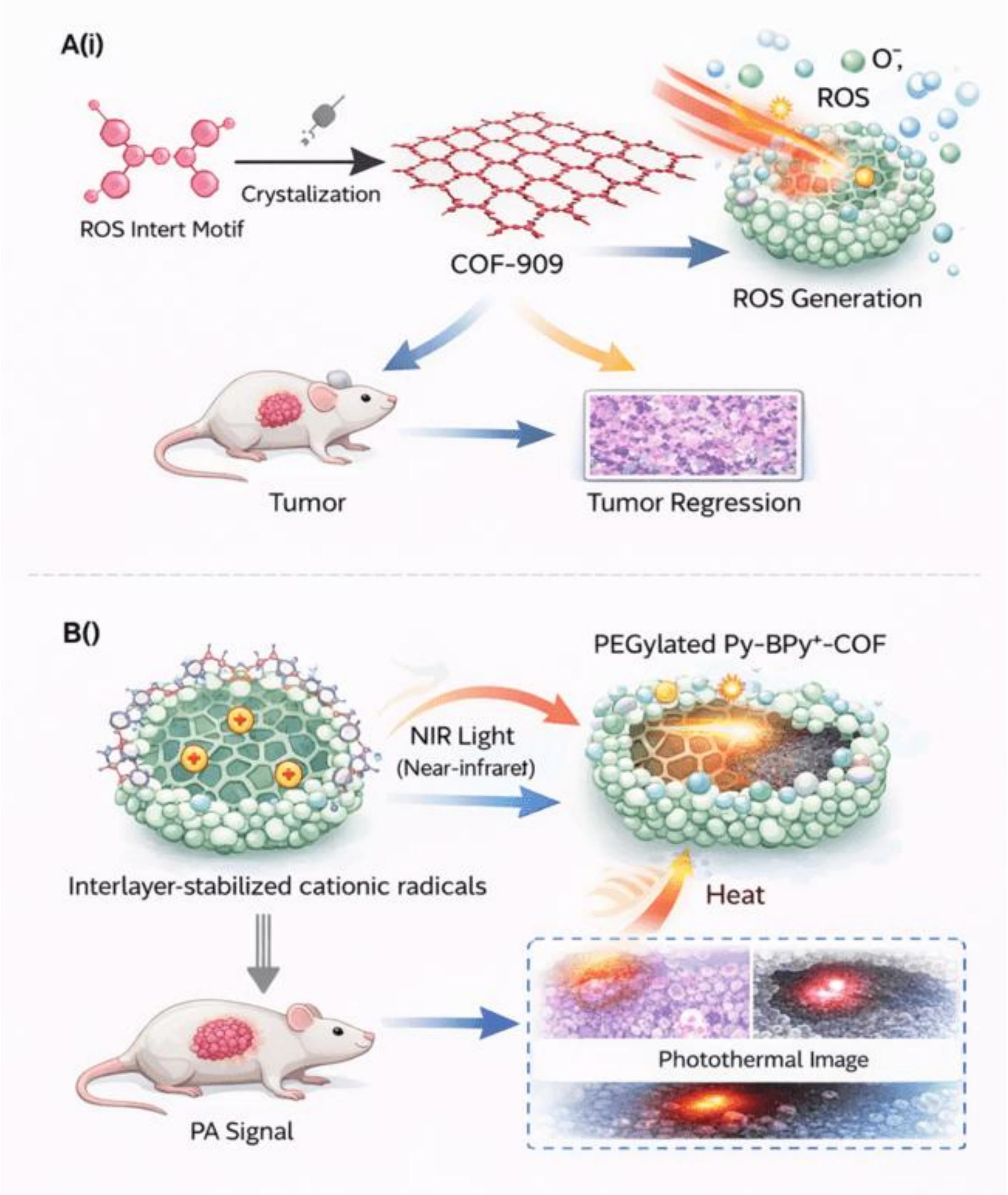

Figure 6. COFs in phototherapy applications. (A) Conceptual illustration of a photoresponsive covalent organic framework (COF) constructed from photodynamically inactive organic building units that assemble into an extended COF network capable of generating reactive oxygen species (ROS) upon light irradiation. Light activation induces ROS production, enabling photodynamic therapeutic effects in tumor tissues. (B) Schematic representation of a functionalized COF designed for photothermal and photoacoustic applications. The ordered COF architecture facilitates near-infrared (NIR) light absorption and efficient photothermal conversion, enabling combined photothermal therapy and imaging-guided treatment through photoacoustic signal generation. Adapted from [88, 89].

representative, and critically analyze the remaining obstacles to translation.

4.1. Photodynamic and photothermal therapy (PDT/PTT) Using COFs

Photodynamic therapy (PDT) and photothermal therapy (PTT) are treatments involving drugs and light to achieve targeted cancer therapy. Photoactive linkers (porphyrins, phthalocyanines, and other π-conjugated units) can be directly added to the framework backbone to create COFs that serve as inherent photosensitizers of photothermal converters, whilst preserving pore space to co-load drugs as shown in Fig. 6. Porphyrinic COFs and exfoliated nanosheets have demonstrated the ability to (i) generate singlet oxygen to act as a PDT biomolecule, (ii) change NIR light to heat to act as a PTT biomolecule, and

(iii) co-deliver chemotherapeutics to synergistically tumour ablate in vivo [73, 77]. Such intrinsic photosystems circumvent certain issues of dye aggregation since quantum yields are maintained by spatially isolating chromophores by the rigid structure [77]. An example is the design of crystalline frameworks, like COF-909, based on a starting PDT-inert building block that becomes active as an ROS generator through crystallization and shows major tumor remission in mouse colorectal cancer models, when irradiated with lasers [88]. Likewise, the COFs that are radical-stabilized, like the Py-BPy+•-COF, can strongly convert light into heat at the near-infrared (NIR) region, allowing it to be used in photoacoustic imaging to guide treatment [64]. These case studies demonstrate how rational molecular design can then be converted to functional phototherapy results. One of the most significant benefits of COFs in PDT/PTT is that the same platform can be used as a therapeutic agent and as an imaging probe, or both therapies and phototherapy can coexist on the same platform. But although small-animal studies are uniform in demonstrating tumor suppression, most are based on short-term studies in small cohorts and infrequently on repeated dosing, chronic toxicity, or biodistribution profiling. In the absence of these, the clinical predictability of phototherapy as a result of COF is unpredictable.

Developments in recent years deal with the biological drawbacks of phototherapy. Lack of oxygen in the tumor environment negatively affects PDT delivery; various groups thus introduce catalase-like nanozymes or oxygen sources into COFs to convert endogenous H_2O_2 into O_2, thereby replenishing oxygen levels and enhancing the production of ROS during light irradiation [73]. The other strategies involve donor-acceptor (DA) intercalation and radical stabilization to enhance photothermal conversion efficiency and NIR window absorption [91, 92]. These engineered COFs have been shown to be superior tumour suppressors in small-animal models over monotherapy controls, although a majority of the literature is in its infancy, using small cohorts.

4.2. Gene delivery (siRNA, DNA, CRISPR-Cas components)

There is a need for nucleic-acid therapeutics carriers that safeguard cargo against nucleases, encourage cellular absorption, and allow cytosolic release. COFs are now emerging as a promising platform for these tasks, provided their design incorporates cationic or anionic linkages that electrostatically bind oligonucleotides. One such example is the iminium-based, positively charged COF, reported by Zhou *et al*., [81] which adsorbed siRNA, evaded lysosomes, and carried siRNA along with a metabolic inhibitor to induce synergistic ferroptosis/apoptosis in fibrosarcoma models [88, 89]. The one-pot synthesis with ambient conditions and ion-exchange processes employed in the same study also provides an example of the working pathways to multifunctional, siRNA-capable COFs.

However, there are still critical engineering issues. The rate-limiting step of intracellular delivery is usually endosomal escape, and this issue is not fully solved in COF systems. Numerous COF-based nucleic-acid carriers are based on co-delivered polymers or pH-responsive motifs to disrupt endosomes; their head-to-head effectiveness with lipid nanoparticles (the clinical standard of siRNA) needs to be studied. Moreover, uniform measures (adsorption capacity, nuclease protection, in vivo biodistribution in primary cells, transfection efficiency in primary cells) should be reported in order to perform meaningful benchmarking.

4.3. Combinations (COFs as Dual Drug + Phototherapy Carriers)

COFs have also been found with one of the most attractive applications in co-delivery, such as chemotherapeutics and photosensitizers, so that several modalities are used in their synergy at the tumor location. COFs of nanoscale were designed to co-load doxorubicin (or other drugs) along with porphyrin units, and under light irradiation, a chemo + PDT/PTT dual action results in tumor killing [77]. The real-world benefit is that COF pores can be used to physically separate various payloads (hydrophobic vs. hydrophilic) and release via stimuli-responsive moieties (pH, redox).

Unexpectedly, more recent, multifunctional designs also incorporate nanozyme catalysis (e.g., Pt, Au nanoparticles) within COF shells to control the tumor microenvironment, breaking down H2O2 to O2 or generating ROS via a Fenton-like reaction, thereby enhancing PDT or chemodynamic therapy [77, 81]. Such multi-mechanism systems are reportedly highly antitumor effective in rodents, but they add to chemical complexities, introduce potential metal retention, and require more toxicology and metabolite identification research before translation.

4.4. Imaging and Theranostics (COFs combined with MRI, fluorescence, PET

The theranostic COF platforms are used to combine therapeutic delivery with diagnostic imaging to track real-time delivery and therapeutic response. Two typical engineering themes are (1) core@shell designs where an imaging core (Fe3O4 to make MRI, Au or radiolabels to make CT/PET) is coated with a porous COF shell to load drugs; and (2) labelled COFs where a fluorescent,

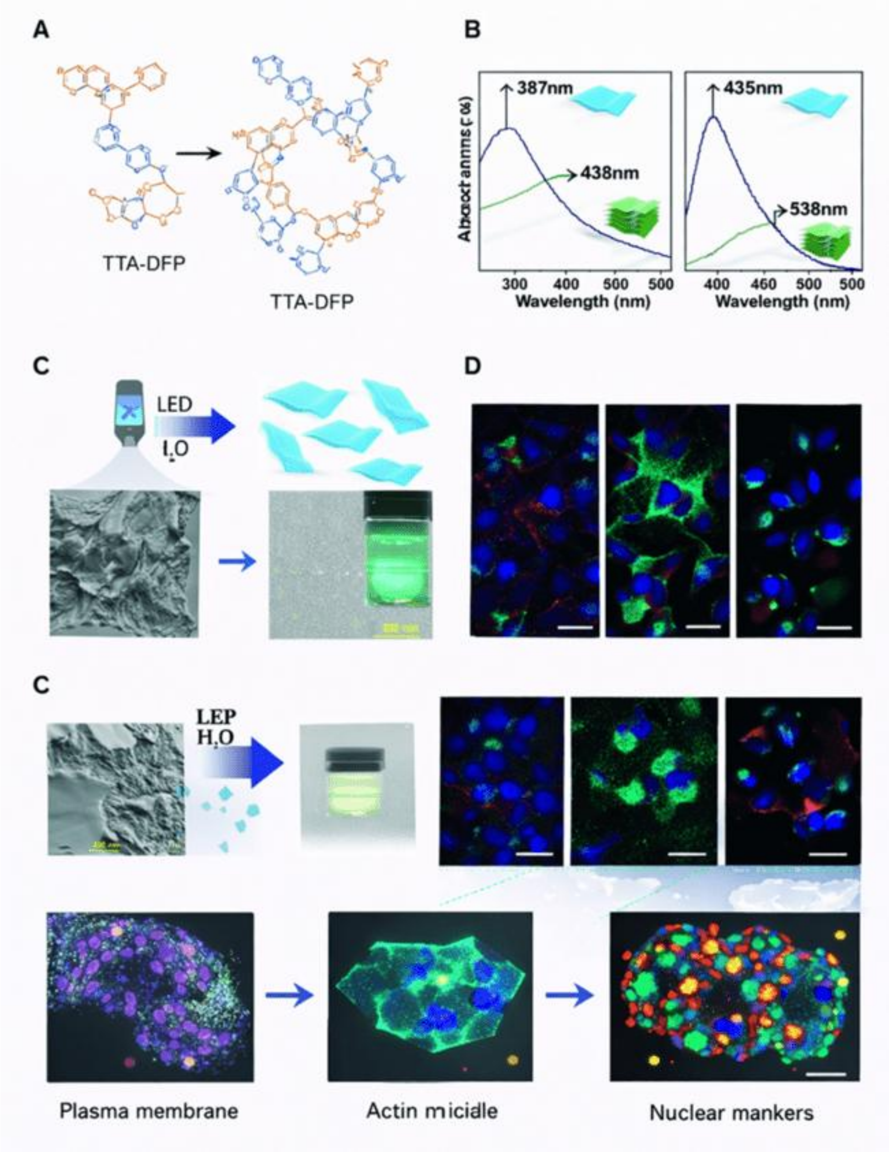

Figure 7. Fluorescent COFs for bioimaging applications. (A) Schematic illustration of the formation of a triazine-based fluorescent covalent organic framework (COF) from organic building blocks, yielding an extended π-conjugated network responsible for photoluminescence. (B) Representative absorption and photoluminescence spectra of the fluorescent COF, showing characteristic excitation and emission features, as well as spectral shifts associated with structural transformation or exfoliation. (C) Conceptual comparison of bulk COF and exfoliated COF nanosheets, illustrating the conversion of layered COF structures into thinner nanosheets in aqueous media and the associated enhancement of fluorescence emission under ultraviolet excitation. (D) Schematic representation of cellular bioimaging using fluorescent COF nanosheets, depicting intracellular localization following cellular uptake and enabling multichannel fluorescence visualization of cellular components. Adapted from [93].

photoacoustic, or PET tag is incorporated into the framework [53, 78]. Core@shell Fe_3O_4 at COF constructs are guided magnetically, with MRI contrast, and combined chemo-photothermal therapy in living organisms [53]. COF-based radiolabeled nanoplatforms are under development with PET tracking, but radiochemistry and in vivo stability need optimization of each tracer.

Direct evaluation of biodistribution and targeting efficacy in preclinical models is only possible with theranostic designs and is priceless in terms of optimization. Other bioluminescent COFs, in addition to metal or radiolabel hybrid systems, purely organic fluorescent COFs have also been explored as bioimaging agents. Indicatively, 2D triazine-based COFs like TTA-DFP can be exfoliated into nanosheets with photoluminescence, which allows the selective visualization of cellular structures in live HeLa cells [93]. As shown in Fig. 7, this points out that the functionality of COFs can be done as an engineered therapeutic carrier as well as an independent fluorescent probe to track intracellular targets or biosensing. However, the introduction of inorganic imaging cores or radioisotopes makes the regulatory routes more difficult and clearance/toxicity more significant, and requires long-term research.

Table 3. Summary of different Covalent Organic Framework (COF) systems that are utilized in drug delivery, photodynamic therapy (PDT) and photothermal therapy (PTT). It presents such major discoveries as the ability to load drugs, tumor rejection, and the formation of ROS, according to previous research. This table gathered the findings of various studies to present the multifunctionality and biological effect of COFs in cancer therapy and bioimaging.

Application	COF platform	Key finding	Ref
Chemo + PDT/PTT	Nanoscale porphyrinic COF co-loaded with DOX.	Synergistic tumor suppression in mice; framework reduces photosensitizer quenching.	77
Tumour-targeted PDT	HA-functionalized porphyrin COF nanosheets.	Enhanced ROS generation and receptor-mediated uptake in vivo.	73
Nanozyme-assisted photocatalysis	Pt-nanozyme-bridged COF-aptamer.	Catalase-like activity relieves hypoxia and strengthens photocatalytic therapy.	73
siRNA + metabolic inhibitor delivery	Iminium-linked cationic COF delivering siRNA.	siRNA adsorption, lysosomal escape, and synergistic tumor regression via ferroptosis.	13
MRI-guided chemo-PTT	Fe_3O_4@COF core@shell.	Magnetic guidance, high DOX loading, turn-off fluorescence reporting.	13
Antibacterial/antiviral (emerging)	Porphyrin-COFs & COF-nanozyme hybrids.	Promising photodynamic antimicrobial and antiviral activity reported; further in vivo validation needed.	

COFs are now a material's desire for a versatile biomedical tool to PDT/PTT, nucleic-acid delivery, multimodal combination therapy, and image-guided theranostics. They can be scaffolded modular, with high payload capacity, and have the capacity to carry catalytic or imaging components. The most critical weaknesses can be summarized as the large-scale synthesis of clinically viable nCOFs, comprehensive PK/BD and prolonged safety information (particularly with respect to hybrid metal-based carriers), and head-to-head comparisons with established vectors (lipid NPs, MOFs).

The difficulty in dealing with these issues, and in particular by using standard assays, extended toxicology, and clear GMP-ready pathways, will dictate whether the COF platforms can shift the challenge of making convincing preclinical demonstrations into clinical translation

5. Biocompatibility, Stability, and Toxicity Concierge

Three parameters, which are interdependent, should be considered as a strict assessment of COFs for application in bio-medical applications, i.e., a stability under physiologic conditions, degradation, and clearance in vivo, and cytotoxicity and immunological behavior of the materials used. The COFs are promising but not yet characterized; the evidence available indicates that some chemistries are promising, but important gaps in knowledge remain that must be bridged to facilitate clinical translation.

5.1. Stability during physiological conditions.

The linkage chemistry is heavily relied on in COF stability. Imine-linked COFs (Schiff bases) are synthetically universal, though they may be hydrolyzed under aqueous or acidic conditions; β-ketoenamine and some strong aromatic condensations offer much better hydrolytic stability [94]. It has been demonstrated through reviews and experimental research that, in simulated physiological conditions, β-ketoenamine COFs remain crystalline and porous than many imine-COFs [94, 95]. However, surface hydrolysis, particle fragmentation, or ligand replacement can occur on even so-called stable COFs during biologically relevant ionic strength and protein-rich media processes, which can change the drug retention and biodistribution. Consequently, any COF designed to be used in biomedicine needs to be preclinically characterized: time-resolved PXRD, BET, dynamic light scattering (DLS) in serum-containing conditions, and TEM/SEM prior to and subsequent to exposure to appropriate buffer and serum.

5.2. Degradability and clearance (in vivo)

Compared with MOFs or polymeric systems, the biodegradation pathways and clearance routes of COFs are also not well explored. Increasingly, animal studies are reporting renal and hepatobiliary clearance of small COF fragments or organic degradation products, although clearance varies depending on particle size, surface chemistry, and the presence of inorganic cores (e.g., Fe_3O_4) [53, 96]. Notably, COFs based on bio-reversible linkages (ester, disulfide-containing tethers) can break down to form smaller fragments that can be excreted (low pH, high GSH) [67]. However, complete ADME data (absorption, distribution, metabolism, and excretion), including the identification of metabolites and mass-balance investigations, are uncommon. Strong in vivo clearance experiments using radiolabeled COFs and longitudinal organ histology would be very necessary to establish safe use.

5.3. Cytotoxicity studies and immunological responses.

When COFs are well-treated and stabilized in terms of washing, their in vitro cytotoxicity is low at concentration ranges applicable in drug delivery. Cellular responses depend on chemical composition: unfunctionalized, large aggregated COFs may cause membrane injury and oxidative stress, but PEGylated or biomimetic-coated COFs are less cytotoxic and more biocompatible [85, 97]. Only sparsely reported immunological interactions involved are opsonization, the activation of the complement system, and the induction of pro-inflammatory cytokines. A limited acute inflammatory response is observed following single doses in a few in vivo studies, whereas repeated-dose immunotoxicity, adaptive immune activation, and the possible development of anti-carrier antibodies are rarely studied. Considering the background of other nanosystems, immunogenicity (cytokine panel, complement activation, and anti-carrier antibody formation) and long-term dosing in relevant animal models should be routine for COFs on the verge of clinical development.

5.4. Comparison with FDA-approved nanocarriers

Compared to established carriers (liposomes, albumin-bound drugs, PLGA), COFs have the benefits of increased and tunable porosity, modular chemistry to stimulus-responsiveness, and metal-free scaffolds (in the case of some designs), but not the decades of toxicological, manufacturing, and regulatory history that support approved platforms [98]. Liposomes and PLGA are systems with well-characterized PK/PD, predictable biodegradation, and established GMO routes; COFs need to match such reliability, biodegrade into safe metabolites, and exhibit scalability for GMO synthesis to compete. Comparative preclinical PK/efficacy/toxicity studies (head-to-head preclinical studies) vs. an FDA-approved carrier are now uncommon but necessary to show added value and acceptable safety margins.

To achieve a translational step forward in this regard, scientists must;

- Select COF linkages with anticipated physiological stability or design in predictable degradation pathways;
- Conduct systematic stability experiments in serum and simulated body fluids;
- Focus on longitudinal biodistribution and mass-balance studies with radio-labelled/or fluorescent tags on clearance;
- Include acute and repeated-dose immunotoxicity studies; and
- Directly compare new COFs with an approved carrier in standardized animal experiments. These practices will significantly reduce biocompatibility uncertainty and shorten the time to informed translational decisions.

6. Difficulties and Gaps in Knowledge

Covalent organic frameworks (COFs) add some special benefits to the list of drug delivery and multifunctional therapeutics. They have a high functionality, tunable chemistry, and modular design that is appealing. However, transferring them from the lab bench to actual biomedical applications has been challenging. This is due to several scientific, technical, and regulatory barriers that still need to be overcome, and it is essential to be aware of the challenges that must be addressed to bring COFs into clinical practice.

6.1. Reproducibility and uniformity of products

The preparation of COFs is a delicate procedure. Their production relies on accurate proportions of monomers, solvents, and reaction circumstances, and any slight modification can result in enormous variations in crystallinity, porosity, particle size, and defect density. These variations have a direct impact on drug loading, release, and biological behavior. Unfortunately, there are numerous academic reports on a best batch only, which has not proven to be reproducible and has not discussed critical quality attributes (CQAs). When it comes to biomedical translation, there can be no concessions when it comes to batch-to-batch consistency. In its place are definite reporting standards (monomer purity, modulators, size distributions, PXRD, and BET data), and solid protocols of synthesis, which can be duplicated across laboratories and eventually become regulated.

6.2. Green manufacturing and scalable

The majority of COFs are currently obtained by means of conventional solvothermal or sealed-vessel techniques. These are sluggish, heavy in solvents, and difficult to scaffold under cGMP conditions. Other options like mechanochemistry, microwave synthesis, or interfacial are promising, but tend to alter the quality of the framework, which subsequently impacts the biological functionality. The industry should also be heavily geared towards creating more sustainable, larger-scale processes that: Scale down small lab recipes to industrial-feasible paths, cut down on solvent and energy consumption, Real-time monitoring of CQAs with process analytical technology (PAT), and demonstrate that highly reproducible nanoscale COFs could be formed on the gram to kilo level.

6.3. Long-term pharmacokinetics and toxicity data are not available

Until now, the majority of safety research indicates that COFs are compatible in cell models and short-term animal models. What, however, is the long-term result? There is still insufficient data on absorption, distribution, metabolism, and excretion (ADME), as well as metabolite formation and repeated-dose toxicology. Hybrid systems that contain metals or inorganic cores attract more concern regarding accumulation and chronic effects. Strong radiolabeled biodistribution data and extended safety trials will be required by regulators prior to the use of COFs in human trials. At this point, they are sparse datasets.

6.4. Absence of standardized biological tests

One of the most serious obstacles on the way to improvement is inconsistency. Different labs use different ratios between drugs and carriers, solvents, release media, dialysis membranes and animal models. This makes it quite difficult to compare or find the good rules of sound design. Agencies like EMA are now demanding the standardization of parameters - size distribution, drug loading and release, surface chemistry, and immune tests (i.e., cytokine panels, complement activation). The science will produce much fragmentary research that cannot be stitched up into a comprehensible picture in their absence

6.5. Regulatory uncertainty

The COFs do not fit into the existing regulatory boxes. Do they contain drugs, devices, biologics, or a combination of products? They are multifunctional, and their lines are blurred. This uncertainty is one of the reasons why it is important to first participate in the dialogue with regulators. The developers should also be capable of defining the primary mode of action and making sure that their preclinical testing plan proceeds along the most appropriate pathway so as to keep the promising nanomaterials away from being on regulatory hold.

6.6. Environmental issues, Supply-Chain, and Cost

COF monomers are usually expensive specialty chemicals and may require intensive handling: solvent purification and solvent use. Of special relevance to large-scale synthesis is solvent utilization and cleaning. The field must move towards an economy of green chemistry, economically efficient supply chains, and life cycle analysis to attain economic and ecological sustainability in order to potentially transition to clinical use. It is essential to address these problems through a collective effort. The community should standardize reporting and biological assay protocols, conduct reproducibility studies, develop key quality traits, scale up solvent-efficient synthetic pathways using PAT, prepare comprehensive ADME and toxicology data, and radiolabeled experiments, and engage regulators early to gain a clear understanding of classification and anticipation. Such gaps will be filled not only to reduce the risk but also to open the path to the goal of objective, evidence-based selection of COFs as a clinical drug carrier.

7. Future Perspectives

Covalent organic structures (COFs) have shown giant possibilities in the laboratory. However, the functioning of these structures has a lot to do with whether research priorities are consistent with clinical and business reality. One can move forward in the research field when the several strategic paths that will result in real translational breakthroughs are prioritized and followed.

7.1. Rational, computation-driven COF design

The traditional COF synthesis is a resource-intensive and laborious process of traditional trial-and-error. Fortunately, with the advancement of high-throughput computation, molecular docking, and AI-driven materials discovery, it is now possible to predict which monomer combinations and pore chemistries will work best in a given application. As an illustration, pore polarity can be paired with drug hydrophobicity with computational screening, or cleavable linkages that react to intracellular stimuli such as glutathione can be engineered. Combined with rapid validation of that prediction, researchers are able to dramatically reduce the time needed to develop them and put resources into the most promising ones [62].

7.2. Emphasis on clinically tractable multifunctionality

Although multifunctionality is one of the strongest selling points of COFs, too much complexity usually slows the clinical translation. To improve on this, a more realistic approach is to aim at low-complexity, high-value multifunctionality, in which a core delivery system is paired with a single clinically relevant added function. As an example, a COF scaffold that is highly drug-loading and controllably releases the drug by pH, or a COF coating to an imaging core to facilitate MRI-guided chemotherapy. These simplified systems minimize regulatory barriers and, nevertheless, have distinct clinical advantages [53, 78].

7.3. Scalable and green manufacturing with PAT integration

The question of scalability is the main question of the future of COFs. The small-scale syntheses currently in place are inadequate for use in industries or clinics. Recyclable and non-toxic solvents, as well as continuous-flow, mechanochemical, or interfacial synthesis, will be necessary to invest in greener methods. Also significant is the incorporation of process analytical technology (PAT), which enables the real-time monitoring of size distribution, polydispersity, and crystallinity in production. Reproducible kilogram-scale synthesis of nanoscale COFs will be a breakthrough, which will be feasible by a strong and intensive partnership between academic teams, process chemists, and business partners [99, 100].

7.4. Standardized preclinical roadmaps and benchmarking

Currently, the COF research is mostly isolated, and various laboratories do not apply comparable protocols that could be compared to each other. It would be helpful to set up standard preclinical roadmaps to have a common point of evaluation. The smallest translational information package would consist of: in vitro serum stability testing, immune compatibility testing (e.g., complement activation), radiolabeled ADME/mass balance, and repeated dose toxicology testing in at least two species. Most importantly, new COF formulations are to be head-to-head compared to the established delivery vehicles, e.g., liposomes or polymeric nanoparticles. This harmonization would not only enhance reproducibility but also expedite regulatory review [67, 101].

7.4. Targeted Clinical Niches and Strategic Regulatory Engagement

Internalized COFs will probably not be used in the early clinical stages as broader and hazardous systemic therapies. Rather, the near-term opportunities (over the next 2-3 years) with the greatest potential include niche applications with great unmet need and controllable risk, including intratumoral adjunct therapies (chemo-photodynamic combinations), imaging-guided theranostics in cancer, or topical/dermatological treatments where systemic exposure is minimal. Earlier interaction with regulators will not only be necessary to provide the correct classification of COFs (drug, device, or combination product) but also to establish an agreement on the requirements for the data, which will reduce the risk of negative regulatory consequences [102].

7.5. Cross-disciplinary consortia and open data

The development in the COF sphere will be accelerated if researchers become more open and cooperative. Cross-disciplinary consortia have the ability to share expertise, to coordinate experimental procedures, and create cumulative datasets that comprise a mix of positive and negative results. Raw characterization data, including BET surface areas, PXRD patterns, particle-size distributions, and batch records, would be highly beneficial to make available publicly so as to increase reproducibility and enable meta-analysis. Such a culture of openness not only increases the rigor of scientific research but also creates confidence among the industrial stakeholders and regulatory forces [62].

The combination of these strategic priorities provides a realistic direction for realizing the COF's lab concepts into clinical products. A rational design combined with simplified multifunctionality, scalable green manufacturing, standardized preclinical testing, clinical entry points, and free collaboration is the cure to advance beyond demonstration of proof of concept towards actual therapeutic use. By so doing, COFs can become high-function, multimodal next-generation precision medicine platforms.

8. Conclusion

Covalent organic frameworks (COFs) unite crystalline order, tunable porosity, and modular chemistry in a way that places them uniquely in the context of next-generation drug delivery and multifunctional therapeutics. In the last ten years, the literature has shown that COFs can be highly loaded with small-molecule drugs, stimulus-responsive release enabled, actively targeted, loaded with photoactive, catalytic, or imaging functional groups to achieve combined therapy and theranostics. Representative applications of porphyrinic COFs to chemo-photo therapy, iminium-linked COFs to siRNA delivery, and Fe_3O_4 core/shell constructs to MRI-guided therapy exemplify the flexibility of the platform and the real preclinical progress made so far.

Although these have encouraging properties, translation into the clinic is currently hindered by a number of implementation issues: synthetic reproducibility and batch consistency; scalable, green manufacturing that can be used in cGMP; incomplete ADME/toxicology data (in particular with metalated or hybrid systems); and regulatory uncertainty around multifunctional constructs.

There is also a lack of homogeneous conduct of experiments that complicates the comparison of cross-studies. To overcome such shortcomings, community implementation of standardized reporting, investments in scalable process chemistry and PAT, rigorous biodistribution, and toxicity studies over the long term, and early regulatory consultation will be required to define product classification and data requirements.

In the future, the most amenable route to clinical impact is pragmatic; focus on low-complexity, high-value designs (such as COFs that can obviously improve payload stability or allow image-guided local therapy), couple computational design with experimental validation to accelerate candidate triage, and seek standardized preclinical packages including head-to-head comparison of approved carriers. Provided that researchers match materials innovation to reproducible manufacturing and sound safety science; the COFs have a realistic chance of advancing beyond compelling laboratory platforms to clinically viable nanomedicines that will enhance the therapeutic precision and multi-modal treatment alternatives

Author contributions

Henrietta Marcel: Investigation, Study conception and Design: Writing-original draft. **Daniel A. Idowu**: Supervision, Writing-Review and Editing, Study Conception. **Adeyinka O. Ademilua**: Investigation, Data Collection and Study conception. **Loveth I. Marcel**: Writing-Review and Editing, Data Collection. **Mohammed I. Abdul-Rahman:** Writing-Review and Editing, Methodology. **Favour S. Fabuyi:** Writing-Review and Editing, Project Administration.

Conflicts of interest

The authors declare no conflict of interest.

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