Advances in Chiral Covalent Organic Frameworks for Enantiomer Separation: Synthesis, Applications, and Future Directions

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Abstract: Chiral drugs, characterized by their enantioselective biological activities and pharmacological effects, necessitate precise separation techniques to ensure therapeutic efficacy and safety. This review systematically summarizes the advancements in chiral separation technologies, with a focus on the application of chiral covalent organic frameworks (CCOFs) in chromatographic enantioseparation. Traditional methods such as crystallization, asymmetric synthesis, and chromatography-based approaches are discussed, highlighting their limitations in scalability, cost, and solvent compatibility. In contrast, CCOFs, emerging as a novel class of chiral stationary phases (CSPs), exhibit exceptional structural tunability, high porosity, and robust stability, enabling efficient enantiomer resolution across gas chromatography (GC), high-performance liquid chromatography (HPLC), and capillary electrochromatography (CEC). Key synthesis strategies for CCOFs—post-synthesis modification, chiral induction, and bottom-up assembly—are critically evaluated, alongside their performance in separating pharmaceuticals, amino acids, and agrochemicals. Recent breakthroughs, including β-cyclodextrin-functionalized COFs and camphorsulfonyl chloride-modified CCOFs, demonstrate superior separation efficiency and reproducibility. This review underscores the potential of CCOFs to address longstanding challenges in chiral separation while identifying future directions for optimizing their design and scalability in industrial applications.

Keywords: Chiral drugs; Enantioseparation; Chromatography; Separation Efficiency

1. Introduction

The inherent chirality of bioactive molecules, such as amino acids and pharmaceuticals, underpins their enantioselective interactions in biological systems. The tragic case of thalidomide—where the (R)-enantiomer alleviated morning sickness while the (S)-enantiomer caused teratogenicity—exemplifies the critical need for enantiopure drug production. Conventional chiral resolution techniques, including crystallization and asymmetric synthesis, are often hindered by high costs, low yields, and technical complexity. Chromatographic methods, particularly those employing chiral stationary phases (CSPs), have emerged as dominant strategies due to their versatility and efficiency. Polysaccharide derivatives, proteins, cyclodextrins, and crown ethers are widely used CSPs, yet limitations such as solvent incompatibility, poor stability, and limited selectivity persist.

Recent advancements in porous materials, notably chiral covalent organic frameworks (CCOFs), offer transformative solutions. CCOFs combine structural precision, high surface areas, and chemical stability with tailorable chiral sites, enabling enhanced enantiomer discrimination. Three primary synthesis approaches—post-synthesis modification, chiral induction, and bottom-up assembly—allow precise integration of chiral functionalities into COF frameworks. Pioneering studies, such as Yan et al.'s β-CD-COF@SiO_2 microspheres for HPLC and Gao et al.'s camphorsulfonyl chloride-modified CCOFs for CEC, highlight their superior separation performance and reproducibility. This review consolidates the progress in CCOF design, synthesis, and chromatographic applications, while addressing remaining challenges in scalability and mechanistic understanding. By bridging material innovation with separation science, CCOFs

hold promise for revolutionizing chiral drug development and analytical enantioseparation.

1.1 Chiral Drugs and Chiral Resolution

Isomers that are non-superimposable mirror images of each other are called enantiomers and can be denoted by the symbols R/SR/S. The term "chirality" is used to describe the stereochemical relationship between such optically active molecules [1]. Chirality is a fundamental characteristic of nature, with essential components of biological macromolecules such as amino acids, DNA, and proteins exhibiting significant chiral properties. Different enantiomers can exhibit substantial differences in metabolic behavior, pharmacological activity, and toxicity, and may even have opposing effects [2]. A notable example is the "thalidomide tragedy" in the 1950s, where the drug thalidomide, used to treat morning sickness, caused severe limb deformities in newborns. Subsequent investigations revealed that while the (R)(R)-enantiomer of thalidomide possessed sedative and antiemetic properties, the (S)(S)-enantiomer was highly teratogenic [3]. Therefore, obtaining single-enantiomer chiral drugs is of critical importance. Common methods for acquiring single-enantiomer chiral drugs include extraction from natural sources, asymmetric synthesis, and chiral resolution. However, natural sources are often difficult to obtain, and asymmetric synthesis is typically hindered by high costs, low yields, and the presence of byproducts. In contrast, chiral resolution techniques are more efficient and well-established.

1.2 Chiral Separation and Chiral Selectors

Chiral resolution techniques encompass four widely used methods: crystallization separation, kinetic separation, chromatographic separation, and membrane-assisted separation. Among these, chromatographic separation is one of the most commonly employed techniques for chiral drug separation, with the chiral stationary phase (CSP) method being one of the most extensively applied and effective approaches in chromatographic separation. The key to this technology lies in the type of chiral selector used [4]. To date, a wide range of chiral selectors have been utilized in the separation and analysis of enantiomers, including polysaccharide derivatives [5], proteins [6], cyclodextrins [7], and crown ethers [8], among others. With advancements in materials chemistry, the emergence of novel porous materials has also provided new opportunities for the development of high-performance CSPs.

1.2.1 Polysaccharides and Their Derivatives

Polysaccharides primarily refer to cellulose and amylose, which are linear helical polymers composed of D-glucose. The hydroxyl groups of the glucose molecules can be partially substituted by benzoate or phenylcarbamate derivatives. Due to their regular helical structures, polysaccharides and their derivatives exhibit high chiral recognition capabilities, making them widely used as chiral selectors in the development of chiral stationary phases (CSPs) for high-performance liquid chromatography (HPLC) and supercritical fluid chromatography (SFC).

In 1939, Henderson et al. reported the first example of enantiomer separation using a chromatographic column with lactose as the chiral selector [9]. During the 1980s and 1990s, significant efforts were focused on modifying the substituents on the main or side chains of polysaccharides to prepare derivatives, thereby expanding their applications in chiral separation. For instance, polysaccharide derivatives such as tribenzoate, triphenylcarbamate, tri-(4-methylbenzoate), and tri-(3,5-dimethylphenylcarbamate) have been widely synthesized. Typically, these materials are coated onto porous silica surfaces to prepare CSPs. This method is simple, rapid, and reproducible, with no specific requirements for the substrate used. However, polysaccharides and their derivatives can only be used with low-polarity solvents, such as alkanes (e.g., n-pentane, n-hexane, n-heptane) and alcohols (e.g., methanol, ethanol, 2-propanol). Swelling or dissolution in other organic solvents can severely affect their stability and shorten their lifespan. To address these issues, covalent bonding methods, such as linking polysaccharides and their derivatives with diisocyanates or vinyl radical polymerization, have been developed. These methods significantly improve the stability of polysaccharides and extend the lifespan of chiral columns. However, the immobilization of polysaccharides on carriers may lead to changes in their conformation or supramolecular structure, which can affect

their chiral recognition capabilities and thus limit their further applications.

1.2.2 Proteins

Proteins exhibit stereoselectivity due to their unique tertiary structures, making them highly promising for the separation of enantiomers. Common protein-based chiral selectors include albumin (e.g., bovine serum albumin (BSA) and human serum albumin (HSA)), glycoproteins (e.g., α1-acid glycoprotein (AGP), antiviral protein (AVI), and riboflavin-binding protein (RfBP)), and enzymes (e.g., trypsin, chymotrypsin, pepsin, and lysozyme) [10].

The general method for preparing protein-based CSPs for chromatographic columns is direct coating. However, chiral selectors applied through this method are prone to desorption. As an alternative, physical adsorption or covalent bonding can be used to immobilize the chiral selectors onto specific substrates. Currently, common substrates include silica-based materials (e.g., silica particles, fused silica capillaries) and zirconia particles.

1.2.3 Cyclodextrins and Their Derivatives

Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucopyranose units linked by α-1,4-glycosidic bonds. They possess a hollow ring structure with a lipophilic inner surface and a hydrophilic outer surface, enabling them to form inclusion complexes in a stereospecific manner. The hydroxyl groups on the edges of the hollow ring vary in acidity and spatial accessibility, allowing for the modification of various substituents at specific sites to generate corresponding derivatives. Additionally, the size of the cavity varies depending on the number of D-glucopyranose units linked by α-1,4-glycosidic bonds. These characteristics significantly increase the interaction sites between CDs and their derivatives with guest molecules, making CDs and their derivatives widely used as chiral selectors in chromatographic separation.

In 2016, Kučerová et al. successfully prepared a sulfobutyl ether-β-cyclodextrin (SBE-β-CD) stationary phase using a coating method, achieving baseline separation of various chiral compounds and peptide isomers [11]. In 2020, Shuang et al. synthesized amino-derivatized β-cyclodextrin and diamido-bridged bis(β-cyclodextrin) and bonded them to the surface of mesoporous silica spheres to prepare CSPs, enabling the separation of 23 pairs of enantiomers, including β-blockers, triazole pesticides, and flavanones [12].

1.2.4 Chiral Crown Ethers

Crown ethers are a class of synthetic polyether molecules known for their high selectivity and affinity toward certain cations, such as alkali ions or protonated primary amines. Since Cram first immobilized chiral crown ethers on silica gel and other carriers [13, 14], many chiral crown ether selectors have been applied to the resolution of α-amino acids and chiral primary amine racemates [14]. In 1987, Sugiura et al. successfully prepared a CSP by coating (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 onto octadecylsilyl-bonded silica gel (ODS) and commercialized it as Crownpak CR [15]. This chiral crown ether-based CSP can be used to resolve various chiral primary amines, including amino acids. However, due to its dynamic coating nature, Crownpak CR has significant limitations in the use of mobile phases. To address these limitations, in 2013, Wonjae Lee et al. developed a novel CSP by covalently bonding (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid to aminopropyl silica gel and applied it to HPLC for enantiomer resolution [16].

1.2.5 Novel Porous Materials

Porous materials play a crucial role in numerous modern scientific and technological fields, and various types of porous materials have been developed to meet the diverse demands of modern industry [17]. Among these, metal-organic frameworks (MOFs), covalent organic frameworks (COFs), and conjugated microporous polymers (CMPs) are particularly noteworthy. MOFs are crystalline structures composed of metal nodes and organic ligands [18], while CMPs are amorphous polymers with extended π-conjugation [19]. COFs, first reported by Yaghi et al. in 2005, are composed of light elements such as C, H, O, N, and B, and feature highly ordered crystalline structures with robust covalent bonds [20].

In 1999, Aoyama et al. first reported the preparation of chiral metal-organic frameworks (CMOFs) [21]. Subsequently, Kim et al. synthesized two novel CMOFs and applied them to enantiomer separation [22]. During the preparation process, chiral groups

can be immobilized on both the metal nodes and the linker units of the MOF framework. In 2009, Kim et al. further synthesized CMOFs using MOF MIL-101 as a precursor and L-proline as the chiral source through covalent coupling reactions, successfully applying them to enantiomer separation [23].

1.3 Covalent Organic Frameworks and Chiral Covalent Organic Frameworks

1.3.1 Overview and Classification of Covalent Organic Frameworks

Covalent organic frameworks (COFs) stand out among various porous materials due to their high surface area, structural tunability, metal-free nature, and excellent stability. They are widely applied in fields such as adsorption, separation, catalysis, sensing, and drug delivery [24]. The synthesis methods for COFs include solvothermal synthesis, ionothermal synthesis, microwave-assisted synthesis, mechanochemical methods, and interfacial synthesis. The key to these methods lies in selecting appropriate organic units and types of bonds, which determine the material's symmetry and pore size. Based on the type of bonds, COFs can be classified into several categories, including boronate ester-linked COFs, imine-linked COFs, imide-linked COFs, phenazine-linked COFs, hydrazone-linked COFs, triazine-linked COFs, and others [25].

1.3.2 Synthesis Strategies for Chiral Covalent Organic Frameworks

Since the first report of chiral covalent organic frameworks (CCOFs), a significant number of CCOFs have been applied to the separation and analysis of enantiomers. Compared to non-chiral COFs, CCOFs exhibit characteristics such as structural order, porosity, and chemical stability, along with unparalleled chiral recognition capabilities that traditional COFs cannot match. Typically, the synthesis strategies for CCOFs are divided into three categories: post-synthesis modification (PSM), chiral induction (CI), and bottom-up approaches.

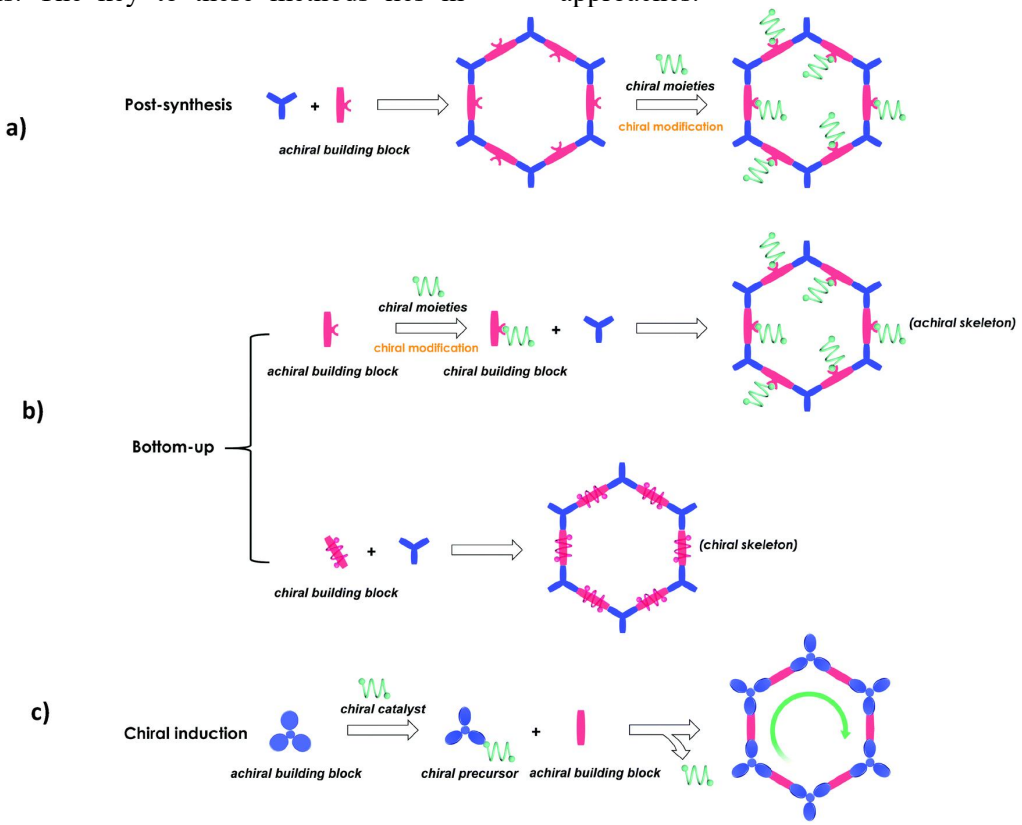

Figure 1. General Strategies for the Design and Synthesis of Chiral Cof Materials [28]

1.3.2.1 Post-Synthesis Modification

Post-synthesis modification refers to the synthesis of chiral covalent organic frameworks (CCOFs) through the modification of non-chiral COF precursors after the organic framework has been formed. The first CCOF synthesized via post-synthesis modification was reported by Jiang et al., who developed an imine-linked porphyrin-based CCOF. By modifying the non-chiral COF framework with (S)-pyrrolidine, they successfully synthesized a CCOF capable of catalyzing Michael addition

reactions [26]. Additionally, anchoring natural biomolecules is another effective approach for synthesizing CCOFs. In 2018, Ma et al. reported a study on the synthesis of CCOFs using natural biomolecules through post-synthesis modification [27]. Their research group covalently immobilized a series of biomolecules, such as lysozyme, tripeptides, and lysine, onto polyimide-based mesoporous non-chiral COFs, successfully introducing chirality into the non-chiral COFs and applying them to separation processes in normal-phase chromatography (NP-HPLC) and reversed-phase chromatography (RP-HPLC).

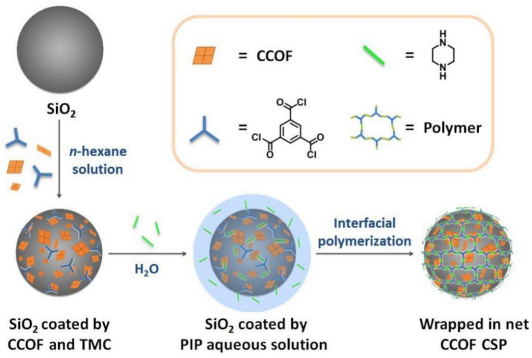

Figure 2. Fabrication Procedures of the "Wrapped in Net" CCOF CSPs. [27]

1.3.2.2 Chiral Induction Method

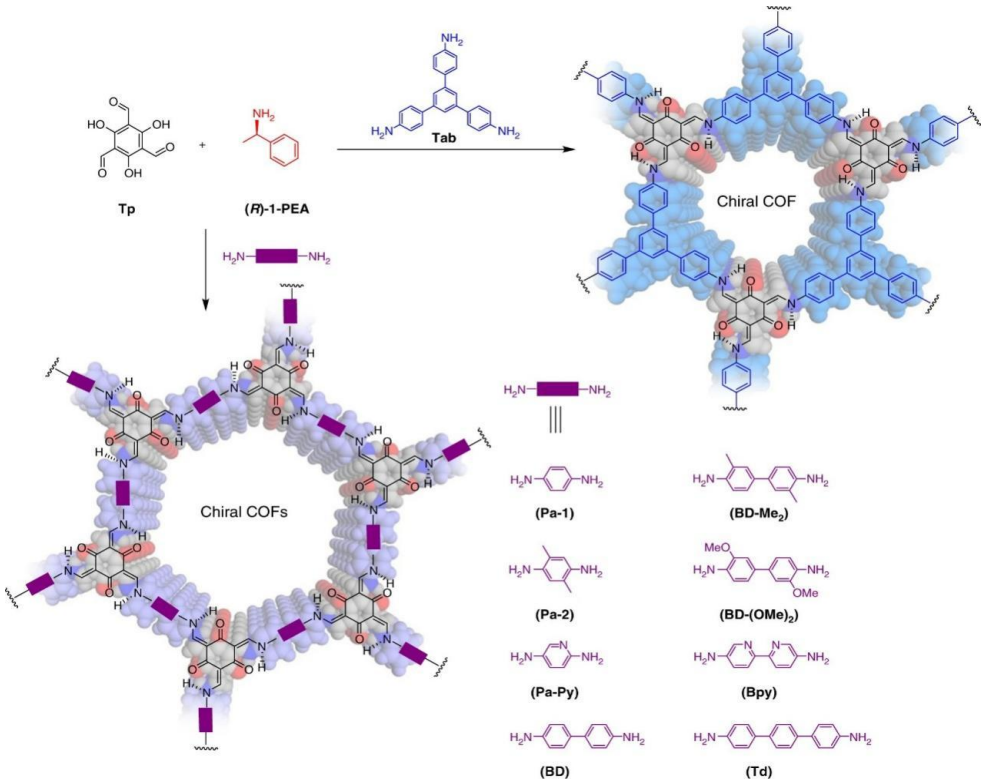

Figure 3. Schematic Representation of the Synthesis of CCOFs. These CCOFs are Formed from Achiral Precursors by Chiral Catalytic Induction. [28]

The chiral induction method refers to the synthesis of chiral covalent organic frameworks (CCOFs) by inducing non-chiral COF precursors with chiral catalysts. Since the shape and properties of CCOF pores are partly determined by the structure and chemical nature of the chiral catalyst, the advantage of chiral induction synthesis lies in its potential to synthesize CCOFs with virtually any desired composition or structural type. In 2018, Cui et al. reported nine CCOFs with controllable chirality [28]. These were synthesized via a solvothermal method using C3C3 - symmetric 2,4,6-trihydroxy-1,3,5-benzenetricarbaldehyde (Tp) and non-chiral diamine or triamine linkers, in the presence of (RR)- or (SS)-1-phenylethylamine (PEA) as the chiral catalyst. Compared to other methods, the induction of CCOF synthesis from non-chiral monomers represents a novel direction with broad application prospects. However, the application of this strategy is limited by the unclear reaction mechanisms, the types of chiral catalysts available, and the selection of COF monomers.

1.3.2.3 Bottom-Up Approach

The bottom-up approach involves introducing functional groups into monomers and directly

constructing chiral covalent organic frameworks (CCOFs) from these functional monomers. Compared to post-synthesis modification, CCOFs obtained through direct synthesis exhibit well-defined structures with precise and uniform chiral sites. CCOF monomers can be categorized into two types based on their structure: monomers with chiral backbones and monomers with non-chiral backbones but chiral substituents.

CCOFs with chiral backbones are assembled directly from optically active organic monomers as building blocks. This method holds the potential to produce CCOFs with higher porosity and more open channels. However, the inherent difficulty in controlling the crystallization of optically pure materials makes the direct synthesis of CCOFs from chiral backbone monomers a significant challenge. To achieve this goal, in 2016, Cui et al. reported a series of CCOFs [30-33] constructed directly from chiral backbone monomers, such as tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) and 1,1′-bi-2-naphthol (BINOL).

CCOFs with non-chiral backbones are synthesized by modifying non-chiral monomers with chiral functional groups, resulting in cavities that incorporate chiral functionalities. In 2016, Yan et al. reported an example of synthesizing CCOFs from non-chiral COFs using the bottom-up approach [29]. They first synthesized a chiral monomer, CTp, by functionalizing Tp with (+)-diacetyl-L-tartaric anhydride ((+)-Ac-L-Ta). Subsequently, CTp was condensed with 1,4-phenylenediamine (Pa-1), 2,5-dimethyl-1,4-phenylenediamine (Pa-2), and benzidine (BD) to produce CCOFs (CTpPa-1, CTpPa-2, and CTpBD).

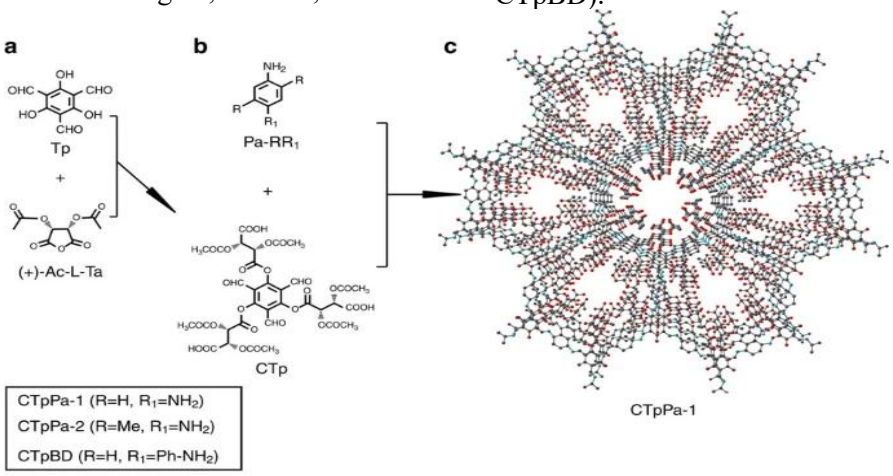

Figure 4. (a) Synthesis of CTp through the Esterification of Tp and (+)-Ac-L-Ta. (b) Synthesis of Chiral COFs through the Condensation of CTp and Pa-RR1. (c) Graphic view of CTpPa-1 (C, Grey; N, Blue; O, red; H is Omitted for Clarity). [29]

1.3.3 Applications of CCOFs in Chromatographic Separation

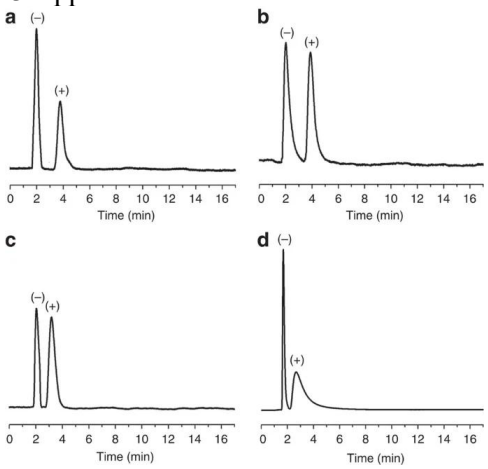

Figure 5. Gas Chromatograms on CTpPa-1-Bound Capillary Column (30 m long × 0.32 mm inner diameter). (a) (±)-1-phenylethanol (200 °C, 1.5 ml min−1 N2); (b) (±)-1-phenyl-1-propanol (200 °C, 2 ml min−1 N2); (c) (±)-limonene (180 °C, 1.5 ml min−1 N2); (d) (±)-methyl lactate (170 °C, 1.5 ml min−1 N2) [29].

Chiral covalent organic frameworks (CCOFs) exhibit significant potential and broad application prospects as chiral selectors for enantiomer separation. In 2016, Yan et al. reported the first application of CCOF materials in gas chromatography (GC) [29]. By functionalizing COFs with (+)-diacetyl-L-tartaric anhydride and employing an in situ growth method, they prepared CCOF-bonded capillary columns. These columns

demonstrated excellent reproducibility and repeatability in enantiomer separation, achieving baseline separation of certain enantiomers within 5 minutes.

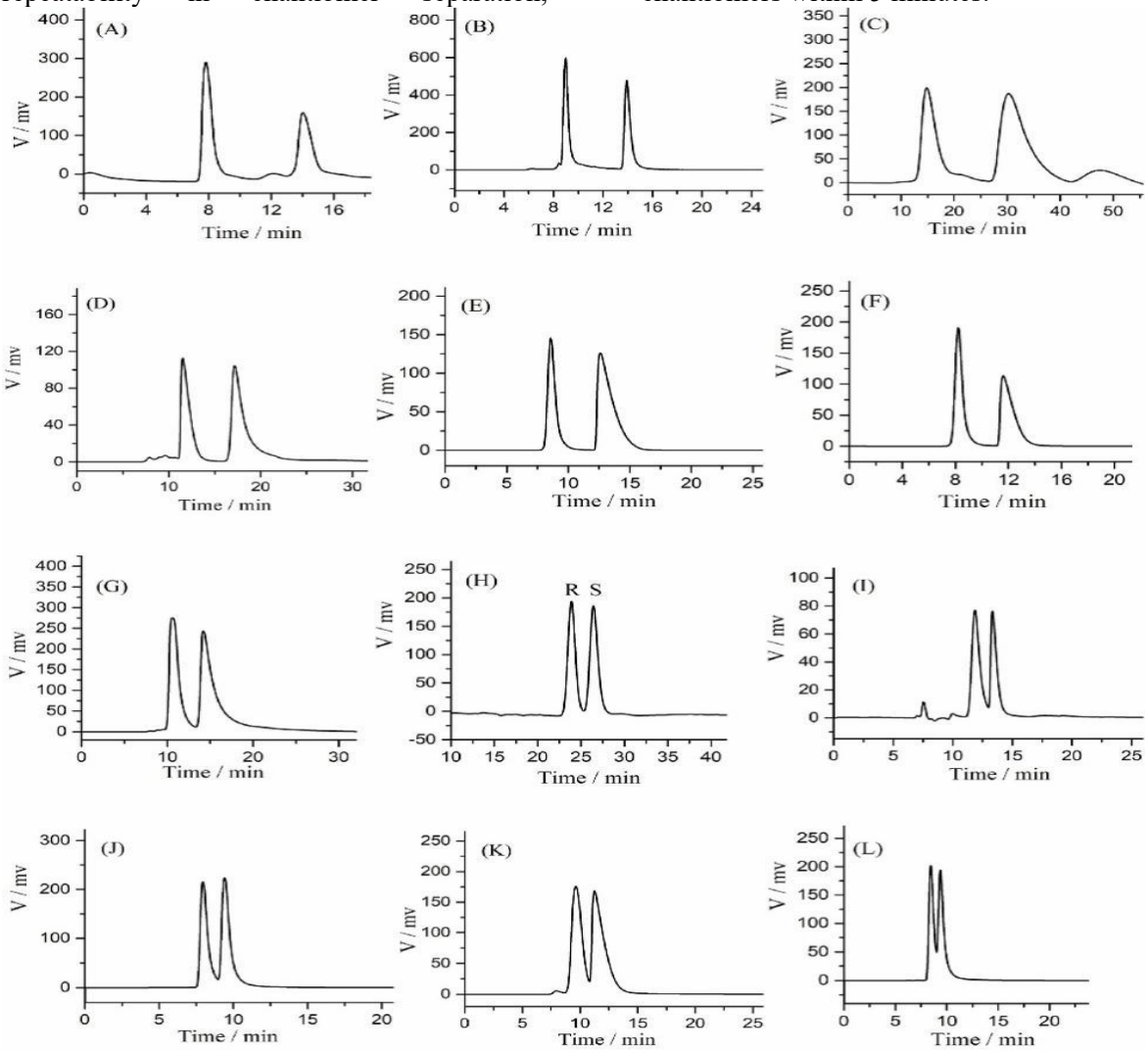

Figure 6. HPLC chromatograms obtained using β-CD-COF@SiO2-packed column (column A, 25 cm length × 2.1 mm i.d.) for the separation of racemic compounds: (A) omeprazole, (B) zopiclone, (C) praziquantel, (D) atenolol, (E) flavanone, (F) clenbuterol hydrochloride, (G) trans-stilbene oxide, (H) benzoin, (I) 1-(4-chlorophenyl)ethanol, (J) clenbuterol hydrochloride, (K) 1,1′ -bi-2-naphthol, and (L) 2-amino-1-butanol[30].

2. Conclusion and Future Perspectives

Chiral covalent organic frameworks (CCOFs) have emerged as groundbreaking materials in the field of enantiomer separation, offering unparalleled advantages in structural designability, high porosity, and chemical robustness. Their integration into chromatographic techniques, such as HPLC, GC, and CEC, has demonstrated exceptional separation efficiency for pharmaceuticals, amino acids, and agrochemicals, surpassing traditional chiral stationary phases in reproducibility and solvent compatibility. The synthesis strategies—post-synthesis modification, chiral induction, and bottom-up assembly—have enabled precise incorporation of chiral functionalities, as exemplified by β-cyclodextrin-functionalized COFs and camphorsulfonyl chloride-modified CCOFs. Despite these advancements, challenges persist in scaling up production, optimizing cost-effectiveness, and fully elucidating the mechanistic interplay between CCOF structures and enantioselective recognition.

Future research should prioritize the development of eco-friendly and scalable synthesis protocols to facilitate industrial adoption. Advanced characterization techniques, such as in situ spectroscopy and

computational modeling, could deepen the understanding of host-guest interactions and guide the rational design of CCOFs with enhanced selectivity. Expanding applications beyond chromatography—for instance, in membrane-based separations or catalytic asymmetric synthesis—may unlock new frontiers in chiral technology. Additionally, long-term stability studies under real-world conditions and performance validation in complex matrices are critical to bridge the gap between laboratory success and commercial viability. By addressing these challenges, CCOFs hold the potential to redefine chiral separation paradigms, fostering safer and more efficient production of enantiopure therapeutics and chemicals.

References

[1] Natarajan R, C. Basak S. Numerical descriptors for the characterization of chiral compounds and their applications in modeling biological and toxicological activities [J]. Current Topics in Medicinal Chemistry, 2011, 11(7): 771-787.

[2] Lorenz H, Seidel-Morgenstern A. Processes to separate enantiomers [J]. Angewandte Chemie International Edition, 2014, 53(5): 1218-1250.

[3] Ridings J E. Teratogenicity Testing: Methods and Protocols [M]. Totowa: Humana Press. 2013: 575-586.

[4] Teixeira J, Tiritan M E, Pinto M M M, et al. Chiral stationary phases for liquid chromatography: recent developments [J]. Molecules, 2019, 24(5): 865.

[5] Fourel I. Enantiomer fraction evaluation of the four stereoisomers of second-generation anticoagulant rodenticides in biological matrices with polysaccharide-based chiral selectors and liquid chromatography tandem mass spectrometry [J]. Journal of Chromatography A, 2022, 1676: 463209.

[6] Millot M C. Separation of drug enantiomers by liquid chromatography and capillary electrophoresis, using immobilized proteins as chiral selectors [J]. Journal of Chromatography B, 2003, 797(1-2): 131-159.

[7] Ma X, Cao J, Yu J, et al. Evaluation of an ionic liquid chiral selector based on sulfobutylether–β–cyclodextrin in capillary electrophoresis [J]. Journal of Molecular Liquids, 2022, 362: 119782.

[8] Hyun M H. Liquid chromatographic enantioseparations on crown ether-based chiral stationary phases [J]. Journal of Chromatography A, 2016, 1467: 19-32.

[9] Karagunis G, Coumoulos G. A new method of resolving a racemic compound [J]. Nature, 1938, 142(3586): 162-163.

[10] Zheng Y, Wang X, Ji Y. Monoliths with proteins as chiral selectors for enantiomer separation [J]. Talanta, 2012, 91: 7-17.

[11] Kučerová G, Procházková H, Kalíková K, et al. Sulfobutylether–β–cyclodextrin as a chiral selector for separation of amino acids and dipeptides in chromatography [J]. Journal of Chromatography A, 2016, 1467: 356-362.

[12] Shuang Y, Zhang T, Li L. Preparation of a stilbene diamido-bridged bis(β–cyclodextrin)–bonded chiral stationary phase for enantioseparations of drugs and pesticides by high performance liquid chromatography [J]. Journal of Chromatography A, 2020, 1614: 460702.

[13] Cram D J. The Design of molecular hosts, guests, and their complexes [J]. Science, 1988, 27(8): 1009-1020.

[14] Zhang X X, Bradshaw J S, Izatt R M. Enantiomeric recognition of amine compounds by chiral macrocyclic receptors [J]. Chemical Reviews, 1997, 97(8): 3313-3362.

[15] Shinbo T, Yamaguchi T, Nishimura K, et al. Chromatographic separation of racemic amino acids by use of chiral crown ether-coated reversed-phase packings [J]. Journal of Chromatography A, 1987, 405: 145-153.

[16] Paik M J, Kang J S, Huang B S, et al. Development and application of chiral crown ethers as selectors for chiral separation in high-performance liquid chromatography and nuclear magnetic resonance spectroscopy [J]. Journal of Chromatography A, 2013, 1274: 1-5.

[17] Mohamed M G, Atayde E C, Matsagar B M, et al. Construction hierarchically mesoporous/microporous materials based on block copolymer and covalent organic framework [J]. Journal of the Taiwan Institute of Chemical Engineers, 2020, 112: 180-192.

[18] Lu X F, Xia B Y, Zang S-Q, et al. Metal–organic frameworks based electrocatalysts

for the oxygen reduction reaction [J]. Angewandte Chemie International Chemie, 2020, 59(12): 4634-4650.

[19] Sánchez-Ruiz A, Sousa-Hervés A, Tolosa Barrilero J, et al. Aggregation-induced emission properties in fully π-conjugated polymers, dendrimers, and oligomers [J].Polymers, 2021, 13(2): 213.

[20] Lyu H, Diercks C S, Zhu C, et al. Porous crystalline olefin-linked covalent organic frameworks [J]. Journal of the American Chemical Society, 2019, 141(17): 6848-6852.

[21] Ezuhara T, Endo K, Aoyama Y. Helical coordination polymers from achiral components in crystals. Homochiral crystallization, homochiral helix winding in the solid state, and chirality control by seeding [J]. Journal of the American Chemical Society, 1999, 121(14): 3279-3283.

[22] Seo J S, Whang D, Lee H, et al. A homochiral metal–organic porous material for enantioselective separation and catalysis [J]. Nature, 2000, 404(6781): 982-986.

[23] Banerjee M, Das S, Yoon M, et al. Postsynthetic modification switches an achiral framework to catalytically active homochiral metal−organic porous materials [J]. Journal of the American Chemical Society, 2009, 131(22): 7524-7525.

[24] Wang R-N, Zhang X-R, Wang S-F, et al. Flatbands in 2D boroxine-linked covalent organic frameworks [J]. Physical Chemistry Chemical Physics, 2016, 18(2): 1258-1264.

[25] Zhuang Z, Shi H, Kang J, et al. An overview on covalent organic frameworks: synthetic reactions and miscellaneous applications [J]. Materials Today Chemistry, 2021, 22: 100573.

[26] Xu H, Chen X, Gao J, et al. Catalytic covalent organic frameworks via pore surface engineering [J]. Chemical Communications, 2014, 50(11): 1292-1294.

[27] Yuan C, Jia W, Yu Z, et al. Are highly stable covalent organic frameworks the key to universal chiral stationary phases for liquid and gas chromatographic separations? [J]. Journal of the American Chemical Society, 2022, 144(2): 891-900.

[28] Han X, Zhang J, Huang J, et al. Chiral induction in covalent organic frameworks [J]. Nature Communications, 2018, 9(1): 1294.

[29] Qian H-L, Yang C-X, Yan X-P. Bottom-up synthesis of chiral covalent organic frameworks and their bound capillaries for chiral separation [J]. Nature Communications, 2016, 7(1): 12104.

[30] Xu N Y, Guo P, Chen J K, et al. Chiral core-shell microspheres β–CD COF @SiO2 used for HPLC enantioseparation [J]. Talanta, 2021, 235: 122754.

[31] Dong Q, Guo X, Qu X, et al. Chiral covalent organic framework-based open tubular capillary electrochromatography column for enantioseparation of selected amino acids and pesticides [J]. Talanta, 2023, 258: 124415.

[32] Guo J-X, Yang C, Yan X-P. “Thiol–ene” click synthesis of chiral covalent organic frameworks for gas chromatography [J]. Journal of Materials Chemistry A, 2021, 9(37): 21151-21157.

[33] Gao K-X, Zhou Z, Yao L, et al. Aspartic acid-assisted size-controllable synthesis of nanoscale spherical covalent organic frameworks with chiral interfaces for inhibiting amyloid–β Fibrillation [J]. ACS Applied Bio Materials, 2022, 5(3): 1210-1221.

