Use of Bile Acids in Pharmacological and Supramolecular Applications

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Keywords: Applications / Bile acids / Molecular recognition / Pharmacology / Receptors

Bile acid-based structures have become increasingly important in different fields of chemistry over recent years, having found applications in pharmacology, supramolecular chemistry and nanoscience. Some interesting studies concerning these applications are reviewed, together with the latest developments in synthetic and analytical methods for bile acid-derived frameworks.

Contents

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1 Introduction

An increasingly important objective in chemistry today is to prepare rationally designed frameworks to serve theoretical or practical purposes. Examples include compounds that are able to recognise and bind other molecules, catalyse transformations, reproduce themselves or otherwise store and process information at the molecular level.[1] In recent years steroidal structures have become increasingly important in a number of fields, such as pharmacology, biomimetic and supramolecular chemistry, and also in nanotechnology. Some reviews on bile acids and other steroidal compounds as architectural components in supramolecular chemistry have been published.[1−7] In this article the main focus is on the latest applications in these fields, while keeping in mind some of the most important older studies.

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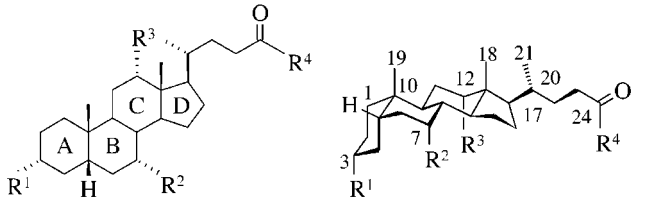
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

2 Structural, Physical and Chemical Properties, Metabolism and Functions of Bile Acids

The most abundant naturally occurring bile acids in higher vertebrates are derivatives of cholanic acid (or cholan-24-oic acid), a (cyclopentano)perhydrophenanthrene ring-containing steroid consisting of 24 carbon atoms (see Figure 1). Bile acids are formed as end products of cholesterol metabolism in the liver. The sterol nucleus undergoes several hydroxylations followed by a loss of an isopropyl group from the side chain, resulting in primary bile acids. Primary bile acids − two of the most common being cholic (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid) and chenodeoxycholic (3α,7α-dihydroxy-5β-cholan-24-oic acid) acids − undergo further chemical alterations to give secondary bile acids, such as deoxycholic (3α,12α-dihydroxy-5β-cholan-24-oic acid), hyodeoxycholic (3α,6α-dihydroxy-5β-cholan-24-oic acid), and lithocholic (3α-hydroxy-5β-cholan-24-oic acid) acids.[8] An important compound from the pharmacological point of view is ursodeoxycholic acid (3α,7β-dihydroxy-5β-cholan-24-oic acid).[9]



	R^1	R^2	R^3	R^4
cholanic acid	H	H	H	OH
cholic acid	OH	OH	OH	OH
chenodeoxycholic acid	OH	OH	H	OH
deoxycholic acid	OH	H	OH	OH
lithocholic acid	OH	H	H	OH
glycocholate	OH	OH	OH	$NHCH_2CO_2^-$
taurocholate	OH	OH	OH	$NHCH_2CH_2SO_3^-$

Figure 1. Structures of the most important bile acids and amino acid conjugates of cholic acid

The two isomeric groups of cholanic acids are 5β- and 5α- (or allo) cholanic acids, the former possessing *cis*- and the latter *trans*-oriented planes of fusion of the A/B rings.[8] The amphiphilic nature of bile acids − a convex hydrophobic upper and a concave hydrophilic α-side combined with a negatively charged side chain − explains the detergent properties of the molecules.[10] Reactions of the bile acids might be expected at their various functional groups. The carboxylic acid group may be esterified, reduced, amidated or subjected to salt formation with metal ions, alkaloids or organic bases. The reactivity of the hydroxy groups towards oxidation is 7-OH > 12-OH > 3-OH and 6-OH > 3-OH. The order of acetylation, hydrolysis, vis-à-vis reduction, or hydrogenation is 3-OH > 7-OH > 12-OH.[8]

In the bile, primary bile acids exist as glycine or taurine conjugates.[8] Bile, which consists of water and dissolved components, such as bile acids, phospholipids, cholesterol, gall pigments and proteins, is concentrated and stored in the gall bladder, which is emptied into the small intestine after food intake. The essential function of bile acids is to participate in the digestion and resorption of fat, fatty acids and lipid-soluble vitamins. The bile acids are almost completely reabsorbed from the intestine, after which they recirculate to the liver via the portal vein. This process is called enterohepatic circulation, which happens 6−15 times per day, and is an important factor in serum cholesterol homeostasis.[10]

3 Pharmacological Applications of Bile Acids

The literature describes a vast amount of pharmacological applications of bile acids and their derivatives, including their use in the treatment of bile acid deficiency and liver diseases and in dissolution of cholesterol gallstones,[11] some promising studies of antiviral properties of bile acids and their sulfate esters[12] and antifungal properties of some bile acid esters,[13] as well as their potential to act as carriers of liver-specific drugs, absorption enhancers, and as cholesterol level lowering agents.[10] The potential medicinal applications of bile acids, their conjugates and complexes as non-opiate analgesics,[14] sensitisers of Gram-negative bacteria to antibiotics[15,16] and radiopharmaceuticals[17] have been discussed. Furthermore, drug-bile acid conjugates for specific drug targeting to the liver and for improving the intestinal absorption of poorly or non-absorbed drugs inspired by the high specificity and capacity of bile acid transport systems during enterohepatic circulation[10,18,19] have been mentioned. Some *N*-substituted amides of lithocholic acid and derivatives of 3α-hydroxy-24-amino-5β-cholane have shown in vitro activity against Gram-positive strains and mycetes.[20]

Polymeric bile acid and insulin conjugate can be used for the production of a treatment for diabetes mellitus.[21] Polymeric and oligomeric bile acids can be used to inhibit bile acid reabsorption from the small intestine, thus reducing the bile acid concentration in the enterohepatic circulation and resulting in a decreased cholesterol level in the serum.[22] Increased levels of loading of a tertiary amine derivative of cholic acid in a series of cross-linked polymers have been observed to result in enhanced binding of taurocholate and in a decreased rate of its release, an interesting observation from the point of view of, for example, the treatment of hypercholesterolemia.[23] The kinetics of degradation and release of active principles of stable and degradable bile acid-based polymers and thermosensitive gels suggest their use as, for example, potential vehicles for controlled release of drugs.[24,25] The synthesis, properties and applications of bile acid-containing polymeric materials with improved biocompatibility for biomedical applications, such as drug delivery systems, stimuli-responsive systems, liquid crystals or dental-filling and bone-repairing materials are described in a review by Zhu and Nichifor;[26] other applications, such as chromatographic supports and photoresists, are also discussed. Sterol-polyamine conjugates as a po-

tential class of antibiotics are represented by a squalamine analogue (Figure 2), exhibiting antimicrobial activities.[27]

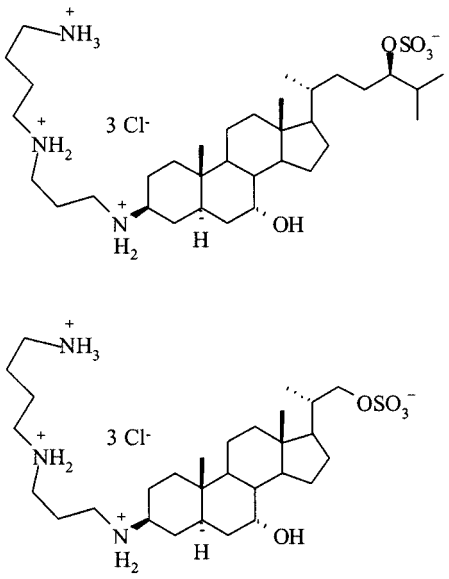


Figure 2. The structures of squalamine (above) and its analogue (below)[27]

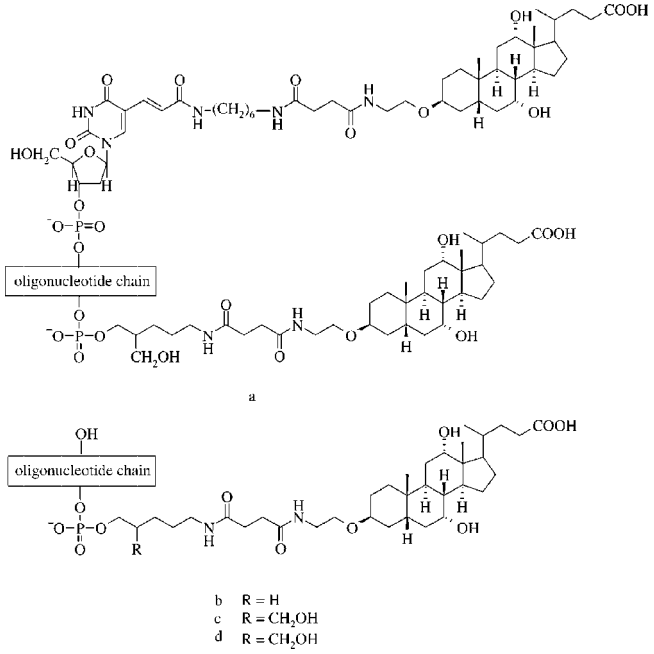


Figure 3. Bile acid-oligodeoxynucleotide conjugates synthesised by Petzinger et al.[36]

Bile acid polyamine conjugates are potential agents in gene therapy[28] because of the Coulombic attraction between the polyamine moieties and the polyphosphate backbone of deoxyribonucleic acid.[29] Burrows et al.[29–31] have published several papers concerning the synthesis of deoxycholic and lithocholic acid-based polyamines and studies of their binding affinities with DNA. Blagbrough and co-workers[28,32,33] have investigated the effects of changes in the stereochemistry and position of the alcohol functional groups on the cholane ring system of bile acids on the relative binding affinities for CT (calf thymus) DNA. Recently they have designed and prepared novel fluorescent molecular probes based on steroid templates that condense DNA and should be useful in monitoring gene delivery in non-viral gene therapy.[34] In vitro identification of cholic acid-binding DNA aptamers could lead to the development of high-affinity ligands capable of special binding to a variety of steroids utilisable as therapeutic and diagnostic tools.[35] Oligodeoxynucleotides represent a new approach in the treatment of cancer or viral infections by specifically affecting different target structures, which is why the observation of increased biliary excretion in vivo in rats of oligodeoxynucleotides covalently conjugated through the 3-OH group to cholic acid (Figure 3) is especially interesting.[36]

An increase in the activity of the 24-quinoline monoester of cholic acid against mouse leukemia cells relative to the 3,24-disubstituted esters in a series of quinoline- and quinoxaline-functionalised mono- and bisintercalator substituted cholic acid derivatives has been observed. This suggests that selective modification of the 24-position in this kind of molecules could provide a potential new class of antitumour agents.[37] Pt^{II}, Pd^{II} and Au^{III} complexes with bile acids and a halide or NH_3 have shown to be promising cytostatic agents.[38] Some of the latest applications in the area of the use of bile acids and their derivatives in cancer therapy are spacer-linked bile acid-*cis*-platin compounds as a model for specific drug delivery[39] and chenodeoxycholylglycinato (CDCG) derivatives of Pt^{II} and Au^{III} with a view to the use of bile acids as shuttles for delivering cytostatic drugs to liver tumours.[40–42] Cytostatic and chemotherapeutic effects have especially been observed in the platinum(II)-bile acid (Bamet) family (see Figure 4).[43,44]

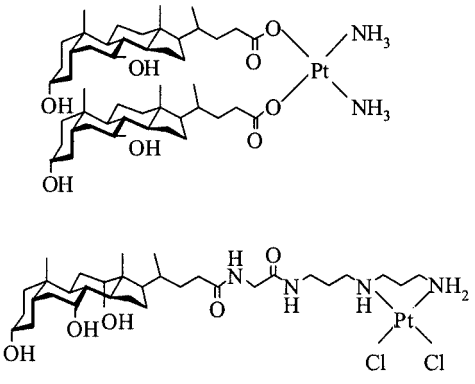


Figure 4. The chemical structures of Bamet-UD2 (above) and Bamet-D3 (below)[43]

Cholic acid and related compounds have shown selective activity against Herpes Simplex Virus Type 2.[45] Additionally, bile acid-based prodrugs have been shown to increase the oral bioavailability of acyclovir in rats.[46] A cholic acid analogue of cosalane, a novel anti-HIV agent, (see Figure 5), has been synthesised to improve the poor oral ab-

sorption of cosalane.[47] Cholic acid has also been exploited as a template for multivalent peptide assembly, which was observed to allow α-helix-bundle formation with a suitable peptide. These α-helix bundles may be useful as mimics of conformational epitopes for vaccine development against, for example, HIV-1.[48]

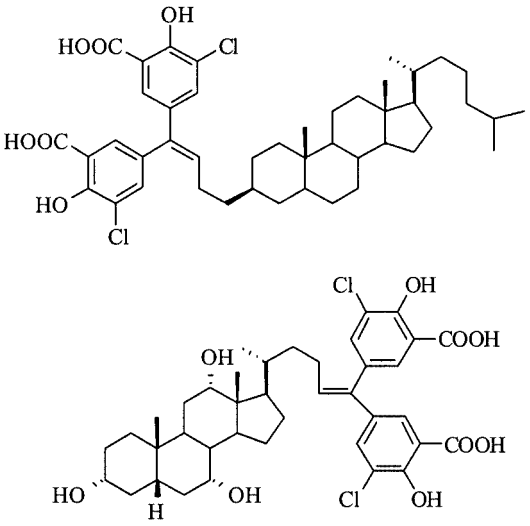


Figure 5. The structures of cosalane, a novel anti-HIV agent (above), and its bile acid analogue (below)[47]

In addition to harnessing the intestinal bile acid uptake pathway to enhance the absorption of poorly absorbed drugs, as well as using the enterohepatic circulation in organ-targeted drug delivery, the bile acid transport system can also be utilised to enhance the systemic bioavailability of orally delivered drugs.[49−51] The use of bile acid conjugates with GABA (γ-aminobutyric acid) analogue drugs or an active metabolite thereof[49] in the treatment of epilepsy, chronic pain and behavioural disorders, as well as that of L-DOPA (L-dihydroxyphenylalanine), AADC (L-aromatic amino acid decarboxylase) inhibitors, and/or COMT (cathechol *O*-methyl transferase) inhibitors[50] in the treatment of Parkinsonism, have been reported.

Bile acid derivatives conjugated with metal ion-chelated complexes have been used successfully as contrast agents in magnetic resonance imaging (MRI). They have been used in MRI assessment of microvascular hyperpermeability in a rat breast tumour, as anti-VEGF (vascular endothelial growth factor) agents,[52] and as blood pool agents for NMR diagnostics.[53−55]

Molecularly imprinted polymers (MIPs) can be used as sequestrants in the gastrointestinal tract as well as in the treatment of various diseases such as atherosclerosis, liver diseases and various diseases in the gastrointestinal tract related to, and/or characterised by, effects of bile acids and their salts.[56] These MIPs can further be used in combination therapy as well as in diagnosing and monitoring of diseases. A bile acid selective recognition portion, achieved by molecular imprinting, in a polymer agent developed by Kitahara and Oka[57] is suitable for use as, for example, a cholesterol-lowering agent.

4 Bile Acids as Building Blocks in Supramolecular Chemistry

4.1 Cyclic Structures

4.1.1 Cholaphanes

Cholaphanes are bile acid-derived macrocycles consisting of two to four bile acid units combined with different spacer molecules. The cholaphanes can be arranged either head-to-tail or head-to-head (Figure 6). In addition to their synthesis and their NMR and molecular modelling characterisation, Bonar−Law and Davis et al. have investigated the carbohydrate-binding properties of cholaphanes.[58−62] Davis et al. have continued the studies of cholaphanes by preparing some cyclocholamides[63,64] as well as by reducing the conformational freedom and improving the solubility of the compounds by creating a new class of cholaphanes with externally directed alkyl chains and truncated side chains.[65] Moreover, Albert and Feigel have prepared steroidal cyclopeptides.[66−68]

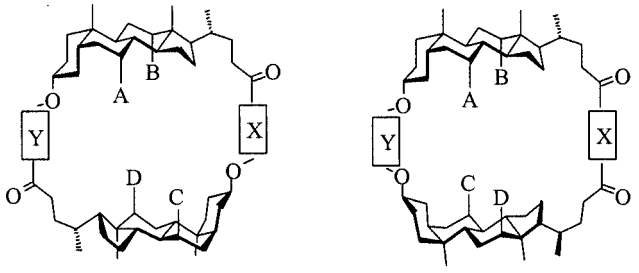
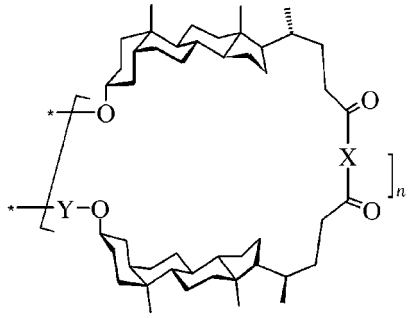


Figure 6. The structures of head-to-tail (left) and head-to-head (right) cholaphanes (A−D = binding/catalytic functionality, X,Y = spacer)

We have synthesised lithocholic acid-based ethane-1,2-diol- or piperazine-bridged head-to-head-cholaphanes in which the ring closure is achieved by use of the Yamaguchi macrolactonisation reaction[69] with aromatic dicarboxylic acids (see Figure 7).[70−74] Cation-binding studies revealed that the pyridine-2,6-dicarboxylic acid-closed cholaphane possessed selective affinity towards potassium ions, whereas the 3,5-isomer showed an affinity for protons and sodium ions.[72] The thiophene-containing cholaphane was observed to have an ability to recognise silver ion over alkali metal, especially potassium, ions.[74] We also examined the conformational preferences and cadmium ion-binding properties of the 2,2′-bipyridine-4,4′-dicarboxylic and pyridine-2,6-dicarboxylic acid-closed macrocycles by variable temperature ^{1}H NMR and multinuclear magnetic resonance techniques.[73] Development of the synthetic strategy led us to apply the one-pot mixed anhydride method,[75,76] also used in the synthesis of *N*-deoxycholyl-L-tryptophan,[77] in the synthesis of 3α,3′α-dihydroxy-5β-cholan-24-oic acid piperazine diamide,[74] an intermediate in the syn-

theses of piperazine-bridged cholaphanes. The time-saving application seems to provide a simple way of synthesising not only mono- but also diamides of bile acids.



	X	Y	n
a	et.glyc.	- OC-C$_6$H$_4$-CO -	2
b	pipe	- OC-C$_6$H$_4$-CO -	1
c	pipe	- OC-C$_5$H$_3$N-CO -	1
d	pipe	- OC-C$_5$H$_3$N-CO -	3
e	pipe	- OC-C$_{10}$H$_6$N$_2$-CO -	1
f	pipe	- OC-C$_4$H$_2$S-CO -	1

Figure 7. The structures of the head-to-head cholaphanes synthesised by us[70–74]

Synthetic strategies for the preparation of cholaphanes have typically involved direct head-to-tail coupling of bile acids by standard macrolactonisation methods or alternatively through the introduction of an amino group at the 3α-position of the steroid, followed by amide bond formation between the steroidal ends.[78] The same cyclisation strategies have been used in the syntheses of head-to-head cholaphanes, giving extremely low yields in both cases. Pandey et al. have reported a combined Cs salt and dicyclohexylcarbodiimide (DCC) method for selective bromoacetylation at the 3α-positions of the dimeric bile acid amides.[79,80] Difficulties in removing cyclohexylurea and low yields inspired Pandey et al. to develop the method further. In their most recent application, bromoacetyl bromide is used in the presence of anhydrous K_2CO_3, resulting in reaction preferentially at the equatorial position to give $> 70\%$ yields of the desired product.[78]

In the development of a host molecule capable of surrounding guests under reaction conditions too severe for amide or ester bonds, Ra et al.[81] have reported synthesis of a cyclic structure in which two lithocholic acid-derived molecules are joined together with two ethane-1,2-diol units (Figure 8).

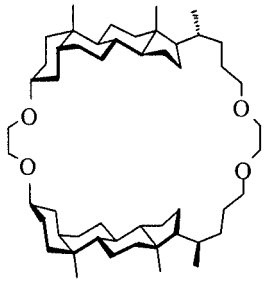


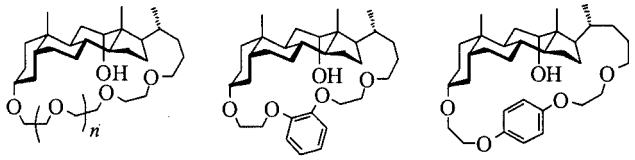
Figure 8. The structure of a cholaphane synthesised by Ra et al.[81]

4.1.2 Other Cyclic Structures

Examples of other cyclic structures involving bile acids reported in the literature and reviewed by Tamminen and Kolehmainen[7] are cyclocholates,[82–101] bile acid-based molecular boxes,[102,103] crown ethers,[104,105] cyclophanes[106–108] and cryptands.[109]

Recently, Dias et al.[110] have defined the solid-state and gas-phase structures of cyclotri(deoxycholate) and cyclotetra(24-norcholate), reporting the first crystallographic determination of macrocycles possessing three or four cholic acid moieties, the latter of which is one of the largest open macrocycles ever subjected to crystallography. The cavities formed channels enclosing large amounts of empty space in the crystal, providing frameworks for the construction of enantioselective hosts as well as chiral ligands or auxiliaries.

In addition to the previously reported bile acid-based crown ethers representing potential alkali metal ion sensors,[104,105] Maitra et al. recently synthesised a novel chola lariat ether with improved alkali metal binding properties.[111] Nair et al.[112,113] have reported interesting results in synthesis, energy minimisation and cation-binding studies of crown ethers derived from deoxycholic acid (Figure 9). Asymmetric Michael reactions in the presence of the hosts **a**, **c** and **d** resulted in moderate asymmetric induction.



a $n = 1$
b $n = 2$ **c** **d**

Figure 9. The structures of the four crown ethers derived from deoxycholic acid by Nair et al.[112,113]

Kikuchi et al. have synthesised steroid cholaphanes bearing four bile acid moieties on a tetraazaparacyclophane skeleton with the ability to bind several naphthalene derivatives effectively in aqueous solutions and in bilayer membranes[108] and have also reported molecular recognition capabilities sensitive to the environment and signal trans-

duction behaviour of steroidal cyclophanes.[114] The molecules studied constitute steroid-based artificial cell-surface receptors.

Li et al.[115] attached three amphiphilic cholic acid or trimethylated cholic acid moieties onto a CTV (cyclotriveratrylene) scaffold. Investigation of their co-aggregation properties by fluorescent studies in water/dimethoxyethane (DME) mixtures showed hydrophobic-lipophilic interaction (HLI) driven intramolecular co-aggregation of cyclotriveratrylenes with cholic acid podants.

Novel tetrasteroidal calix[4]pyrroles containing steroidal components (Figure 10) were found to exist in the forms of four configurational isomers. Enhanced enantioselectivity of the αααβ configurational isomer of compound **c** in the case of some carboxylic acids was detected, indicating the utility of these compounds in effecting the enantioselective recognition of appropriate organic anions.[116] A steroid-porphyrin receptor was demonstrated to exhibit effective saccharide binding in aqueous media, resulting in preferential complexation of oligosaccharides.[117]

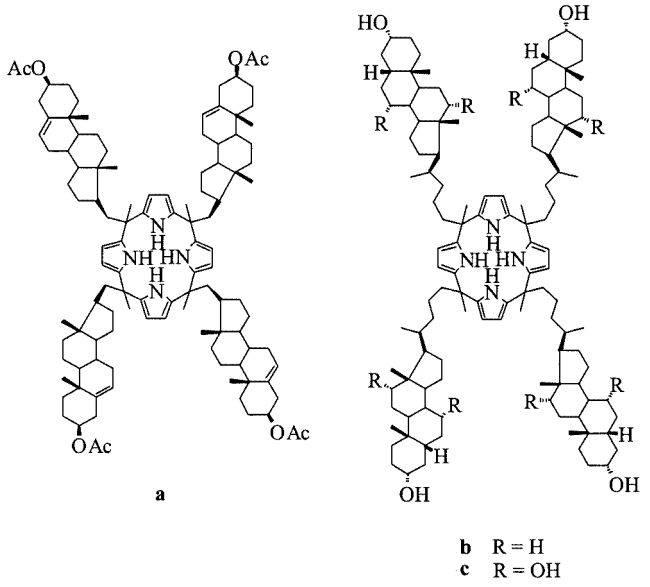


Figure 10. The structures of the steroid-containing calix[4]pyrroles[116]

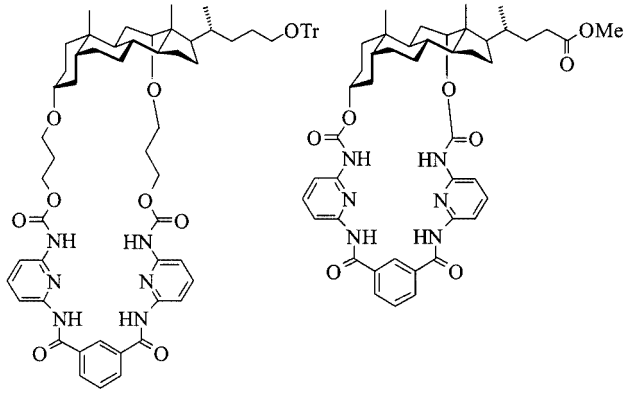


Figure 11. Deoxycholate-based macrocyclic receptors[118]

A synthesis and the barbiturate-cinnamic acid-binding properties of a series of macrocyclic receptors possessing an (*R*)-BINOL or a modified deoxycholate moiety (see Figure 11) as the chiral unit connected to a barbiturate-binding domain with varying lengths of spacers was reported by Skrydstrup et al.[118] They also studied the possibility of employing the macrocycles in asymmetric syntheses for performing 1,3-cycloadditions between arylnitrile oxides and receptor-bound cinnamate moieties.

4.2 Acyclic Structures

The first dimeric bile acid-based framework, consisting of two cholic acid molecules forming an acyclic cleft type structure, was published by McKenna et al.[119] Kohmoto et al. observed that 2,6-bis(hydroxymethyl)naphthalene molecule (acting as a guest) induced a cleft-type conformation in a cholic acid-derived dimeric host.[120] Maitra et al. have synthesised several semi-rigid molecular tweezers based on bile acids and studied their recognition properties.[103,121–124] Recently, they have prepared three novel deoxycholic acid-based tweezers capable of binding electron-deficient aromatic compounds. They have also determined the thermodynamic parameters for the binding.[125]

Several bile acid-based molecular clefts have been synthesised by our group.[70–73,126–129] The structures, conformational preferences and Ag^+ cation-binding properties of the synthesised molecules have been studied both experimentally and theoretically. We have also reported the synthesis, structural characterisation and cation/anion-binding properties of a novel bile acid-amino acid conjugate, *N*-deoxycholyl-L-tryptophan (Figure 12).[77] The structures of the ligand and its cadmium adduct under different pH conditions and at various cadmium perchlorate concentrations were determined by multinuclear magnetic resonance spectroscopic and by ESI-TOF MS techniques. Semiempirical PM3 and ab initio/HF molecular modelling studies were also performed. The synthesised compound could have potential to act as a prodrug, since L-tryptophan is a precursor of serotonin, well known as a neurotransmitter.

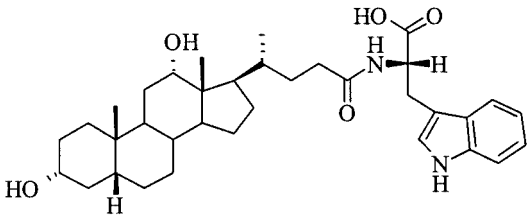


Figure 12. The structure of *N*-deoxycholyl-L-tryptophan[77]

We have recently synthesised three steroidal dipyrromethanes (Figure 13), starting from lithocholic acid, and have characterised the structures of the compounds.[130] Because dipyrromethanes are important precursors in syntheses of calix[4]pyrroles, porphyrins and other macrocycles, it is suggested that the synthesised molecules may be utilisable as precursors for pyrrole-steroidal macrocycles.

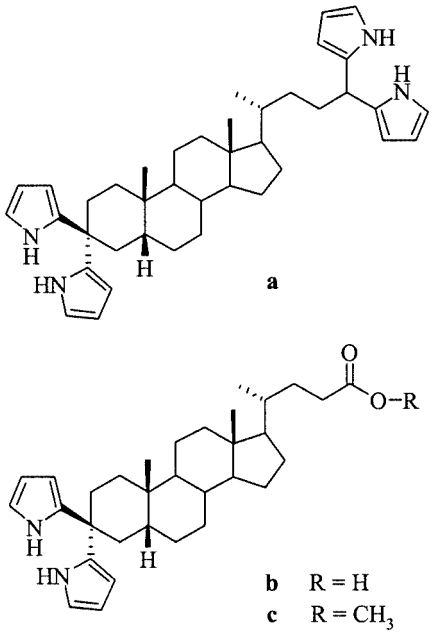


Figure 13. The structures of steroidal dipyrromethanes utilisable as precursors for pyrrole-steroidal macrocycles[130]

Synthesis of anionic facial amphiphiles derived from cholic acid (Figure 14), utilisable in, for example, solubilisation of hydrophobic molecules, permeabilisation of membranes and as structural components in supramolecular frameworks has been reported by Savage et al., together with investigations of the aggregation properties of the molecules.[131]

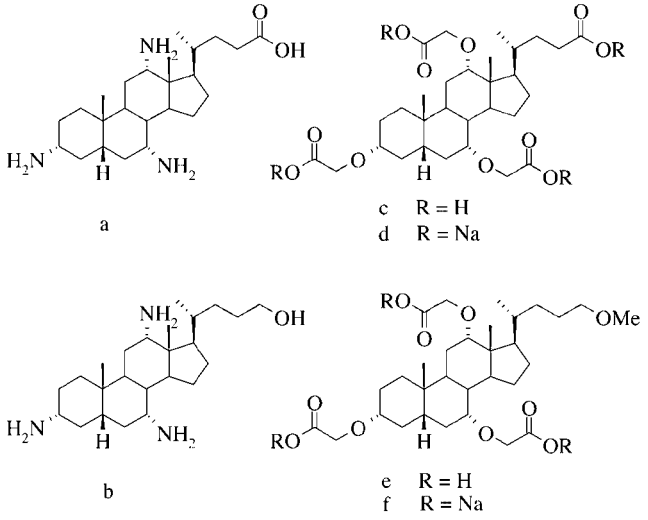


Figure 14. The structures of cholic acid-derived facial amphiphiles synthesised by Savage et al.[131]

Antimicrobial activity against both Gram-positive and Gram-negative bacteria of two molecules of a series of cholic acid-derived novel facial amphiphiles with a permanent ionic character has been reported by Marcelis et al.[132] Recently, Deshpande et al.[133] have found that certain dimeric steroids derived from cholic and deoxycholic acids show antifungal and antiproliferative effects when tested in vitro. Kikuchi et al.[134] have designed artificial signalling systems consisting of an amino group-containing bile acid derivative acting as a steroidal receptor molecule, a bilayer-forming synthetic lipid, and pig heart L-lactate dehydrogenase (LDH). In these systems the artificial receptor was able to switch on enzymic activity through accompanying double-signal recognition and phase reorganisation, which means that these supramolecular vesicles were acting as nano-reactors.

4.2.1 Enantioselective Receptors

The design of bile acid-based receptor molecules capable of enantioselective recognition is of considerable interest, especially because of the need for enantiomerically pure compounds in the pharmaceutical and chemical industries.[135,136] The steroidal guanidinium cations of the general form represented in Figure 15, designed by Davis et al.,

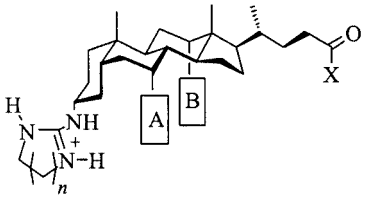


Figure 15. The general form of steroidal guanidinium cations[136]

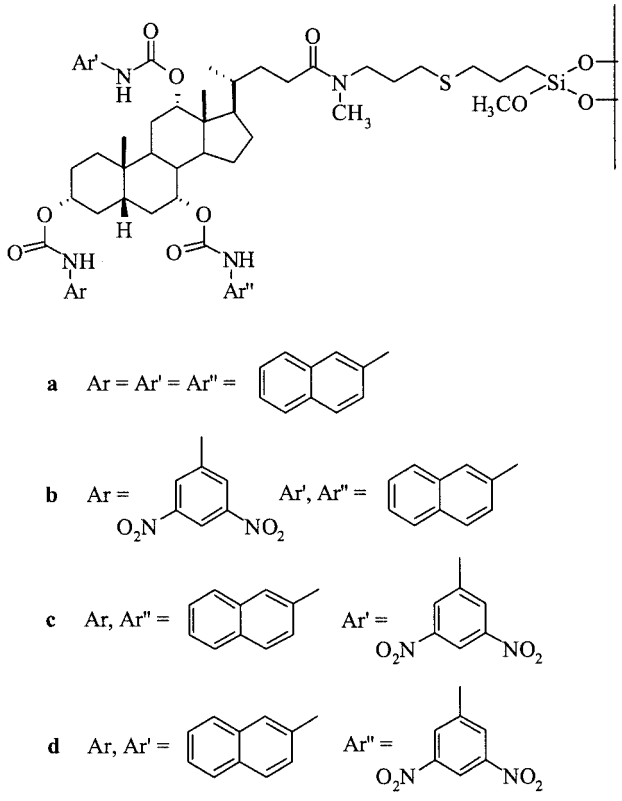


Figure 16. Examples of bile acid-based chiral stationary phases (CSPs)[143]

have proved to be a promising new class in this area.[135−137] These cholic acid-based receptor molecules are able to extract *N*-acetyl-α-amino acids from aqueous into organic media with encouraging enantioselectivities.

The chirality of the steroidal skeleton has prompted the use of bile acids as chiral templates in asymmetric syntheses. 1,1′-Binaphthyl-2,2′-diol derivatives have been synthesised with encouraging enantioselectivities by use of deoxycholic acid as a template.[138] Both enantiomers of 1-phenylethane-1,2-diol have been synthesised by use of phenylglyoxalates derived from bile acids with good to excellent enantiomeric excess.[139] Bile acid inducers possessing a carbonyl function at position C3 and specific and stereochemically appropriate substituents at positions C7 and C12 have been shown to have a large effect on the reactivity and selectivity of asymmetric epoxidation reactions with Oxone.[140] Differently substituted cholic and deoxycholic acid derivatives covalently attached to silica gel have been synthesised and used as chiral stationary phases (CSPs) for the HPLC separation of enantiomers (for an example see Figure 16). The enantiodiscriminating properties exhibited by, and the mechanisms of chiral recognition of, this kind of bile acid-derived CSPs have been further elucidated.[141−145]

4.2.2 Bile Acid-Based Ionophores

Regen et al.[146−149] have synthesised a family of bile acid-based conjugates exhibiting significant activities in transport of Na^+ ions across liposomal membranes. They have observed that transport-active dimers are formed in all cases, and suggest an antiport mechanism of transport. They have also systematically investigated the influence of facial hydrophilicity on the transport activity. Selectivity towards the thickness of the membrane and osmotically-stressed phospholipid bilayers has been detected, offering potential therapeutic applications, such as new classes of antibiotics less susceptible toward resistance.[146−149]

Tecilla and De Riccardis et al.[150,151] have designed and synthesised a C_2-symmetric bis(20*S*)-5α-23,24-bisnorchol-16-ene-3β,6α,7β-triol-22-terephthaloate (see Figure 17), active as a Na^+-transporting transmembrane channel. They also reported the synthesis of sterol-polyether conjugates, in which two rigid 3β-hydroxy-5α-23,24-bis(norcholanic) units and two flexible hydrophilic oligo(ethylene glycol) chains were attached to an L-treitol spacer. When incorporated into phospholipid vesicles the compounds showed enhanced Na^+ transport capability.[152]

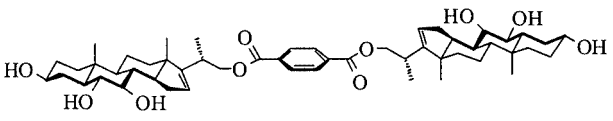


Figure 17. The structure of the C_2-symmetric bis[(20*S*)-5α-23,24-bisnorchol-16-ene-3β,6α,7β-triol-22-terephthaloate], active as a Na^+-transporting transmembrane channel[150,151]

Kobuke and co-workers[153−155] have designed artificial ion channels based on cholic acid derivatives and investigated the single-ion channel currents of the compounds. Additionally, they have introduced a novel artificial ion channel consisting of a macrocyclic resorcin[4]arene and four amphiphilic cholic acid-derived moieties (Figure 18).[156] In a bilayer membrane these molecules would be expected to form a tail-to-tail coupled pair to afford a transmembrane channel with a long-lasting open state.

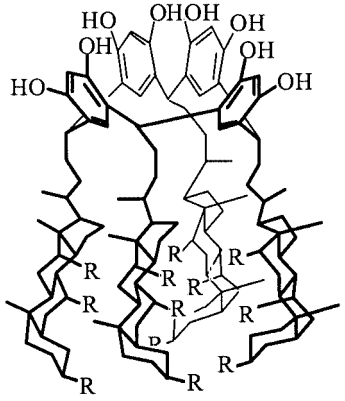


Figure 18. Structure of an artificial ion channel consisting of resorcin[4]arene and four amphiphilic cholic acid-derived groups[156]

Nam and co-workers[157,158] report syntheses and investigations of potentiometric performances of deoxycholic acid-based selective electrodes. A carbonate-selective electrode was shown to provide accurate oceanic total CO_2 determination with clear advantages over conventional methods.[157] Pyun et al.[159] have designed cholic acid-derived carbonate ionophores containing one to three trifluoroacetylbenzoyl (TFAB) moieties at the 3α-, 7α- and 12α-positions as well as a long-chain dialkylamide group attached to the carboxyl group of cholic acid. They observed enhanced affinities towards carbonate ions in the cases of compounds possessing two or three TFAB moieties. The tweezer-type neutral carrier-based calcium-selective membrane electrode synthesised by Nam et al. showed remarkably reduced anionic interference relative to ETH 129 and ETH 1001, the best known calcium-selective neutral carriers, and can, for example, be applied in clinical analyses.[158]

Davis et al. have designed cholic acid-based anion-binding receptors[160] and have found that methyl and octyl cholates bind tridentate oxoanions as sulfonates through hydrogen bonding involving the three hydroxy groups of the cholic acid moiety.[161] Modifications of their original bile acid-derived anionophore designs[160] have resulted in several new anionophores with remarkably improved properties.[162,163] Davis and Joos have recently published an article summarising the use of steroids, especially cholic acid, in the area of anion recognition.[164]

4.2.3 Molecular Umbrellas Derived from Bile Acids

Molecular umbrellas are a novel class of molecules with potential to function as vehicles for transporting hydro-

philic compounds across phospholipid bilayers by means of a shielded conformation that hides the hydrophilicity of the attached agent from the hydrophobic core of a lipid bilayer.[165] Two- and four-walled molecular umbrellas containing cholic acid and spermidine have been synthesised, and their abilities to transport hydrophilic peptide and thiolated AMP and ATP across liposomal membranes have been investigated.[165–167] Double- and quadruple-walled cholic acid-containing molecular umbrella-spermine conjugates have shown enhanced affinities towards DNA at physiological salt concentrations and a highly cooperative character of binding. These properties may prove very useful from the point of view of rational drug design.[168] Compelling evidence of an umbrella mechanism in the transport of bile acid-based structures has been presented.[169] Examples of double- and quadruple-walled molecular umbrellas are shown in Figure 19. In a development of low-molecular-weight synthetic translocases, cholate bis(phenylureas) proved to be promising promoters of phosphatidylcholine translocation across vesicle and cell membranes.[170]

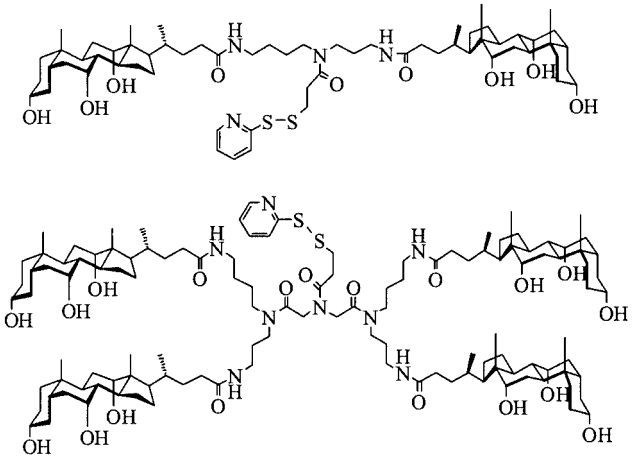


Figure 19. Examples of double- and quadruple-walled bile acid-based molecular umbrellas synthesised by Regen et al.[166]

4.2.4 Bile Acids as Gelling Agents

Organogels find applications in a wide variety of areas, including medicine, pharmacology, cosmetics, hardeners of spilled toxic solvents and environmental clean-up, which is why the observation by Miyata et al. during their investigations concerning the inclusion compounds of cholic acid and its derivatives, according to which *N*-isopropylcholamide was able to form gels in aromatic solvents in the presence of methanol,[171] was particularly interesting.

Since then, Maitra et al.[172] have reported the ability of some bile acids, substituted with aromatic donors at the 3-position, to gelate certain organic solvents (primarily alcohols) in the presence of trinitrofluorenone as an acceptor. The electron donor-acceptor interaction was established as a requirement for the gelation process. They have also reported the ability of a novel tripodal cholic acid derivative (Figure 20) to form gels in aqueous media and have discovered that the gelation process creates highly hydrophobic pockets[173] with potential to be utilised for selective chemical transformations. Additionally, the rotational dynamics of polarity-sensitive fluorescent dyes in a gel derived from the tripodal cholic acid derivative were investigated.[174]

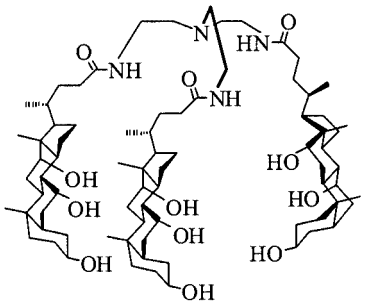


Figure 20. The structure of the tripodal cholic acid derivative with organogelator properties[173]

They have also reported results concerning the first bile acid-based cationic surfactant-gelators.[175] Their studies revealed that the presence of a hydrophilic functionality on the side chain of deoxycholic acid may result in thickening of aqueous liquids, and that the number of hydroxy groups on the bile acid backbone, as well as the presence of the amide linkage, may play an important role in gelation.[175]

Sudhölter and Marcelis et al.[176,177] have investigated the organogelator properties of bile acid-based low molecular weight compounds. They found that several *N*-(cholyl)amino acid alkyl esters could act as organogelators for aromatic solvents and cyclohexene, resulting in stable, transparent and thermoreversible gels.[176] Hydrogen bonds and the chiral centre at the amino acid α-carbon were observed to affect the gelation properties of the compounds. Furthermore, results similar to those of Maitra et al.[175] concerning the importance of the amide bond and several hydroxy groups of the bile acid component in the gelation process have been reported.

A phenanthroline amide of cholic acid was found to be a powerful gelating agent by Král and Drašar et al.[178] The gelation properties were observed to change dramatically as a phenanthroline-zinc(II) 2:1 complex was formed. We have observed that 2-hydroxyethylamides of lithocholic and deoxycholic acids are effective gelators in chlorinated organic solvents, whereas the corresponding 3-hydroxypropylamides (see Figure 21) form gels in aromatic solvents.[179] Ac-

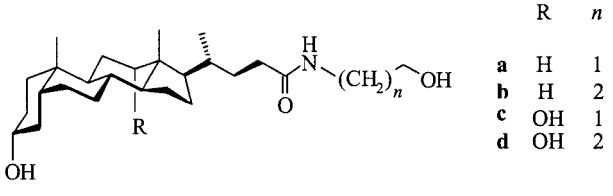


Figure 21. The structures of 2-hydroxyethyl- and 3-hydroxypropylamides of lithocholic and deoxycholic acids with gelator properties[179]

cording to our investigations, both derivatives thicken neutral and acidic water solutions.

4.2.5 Inclusion Compounds of Bile Acids

In inclusion compounds, the host molecules form open cavities accommodated by guest compounds.[180] Bile acids have shown a special tendency to form inclusion compounds with different guest molecules. Deoxycholic acid has been known as a classical host for a long time. Cholic acid forms channel-type inclusion compounds, whereas chenodeoxycholic acid has large hexagonal cavities for accommodating organic guests. Lithocholic acid does not yet seem to form inclusion compounds.[181]

So far Miyata and co-workers have obtained over three hundred crystal structures of bile acids and their derivatives with a variety of organic substances.[181−188] Recently, they have reported a systematic investigation of the crystal structures of inclusion compounds of cholic acid with monosubstituted benzenes.[189] In further studies, competitive recrystallisation experiments of cholic acid from 1:1 binary mixtures of different monosubstituted benzenes[180] and from mixtures of *o*-, *m*- and *p*-xylenes[190] were performed. The latter study is the first to describe the mechanisms of selective and unselective enclathration of guest compounds with flexible host frameworks. Interesting results concerning the extremely specific recognition of ethylene glycol by *N*-deoxycholamide,[191] the enantioselective enclathration of (2*R*,3*S*)-3-methylpentanol in the channel-like cavity of 3-epideoxycholic acid, interpreted by the four-location model for chiral recognition,[192] as well as hierarchical helical tape assemblies in inclusion crystals of bile acids and their derivatives[181] have also recently been reported.

A channel structure of an ursodeoxycholic acid-phenanthrene inclusion complex, characterised by a mesh-like framework with a complicated hydrogen bond network, resulting in higher guest selectivity of the ursodeoxycholic acid in the complex formation, has been reported by Yamamoto et al.[193] This structure clearly differs from the previously reported inclusion complexes of cholic and deoxycholic acids.

The effect of β-orientation of the 3-OH group on the formation of crystalline inclusion compounds has been studied by Vázquez Tato et al.[194] They observed that the crystals of iso-deoxycholic acid, the 3β-hydroxy epimer of deoxycholic acid, did not contain any guest molecules when recrystallised from *p*-xylene, thus clearly differing from the crystals of deoxycholic acid, which were recrystallised from *o*-, *m*-, and *p*-xylene with a host guest ratio of 2:1.

Fantin et al. have used dehydrocholic acid as a chiral host for the optical resolution of aryl alkyl sulfoxides by inclusion.[195] They have also investigated the optical resolution complexation capabilities of cholic and deoxycholic acids with cyclic ketones and observed the formation of inclusion compounds enabling enantiomer separation.[196] Photochromic crystals have been suggested as data storage devices, for example, which is why the results concerning the photochromic properties of inclusion crystals of deoxycholic acid and its amide and alcohol derivatives with *N*-salicylideneaniline reported by Kawato and co-workers[197] are particularly noteworthy. Prout and Heyes et al.[198] have observed a gradual phase transition on heating in an inclusion complex of deoxycholic acid and ferrocene.

4.2.6 Bile Acids in Combinatorial Chemistry

Combinatorial libraries offer a powerful tool for investigation of selective interactions between a host and a guest.[199] Bile acids have been used in the traditional combinatorial chemistry approach by, for example, Still et al.,[200,201] who have synthesised a library of peptidosteroids based on both chenodeoxycholic and allo-chenodeoxycholic acids and have investigated the ability of the receptors to bind enkephalins, by Wess et al.[202] and also by Davis et al.[203] Traditional combinatorial libraries have also been created by Høeg-Jensen,[204] who presented a method for solid-phase and combinatorial synthesis of a cholic acid scaffold substituted with peptide, pseudo-peptide and/or peptoid chains, and by Secundo et al.,[205] who created a library of 39 bile acid derivatives by a combinatorial biocatalytic approach. Lukeman and Sanders[206] have generated dynamic combinatorial libraries (DCLs) based on methyl deoxycholate monomers bearing directional recognition functionalities towards metal centres. Bile acid-containing polymers can also be used in the design of new receptors for combinatorial chemistry, as mentioned in a review by Zhu and Nichifor.[26]

4.2.7 Steroidal Oligomers and Polymers

In addition to the pharmacological applications of bile acid-based polymers[21−26,56,57] described above, bile acids have also found use in some other oligo- and polymeric structures. The first bile acid-based dendrons, based on acetoxy-functionalised cholic and deoxycholic acids and a convergent method resulting in a heptamer, a nonamer and a decamer, were reported by Maitra et al.[207,208] The free carboxylic acid groups of some of the synthesised dendrons, combined with their chirality, enable the use of these molecules for further transformations into functional dendritic species.

In collaboration with Rissanen's group,[209] we have synthesised first- and second-generation dendrons, capable of functioning as model compounds for possible drug carriers, from 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) and lithocholic acid by a convergent method (Figure 22). It is suggested that the drug, which is simulated by the benzyl protecting group of bis-MPA, is surrounded by an "umbrella" of the dendritic moieties. In addition, the solubility of dendrons of this kind can also be modified by altering the bile acid residue or the external surface.

We unexpectedly observed the formation of lithocholic acid-based tetramers[73] (see Figure 23) as by-products in Yamaguchi macrolactonisation reactions[69] between lithocholic acid piperazine diamide and some aromatic dicarboxylic acids, suggesting some kind of self-assembly tendency of the reacting species. Since the four steroidal units

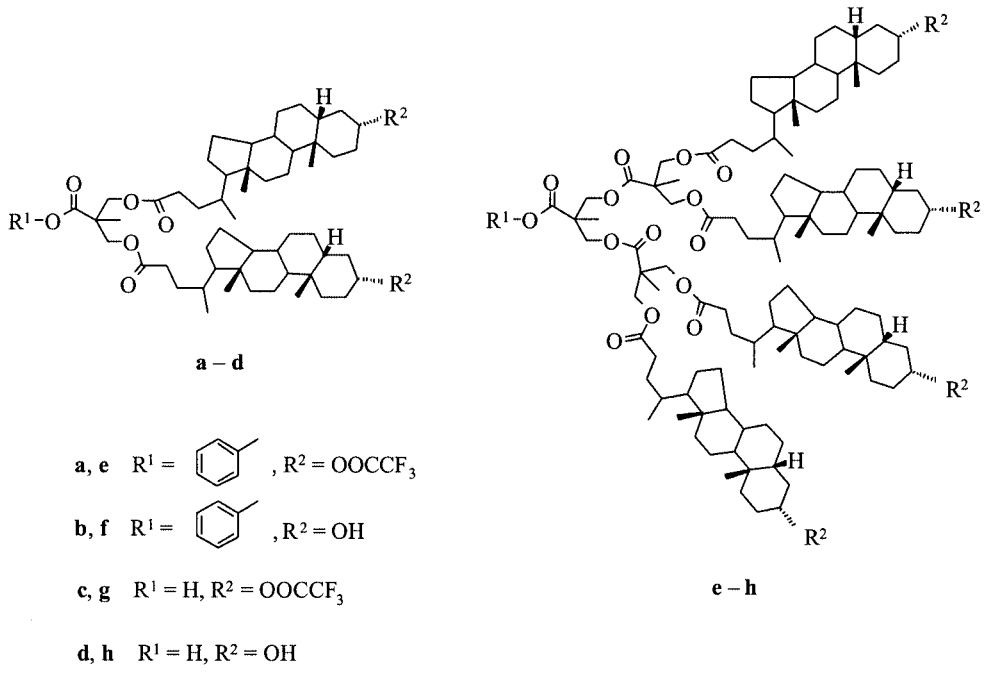


Figure 22. The structures of lithocholic acid-based dendrons representing model compounds for possible drug carriers[209]

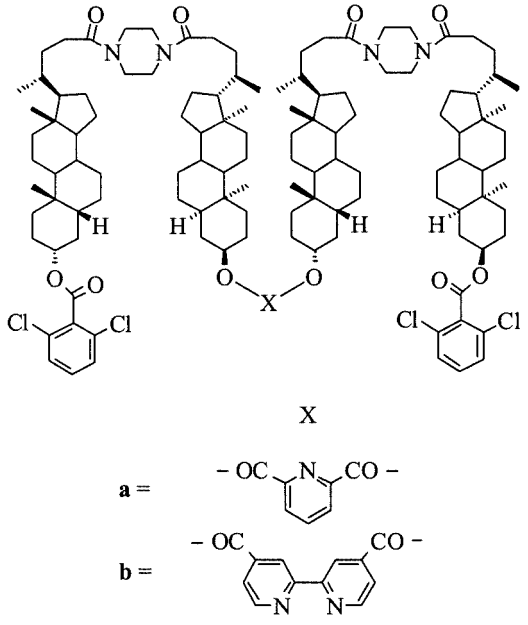


Figure 23. The structures of lithocholic acid-based tetramers formed as by-products in Yamaguchi macrolactonisation reactions of lithocholic acid piperazine diamide and some aromatic dicarboxylic acids[73]

linked by amide bonds by use of the linear chaining method by Černý et al.[210] have been suggested to reach the limit of 40 Å corresponding to the thickness of a lipid bilayer, the structures formed as by-products in the present case might also find use in facilitation of the transport of ions or small molecules across lipid bilayers. In addition to the detailed structural characterisation of these oligomers, their ability to interact with cations was also investigated.[73]

Thermosensitive polymers with a marked chemical and physical response to a relatively weak stimulus, and thus useful in industrial, medical, and biotechnological applications, have been obtained by the synthesis of copolymers of *N*-alkylacrylamides with acrylamide or methacrylamide derivatives of cholic acid.[211,212]

5 Conclusions and Prospects

Bile acids are versatile building blocks for the design of frameworks capable of ionic and molecular recognition. They have been used as chiral templates in asymmetric syntheses and have been observed to act as organogelators, offering potential applications in medicine, pharmacology, cosmetics, material science and environmental clean-up. Bile acid-based compounds have found use in transport of ions and molecules across phospholipid bilayers. Inclusion complexes and combinatorial libraries based on bile acids are useful in, for example, investigations of selective interactions between a host and a guest. A vast amount of interesting medical applications, such as potential cancer and HIV therapeutic agents, based on bile acids have been reported.

We have applied new synthetic techniques, such as power ultrasound and microwave techniques, in esterification reactions of bile acids with promising results.[213,214] Since these techniques increase the reaction rates, affect the distribution of the reaction products and improve the yields, they are interesting methods from both the economic and the environmental points of view. Difficulties in growing single crystals of bile acids and their derivatives suitable for X-ray structural analysis has resulted in the exploitation of X-ray powder diffraction methods for investigation of the solid-

state structures of the molecules.[179] We have also obtained promising results in the calculation of ^{13}C and ^{17}O NMR chemical shifts at the DFT/GIAO level for the optimised structures of some methyl 5β-cholan-24-oates[215−217] and have also been able qualitatively to predict the ^{13}C NMR chemical shift changes induced by cation complexation of bile acids.[126,218] The theoretical methods may prove useful in, for example, interpretation of complicated experimental spectra.

The observation[219] that bile acids transcriptionally regulate their biosynthesis and enterohepatic transport mediated by the farnesoid X receptor (FXR) suggests an expanded model for the regulation of cholesterol homeostasis by nuclear receptors. The finding that FXR and LXR Alpha (liver X receptor) function as key regulators in cholesterol and bile acid homeostasis has significance for the discovery of drugs targeted against these receptors and opens new and inspiring insights concerning research into bile acids and molecular structures derived from them.

An active and versatile research effort on bile acids, their derivatives and their potential applications continues. The obtained results are important in the areas of drug preparation and biological response and can be utilised in, for example, the design of organ-targeted supramolecular drug carriers. Bile acid-based systems are important for detailed understanding of the functioning of natural systems and for the development of new chemical and pharmacological applications.

Acknowledgments

E. V. gratefully acknowledges financial support from the University of Jyväskylä Faculty of Mathematics and Science, the Magnus Ehrnrooth Foundation of the Finnish Society of Sciences and Letters, the Finnish Cultural Foundation and Masaryk University.

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Received November 3, 2003

