Trends in Analytical Chemistry 118 (2019) 779–792

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

Chiral liquid chromatography and capillary electrochromatography: Trends from 2017 to 2018

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ARTICLE INFO

Article history:
Available online 16 July 2019

Keywords:
Capillary electrochromatography
Chiral selectors
Chiral stationary phases
Liquid chromatography
Low molecular mass compounds
Metal-organic framework
Oligomers
Polymers
Polysaccharides
Drugs

ABSTRACT

Chiral separation remains an important area of research in analytical chemistry. This review recognises the use of different chiral selectors for chiral liquid chromatography and capillary electrochromatography. For the past two years (2017–2018), there was high activity in the development of chiral chromatographic materials and methods as shown by the 93 research and 9 review articles covered. Based on the covered papers, we categorised chiral selectors as low molecular mass, oligomeric, polymeric and metal/covalent organic framework entities. Popular research topics are on liquid chromatography (76 papers), new chiral selectors and stationary phases (56 papers) and polymeric chiral selectors (38 papers). Only 13 research articles were on applications and most papers were on fundamental studies that showed separation of racemic drugs and other model compounds.

1. Introduction

Chirality is a naturally occurring phenomenon, where a molecule has a strong space-specific orientation. A pair of non-superimposable molecules are called enantiomers. Enantiomers have the same physical and chemical characteristics, except for rotation of plane-polarised light and reaction to chiral reagents. The three-dimensional arrangement of a chiral molecule also affects its interactions with enzymes and receptors. Thus, enantiomers may have different biological activities or potencies, e.g., atorvastatin whose (3*R*,5*R*) isomer is a hundred times more effective for inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A reductase activity than its (3*S*,5*R*) isomer [1]. Thus, there is much interest in the separation of enantiomers.

In the analytical separation techniques of liquid chromatography (LC) and capillary electrochromatography (CEC), the chiral selector (CS) is the chiral component of the separation system capable of interacting selectively with the enantiomers to be separated [2]. The basis of separation by CSs is the formation of a host-guest complex by non-covalent interactions, i.e., dipole, electrostatic, hydrogen bonding, hydrophobic and steric. Oftentimes, the differences in binding energy between the two enantiomers and a CS is small, making separations difficult [3,4]. Lämmerhofer classified CSs in LC as macromolecular, macrocyclic and low-molecular mass compounds [5]. In this review on LC and CEC, CSs were organised based on the published articles into several categories; low molecular mass, oligomers, polymers and metal/covalent organic frameworks (MOF/COF).

Chiral LC and CEC (also considered as a mode of capillary electrophoresis (CE)) typically uses a chiral column for chiral separation. The column contains a chiral stationary phase (CSP) by coating or by immobilising a CS onto the surface of a solid support [2]. The difference between LC and CEC is that the mobile phase is flowed through the column by pressure and voltage, respectively. In CEC, retention of charged analytes is also affected by the analytes' electrophoretic migration. However, chiral recognition is only from the interaction of the analytes with a CSP. Classical columns are fully packed with CSPs, but there are advanced columns such as open-tubular (OT) columns where the CSPs are coated onto the walls of the column [6]. In OT-LC and OT-CEC, very narrow inner diameter (i.d.) (e.g., ≤10 μm) columns with an ample coating thickness are required to give optimum performance [6–8].

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https://doi.org/10.1016/j.trac.2019.07.011
0165-9936/

Abbreviations

H_2bbimb	1,3-bis(2-benzimidazol)benzene
ACN	acetonitrile
NH_2-MSN	amino-modified mesoporous silica
Boc	tert-Butyloxycarbonyl protecting group
CD	cyclodextrin
CE	capillary electrophoresis
CEC	capillary electrochromatography
CS	chiral selector
CSP	chiral stationary phase
COF	covalent organic framework
Dabco	1,4-diazabicyclo[2.2.2]-octane
DEA	diethylamine
DMF	*N*,*N*-dimethylformamide
EDMA	ethylene dimethacrylate
DNB-epi-AQn	3,5-dinitrobenzoyl-9-amino-9-deoxy-9-epiquinine
EOF	electroosmotic flow
Fmoc	fluorenylmethyloxycarbonyl chloride
GMA	glycidyl methacrylate
HPMA-Cl	3-chloro-2-hydroxypropylmethacrylate
i.d.	inner diameter
IPA	2-propanol or isopropyl alcohol
LC	liquid chromatography
META	[2-methacryloyloxy)ethyl] trimethylammonium chloride
MIP	molecularly imprinted polymer
MOF	molecular organic framework
OT-CEC	open-tubular capillary electrochromatography
OT-LC	open-tubular liquid chromatography
RP	reversed-phase
SEM	scanning electron microscopy
tBuCQN	tert-butylcarbamoylquinine
TEAA	triethylammonium acetate
TFA	trifluoroacetic acid

Research articles (2017–2018): The objective of this review is to survey and analyse the developments in chiral selectors for use in LC and CEC from 2017 to 2018. We primarily used the search parameters, "alkaloids", "amino alcohols", "antibiotics", "bovine serum albumin", "capillary electrochromatography", "chiral crown ethers", "chiral ligand", "covalent organic frameworks", "cyclodextrins", "liquid chromatography", "metal organic frameworks", "pepsin", "polymers", "polysaccharides" and "chiral separation" in Scopus. Fig. 1 summarises the selected results, showing the categories (and specific topics in the figure caption) and number of papers found. The CS categories of MOF/COF, low molecular mass, oligomeric and polymeric CSs comprised 6%, 22%, 31% and 41% of the total 93 research articles covered, respectively. A few papers reported MOFs (5%) and COF (1%). Low molecular mass selectors are based on amino alcohols/acids (l1) (1%), other (l2) (1%), chiral ligands (l4) (3%) and alkaloids (l5) (14%). Two papers utilised both polysaccharide- and alkaloid-based CSs (l3) (2%). Oligomeric CSs are based on native CDs (o1) (6%), cyclic oligomers (o2) (8%), derivatised CDs (o3) (9%) and glycopeptide antibiotics (o4) (9%). Majority or the papers reported polymeric CSs, which are based on nucleic acids (p1) (1%), amylose & cellulose (p2) (3%), chitosan (p3) (3%), proteins (p4) (3%), synthetic polymers (p5) (4%), amylose (p6)

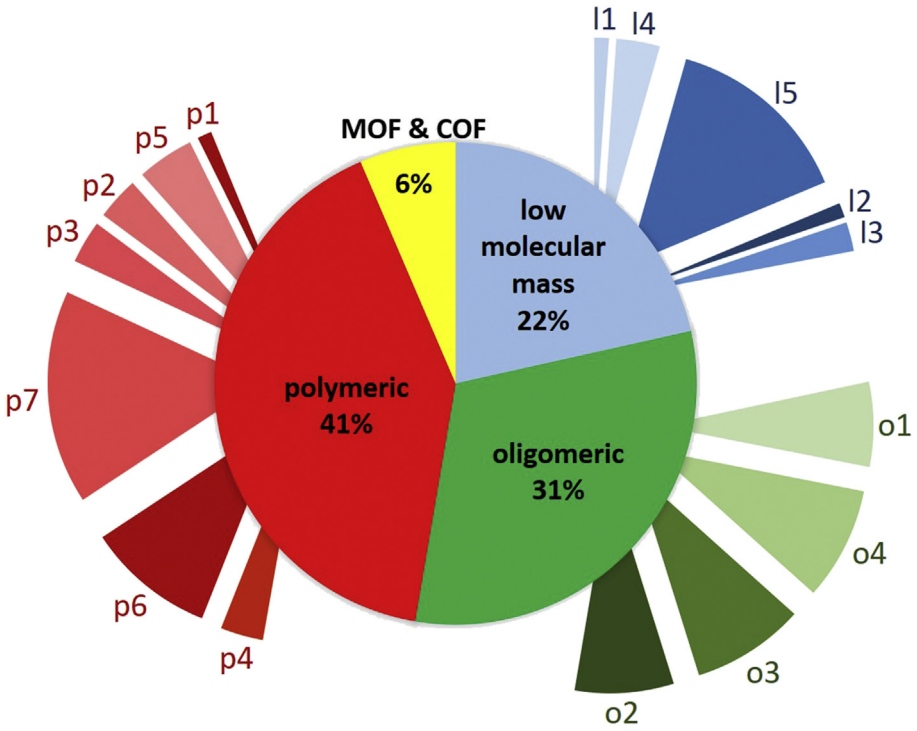

Fig. 1. Chiral selectors in LC and CEC (2017–2018). Total of 93 research articles. Legends: l1: amino alcohols/acids, l2: other, l3: polysaccharide and alkaloids, l4: chiral ligands, l5: alkaloids, o1: native CDs, o2: cyclic oligomers, o3: derivatised CDs, o4: glycopeptide antibiotics, p1: nucleic acids, p2: amylose & cellulose, p3: chitosan, p4: proteins, p5: synthetic polymers, p6: amylose, p7: cellulose.

(10%) and cellulose (p7) (16%). Clearly, sugar-based polymeric CSs were dominant (32% of all papers covered) among the polymeric CSs. The sugar-based polymeric CSs also outnumbered the broader categories of oligomeric and low molecular mass CSs.

Majority of the reported studies (82% or 76 papers) were in LC. 35 studies used commercial chiral columns. 1 paper used a CS as a mobile phase additive and a commercial achiral column. 5, 17, 24 and 30 papers were on MOF/COF, low molecular mass, oligomeric and polymeric CSs, respectively. There were 16 papers in CEC. 1, 3, 4 and 7 paper/s were on MOF, low molecular mass, oligomeric and polymeric CSs, respectively. In general, there were more papers on the development of new CSs or CSPs (40 papers in LC and 15 papers in CEC, 60% of all papers). This suggests sustained interest in materials research in this area. The targeted analytes were mainly pharmaceutical or illicit drugs but also pesticides and biomolecules.

Review articles (2017–2018): Using the same search parameters, there were nine reviews that are relevant to chiral chromatography. Synthetic strategies and applications of MOFs and COFs to chiral separation were reviewed by Bhattacharjee and co-workers [9] and Liu and co-workers [10], respectively. Low molecular mass CSs were reviewed by Fernandes and co-workers (general) [11], Hyun (amino alcohols as chiral ligands) [12] and Ilisz and co-workers (alkaloids) [13]. Selected polysaccharide-based CSPs either for LC or CEC were reviewed by three groups [14–16]. In LC, the chiral recognition ability and mechanisms of coated vs. immobilised polysaccharide CSPs were reviewed by Padró and Keunchkarian [14]. The development of chitosan- and cyclofructan-based CSPs were covered by Xie and Yuan [15]. In CEC, the applications of amylose- and cellulose-based CSPs in real sample analysis were discussed by D'Orazio and co-workers [16]. The use of molecularly imprinted polymers (MIPs) in LC and CEC was surveyed by Rutkowska and co-workers [17]. Clearly, the majority of the abovementioned reviews have focused on very specific aspects of the CSs or separation platform. This review therefore discusses the major developments in chiral separations in both LC and CEC using different CSs and CSPs. A review on CSs as soluble additives in CE is found elsewhere [18].

2. Low molecular mass selectors

The low molecular mass selectors were amino alcohols/acids, chiral alkaloids, metal-ligands and others. During this review, one study prepared Pirkle-type CSPs for LC based on an amino alcohol (*S*-leucinol) and two amino acids (*R*-phenylglycine and *S*-leucine), with the amino acids being more effective for enantioseparation of π-acidic, π-basic, aromatic and oxazolidinone analytes [19]. Separations were based on a combination of different non-covalent bonding interactions such as hydrogen bonding, dipole-dipole stacking and face-to-face or face-to-edge π-π interactions.

It has been >60 years since chiral alkaloids from *Cinchona* were implemented as CS by Grubhofer and Schleith for the chiral separation of mandelic acid [20]. Therefore, it is not surprising to find *Cinchona* alkaloid-based commercial columns for LC. Table 1 summarises these quinine or quinidine-based columns (7 papers), their application and the associated references [21–27]. In addition, during this review period, there were additional 6 papers that developed derivatised *Cinchona* alkaloids for LC of various analytes. These were 3,5-dinitrobenzoyl-9-amino-9-deoxy-9-epiquinine (DNB-epi-AQn) [28], *tert*-butylcarbamoylquinine (tBuCQN) [29,30] and tBuCQN modified with dichlorophenyl, propargyl, *n*-propyl or triazolomethylene [31], *O*-9-(3,5-bis(trifluoromethyl)phenyl) [32] and *O*-9-(2,6,-diisopropylphenylcarbamoyl) [33] groups. Notably, the effect of particle size and morphology on separation was demonstrated using new sub-2 μm fully porous particles and 2.7 μm superficially porous particles of tBuCQN. These innovative particle technologies provided faster and more efficient separation of test analytes compared to benchmark 5 μm fully porous particles [29]. This is shown in Fig. 2 including the structure of tBuCQN-based CSP (inset). In another study with tBuCQN derivatives, the authors found that immobilisation chemistry does not influence the elution order of the tested acidic analytes but could affect selector coverage [31]. In general, the mechanism of chiral separation of alkaloid type CSs is based on ion exchange with the ionisable group of the alkaloid derivatives. However, DNB-epi-AQn also contains multiple π-donor/π-acceptor units which may contribute to the chiral separation mechanism, and thus it was considered as a hybrid selector.

Efforts to develop more efficient CSs lead researchers to explore other alkaloids as potential CSs. Following earlier work on brucine [34], other terrestrial plant-sourced alkaloid strychnine [35] and codeine [36] was developed for LC and CEC, respectively. The immobilised strychnine had a permanently ionised nitrogen atom that is desired for chiral separations due to its strong anion exchange capabilities [35]. The codeine immobilised on a glycidyl methacrylate-based monolithic support gave rise to a high thiol group density, which provided high chiral selector coverage [36].

Chiral ligands as CSs have been proposed by Davanakov since the early 1970s [37]. Mechanism of chiral separation with these CSs is based on chiral ligand exchange. The chiral ligands in the CSP form complexes with a metal ion (added into the mobile phase) and analytes. The analyte enantiomer that forms a more stable complex is thus more retained, causing the separation of enantiomeric mixtures. The new ligand *N*-decyl-*S*-trityl-*R*-cysteine [38] and poly(methacryloyl-L-arginine methyl ester) [39] was developed for LC and CEC, respectively. Copper or zinc was used in the mobile phase for the separation of native and derivatised amino acids. A commercially available chiral ligand exchange column with a proprietary ligand (Supelco Astec CLC-D) was used for the analysis of D-lactic acid [40].

The CS considered here as "other" is the low molecular weight and cyclic chiral compound azithromycin, which is a 15-membered lactone ring containing several functionalities and multiple chiral centres. This chiral antibiotic was previously reported as a CS in CE [41] and was recently applied as CSP in CEC for anionic drugs [42]. The new work was however motivated by the success of the implementation of antibiotic-based CSs on zirconia hybrid sol-gel monoliths by the same research group. They observed enhanced performance with these monoliths based on the homogenous distribution of the CS into the support.

3. Oligomeric selectors

Oligomers are molecules of intermediate relative molecular mass, the structure of which essentially comprises a small plurality of units derived, actually or conceptually, from molecules of lower relative molecular mass [2]. The number of repeating units in oligomers is not precisely defined but is generally set between three to ten. The oligomers covered here were oligosaccharides, glycopeptide antibiotics, crown ethers and calix[4]arenes.

3.1. Oligosaccharides

Oligosaccharides contain three to ten repeating sugar monomers. Among these, cyclodextrins (CDs) are cyclic oligosaccharides containing between six to eight repeating glucose units linked together by an α(1 → 4) glycosidic bond. CDs have a toroidal cone structure with a hydrophobic cavity and a hydrophilic surface. Molecules interact with the hydrophobic cavity in a stereospecific manner via non-covalent interactions, which gives CDs the ability to discriminate between enantiomers. Only small molecules can

Table 1
Commercial columns with different macromolecules as CSPs based on CD, amylose, cellulose and others; application and references.

CS	Trade name (manufacturer)	Analyte molecule	Ref.
Alkaloid-based			
O-9-(tert-butylcarbamoyl) quinidine	Chiralpak QD-AX (Daicel)	short chain aliphatic hydroxycarboxylic acids	[23]
		2-hydroxyadipic acid, malic acid	[24]
		N^{α}-Fmoc/Boc amino acid derivatives of natural and unnatural amino acids	[25]
O-9-(tert-butylcarbamoyl) quinine	Chiralpak QN-AX (Daicel)	short chain aliphatic hydroxycarboxylic acids	[23]
		2-hydroxy-monocarboxylic acids	[24]
		N^{α}-Fmoc/Boc amino acid	[26]
quinine combined with (*S*,*S*)-*trans*-2-aminocyclohexanesulfonic acid	Chiralpak ZWIX(+) (Daicel)	cyclic β-amino acids, related cyclic β-aminohydroxamic acids	[21]
		basic and ampholytic indole analogues	[22]
		limonene-based carbocyclic β-amino acids	[27]
		short chain aliphatic hydroxycarboxylic acids	[23]
quinidine combined with (*R*,*R*)-*trans*-2-aminocyclohexanesulfonic acid	Chiralpak ZWIX(−) (Daicel)	limonene-based carbocyclic β-amino acids	[27]
		N^{α}-Fmoc/Boc amino acid	[26]
		short chain aliphatic hydroxycarboxylic acids	[23]
		citramalic acid and 2-isopropylmalic acid	[24]
		cyclic β-amino acids, related cyclic β-aminohydroxamic acids	[21]
		basic and ampholytic indole analogues	[22]
Chiral ligand-based			
proprietary chiral ligand	Supelco Astec CLC-D (Sigma Aldrich)	D-lactic acid	[40]
CD-based			
permethyl-β-CD	Nucleodex-β-PM (Macherey-Nagel)	aryloxyphenoxy-proprionate herbicides	[57]
Glycopeptide antibiotics-based			
N,*S*-dioctyl-D-penicillamine	Chirex® 3126 (D)-penicillamine (Phenomenex)	carnosine	[61]
modified macrocyclic glycopeptide	Nicoshell (AZYP)	verubecestat API	[59]
		40 tobacco alkaloids and tobacco-specific nitrosamine metabolites	[62]
ristocetin	Chirobiotic™ R (Astec)	phenylalanine	[63]
teicoplanin	Chirobiotic™ T (Astec)	phenylalanine	[63]
		carnosine	[61]
		14 drugs and 8 metabolites	[60]
	Teicoshell (AZYP)	verubecestat intermediates	[59]
vancomycin	Vancoshell (AZYP)	40 tobacco alkaloids and tobacco-specific nitrosamine metabolites	[62]
Chiral crown ether-based			
(+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid	Chirosil NT-RCA(+) (RS Tech)	proline and pipecolic acid	[67]
		methoxyphenamine and its analogues	[68]
S-(1,1′-binaphthyl)-20-crown-6	Crownpak CR-I(+) (Daicel)	proteinogenic amino acids (except DL-proline)	[69]
R-(1,1′-binaphthyl)-20-crown-6	Crownpak CR-I(−) (Daicel)		
Amylose-based			
amylose tris(5-chloro-2-methylphenylcarbamate)	Chiralpak AY-RH (Daicel)	two novel diazenes	[87]
amylose tris (3,5-dimethylphenylcarbamate)]	Chiralpak IA (Daicel)	apremilast	[82]
		ten anti-cholinergic drugs	[85]
		7-[(1-alkylpiperidin-3-yl)methoxy]coumarin derivatives	[86]
	Chiralpak AD (Daicel)	tofisopam	[81]
	Chiralpak AD-H (Daicel)	various sulfinamide derivatives	[88]
	Lux Amylose 1 (Phenomenex)	various racemates	[80]
amylose tris(5-chloro-3-methylphenylcarbamate)	Lux Amylose 2 (Phenomenex)	helical chromenes	[84]
amylose tris(3-chlorophenylcarbamate)	Chiralpak ID (Daicel)	eight anti-cholinergic drugs	[76]
amylose tris(3-chloro-5-methylphenylcarbamate)	Chiralpak IG (Daicel)	various racemates	[83]
Cellulose-based			
cellulose tris (3,5-dimethylphenylcarbamate)	Lux® Cellulose-1 (Phenomenex)	1-naphthylamides	[95]
cellulose tris(3-chloro-4-methylphenylcarbamate)	Lux® Cellulose-2 (Phenomenex)	chiral psychoactive drugs	[99]
cellulose tris(4-methylbenzoate)	Lux® Celluose-3 (Phenomenex)	dextromepromazine and related substances	[96]
		levompromazine sulfoxide	
		2-methoxyphenothiazine	
	Chiralcel OJ (Daicel)	racecadotril	[98]
cellulose tris(3,5-dimethylphenylcarbamate)	Chiralcel OD-H (Daicel)	various sulfinamide derivatives	[88]
	Chiral ART Cellulose-SB (YMC America)	various pharmaceuticals	[74]
cellulose tris(4-chloro-3-methylphenylcarbamate)	Lux® Cellulose-4 (Phenomenex)	helical chromenes	[84]
cellulose tris(3,5 dichlorophenylcarbamate)	Chiralpak IC (Daicel)	alvimopan	[94]
		AT1 blockers with 6-substituted carbamoyl benzimidazoles	[97]
		eight azole antifungals	[100]
	Lux i-Cellulose 5 (Phenomenex)	various racemates	[80]

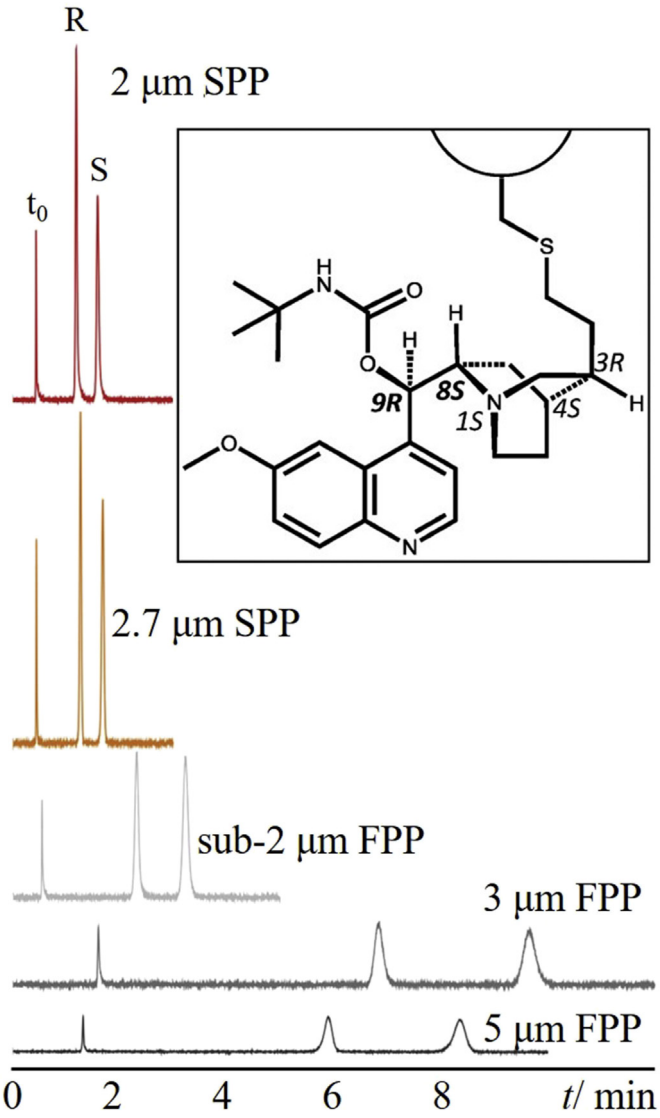

Fig. 2. Influence of particle size and morphology on the separation of fluorenylmethyloxycarbonyl chloride-derivatised phenylalanine racemate. Particle size and morphology is indicated beside each chromatogram. Inset shows the CSP based on tBuCQN. Abbreviations: FPP: fully porous particle; SPP: superficially porous particle. Other experimental conditions are found in Figure 2 of reference [29]. Reprinted with permission from Ref. [29].

enter the cavity due to the limited cavity size. The native CDs are α-, β- and γ-CD, with 6, 7 and 8 number of glucose units, respectively. The cavity diameter (narrow/wide rim) increases from α- (0.47/0.52 nm), β- (0.60/0.64 nm) to γ-CD (0.75/0.83 nm). Native CDs have been modified to improve its chiral selection ability and solubility [43], especially β-CD which is the least soluble in aqueous-based solvents.

3.1.1. Native CDs

β-CD was immobilised into silica to investigate the effect of surface orientation (wider or narrower mouth facing the mobile phase) on separation of 30 model racemates by reversed-phase (RP)-LC [44]. Click chemistry was used to anchor the derivatised β-CD, mono(2^A-azido-2^A-deoxy)-β-CD onto alkynyl silica. More analytes were separated with the wider rim facing the mobile phase. Reversal of elution was observed with the change of surface orientation. Molecular dynamics simulation was also used to explain the separation, with hydrogen bonding and hydrophobic interaction as the major players that bring separation.

In two papers, alternating layers of gold nanoparticles and a β-CD derivative were assembled onto a modified fused silica capillary with the β-CD as the final layer [45,46]. Meanwhile, β-CD was bonded onto a periodic mesoporous organosilica [47] and a methacrylate-based polymer [48]. In a separate study, a β-CD/polydopamine composite was prepared [49]. These materials were immobilised on the inner walls of fused silica capillaries for chiral OT-CEC and OT-LC. Separations were obtained in wide i.d. capillaries (≥50 μm) with very thin coatings as CSPs, which are atypical in OT-CEC and OT-LC.

3.1.2. Modified/derivatised CDs

Functionalisation could provide additional non-covalent bonding forces beyond the capability of native CDs [50]. β-CDs have shown superior performance over other CDs, and its functionalisation has been of research interest. With these in mind, novel β-CDs with different functionalities have been prepared, namely, three phenylcarbamoylated β-CDs [51], perphenylcarbamoylated β-CD derivatives [52–54], *N*-benzyl-phenethylamino-β-CD [55] and cationic β-CD clicked bilayer [54]. Specifically, 3,5-dimethylphenylcarbamoylated β-CD was incorporated into amino-functionalised spherical mesoporous silica for nano-RP-LC and CEC for separation of various flavanones [56]. Fig. 3(A) shows the synthetic pathway to prepare β-CD derivative from native β-CD. The derivative was immobilised into the amino-functionalised spherical mesoporous silica (with "3D wormhole-like porous framework"). Fig. 3(B) shows the scanning electron microscopy (SEM) image of a nicely packed 100 μm i.d. column. Fig. 3(C) compares the chiral separation of flavone via nano-LC and CEC using the same column. The separations under the conditions used were faster by LC due to the faster flow rate compared to the electroosmotic flow (EOF) in CEC. Also, more racemates were baseline separated in LC compared to CEC.

A commercially-available chiral column based on a permethyl-β-CD (Nucleodex-β-PM) was used for the separation of aryloxyphenoxy-propionate herbicides [57] while carboxymethyl-β-CD was used as a mobile phase additive with a commercially-available RP column for analysis of indanone and tetralone derivatives commonly found in natural products [58]. Notably with the study using a CD as mobile phase additive, very successful separations were obtained, but with moderately long analysis times [58].

3.2. Glycopeptide antibiotics

Glycopeptide antibiotics are glycosylated modified peptides. Eremomycin, teicoplanin and vancomycin (and its Edman degradation product) are glycopeptide antibiotics considered in this review. Ristocetin, modified penicillamine and Nicoshell (a proprietary CSP) in LC are mentioned in Table 1 [59–63]. Glycopeptide antibiotics have diverse functional groups that allow multiple molecular interactions. While it is difficult to ascertain the chiral recognition mechanism of glycopeptide antibiotics, it is thought that its ionisable groups play an important role in its interaction with analytes. Also, the aromatic ring association with these antibiotics immobilises the peptide backbone. This creates multiple inclusion sites that influence selectivity. The resulting CSPs are stable and efficient in LC at normal and reversed phase modes. The carboxylic acid group in vancomycin is important for recognition of amines, while the amine group in teicoplanin and its aglycone is thought to be important for recognition of acids.

A report described the fabrication of a mixed eremomycin- and vancomycin-immobilised CSP [64] and was found to separate β-

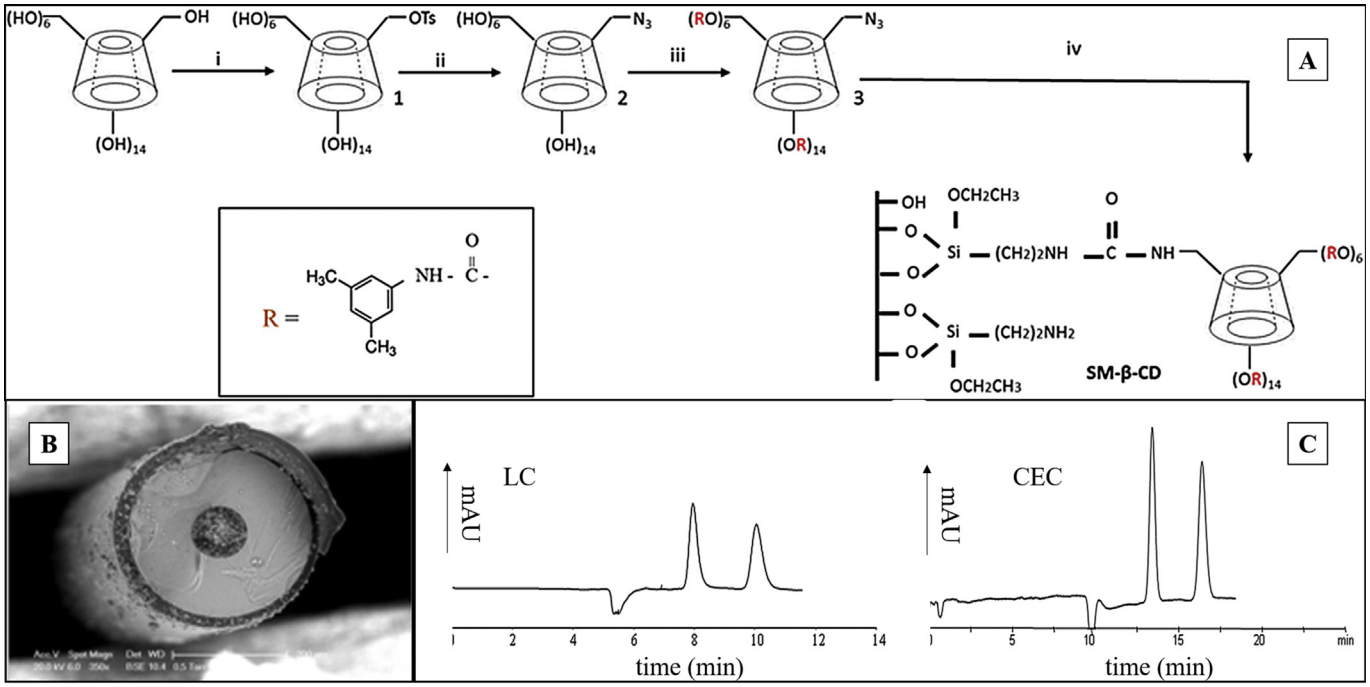

Fig. 3. (A) Schematic of preparation of β-CD derivative and immobilisation into mesoporous silica. (B) Representative SEM image of packed LC/CEC column. (C) Representative LC and CEC analyses of flavanone. Capillary dimensions 20 cm × 100 μm i.d.; mobile phase MeOH/H_2O, 10 mM ammonium acetate pH 4.5 (90:10, v/v); flow rate 281 nL/min. More details are found in Table 1 and Figure 6 of reference [56]. Reprinted with permission from Ref. [56].

blockers and amino acids enantiomers. In another report, the Edman degradation product (the terminal amide was reduced to an amine group) of vancomycin as CSP in LC was described [65]. The new CSP was able to recognise more analytes compared to Nicoshell™, Teicoshell™ (teicoplanin-based) and Vancoshell™ (vancomycin-based) although it was Teicoshell™ that gave better chiral resolutions. Meanwhile, zwitterionic teicoplanin and vancomycin CSPs were bonded to ≤2 μm fully porous silica particles and were evaluated for analysis of chiral compounds [66]. The analytes were better resolved compared to their commercial counterparts, TeicoShell™ and VancoShell™. The zwitterionic feature of the CSPs also allowed for the simultaneous analysis of the corresponding counterions.

3.3. Cyclic oligomers

Cyclic oligomers included in this review are chiral crown ethers [67–70] and calix[4]arenes [71–73]. These compounds were all applied as CSPs in LC. Chiral crown ethers based on 20-crown-6 are well known to resolve enantiomers with primary amine groups, which interact with the cavity of the crown ether [67,68]. On the other hand, crown ethers based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid can also resolve enantiomers with secondary amine groups, which interact with the carboxylate group of the crown ether [68]. New acridino-18-crown-6 and acridino-21-crown-7 ethers containing a carboxyl group at position 9 of the acridine ring was synthesised and evaluated for the analysis of aralkylamines and α-amino acid esters [70]. The new CS has an extended aromatic system that adds rigidity to the crown ether framework. The aromatic system also allows for π-π interaction with analytes, but its benefits for separation were not verified.

Table 1 summarises the chiral crown ether-based columns that are commercially available, their application and associated reference [67–69]. Crownpak CR-I(+) and CR-I(−) (Daicel) are based on (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6, while Chirosil RCA(+) and Chirosil NT-RCA(+) (RS Tech) are based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid. Chirosil NT-RCA(+) is an improvement to Chirosil RCA(+). The former has an *N*-methylated amide linker, which eliminates hydrogen bonding between itself and the oxygens in the crown ether. This removes any competition for interactions and improved resolution of proline, pipecolic acid and methoxyphenamine [67,68].

Calix[4]arenes are cyclic oligomers composed of phenol units linked by methylene bridges at positions ortho to the hydroxyl group. Like cyclodextrins and chiral crown ethers, calix[4]arenes form inclusion complexes with analytes. Addition of functional groups at one edge of the calix[4]arene structure (*para* position to the hydroxyl group) could provide a better environment for interaction with chiral molecules as they become included into the new structure. Perhaps inspired by these, three new calix[4]arene derivatives: L-alanine- [71] and deoxycholate-functionalised calix[4]arene [72] and aza-15-crown-5-capped 3-*C*-methylcalix[4]resorcinarene [73] were synthesised to make CSPs for LC. Unlike the latter derivative, the first two calix[4]arene derivatives were specifically designed to contain chiral moieties. Notably, deoxycholate-functionalised calix[4]arene-based CSP showed better performance over deoxycholate only-based CSP (see Fig. 4). The aza-15-crown-5-capped 3-*C*-methylcalix[4]resorcinarene has two recognition moieties: 3-*C*-methylcalix[4]resorcinarene and aza-15-crown-5. It was claimed that the resulting CSP provided very good resolutions for the tested compounds. However, the commonly used model analytes are easily separable using LC with other CSs [64,74,75].

4. Polymeric selectors

4.1. Polysaccharides

Polysaccharides contain more than ten monosaccharide residues linked by glycosidic bonds. Homopolysaccharides from D-

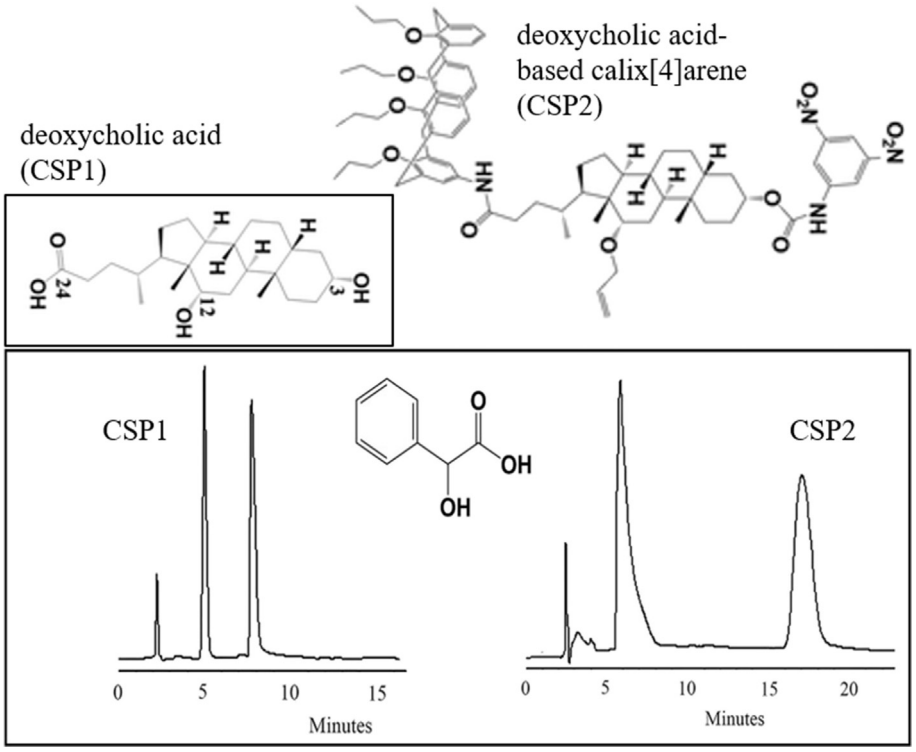

Fig. 4. Structures of deoxycholic acid and deoxycholic acid-based calix[4]arene which were functionalised into CSP1 and CSP2, respectively. Enhanced chiral separation of DL-mandelic acid using CSP2 vs. CSP1. Column dimensions 250 mm × 4.0 mm i.d.; mobile phase hexane/IPA/TFA (95:5:0.1, v/v/v); flow rate 1 mL/min. More details are found in Table 1 of reference [72]. Reprinted with permission from Ref. [72].

glucose (amylose and cellulose) and heteropolysaccharides (chitosan) were used as CSs in LC and CEC. Polysaccharide CSPs are among the most popular choice due to their known versatility in separating organic compounds. They are not applicable as mobile phase additives due to their poor solubility. The ability of polysaccharide CSPs to discriminate enantiomers is due to their chirality arising from the presence of several stereogenic centres of the glucopyranose unit, the helical twist of the polymer backbone and the alignment of adjacent polymer chains forming ordered regions [5].

4.1.1. Amylose

Amylose is linked together by an α(1 → 4) glycosidic bond and has a helical three-dimensional structure. Amylose is functionalised with various substituents at the 2, 3, and 6 positions of the glucose unit, commonly by phenylcarbamate substituents. The resulting amylose derivatives are hydrophobic left-handed helices that provide a steric environment. This allows enhanced recognition between enantiomers. They have functional groups enabling weak selector-analyte interactions that are driven by hydrophobic and hydrogen bonding.

Interactions with amylose-based CSPs was studied using LC [76,77]. The chiral recognition abilities of six new amylose derivatives (coated on 3-aminopropyl silica gels) with a benzoate at 2-position and two different phenylcarbamates at 3- and 6-positions were evaluated. The amylose 2-benzoate-3-(phenylcarbamate/4-methylphenylcarbamate)-6-(3,5-dimethylphenylcarbamate) exhibited similar performance to commercially available Chiralpak AD [77]. In the other study, the recognition mechanisms of the commercially-available column Chiralpak ID was studied by molecular modelling using AutoDock [76]. Their results verify that substituent size, substitution patterns, and interactions (hydrogen bonds and hydrophobic) played a crucial role for separation. Meanwhile, the performance of the previously reported CSP, amylose 3,5-dimethylphenylcarbamate [78] was evaluated in nano-LC, CEC and pressure-assisted CEC modes. The pressure-assisted CEC mode provided the best chromatographic efficiency for the selected flavanone racemates [79].

Table 1 summarises the amylose-based columns commercially available, their application and the associated reference for this review period [76,80–88]. The columns were mostly based on tris-substituted (i.e., positions 2, 3 and 6 of the sugar monomer have the same substituent) derivatives.

4.1.2. Cellulose

Unlike amylose, cellulose is linked together by β(1 → 4) glycosidic bonds. Cellulose has a linear three-dimensional structure, rendering its limited solubility in aqueous solutions. Similar to amylose, cellulose is functionalised with various substituents at the 2, 3, and 6 positions of the glucose unit commonly by phenylcarbamate and benzoate substituents. The resultant molecules are hydrophobic right-handed helices that provide a steric environment for recognition between enantiomers. Certain functionalisations allow for weak selector-analyte interactions that are driven by hydrophobic and hydrogen bonding interactions.

In LC, CSs are typically coated or immobilised onto a silica surface. Motivated by the stability and increased chromatographic capacity provided by nanoparticles on coated-type CSPs, cellulose was coated onto the surfaces of reduced graphene oxide-modified [89] and silver nanoparticles-modified silica [90]. These innovative coatings showed better performance over the commercially available silica supported CSPs for various racemates. For example, the separation factor values of graphene oxide-modified and silver nanoparticles-modified silica were >2, while that of Chiralcel OD was <2 [91]. Meanwhile, more test enantiomers were separated using immobilised-type CSPs [80].

The separation capability of CSPs with cellulose derivatives depends on the nature of the substituents on aromatic moieties at the 2-, 3- and 6-positions of the sugar unit. These substituents modify the structure and polarity (including local polarity) of the derivatives. Thus, several studies have evaluated the performance of celluloses derivatised with benzoates [92], phenylcarbamates [93] and carbamates [91] in LC. Among the 24 benzoate derivatives studied, cellulose 4-methylbenzoate and 3-methylbenzoate separated the largest number of compounds considered in the report [92]. The presence of electron-donating methyl provides electron density to the phenyl group. This enhanced π-π interactions. In another study, the emphasis was on the interactions between 18 different tris-substituted cellulose derivatives and 14 chiral sulfoxide molecules [93]. As expected, different functionalities at different positions affected the recognition, e.g., presence of bulky and methyl/chloro groups reduced and improved selectivity, respectively under certain experimental conditions.

While the above studies were on changing one substituent only, the effect of more than one substituent at specific positions of the glucose unit (2-, 3-, and 6-) was also investigated and proved to be a valuable approach for improved separation [91]. When two different substituents (e.g., 3,5-dimethylphenylcarbamate, 3,5-dichlorophenylcarbamate, 4-chlorophenylcarabamate, and cyclohexylcarbamate) are combined, it was suggested that the enantioseparation was better because of the different recognition mechanisms of the two different carbamate groups. In addition, the resulting CSPs were superior when compared to a commercially available cellulose-based column.

Table 1 summarises the commercially available cellulose-based columns, their application and associated reference for this review period [74,80,84,88,94–100]. Similar to amyloses, they were mostly based on tris-substituted (i.e., positions 2, 3 and 6 of the sugar monomer have the same substituent) derivatives.

There were two reports on the application of cellulose derivatives for CEC. Cellulose tris(3,5-dimethylphenylcarbamate) was coated onto a glycidyl methacrylate-based monolith for the separation of several acidic, basic and neutral racemates [101]. Photografting of the monolith with [(2-methacryloyloxy)ethyl] trimethylammonium chloride was done to incorporate quaternary ammonium groups onto the support. This provided a larger number of hydrogen bonding sites for the attachment of the cellulose derivative. In another study, a special nanocellulose crystal-sol mixture was coated onto the inner walls of a fused silica capillary [102]. SEM images showed a thin coating inside a particularly wide (75 μm) i.d. capillary, but the column was reported to affect OT-CEC enantioseparation of the thirteen different racemates tested. A thin coating of cationic β-CD also only affected the EOF in CE [103]. In addition, the coating was not via the traditional layer-by-layer approach where a positive layer is typically coated over a negative layer and vice-versa.

4.1.3. Chitosan

Chitosan is produced from the partial deacetylation of chitin that is composed of *N*-acetyl-*D*-glucosamine units linked together by β(1 → 4) glycosidic bonds. It has very similar structure to cellulose, except the 2-position in the glucose unit contains an amino or acetamido group rather than a hydroxyl group. Chitosan and its derivatives have been considered as promising CSs; however, studies on their applications to chiral analytes have been limited [15]. Nevertheless, there were three reports from the same group on new chitosan derivatives, namely, chitosan 3,6-bis(4-methylphenylcarbamate)-2-(isobutylurea) and chitosan 3,6-bis(3-chloro-4-methylphenylcarbamate)-2-(isobutylurea) [104], chitosan bis(phenylcarbamate)-(*N*-cyclohexylformamide)s and chitosan bis(phenylcarbamate)-(*N*-hexanamide)s [105], and chitosan 3,6-bis(arylcarbamate)-2-(p-methylbenzylurea)s [106]. Coated-type CSPs were prepared. The suggested advantage of chitosan derived CSPs is their wide solvent tolerance, allowing the use of so-called "unusual solvents". Notably, two derivatives of chitosan 3,6-bis(arylcarbamate)-2-(isobutylurea) were found to have similar performance to Chiralcel OD, a cellulose-based column [104].

4.2. Proteins

Proteins are heteropolymers of amino acids linked together by peptide bonds. Its three-dimensional structure depends on the nature and order of amino acid residues. Proteins have several functions including small molecule recognition in biological systems. The stereospecificity of protein-analyte interactions led to the development of proteins as CSs. However, proteins have limited physicochemical stability, especially in high organic solvent environments and temperature used in chiral chromatography. Moreover, low sample loading capacity due to a limited number of binding sites and low molar concentration per CS binding site were issues that lead to poor separations. For these reasons the popularity of protein CSPs for LC and CEC have declined over the years [5].

Monoliths as a CSP support may help alleviate the low sample loading capacity and low molar concentration per CS binding site; thus, there is sustained interest in the development of protein-based monolithic CSPs in CEC. Monoliths are typically easy to prepare, permeable and have low resistance to mass transfer [107]. Pepsin was functionalised onto a monolith obtained from co-polymerisation of amino-modified mesoporous silica nanoparticles, glycidyl methacrylate and ethylene dimethacrylate [108]. The nanoparticles improved the loading of pepsin into the monolith matrix, hence the improved interaction between pepsin and enantiomers. The same research group fabricated a mixed CSP monolith made up of cellulase and human serum albumin on a poly(glycidylmethacrylate-co-ethylene glycol dimethacrylate) monolith [109]. The mixed CSP was able to separate more test analytes than the individual CSPs. In both studies, however, stability of columns reported was limited, i.e., 60–100 runs, which can be performed within a few days only. Meanwhile, lysozyme was immobilised into covalent organic frameworks (COFs) [110]. This was motivated by the group's earlier success with immobilising lipase into the COF [111]. The COFs provided a protective environment, which prevented the denaturation and leaching of lysozyme.

4.3. Nucleic acids

Nucleic acids are heteropolymers of nucleotide bases linked together by a sugar-phosphate backbone. One paper utilised a 365-base pair deoxyribonucleic acid fragment from *Salmonella enterica* as CS [112]. The CSP coating was prepared by sequentially immobilising polydopamine/gold nanoparticles and the CS on a glass microfluidic channel using layer-by-layer assembly. Although the coating is expected to be too thin to allow OT-CEC, chiral separation of Cy5-labelled tryptophan was reported.

4.4. Synthetic polymers

There were two reports on the application of synthetic polymers for chiral LC or CEC. First, a set of polymers with a phenylacetylene repeating unit containing an L-phenylalanine ester pendant was prepared and utilised as a CSP in LC [113]. The polymers were either coated or immobilised onto silica with the immobilised CSPs showing better performance. The immobilised CSP labelled as iCSP 2 was found to have comparable performance versus six commercially available Daicel Chiralpak or Chiralcel columns for the separation of one target racemate. These separations were, however,

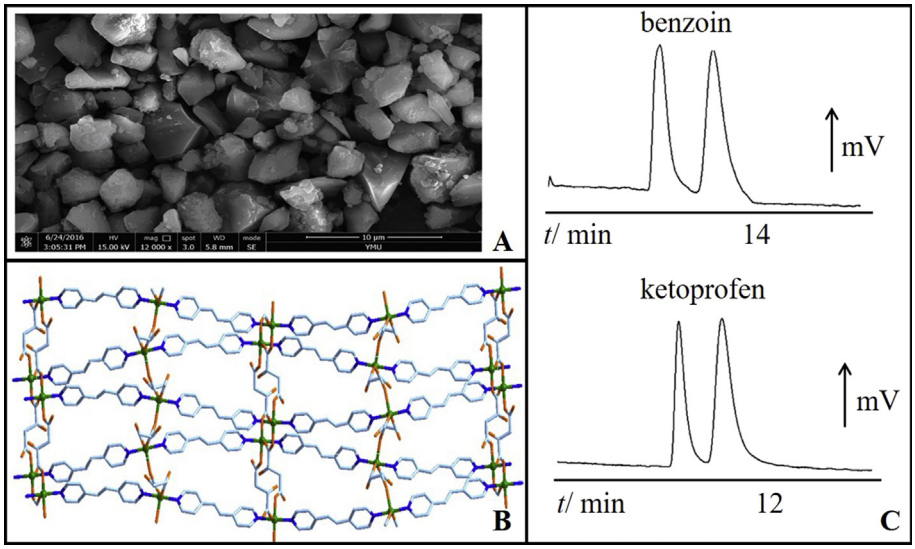

Fig. 5. (A) SEM image of prepared homochiral MOF crystals with a uniform cubic shape and average particle size of 5–10 μm (B) Framework structure of $[Cu(S\text{-mal})(bpe)]_n$ (C) LC chromatograms of benzoin and ketoprofen on MOF columns. Column dimensions 250 mm × 2.0 mm i.d.; mobile phase (benzoin) hexane/IPA (99:1, v/v), (ketoprofen) hexane/IPA (95:5, v/v); flow rate 1 mL/min. More details are found in Figure 2 of reference [121]. Reprinted with permission from Ref. [121].

obtained with environmentally harmful organic solvents such as hexane and chloroform. In the other study, poly-levadopa was deposited onto the walls of a 75 μm capillary for OT-CEC separation of several model racemates [114]. The column with thin coating observed via SEM results was claimed to affect OT-CEC enantioseparation of the tested racemates.

The high selectivity of molecularly imprinted polymers (MIP) make them an attractive platform for chiral separations of very important target molecules. The MIPs using *R*-1,1′-binaphthalene-2-naphthol [115] and *R*-mandelic acid and L-histidine [116] as template molecules was used as CSPs for LC and CEC, respectively. The reported LC separation of 1,1′-binaphthalene-2-naphthol was characteristically long (60 min at 20°C). On one hand, the elegant use of magnetic MIPs that can be easily placed at the separation channels of a microchip allowed the electrochromatographic separation of mandelic acid and histidine racemates.

5. Metal and covalent organic frameworks

Metal organic frameworks (MOFs) are coordination networks with an open framework containing potential voids [117]. They are typically solid materials constructed from inorganic metal ions or metal clusters and multitopic organic ligands. Covalent organic frameworks (COFs) are extended porous crystalline polymers assembled from organic building blocks with light elements through covalent bonds [118]. MOFs and COFs have several unique features such as large specific surface area, accessible tunnels and cavities and excellent chemical and thermal stability. These make them attractive materials for chiral separation [9].

In this review period, five papers reported the use of MOFs. The use of a bare or silica-immobilised MOF CSP was investigated using a known MOF based on Nd^{3+} as metal ion and D-camphoric acid, H_2O and Cl^- as ligands [119]. The packed columns with silica-immobilised MOF CSP had regular shape and more uniform particle size, thus more racemates were separated in comparison to its bare counterpart. From two papers, a total of three new MOFs were prepared from the metal ions Zn^{2+}, Co^{2+} and Cu^{2+} coordinated with the ligands L-tyr, L-glu or *S*-malic acid and *trans*-1,2-bis(4-pyridyl)ethylene, respectively [120,121]. Fig. 5(A), (B) show the SEM image and the framework structure of the MOF $[Cu(S\text{-mal})(bpe)]_n$ [121]. Fig. 5(C) shows the successful separation of two racemates with this MOF.

In addition, there were two unique MOFs. One was based on K^+ as metal ion and γ-CD as ligand [122]. The other was a homochiral zeolitic MOF having a final formula of $[(Cu_4I_4)(dabco)_2]\cdot[Cu_2(bbimb)]\cdot 3DMF$ (dabco = 1,4-diazabicyclo[2.2.2]-octane, H_2bbimb = 1,3-bis(2-benzimidazol)benzene, DMF = *N*,*N*-dimethylformamide) [123]. Although the individual components of this MOF are achiral, the helical structure of the MOF allowed chiral recognition.

A challenge on the use of typical MOFs for many chemical purposes, especially in LC is susceptibility to water [124]. A true water-stable MOF is an uncommon CSP in LC. Water disrupts the structure of the reported MOFs, and thus extremely harmful or non-green organic solvent (i.e., hexane, dichloromethane) based mobile phases were implemented in all the covered as well as many previous studies [125,126]. We encourage the development of water stable MOFs as CS in LC and CEC.

One study was successful in preparing two chiral COFs by condensation of a symmetric tetraaryl-1,3-dioxolane-4,5-dimethanol-derived tetraaldehyde and tetra(4-aniliyl)methane [127]. This is a remarkable achievement because of the problems associated with the preparation of chiral COFs having a balance between asymmetry and crystallinity [10]. However, the problem with the results was the ~5 min-long peak widths and long analysis times.

6. Applications to real samples

Out of the 93 covered papers, only 13 papers (14% of total papers) presented real world applications. Table 2 summarises these 13 papers, which were grouped according to type of analyte, i.e., small molecule pharmaceutical drugs or drug intermediates, amino acids and a small organic acid. For each paper, the CS and CSP of the optimum chiral column, separation mode, mobile phase, analyte, application and appropriate reference were listed. The drugs were mainly in formulations, but also as intermediates and in environmental samples. They were analysed mostly by RP-LC using commercially available chiral columns. The mobile phases implemented were typical, e.g., using short chain alcohols. In the case of method development for pharmaceutical formulations, several

Table 2
Real sample applications of various CSs in LC and CEC[b].

CS[a]	CSP[a]	separation mode/mobile phase	analyte	application	ref.
small molecule pharmaceutical drugs or drug intermediates					
amylose tris (3,5-dimethylphenylcarbamate)	Chiralpak AD (Daicel)	RP-LC MeOH/IPA (85:15, v/v)	*R*- and *S*-tofisopam	analysis of tofisopam isomers in a commercial tablet	[81]
cellulose tris (4-methylbenzoate)	Chiralcel OJ (Daicel)	RP-LC 100% MeOH	*R*- and *S*-racecadotril	analysis of racecadotril enantiomers in commercially available capsules and granules	[98]
teicoplanin	Teicoshell (AZYP)	RP-LC 1% TEAA/MeOH (50:50 v/v) RP-LC 2% TEAA/MeOH (75:25 v/v) RP-LC 2% TEAA/MeOH (70:30 v/v) RP-LC 2% TEAA/MeOH (70:30 v/v) RP-LC 0.1% H_3PO_4/MeOH (70:30 v/v)	verubecestat synthetic intermediate 1 verubecestat synthetic intermediate 2 verubecestat synthetic intermediate 3 verubecestat synthetic intermediate 4 verubecestat synthetic intermediate 5	enantiopurity analysis of the entire verubecestat synthetic route	[59]
(proprietary CSP)	Nicoshell (AZYP)	RP-LC 1.0% TEAA/ACN (40:60 v/v)	verubecestat final API		
teicoplanin	Chirobiotic T (Astec)	RP-LC 10 mM NH_4OAc, pH 4.2/MeOH (70:30 v/v)	carboxyibuprofen, chloramphenicol, 2-hydroxyibuprofen, ibuprofen, ifosfamide, indoprofen, ketoprofen, naproxen and praziquantel	analysis of pharmacologically active compounds in influent and effluent wastewaters and river water	[60]
cellulose tris (4-methylbenzoate)	Lux Cellulose-3 (Phenomenex)	RP-LC 0.1% DEA in MeOH	dextromepromazine, 2-methoxyphenothiazine, levomepromazine sulfoxide, levomepromazine	analysis of levomepromazine maleate or levomepromazine HCl in commercial 25 mg film-coated tablets or injection solutions, respectively	[96]
β-CD	gold nanoparticles/thiols β-CD	CEC 25 mM Tris-H_3PO_4 buffer containing 5% ACN, pH 5.0	meptazinol	analysis of racemic meptazinol in spiked human urine sample	[45]
pepsin	pepsin-modified poly(GMA-EDMA-NH_2-MSN) monolith	CEC 15 mM NH_4OAc-HOAc buffer, pH 4.2	amlodipine besylate, levamlodipine besylate	analysis of amlodipine besylate and levamlodipine besylate tablets	[108]
amino acids					
teicoplanin	Chirobiotic T (Astec)	RP-LC ACN/H_2O (75:25, v/v)	D- and L-phenylalanine	analysis of phenylalanine enantiomers in samples of energy drinks and dietary supplements	[63]
(*S*/*R*)-(1,1′-binaphthyl)-20-crown-6	CROWNPAK CR-I(+)/CROWNPAK CR-I(−) (Daicel)	HILIC ACN/EtOH/H_2O/TFA (80:15:5:0.5, v/v/v/v)	D- and L-alanine, arginine, asparagine, aspartic acid, glutamic acid, histidine, isoleucine, leucine, methionine, phenylalanine, serine, tyrosine, valine	amino acid profiling in black vinegar	[69]
β-CD	β-CD bound poly(HPMA-Cl-EDMA)	HILIC 85%ACN:10%MeOH: 5% H_2O in 0.1% (v/v) TFA	aspartic acid, glutamic acid, histidine, isoleucine, phenylalanine, proline, tryptophan, tyrosine	enantioseparation and analysis of amino acids in apple juice	[48]
N-decyl-*S*-trityl-(*R*)-cysteine	*N*-decyl-*S*-trityl-(*R*)-cysteine coated to octadecyl-silica	chiral ligand exchange LC 1.0 mM $CuSO_4$	L-leucine	enantioselective analysis of a commercially available L-leucine-containing tablet	[38]
poly (methacryloyl-L-arginine methyl ester) moiety (as immobilised chiral ligand) and Zn^{2+} (as the central ion)	poly(maleic anhydride-styrene-methacryloyl-L-arginine methyl ester)	chiral ligand exchange CEC 100.0 mM boric acid, 10.0 mM NH_4OAc, 4.0 mM $ZnSO_4$ and 4.0 mM L-arginine, pH 8.0	L-glutamine	glutaminase kinetics study	[39]
small organic acid					
Proprietary chiral ligand	Supelco Astec CLC-D (Sigma Aldrich)	chiral ligand exchange LC 7 mM $CuSO_4$ (anhydrous) in 1.0 mM CH_3COOH containing 4% MeOH	D-lactic acid	analysis of D-lactic acid in Ringer-lactate solution	[40]

[a] CS and CSP of the optimum chiral column only. There could be more than one column evaluated in the studies.
[b] Abbreviations: ACN – acetonitrile, DEA – diethylamine, EDMA – ethylene dimethacrylate, EtOH – ethanol, GMA – glycidyl methacrylate, HPMA-Cl – 3-chloro-2-hydroxypropylmethacrylate, IPA – 2-propanol, MeOH – methanol, NH_2-MSN – amino-modified mesoporous silica, TEAA - triethylammonium acetate, TFA – trifluoroacetic acid.

chiral columns were usually evaluated and compared. The column with optimum performance or many advantages was chosen [81,96,98]. For example, Niedermeier and co-workers evaluated seven chiral columns, including two Lux® Amylose and five Lux® Cellulose columns during analytical separation (including chiral) method development for dextromepromazine and related substances in two formulations. Using a screening mobile phase of 0.1% diethylamine in methanol flowed at 2 mL/min, the column which satisfactorily separated the enantiomers and related substances was chosen, i.e., Lux® Cellulose-3. Meanwhile for intermediates

with analogous structures, e.g., verubecestat intermediates, method development could be performed with one chiral column while modifying the composition of the mobile phase to impart the desired chiral resolution [59].

The five papers on amino acids were in food products and supplements (see Table 2). In contrast to application studies for drugs, chiral separation of amino acids was conducted using commercial and laboratory-developed CSPs. Various separation modes such as RP-LC [63], hydrophilic interaction LC (HILIC) [48,69] and chiral ligand exchange LC (CLE-LC) [38] and CEC (CLE-CEC) [39] were implemented. Most of the methods implemented ACN-based mobile phases. However, methods employing CLE-LC [38] and CLE-CEC [39] used more environmentally-friendly aqueous-based mobile phases. A rigorous study that separated more than ten amino acids were conducted using CROWNPAK CR-I(+)/CROWNPAK CR-I(−) [69].

Interestingly, there were three studies with phenylalanine as a target chiral analyte in different samples (apple juice, black vinegar and food supplements). Separation was by either RP-LC or HILIC mode that used non-environmentally friendly ACN-based mobile phases. In terms of chiral resolution, CROWNPAK CR-I(+)/CROWNPAK CR-I(−) [69] showed better performance over Chirobiotic T [63] or prepared β-CD-based columns [48]. The separation was also considerably faster (~3 min plus conditioning) with CROWNPAK CR-I(+)/CROWNPAK CR-I(−). A major issue with many chiral columns is the limited number of injections that can be performed before column performance deterioration. However, all three studies did not determine column deterioration.

In particular, in the chiral nano-OT-LC work reported [48], the coating was too thin to allow retention. Also, the mobile phase was unreasonably mobilised at very high pressures (i.e., 40 bar or 4 MPa) on a 15 cm-long and 75-μm i.d. OT capillary column. This means that the void time will be less than 1 s and chiral separation is less likely.

7. Conclusion and future prospects

Chiral separation in LC and CEC was an active research area during 2017–2018, with an average of 47 papers a year. A main focus was the development of new materials and on LC. Commercial chiral LC columns that employed various materials including alkaloids, amyloses, celluloses, chiral crown ethers, chiral ligands, cyclodextrins and glycopeptide antibiotics accounted for 35 papers. Only one study was on the approach that used a CS as mobile phase additive in LC, probably due to the notion that this approach typically gives poor separation power. The use of chiral methods to determine enantiomeric excess was limited. Most methods demonstrated separation of racemates. There were also some very surprising results especially in the OT-CEC format where thin coatings inside ≥50 μm i.d. capillaries were reported to afford separations.

Chiral chromatography often uses harmful organic solvents, including hexane and acetonitrile. However, during this review, there were no specific greening efforts for chiral separations, although miniaturisations such as nano-LC studies were reported. We hope to see future studies on not only pushing excellent enantiomeric separations and applications to specific enantiomers, but also to develop chiral separation methods that minimise generation of chemical waste. MOFs with high stability in aqueous environments will be an interesting area of investigation. We found two interesting reports that developed novel CSs that are pseudophases (i.e., imprinted micelles [128] and liposomes [129]), but they have not been implemented in any separation platform. In our research group, we are currently developing green chiral methods using pseudophases in nano-OT-LC.

Acknowledgements

This work was supported by the Australian Research Council [DP180102810, 2018].

References

[1] B. Roth, U.S.P. Office, in: [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid, its lactone Form and Salts Thereof. United States, 1993.
[2] A.D. McNaught, A. Wilkinson, A.D. McNaught, P. International Union of, C. Applied, Compendium of Chemical Terminology : IUPAC Recommendations/compiled by Alan D. McNaught and Andrew Wilkinson, second ed., Blackwell Science, Oxford [Oxfordshire]; Boston, 1997.
[3] K.F. Morris, B.A. Becker, B.C. Valle, I.M. Warner, C.K. Larive, Use of NMR binding interaction mapping techniques to examine interactions of chiral molecules with molecular micelles, J. Phys. Chem. B 110 (2006) 17359–17369.
[4] H.H. Yarabe, J.K. Rugutt, M.E. McCarroll, I.M. Warner, Capillary electrophoretic separation of binaphthyl enantiomers with two polymeric chiral surfactants: ^{1}H-nuclear magnetic resonance and fluorescence spectroscopy study, Electrophoresis 21 (2000) 2025–2032.
[5] M. Lämmerhofer, Chiral recognition by enantioselective liquid chromatography: mechanisms and modern chiral stationary phases, J. Chromatogr. A 1217 (2010) 814–856.
[6] R.T. Kennedy, M.D. Oates, B.R. Cooper, B. Nickerson, J.W. Jorgenson, Microcolumn separations and the analysis of single cells, Science 246 (1989) 57–63.
[7] W.J. Cheong, F. Ali, Y.S. Kim, J.W. Lee, Comprehensive overview of recent preparation and application trends of various open tubular capillary columns in separation science, J. Chromatogr. A 1308 (2013) 1–24.
[8] J.P. Quirino, F.M. Tarongoy, Liquid chromatography with micelles in open-tube capillaries, Green Chem. 20 (2018) 2486–2493.
[9] S. Bhattacharjee, M.I. Khan, X. Li, Q.L. Zhu, X.T. Wu, Recent progress in asymmetric catalysis and chromatographic separation by chiral metal-organic frameworks, Catalysts 8 (2018).
[10] G. Liu, J. Sheng, Y. Zhao, Chiral covalent organic frameworks for asymmetric catalysis and chiral separation, Sci. China Chem. 60 (2017) 1015–1022.
[11] C. Fernandes, Y.Z. Phyo, A.S. Silva, M.E. Tiritan, A. Kijjoa, M.M.M. Pinto, Chiral stationary phases based on small molecules: an update of the last 17 years, Separ. Purif. Rev. 47 (2018) 89–123.
[12] M.H. Hyun, Liquid chromatographic ligand-exchange chiral stationary phases based on amino alcohols, J. Chromatogr. A 1557 (2018) 28–42.
[13] I. Ilisz, A. Bajtai, W. Lindner, A. Péter, Liquid chromatographic enantiomer separations applying chiral ion-exchangers based on *Cinchona* alkaloids, J. Pharm. Biomed. Anal. 159 (2018) 127–152.
[14] J.M. Padró, S. Keunchkarian, State-of-the-art and recent developments of immobilized polysaccharide-based chiral stationary phases for enantioseparations by high-performance liquid chromatography (2013-2017), Microchem. J. 140 (2018) 142–157.
[15] S.M. Xie, L.M. Yuan, Recent development trends from chiral stationary phases based on chitosan derivatives, cyclofructan derivatives and chiral porous materials in high performance liquid chromatography, J. Sep. Sci. 42 (2018) 6–20.
[16] G. D' Orazio, M. Asensio-Ramos, C. Fanali, Enantiomers separation by capillary electrochromatography using polysaccharide-based stationary phases, J. Sep. Sci. 42 (2019) 360–384.
[17] M. Rutkowska, J. Płotka-Wasylka, C. Morrison, P.P. Wieczorek, J. Namieśnik, M. Marć, Application of molecularly imprinted polymers in analytical chiral separations and analysis, Trends Anal. Chem. 102 (2018) 91–102.
[18] R.B. Yu, J.P. Quirino, Chiral Selectors in Capillary Electrophoresis: Trends during 2017-2018, Molecules, 2019.
[19] J. Yu, D.W. Armstrong, J.J. Ryoo, Synthesis of new C3 symmetric amino acid- and aminoalcohol-containing chiral stationary phases and application to HPLC enantioseparations, Chirality 30 (2018) 74–84.
[20] N. Grubhofer, L. Schleith, Modified ion exchangers as specific adsorbents, Naturwissenschaften 40 (1953) 508–512.
[21] A. Bajtai, B. Fekete, M. Palkó, F. Fülöp, W. Lindner, M. Kohout, I. Ilisz, A. Péter, Comparative study on the liquid chromatographic enantioseparation of cyclic β-amino acids and the related cyclic β-aminohydroxamic acids on *Cinchona* alkaloid-based zwitterionic chiral stationary phases, J. Sep. Sci. 41 (2018) 1216–1223.
[22] A. Bajtai, G. Lajkó, I. Szatmári, F. Fülöp, W. Lindner, I. Ilisz, A. Péter, Dedicated comparisons of diverse polysaccharide- and zwitterionic *Cinchona* alkaloid-based chiral stationary phases probed with basic and ampholytic indole analogs in liquid and subcritical fluid chromatogrpahy mode, J. Chromatogr. A 1563 (2018) 180–190.
[23] C. Calderón, M. Lämmerhofer, Chiral separation of short chain aliphatic hydroxycarboxylic acids on cinchonan carbamate-based weak chiral anion exchangers and zwitterionic chiral ion exchangers, J. Chromatogr. A 1487 (2017) 194–200.

[24] C. Calderón, C. Santi, M. Lämmerhofer, Chiral separation of disease biomarkers with 2-hydroxycarboxylic acid structure, J. Sep. Sci. 41 (2018) 1224–1231.
[25] Y. Komaravolu, V.R. Dama, T.C. Maringanti, Development of novel enantioselective HPLC methods for the determination of optical purity of N^{α}-Fmoc/Boc amino acid derivatives (N^{α}-PADs) of natural and unnatural amino acids: an analytical strategy for the key starting materials of therapeutic peptides, Anal. Methods. 10 (2018) 2481–2493.
[26] G. Lajkó, N. Grecsó, G. Tóth, F. Fülöp, W. Lindner, I. Ilisz, A. Péter, Liquid and subcritical fluid chromatographic enantioseparation of N^{α}-Fmoc proteinogenic amino acids on *Quinidine*-based zwitterionic and anion-exchanger type chiral stationary phases. A comparative study, Chirality 29 (2017) 225–238.
[27] G. Lajkó, T. Orosz, I. Ugrai, Z. Szakonyi, F. Fülöp, W. Lindner, A. Péter, I. Ilisz, Liquid chromatographic enantioseparation of limonene-based carbocyclic β-amino acids on zwitterionic *Cinchona* alkaloid-based chiral stationary phases, J. Sep. Sci. 40 (2017) 3196–3204.
[28] M. De Martino, G. Bencivenni, A. Mazzanti, S. Menta, O.H. Ismail, R. Sabia, A. Ciogli, 3,5-dinitrobenzoyl-9-amino-9-deoxy-9-epiquinine as Pirkle-anion exchange hybrid-type chiral selector in high-performance liquid chromatography, Chromatographia 80 (2017) 751–762.
[29] K. Schmitt, U. Woiwode, M. Kohout, T. Zhang, W. Lindner, M. Lämmerhofer, Comparison of small size fully porous particles and superficially porous particles of chiral anion-exchange type stationary phases in ultra-high performance liquid chromatography: effect of particle and pore size on chromatographic efficiency and kinetic performance, J. Chromatogr. A 1569 (2018) 149–159.
[30] U. Woiwode, A. Sievers-Engler, A. Zimmermann, W. Lindner, O.L. Sánchez-Muñoz, M. Lämmerhofer, Surface-anchored counterions on weak chiral anion-exchangers accelerate separations and improve their compatibility for mass-spectrometry-hyphenation, J. Chromatogr. A 1503 (2017) 21–31.
[31] M. Kohout, S. Wernisch, J. Tůma, H. Hettegger, J. Pícha, W. Lindner, Effect of different immobilization strategies on chiral recognition properties of *Cinchona*-based anion exchangers, J. Sep. Sci. 41 (2018) 1355–1364.
[32] F. Ianni, L. Pucciarini, A. Carotti, A. Gioiello, R. Galarini, S. Natalini, R. Sardella, W. Lindner, B. Natalini, Improved chromatographic diastereoresolution of cyclopropyl dafachronic acid derivatives using chiral anion exchangers, J. Chromatogr. A 1557 (2018) 20–27.
[33] U. Woiwode, M. Ferri, N.M. Maier, W. Lindner, M. Lämmerhofer, Complementary enantioselectivity profiles of chiral cinchonan carbamate selectors with distinct carbamate residues and their implementation in enantioselective two-dimensional high-performance liquid chromatography of amino acids, J. Chromatogr. A 1558 (2018) 29–36.
[34] K. Záruba, V. Král, Quaternized brucine as a novel chiral selector, Tetrahedron Asymmetry 13 (2002) 2567–2570.
[35] D. Sýkora, J. Vozka, E. Tesařová, K. Kalíková, M. Havlík, P. Matějka, V. Král, Immobilized strychnine as a new chiral stationary phase for HPLC, Electrophoresis 38 (2017) 1956–1963.
[36] E.J. Carrasco-Correa, M. Ferri, U. Woiwode, Y. Ma, J.M. Herrero-Martínez, G. Ramis-Ramos, W. Lindner, M. Lämmerhofer, Zwitterionic codeine-derived methacrylate monoliths for enantioselective capillary electrochromatography of chiral acids and chiral bases, Electrophoresis 39 (2018) 2558–2565.
[37] V.A. Davankov, S.V. Rogozhin, Ligand chromatography as a novel method for the investigation of mixed complexes: stereoselective effects in α-amino acid copper(II) complexes, J. Chromatogr. A 60 (1971) 280–283.
[38] A. Carotti, F. Ianni, E. Camaioni, L. Pucciarini, M. Marinozzi, R. Sardella, B. Natalini, *N*-Decyl-*S*-trityl-(*R*)-cysteine, a new chiral selector for "green" ligand-exchange chromatography applications, J. Pharm. Biomed. Anal. 144 (2017) 31–40.
[39] L. Zhao, J. Qiao, K. Zhang, D. Li, H. Zhang, L. Qi, Construction of chiral ligand exchange capillary electrochromatography for d,L-amino acids separation and its application in glutaminase kinetics study, J. Chromatogr. A 1548 (2018) 104–110.
[40] M.M.K. Sharaf El-Din, K.A.M. Attia, M.W.I. Nassar, M.M.Y. Kaddah, Development and validation of a copper ligand-exchange chromatographic method for the estimation of D-lactic acid in Ringer-lactate solution, Talanta 189 (2018) 86–91.
[41] A.P. Kumar, J.H. Park, Azithromycin as a new chiral selector in capillary electrophoresis, J. Chromatogr. A 1218 (2011) 1314–1317.
[42] S. Dixit, I.S. Lee, J.H. Park, Carbamoylated azithromycin incorporated zirconia hybrid monolith for enantioseparation of acidic chiral drugs using non-aqueous capillary electrochromatograpy, J. Chromatogr. A 1507 (2017) 132–140.
[43] M. Cecilio Fonseca, R.C. Santos da Silva, C.S. Nascimento Jr., K. Bastos Borges, Computational contribution to the electrophoretic enantiomer separation mechanism and migration order using modified β-cyclodextrins, Electrophoresis 38 (2017) 1860–1868.
[44] X. Li, X. Yao, Y. Xiao, Y. Wang, Enantioseparation of single layer native cyclodextrin chiral stationary phases: effects of cyclodextrin orientation and a modeling study, Anal. Chim. Acta 990 (2017) 174–184.
[45] L.L. Fang, P. Wang, X.L. Wen, X. Guo, L.D. Luo, J. Yu, X.J. Guo, Layer-by-layer self-assembly of gold nanoparticles/thiols β-cyclodextrin coating as the stationary phase for enhanced chiral differentiation in open tubular capillary electrochromatography, Talanta 167 (2017) 158–165.
[46] L. Zhou, S. Jiang, X. Zhang, L. Fang, X. Guo, Preparation of β-cyclodextrin-gold nanoparticles modified open tubular column for capillary electrochromatographic separation of chiral drugs, Electrophoresis 39 (2018) 941–947.
[47] D. Guo, M. Liu, S. Zhong, Y. Dong, X. Li, Preparation and evaluation of β-cyclodextrin functionalized periodic mesoporous organosilica open tubular capillary columns, Anal. Methods 9 (2017) 4151–4156.
[48] C. Aydoğan, Chiral separation and determination of amino acid enantiomers in fruit juice by open-tubular nano liquid chromatography, Chirality 30 (2018) 1144–1149.
[49] H. Guo, X. Niu, C. Pan, T. Yi, H. Chen, X. Chen, A novel in situ strategy for the preparation of a β-cyclodextrin/polydopamine-coated capillary column for capillary electrochromatography enantioseparations, J. Sep. Sci. 40 (2017) 2645–2653.
[50] J.M. Saz, M.L. Marina, Recent advances on the use of cyclodextrins in the chiral analysis of drugs by capillary electrophoresis, J. Chromatogr. A 1467 (2016) 79–94.
[51] C. Lin, J. Fan, W. Liu, X. Chen, L. Ruan, W. Zhang, A new single-urea-bound 3,5-dimethylphenylcarbamoylated β-cyclodextrin chiral stationary phase and its enhanced separation performance in normal-phase liquid chromatography, Electrophoresis 39 (2018) 348–355.
[52] X. Li, J. Li, Q. Kang, Y. Wang, Polarity tuned perphenylcarbamoylated cyclodextrin separation materials for achiral and chiral differentiation, Talanta 185 (2018) 328–334.
[53] J. Tang, Y. Lin, B. Yang, J. Zhou, W. Tang, Functionalities tuned enantioselectivity of phenylcarbamate cyclodextrin clicked chiral stationary phases in HPLC, Chirality 29 (2017) 566–573.
[54] J. Zhou, B. Yang, J. Tang, W. Tang, A cationic cyclodextrin clicked bilayer chiral stationary phase for versatile chiral separation in HPLC, New J. Chem. 42 (2018) 3526–3533.
[55] L. Li, B. Cheng, R. Zhou, Z. Cao, C. Zeng, L. Li, Preparation and evaluation of a novel N-benzyl-phenethylamino-β-cyclodextrin-bonded chiral stationary phase for HPLC, Talanta 174 (2017) 179–191.
[56] M. Silva, D. Pérez-Quintanilla, S. Morante-Zarcero, I. Sierra, M.L. Marina, Z. Aturki, S. Fanali, Ordered mesoporous silica functionalized with β-cyclodextrin derivative for stereoisomer separation of flavanones and flavanone glycosides by nano-liquid chromatography and capillary electrochromatography, J. Chromatogr. A 1490 (2017) 166–176.
[57] E. Lubomirsky, J.M. Padró, H. Di Loreto, C.B. Castells, Chiral separation of aryloxyphenoxy-propionate herbicides in a permethyl-β-cyclodextrin based column. Influence of temperature and mobile phase composition on enantioselectivity, Electrophoresis 38 (2017) 1948–1955.
[58] X. Hu, X. Guo, S. Sun, B. Zhu, J. Yu, X. Guo, Enantioseparation of nine indanone and tetralone derivatives by HPLC using carboxymethyl-β-cyclodextrin as the mobile phase additive, Chirality 29 (2017) 38–47.
[59] C.L. Barhate, D.A. Lopez, A.A. Makarov, X. Bu, W.J. Morris, A. Lekhal, R. Hartman, D.W. Armstrong, E.L. Regalado, Macrocyclic glycopeptide chiral selectors bonded to core-shell particles enables enantiopurity analysis of the entire verubecestat synthetic route, J. Chromatogr. A 1539 (2018) 87–92.
[60] D. Camacho-Muñoz, B. Kasprzyk-Hordern, Simultaneous enantiomeric analysis of pharmacologically active compounds in environmental samples by chiral LC–MS/MS with a macrocyclic antibiotic stationary phase, J. Mass Spectrom. 52 (2017) 94–108.
[61] L. Fumagalli, L. Pucciarini, L. Regazzoni, E. Gilardoni, M. Carini, G. Vistoli, G. Aldini, R. Sardella, Direct HPLC separation of carnosine enantiomers with two chiral stationary phases based on penicillamine and teicoplanin derivatives, J. Sep. Sci. 41 (2018) 1240–1246.
[62] G. Hellinghausen, D. Roy, Y. Wang, J.T. Lee, D.A. Lopez, C.A. Weatherly, D.W. Armstrong, A comprehensive methodology for the chiral separation of 40 tobacco alkaloids and their carcinogenic *E*/*Z*-(*R*,*S*)-tobacco-specific nitrosamine metabolites, Talanta 181 (2018) 132–141.
[63] A. Lomenova, K. Hroboňová, Comparison of HPLC separation of phenylalanine enantiomers on different types of chiral stationary phases, Food Anal. Methods (2018) 1–10.
[64] I.A. Fedorova, E.N. Shapovalova, O.A. Shpigun, Separation of β-blocker and amino acid enantiomers on a mixed chiral sorbent modified with macrocyclic antibiotics eremomycin and vancomycin, J. Anal. Chem. 72 (2017) 76–82.
[65] G. Hellinghausen, D.A. Lopez, J.T. Lee, Y. Wang, C.A. Weatherly, A.E. Portillo, A. Berthod, D.W. Armstrong, Evaluation of the Edman degradation product of vancomycin bonded to core-shell particles as a new HPLC chiral stationary phase, Chirality 30 (2018) 1067–1078.
[66] O.H. Ismail, M. Antonelli, A. Ciogli, M. De Martino, M. Catani, C. Villani, A. Cavazzini, M. Ye, D.S. Bell, F. Gasparrini, Direct analysis of chiral active pharmaceutical ingredients and their counterions by ultra high performance liquid chromatography with macrocyclic glycopeptide-based chiral stationary phases, J. Chromatogr. A 1576 (2018) 42–50.
[67] E.S. Cho, J.Y. Sung, J.S. Jin, M.H. Hyun, Liquid chromatographic resolution of proline and pipecolic acid derivatives on chiral stationary phases based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid, J. Sep. Sci. 41 (2018) 1192–1198.
[68] H. Jeon, M.H. Hyun, Resolution of methoxyphenamine and its analogues on a chiral stationary phase based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid, J. Sep. Sci. 41 (2018) 4281–4285.
[69] Y. Konya, M. Taniguchi, M. Furuno, Y. Nakano, N. Tanaka, E. Fukusaki, Mechanistic study on the high-selectivity enantioseparation of amino acids

using a chiral crown ether-bonded stationary phase and acidic, highly organic mobile phase by liquid chromatography/time-of-flight mass spectrometry, J. Chromatogr. A 1578 (2018) 35–44.
[70] T. Németh, G. Dargó, J.L. Petró, Z. Petrik, S. Lévai, B. Krámos, Z. Béni, J. Nagy, G.T. Balogh, P. Huszthy, T. Tóth, Synthesis and pKa determination of new enantiopure dimethyl-substituted acridino-crown ethers containing a carboxyl group: useful candidates for enantiomeric recognition studies, Chirality 29 (2017) 522–535.
[71] S. Yaghoubnejad, K. Tabar Heydar, S.H. Ahmadi, R. Zadmard, Preparation and evaluation of a chiral HPLC stationary phase based on cone calix[4]arene functionalized at the upper rim with L-alanine units, Biomed. Chromatogr. 32 (2018).
[72] S. Yaghoubnejad, K. Tabar Heydar, S.H. Ahmadi, R. Zadmard, N. Ghonouei, Preparation and evaluation of a deoxycholic-calix[4]arene hybrid-type receptor as a chiral stationary phase for HPLC, J. Sep. Sci. 41 (2018) 1903–1912.
[73] M. Ma, Q. Wei, M. Meng, J. Yin, Y. Shan, L. Du, X. Zhu, S.F. Soh, M. Min, X. Zhou, X. Yin, Y. Gong, Preparation and application of aza-15-crown-5-capped methylcalix[4]resorcinarene-bonded silica particles for use as chiral stationary phase in HPLC, Chromatographia 80 (2017) 1007–1014.
[74] K. Kalíková, M. Martínková, M.G. Schmid, E. Tesařová, Preparation and application of aza-15-crown-5-capped methylcalix[4]resorcinarene-bonded silica particles for use as chiral stationary phase in HPLC, J. Sep. Sci. 41 (2018) 1471–1478.
[75] L. Wang, S. Dong, F. Han, Y. Zhao, X. Zhang, X. Zhang, H. Qiu, L. Zhao, Spherical β-cyclodextrin-silica hybrid materials for multifunctional chiral stationary phases, J. Chromatogr. A 1383 (2015) 70–78.
[76] M. Li, B. Zhang, J. Yu, J. Wang, X. Guo, Enantiomeric separation and simulation study of eight anticholinergic drugs on an immobilized polysaccharide-based chiral stationary phase by HPLC, New J. Chem. 42 (2018) 11724–11731.
[77] S. Tang, Z. Jin, B. Sun, F. Wang, W. Tang, Preparation and evaluation of regioselectively substituted amylose derivatives for chiral separations, Chirality 29 (2017) 512–521.
[78] C. Fanali, S. Fanali, B. Chankvetadze, HPLC separation of enantiomers of some flavanone derivatives using polysaccharide-based chiral selectors covalently immobilized on silica, Chromatographia 79 (2016) 119–124.
[79] G. D'Orazio, C. Fanali, M. Karchkhadze, B. Chankvetadze, S. Fanali, Enantiomeric separation of some chiral analytes using amylose 3,5-dimethylphenylcarbamate covalently immobilized on silica by nano-liquid chromatography and capillary electrochromatography, J. Chromatogr. A 1520 (2017) 127–134.
[80] N. Beridze, E. Tsutskiridze, N. Takaishvili, T. Farkas, B. Chankvetadze, Comparative enantiomer-resolving ability of coated and covalently immobilized versions of two polysaccharide-based chiral selectors in high-performance liquid chromatography, Chromatographia 81 (2018) 611–621.
[81] M. Foroughbakhshfasaei, Z.I. Szabó, A. Mirzahosseini, P. Horváth, G. Tóth, Enantiomeric quality control of *R*-Tofisopam by HPLC using polysaccharide-type chiral stationary phases in polar organic mode, Electrophoresis 39 (2018) 2566–2574.
[82] M. Foroughbakhshfasaei, Z.I. Szabó, G. Tóth, Validated LC method for determination of enantiomeric purity of apremilast using polysaccharide-type stationary phases in polar organic mode, Chromatographia (2018) 1–9.
[83] A. Ghanem, C. Wang, Enantioselective separation of racemates using CHIRALPAK IG amylose-based chiral stationary phase under normal standard, non-standard and reversed phase high performance liquid chromatography, J. Chromatogr. A 1532 (2018) 89–97.
[84] F. Ianni, S. Scorzoni, P.L. Gentili, A. Di Michele, M. Frigoli, E. Camaioni, F. Ortica, R. Sardella, Chiral separation of helical chromenes with chloromethyl phenylcarbamate polysaccharide-based stationary phases, J. Sep. Sci. 41 (2018) 1266–1273.
[85] M. Li, Y. Zhao, L. Zhou, J. Yu, J. Wang, X. Guo, Study of the enantiomeric separation of the anticholinergic drugs on two immobilized polysaccharide-based chiral stationary phases by HPLC and the possible chiral recognition mechanisms, Electrophoresis 39 (2018) 1361–1369.
[86] L. Pisani, M. Rullo, M. Catto, M. de Candia, A. Carrieri, S. Cellamare, C.D. Altomare, Structure–property relationship study of the HPLC enantioselective retention of neuroprotective 7-[(1-alkylpiperidin-3-yl)methoxy] coumarin derivatives on an amylose-based chiral stationary phase, J. Sep. Sci. 41 (2018) 1376–1384.
[87] T. Vojtylová, V. Hamplová, Z. Galewski, I. Korbecka, D. Sýkora, Chiral separation of novel diazenes on a polysaccharide-based stationary phase in the reversed-phase mode, J. Sep. Sci. 40 (2017) 1465–1469.
[88] Q. Zeng, Q. Wen, Y. Xiang, L. Zhang, Chromatographic enantioseparation of chiral sulfinamide derivatives on polysaccharide-based chiral stationary phases, J. Chromatogr. A 1571 (2018) 240–244.
[89] Y. Li, Q. Li, N. Zhu, Z. Gao, Y. Ma, Cellulose type chiral stationary phase based on reduced graphene oxide@silica gel for the enantiomer separation of chiral compounds, Chirality 30 (2018) 996–1004.
[90] Y. Li, N. Zhu, Y. Ma, Q. Li, P. Li, Preparation of polysaccharide-based chiral stationary phases on SiO_2@Ag core–shell particles by means of coating and intermolecular polycondensation and comparative liquid chromatography enantioseparations, Anal. Bioanal. Chem. 410 (2018) 441–449.
[91] J. Shen, F. Wang, W. Bi, B. Liu, S. Liu, Y. Okamoto, Synthesis of cellulose carbamates bearing regioselective substituents at 2,3- and 6-positions for efficient chromatographic enantioseparation, J. Chromatogr. A 1572 (2018) 54–61.
[92] L. Chang, J. Zhang, W. Chen, M. Zhang, C. Yin, W. Tian, Z. Luo, W. Liu, J. He, J. Zhang, Controllable synthesis of cellulose benzoates for understanding of chiral recognition mechanism and fabrication of highly efficient chiral stationary phases, Anal. Methods 10 (2018) 2844–2853.
[93] Z. Shedania, R. Kakava, A. Volonterio, T. Farkas, B. Chankvetadze, Separation of enantiomers of chiral sulfoxides in high-performance liquid chromatography with cellulose-based chiral selectors using methanol and methanol-water mixtures as mobile phases, J. Chromatogr. A 1557 (2018) 62–74.
[94] N.H. Dhekale, D.B. Gunjal, A.H. Gore, Y. Komaravolu, K. Hima Bindu, G.B. Kolekar, Stereoselective HPLC separation of alvimopan on cellulose-based immobilized polysaccharide as a chiral stationary phase, Chirality 30 (2018) 982–987.
[95] M.F. Islam, S. Adhikari, M.J. Paik, W. Lee, Liquid chromatographic enantiomer separation of 1-naphthylamides of chiral acids using several amylose- and cellulose-derived chiral stationary phases, Arch. Pharmacal Res. 40 (2017) 350–355.
[96] S. Niedermeier, I. Matarashvili, B. Chankvetadze, G.K.E. Scriba, Simultaneous determination of dextromepromazine and related substances 2-methoxyphenothiazine and levomepromazine sulfoxide in levomepromazine on a cellulose tris(4-methylbenzoate) chiral column, J. Pharm. Biomed. Anal. 158 (2018) 294–299.
[97] R. Su, Z. Hou, L. Sang, Z.M. Zhou, H. Fang, X. Yang, Enantioseparation of angiotensin II receptor type 1 blockers: evaluation of 6-substituted carbamoyl benzimidazoles on immobilized polysaccharide-based chiral stationary phases. Unusual temperature behavior, J. Chromatogr. A 1515 (2017) 118–128.
[98] Z.I. Szabó, M. Foroughbakhshfasaei, B. Noszál, G. Tóth, Enantioseparation of racecadotril using polysaccharide-type chiral stationary phases in polar organic mode, Chirality 30 (2018) 95–105.
[99] M. Taschwer, J. Grascher, M.G. Schmid, Development of an enantioseparation method for novel psychoactive drugs by HPLC using a Lux® Cellulose-2 column in polar organic phase mode, Forensic Sci. Int. 270 (2017) 232–240.
[100] B. Zhu, F. Zhao, J. Yu, Z. Wang, Y. Song, Q. Li, Chiral separation and a molecular modeling study of eight azole antifungals on the cellulose tris(3,5-dichlorophenylcarbamate) chiral stationary phase, New J. Chem. 42 (2018) 13421–13429.
[101] R. Noel Echevarria, E.J. Carrasco-Correa, S. Keunchkarian, M. Reta, J.M. Herrero-Martinez, Photografted methacrylate-based monolithic columns coated with cellulose tris(3,5-dimethylphenylcarbamate) for chiral separation in CEC, J. Sep. Sci. 41 (2018) 1424–1432.
[102] S. Dong, Y. Sun, X. Zhang, H. Li, G. Luo, L. Zhao, Nanocellulose crystals derivative-silica hybrid sol open tubular capillary column for enantioseparation, Carbohydr. Polym. 165 (2017) 359–367.
[103] J.P. Quirino, A cationic β-cyclodextrin as a dynamic coating for the separation of proteins in capillary electrophoresis, J. Sep. Sci. 40 (2017) 4835–4838.
[104] S. Liang, S.H. Huang, W. Chen, Z.W. Bai, High-performance chiral stationary phases based on chitosan derivatives with a branched-chain alkyl urea, Anal. Chim. Acta 985 (2017) 183–193.
[105] S. Tang, J.D. Liu, W. Chen, S.H. Huang, J. Zhang, Z.W. Bai, Performance comparison of chiral separation materials derived from *N*-cyclohexylcarbonyl and *N*-hexanoyl chitosans, J. Chromatogr. A 1532 (2018) 112–123.
[106] S. Tang, X. Mei, W. Chen, S.H. Huang, Z.W. Bai, A high-performance chiral selector derived from chitosan (p-methylbenzylurea) for efficient enantiomer separation, Talanta 185 (2018) 42–52.
[107] J.P. Quirino, M.T. Dulay, B.D. Bennett, R.N. Zare, Strategy for on-line preconcentration in chromatographic separations, Anal. Chem. 73 (2001) 5539–5543.
[108] S. Xu, R. Mo, C. Jin, X. Cui, R. Bai, Y. Ji, Mesoporous silica nanoparticles incorporated hybrid monolithic stationary phase immobilized with pepsin for enantioseparation by capillary electrochromatography, J. Pharm. Biomed. Anal. 140 (2017) 190–198.
[109] S. Xu, Y. Wang, Y. Tang, Y. Ji, A protein-based mixed selector chiral monolithic stationary phase in capillary electrochromatography, New J. Chem. 42 (2018) 13520–13528.
[110] S. Zhang, Y. Zheng, H. An, B. Aguila, C.X. Yang, Y. Dong, W. Xie, P. Cheng, Z. Zhang, Y. Chen, S. Ma, Covalent organic frameworks with chirality enriched by biomolecules for efficient chiral separation, Angew. Chem. Int. Ed. 57 (2018) 16754–16759.
[111] Q. Sun, C.-W. Fu, B. Aguila, J. Perman, S. Wang, H.-Y. Huang, F.-S. Xiao, S. Ma, Pore environment control and enhanced performance of enzymes infiltrated in covalent organic frameworks, J. Am. Chem. Soc. 140 (2018) 984–992.
[112] Y. Zhang, Y. Zhang, W. Chen, Y. Zhang, L. Zhu, P. He, Q. Wang, Enantiomeric separation of tryptophan by open-tubular microchip capillary electrophoresis using polydopamine/gold nanoparticles conjugated DNA as stationary phase, Anal. Methods 9 (2017) 3561–3568.
[113] Y. Zhou, C. Zhang, Q. Geng, L. Liu, H. Dong, T. Satoh, Y. Okamoto, Immobilization of helical poly(phenylacetylene)s having L-phenylalanine ethyl ester pendants onto silica gel as chiral stationary phases for HPLC, Polymer 131 (2017) 17–24.
[114] H. Guo, Y. Sun, X. Niu, N. Wei, C. Pan, G. Wang, H. Zhang, H. Chen, T. Yi, X. Chen, The preparation of poly-levodopa coated capillary column for capillary electrochromatography enantioseparation, J. Chromatogr. A 1578 (2018) 91–98.

[115] H. Dong, D. Zhang, H. Lin, Y. Wang, L. Liu, M. Zheng, X. Li, C. Zhang, J. Li, P. Zhang, J. So, A surface molecularly imprinted polymer as chiral stationary phase for chiral separation of 1,1′-binaphthalene-2-naphthol racemates, Chirality 29 (2017) 340–347.
[116] L.L. Wu, R.P. Liang, J. Chen, J.D. Qiu, Separation of chiral compounds using magnetic molecularly imprinted polymer nanoparticles as stationary phase by microchip capillary electrochromatography, Electrophoresis 39 (2018) 356–362.
[117] R. Batten Stuart, R. Champness Neil, X.-M. Chen, J. Garcia-Martinez, S. Kitagawa, L. Öhrström, M. O'Keeffe, M. Paik Suh, J. Reedijk, Terminology of Metal–Organic Frameworks and Coordination Polymers, IUPAC Recommendations 2013, 2013, p. 1715.
[118] A.P. Côté, A.I. Benin, N.W. Ockwig, M. O'Keeffe, A.J. Matzger, O.M. Yaghi, Chemistry: porous, crystalline, covalent organic frameworks, Science 310 (2005) 1166–1170.
[119] P. Zhang, L. Wang, J.H. Zhang, Y.J. He, Q. Li, L. Luo, M. Zhang, L.M. Yuan, Homochiral metal-organic framework immobilized on silica gel by the interfacial polymerization for HPLC enantioseparations, J. Liq. Chromatogr. Relat. Technol. 41 (2018) 903–909.
[120] S. Xie, C. Hu, L. Li, J. Zhang, N. Fu, B. Wang, L. Yuan, Homochiral metal-organic framework for HPLC separation of enantiomers, Microchem. J. 139 (2018) 487–491.
[121] J.H. Zhang, R.Y. Nong, S.M. Xie, B.J. Wang, P. Ai, L.M. Yuan, Homochiral metal-organic frameworks based on amino acid ligands for HPLC separation of enantiomers, Electrophoresis 38 (2017) 2513–2520.
[122] C.X. Yang, Y.Z. Zheng, X.P. Yan, γ-Cyclodextrin metal-organic framework for efficient separation of chiral aromatic alcohols, RSC Adv. 7 (2017) 36297–36301.
[123] C. Pan, W. Lv, X. Niu, G. Wang, H. Chen, X. Chen, Homochiral zeolite-like metal-organic framework with DNA like double-helicity structure as stationary phase for capillary electrochromatography enantioseparation, J. Chromatogr. A 1541 (2018) 31–38.
[124] X.Y. Liu, S.J. Pai, S.S. Han, ReaxFF molecular dynamics simulations of water stability of interpenetrated metal–organic frameworks, J. Phys. Chem. C 121 (2017) 7312–7318.
[125] Z.X. Fei, M. Zhang, J.H. Zhang, L.M. Yuan, Chiral metal-organic framework used as stationary phases for capillary electrochromatography, Anal. Chim. Acta 830 (2014) 49–55.
[126] M. Zhang, X. Chen, J. Zhang, J. Kong, L. Yuan, A 3D homochiral MOF [Cd_2(d-cam)$_3$]•2Hdma•4dma for HPLC chromatographic enantioseparation, Chirality 28 (2016) 340–346.
[127] X. Han, J. Huang, C. Yuan, Y. Liu, Y. Cui, Chiral 3D covalent organic frameworks for high performance liquid chromatographic enantioseparation, J. Am. Chem. Soc. 140 (2018) 892–895.
[128] J.K. Awino, Y. Zhao, Imprinted micelles for chiral recognition in water: shape, depth, and number of recognition sites, Org. Biomol. Chem. 15 (2017) 4851–4858.
[129] Y. Okamoto, Y. Kishi, K. Suga, H. Umakoshi, Induction of chiral recognition with lipid nanodomains produced by polymerization, Biomacromolecules 18 (2017) 1180–1188.