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Syntheses and structural study of bile acid amidoalcohols

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ABSTRACT

Preparation, structural and thermoanalytical characterization of fourteen *N*-hydroxyalkyl 5β-cholan-24-amides have been performed in this study. The utilized techniques include liquid state and CP-MAS ^{13}C NMR spectroscopy, thermogravimetry, differential scanning calorimetry, and also powder and single crystal X-ray crystallography. The results were discussed and compared to each other and also to previous findings on similar compounds. One pure hydrate form was obtained. Six new single crystal structures were determined, including one hydrated chloroform solvate. Decomposition temperatures were found to correlate with the side chain length, and the number of the hydroxyl groups. The spatial direction of the groups in the steroid skeleton was also found to be relevant in predicting the thermal properties of bile acid amidoalcohols studied.

1. Introduction

Bile acids are readily available and low cost starting materials, with enantiomeric purity and biological activity, which makes them desirable steroidal compounds in synthetic chemistry and they are widely applied [1]. The pharmacological interest of bile acids is directed on the fact that hepatic cells can specifically recognize these natural ligands of enterohepatic circulation [2]. Some bile acid derivatives have an ability to act as enantiomer differentiating host molecule in inclusion processes [3–5]. The ability to gel organic solvents [6–10] and aqueous liquids [11–13] is also significant. Owing to these properties, bile acids are ideal building blocks in construction of novel molecular and supramolecular assemblies for molecular recognition.

The exact solid state structures of bile acids and their derivatives are often difficult to obtain because they frequently solidify out from solutions in forms unsuitable for single crystal X-ray structural studies. However, NMR crystallography [14,15] together with powder X-ray diffraction opens a direct and pharmaceutically very important scope for studies of bile acid derivatives in the solid state. These studies enable characterization of the structures, including possible polymorphs and pseudopolymorphs, of many bile acid derivatives, particularly when utilized together with TG and DSC. There are not many reports on ^{13}C CP-MAS NMR spectral studies of bile acids or their derivatives found in the literature. Isolated *N*-(3-hydroxypropyl) 3α,12α-dihydroxy-5β-cholan-24-amide and its monohydrates were recently characterized by us [16]. Few reports on ^{13}C CP-MAS NMR studies of inclusion or binding interactions of bile acids are also found, including interactions with barley β-D-glucan [17], carrot fiber [18], 2,3-dimethylbutadiene [19], ferrocene [20,21], *R*-, and *S*-camphor (and their mixtures) [21], as well as γ-valerolactone [22,23]. Since the middle fifties many reports of powder X-ray diffraction studies of bile acids and their derivatives have been published. The topics like inclusion processes [e.g. 4,5,24–29], polymorphism [e.g. 15,30,31], crystallinity and amorphization [e.g. 32–34], as well as bile acid containing polymers [e.g. 35–37] are, for example, reported. Hundreds of single crystal struc-

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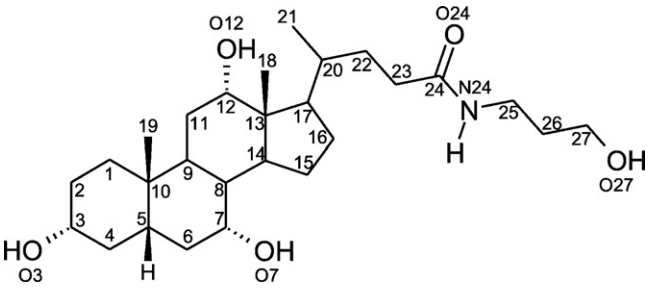
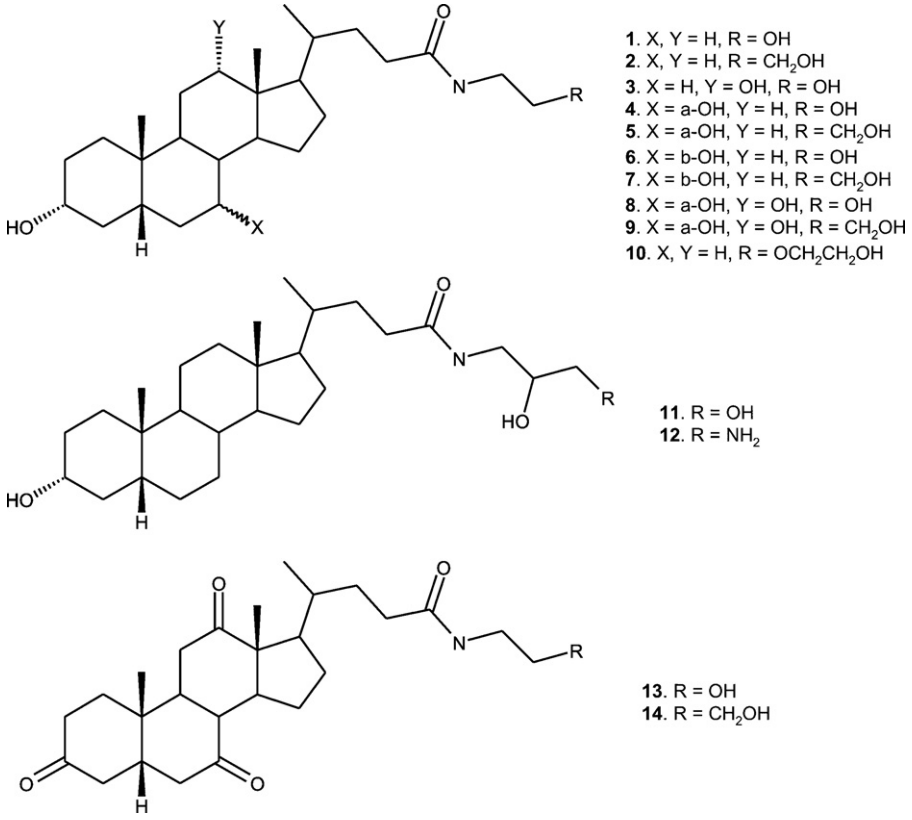


Scheme 1 – General structure and numbering. *N*-(3-Hydroxypropyl) 3α,7α,12α-trihydroxy-5β-cholan-24-amide (9) as a model compound.

tures containing bile acid moiety are found from CSD database [38], containing single molecules, solvates, or inclusion complexes.

The synthesis and structures of *N*-(2-hydroxyethyl) and *N*-(3-hydroxypropyl) amides of 3α-hydroxy-5β-cholan-24-oic (lithocholic, LCA) and 3α,12α-dihydroxy-5β-cholan-24-oic (deoxycholic, DCA) acids as well as their gelation properties were investigated and discussed in our previous studies [16,39]. Bile acid amidoalcohols (Scheme 1) have proven to be biologically interesting and active compounds. Some bile acid amidoalcohols are found to act as antimicrobials and antifungals [40] and could possibly be used in therapeutic treatment of inflammations and diseases [41–45]. These compounds can have an effect on ileal bile salt transport system [46]. One study shows, that pathogenic strains could also biotransform human cholic acid (CA) derivatives to *N*-(2-hydroxyethyl) 3α,7α,12α-trihydroxy-5β-cholan-24-amide [47]. The ability of these compounds to gel organic solvents is also significant [5,8]. *N*-(2-Hydroxyethyl) cholanamide moieties have also been used in preparation of novel biodegradable amphiphilic copolymers [48] and selective high-affinity ligands [49].

Absolute configuration and conformational equilibrium are crucial factors for the function of biologically and pharmacologically active compounds. In case of common bile acids (5β-cholan-24-oic acids) the steroidal back bone possesses its unique chirality owing to several enzymic transformations starting form cholesterol. The variable number of hydroxyl substituents affects the solubility, surface activity, and amphibility of these steroidal compounds as well. Furthermore, steroidal ring system typically remains in the same conformation [50]. *iso*-Pentyl carboxylic acid side chain exhibiting conformational freedom will also influence on their activity [51,52] and adopt more or less well-defined state or equilibrium depending on its environment (liquid, amorphous solid, or well organized crystal). Therefore, it is interesting to study how the conformationally restricted, planar peptide bond in their amide derivatives (or peptido mimetics) will affect their properties such as structures and polymorphism, e.g. Multi-technical approach by well-established experimental methods like spectroscopy, crystallography and thermal analysis, become indispensable in purposes to characterize these structural properties. Solid state structures of these compounds are mainly unexplored and, for example, only our single crystal structures of *N*-(3-hydroxypropyl) 3α,12α-



Scheme 2 – Structures of compounds 1–14.