Journal of Molecular Structure 892 (2008) 53–57

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Synthesis and characterization of novel bile-acid – heteroaryl conjugates with *N*-(2-aminoethyl)amido linker

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ARTICLE INFO

Article history:
Received 17 April 2008
Received in revised form 25 April 2008
Accepted 25 April 2008
Available online 11 May 2008

Keywords:
Bile acids
Heteroaromatics
^{13}C NMR chemical shifts
X-ray diffraction
Thermal analysis

ABSTRACT

Four novel bile acid conjugates *N*-[2-([2,2′]-bithiophen-5-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide (**1**), *N*-[2-([2,2′]-bithiophen-5-ylmethyl)aminoethyl]-3α,7α,12α-trihydroxy-5β-cholan-24-amide (**2**), *N*-[2-(1*H*-pyrrol-2-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide (**3**), *N*-[2-(pyridin-2-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide (**4**) have been synthesized in moderate to good yields, and their structures have been characterized by ^{1}H, ^{13}C, ^{13}C DEPT-135, PFG ^{1}H,^{13}C HMQC, and PFG ^{1}H,^{13}C HMBC NMR spectra. Their molecular weights and elemental compositions have been determined by ESI-TOF mass spectrometry and elemental analyses. Crystal structure of **1** characterized with orthorhombic $P2_12_12_1$ space group has also been determined.

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1. Introduction

Bile acids are natural surfactants, which assist in solubilization, digestion and resorption of lipids and lipid soluble vitamins. In addition, bile acids and their derivatives are potential carriers for liver specific drugs and some of them can be used as cholesterol lowering agents [1] and in treatment of bile acid deficiency and liver diseases [2]. Recently, many pharmaceutical and supramolecular applications of bile acid derivatives have also been reported [3]. Preparation and characterization of bile acid conjugates with various heteroaromatic compounds such as nitrogen and sulfur heterocycles are reported earlier by us [4–8]. Among them thiophene in addition to its pharmaceutical applications [9], has been frequently used in electronic and optoelectronic devices [10].

2. Experimental

2.1. Spectroscopy

NMR experiments were run on a Bruker Avance DRX 500 FT NMR spectrometer equipped with a *z*-gradient accessory and a 5 mm diameter inverse detection probehead working at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C, respectively. The ^{1}H NMR chemical shifts are referenced to the resonance of $CHCl_3$ [$\delta(^{1}H)$ = 7.26 ppm from int. TMS]. ^{13}C NMR chemical shifts are referenced to the center peak of $CDCl_3$ triplet [$\delta(^{13}C)$ = 77.00 ppm from int. TMS]. Complete lists of the NMR acquisition and processing parameters are available from E.K. on request. Mass spectrometric measurements were performed using a Micromass LCT time of flight (TOF) mass spectrometer with electrospray ionization (ESI). Elemental analysis was performed using a VarioEL III elemental analyzer.

2.2. X-ray crystallography

The single crystal X-ray structural data of compound **1**, crystallized from methanol, was collected with Bruker–Nonius Kappa APEX-II diffractometer at 123.0 ± 0.1 K using graphite monochromatized MoK_α radiation (λ = 0.71073 Å) and COLLECT [11] data collection software. Data was processed with DENZO-SMN [12]. The structure was solved by direct methods, using SIR2002 [13], and refined on *F*2, using SHELXL-97 [14]. The reflections were corrected for Lorenz polarization effects and absorption correction was not used. The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms. The figures were drawn with ORTEP-3 [15] and MERCURY [16]. Other experimental X-ray data are shown in Table 1. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-684960. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

2.3. Differential scanning calorimetry

Thermal transitions of the compounds were determined on power compensation type Perkin Elmer PYRIS DIAMOND DSC.

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doi:10.1016/j.molstruc.2008.04.057

Table 1
Crystal data and structure refinement parameters of **1**

	1
Empirical formula	$C_{35}H_{52}N_2O_2S_2$
Formula weight	596.91
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	7.05300 (10)
b (Å)	15.6665(4)
c (Å)	29.8895(7)
α,β,γ (°)	90
Volume (Å^3)	3302.66(12)
Z	4
Density$_{calc}$ (Mg/m^3)	1.200
Abs. coefficient (mm^{-1})	0.194
$F(000)$	1296
θ Range (°)	1.88–25.00
Index ranges	$-8 \leqslant h \leqslant 0$ $-18 \leqslant k \leqslant 18$ $-35 \leqslant l \leqslant 35$
Reflections collected	11585
Internal consistency	0.1648
Data/restraints/parameters	3341/18/371
Goodness-of-fit on F^2	1.084
Final R indices [$I > 2\sigma(I)$]	
R_1	0.0719
wR_2	0.1266
R indices (all data)	
R_1	0.1050
wR_2	0.1400
Largest diffraction	
Peak (eÅ^{-3})	0.39
Hole (eÅ^{-3})	−0.31

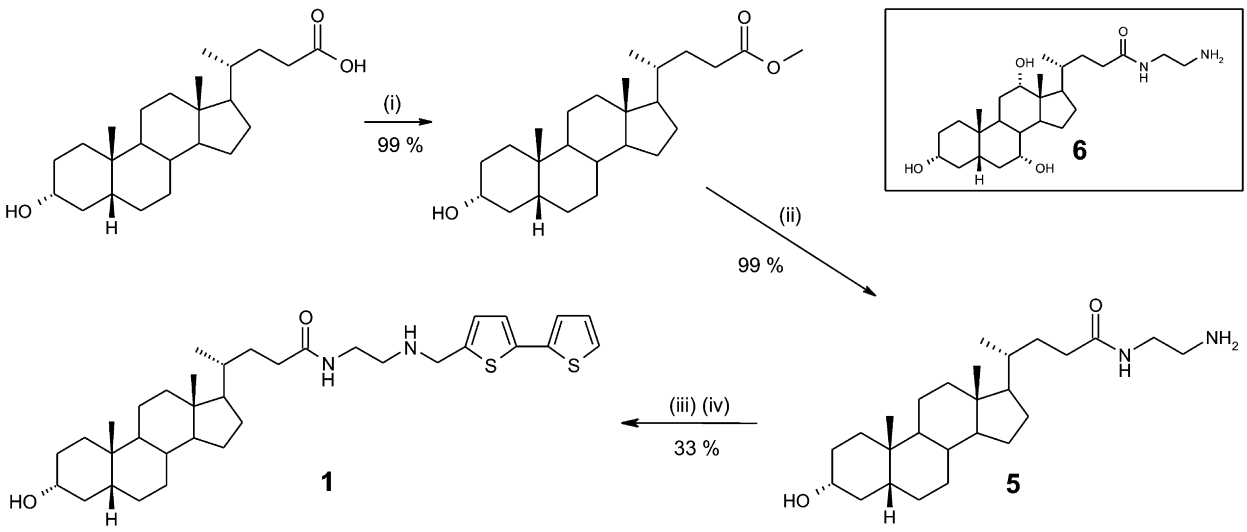
The measurements were carried out under nitrogen atmosphere (flow rate 50 mL min^{-1}) using 50 μL sealed aluminum sample pans. The sealing was made by using a 30 μL aluminum pan with capillary holes to ascertain good thermal contact between the sample and pan, and to minimize the free volume inside the pan. The temperature calibration was made using two standard materials (*n*-decane, In) and energy calibration by an indium standard (28.45 J g^{-1}). Typically, following temperature profile was used for each sample: a sample was heated from 0 to either 160 or 180 °C with a heating rate of 10 °C/min, followed by 1 min hold at the end temperature, and cooled down to −40 °C with a rate of 10 °C/min. The heating–cooling cycle was repeated once. The sample was held at −40 °C for 5 min before initiation of a next cycle. The melting temperature (T_m), was obtained as an extrapolated onset. The glass transition temperature (T_g) was obtained at a half-step temperature of a ΔC_p change. Uncertainty for measured temperatures was less than 0.7 °C for all measurements. Sample weights of ~1–4 mg were used on the measurements. The sample weight was checked afterwards to monitor a weight loss that may have occurred during the scans.

2.4. Synthesis

Bile acid methyl esters were synthesized according to the previously reported procedure [17]. Amides **5** and **6** were synthesized from methyl esters using 10-fold excess of 1,2-diaminoethane [18]. Synthetic route to **1** starting from lithocholic acid is presented in Scheme 1. All reagents and solvents (purity ⩾96% or better) were purchased from Sigma–Aldrich or Fluka and used without further purification.

2.4.1. *N*-[2-([2,2′]-bithiophen-5-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide **1**

N-(2-aminoethyl)-3α-hydroxy-5β-cholan-24-amide **5** 500 mg (1.19 mmol) and 2,2′-bithiophenyl-5-carbaldehyde 250 mg (1.29 mmol) were dissolved in 20 mL of methanol, and the solution was stirred at rt for 1d. Formed Schiff base was reduced by $NaBH_4$ 150 mg (3.96 mmol) added during 5 min and stirring was continued for 30 min. Then another 150 mg of $NaBH_4$ was added and the mixture was stirred for additional 1.5 h. Solvent was evaporated and the product was dissolved in CH_2Cl_2 and transferred into separatory funnel with water. About 2 M aq. HCl was added until the water layer was neutralized. Organic layer was washed with water and dried over anhyd. Na_2SO_4. Product was purified by column chromatography (silica gel, 0.040–0.063 mm; eluents: CH_2Cl_2 and CH_2Cl_2:MeOH 95:5). Recrystallization from CH_3CN gave pure product 235 mg (33%). ^{1}H NMR in $CDCl_3$: $\delta = 0.62$ (3H, s), 0.91 (3H, s), 0.91 (3H, d), 0.93–1.90 (28H), 2.03–2.12 (1H, m), 2.20–2.29 (1H, m), 2.81 (2H, t), 3.35 (2H, q), 3.61 (1H, m), 3.95 (2H, d), 6.00 (1H, t), 6.81 (1H, d), 6.99 (1H, t), 7.00 (1H, d), 7.12 (1H, dd), 7.19 (1H, dd). MS: $m/z = 597$ $[M+H]^+$, 619 $[M+Na]^+$. MW ($C_{35}H_{52}N_2O_2S_2$) = 596.94. Elemental analysis: calcd. (%) for $C_{35}H_{52}N_2O_2S_2$: C, 70.42; H, 8.78; N, 4.69. Found C, 70.23; H, 8.91; N, 4.08.



Scheme 1. Synthetic route to **1**. Reagents and condition: (i) MeOH, conc. H_2SO_4, reflux overnight; (ii) 1,2-diaminoethane, MeOH, reflux 48 h; (iii) 2,2′-bithiophenyl-5-carbaldehyde, $CHCl_3$, rt 1 day; (iv) $NaBH_4$, MeOH, rt 2 h. Insert: structure of intermediate **6**.

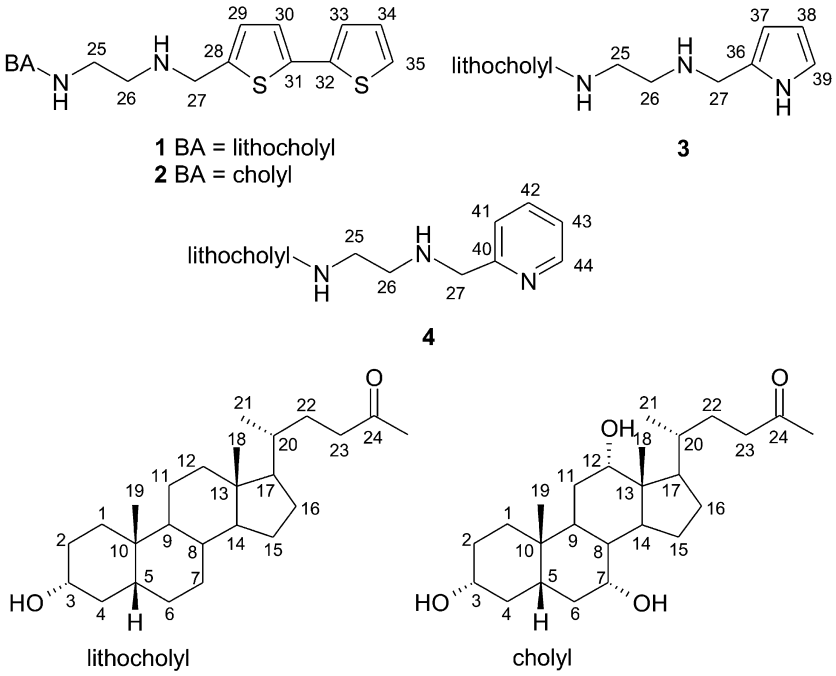


Fig. 1. Structures and numbering of **1–4**.

*2.4.2. N-[2-([2,2′]-bithiophen-5-ylmethyl)aminoethyl]-3α,7α,12α-trihydroxy-5β-cholan-24-amide. **2***

N-(2-aminoethyl)-3α,7α,12α-trihydroxy-5β-cholan-24-amide **6** 500 mg (1.11 mmol) and 2,2′-bithiophenyl-5-carbaldehyde 230 mg (1.18 mmol) were dissolved in 20 mL of methanol. Synthesis was continued as described for **1**. Product was purified by column chromatography (silica gel, 0.040–0.063 mm; eluents: CH_2Cl_2:MeOH 95:5, 90:10, 80:20). Yield 460 mg (66%). ^{1}H NMR in $CDCl_3$: δ = 0.64 (3H, s), 0.85 (3H, s), 0.94 (1H, m), 0.97 (3H, d), 1.00–1.93 (23H), 2.05–2.28 (4H), 2.80 (2H, t), 3.34 (2H, t), 3.36 (1H, m), 3.80 (1H, d), 3.92 (1H, s), 3.94 (2H, s), 6.52 (1H, br), 6.81 (1H, d), 6.98 (1H, t), 6.99 (1H, d), 7.11 (1H, dd), 7.18 (1H, dd). MS: *m/z* = 629 $[M+H]^+$, 651 $[M+Na]^+$. M.W. ($C_{35}H_{52}N_2O_4S_2$) = 628.94. Elemental analysis: calcd. (%) for $C_{35}H_{52}N_2O_4S_2$: C, 66.84; H, 8.33; N, 4.45. Found C, 66.94; H, 8.47; N, 4.08.

*2.4.3. N-[2-(1H-pyrrol-2-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide. **3***

N-(2-aminoethyl)-3α-hydroxy-5β-cholan-24-amide **5** 500 mg (1.19 mmol) and pyrrole-2-carbaldehyde 130 mg (1.37 mmol) were dissolved in 20 mL of methanol. Synthesis was continued as described for **1**. Product was purified by column chromatography (silica gel, 0.040–0.063 mm; eluent: CH_2Cl_2:MeOH 70:30). Yield 226 mg (38%). ^{1}H NMR in $CDCl_3$: δ = 0.64 (3H, s), 0.92 (3H, s), 0.92 (3H, d), 0.93–2.00 (28H), 2.02–2.13 (1H, m), 2.19–2.27 (1H, m), 2.76 (2H, t), 3.34 (2H, q), 3.61 (1H, m), 3.80 (2H, s), 6.00 (1H, t), 6.04 (1H, br), 6.12 (1h, q), 6.74 (1H, m), 8.93 (1H, br). MS: *m/z* = 498 $[M+H]^+$, 520 $[M+Na]^+$. M.W. ($C_{31}H_{51}N_3O_2$) = 497.77. Elemental analysis: calcd. (%) for $C_{31}H_{51}N_3O_2{\cdot}0.5\ CH_3OH$: C, 73.64; H, 10.40; N, 8.18. Found C, 73.75; H, 10.11; N, 7.75.

*2.4.4. N-[2-(pyridin-2-ylmethyl)aminoethyl]-3α-hydroxy-5β-cholan-24-amide. **4***

N-(2-aminoethyl)-3α-hydroxy-5β-cholan-24-amide **5** 500 mg (1.19 mmol) and pyridine-2-carbaldehyde 120 μL (1.26 mmol) were dissolved in 20 mL of methanol. Synthesis was continued as described for **1**. Product was purified by column chromatography (silica gel, 0.040–0.063 mm; eluents: CH_2Cl_2:MeOH 98:2, 80:20). Yield 360 mg (59%); mp. 161 °C. ^{1}H NMR in $CDCl_3$: δ = 0.61 (3H, s), 0.89

Table 2
^{13}C NMR chemical shifts of **1–4** (ppm from int. TMS) in $CDCl_3$ at 303 K

Carbon	1	2	3	4
1	35.4	34.7	35.4	35.4
2	30.6	30.5	30.6	30.6
3	71.8	71.8	71.8	71.7
4	36.5	39.7	36.5	36.5
5	42.1	41.5	42.1	42.1
6	27.2	35.3	27.2	27.2
7	26.4	68.4	26.4	26.4
8	35.9	39.5	35.9	35.9
9	40.5	26.4	40.5	40.5
10	34.6	34.7	34.6	34.6
11	20.8	28.2	20.8	20.8
12	40.2	73.0	40.2	40.2
13	42.7	46.4	42.7	42.8
14	56.5	41.7	56.5	56.5
15	24.2	23.3	24.2	24.2
16	28.2	27.6	28.2	28.2
17	56.0	46.5	56.0	56.1
18	12.0	12.4	12.0	12.1
19	23.4	22.4	23.4	23.4
20	35.5	35.4	35.5	35.5
21	18.4	17.5	18.4	18.4
22	31.8	31.6	31.8	31.9
23	33.7	33.1	33.6	33.7
24	173.7	174.3	174.1	173.8
25	39.0	39.0	38.9	39.0
26	47.8	47.8	48.1	48.4
27	48.2	48.0	45.8	54.4
28	143.4	142.9	–	–
29	125.6	125.8	–	–
30	123.3	123.3	–	–
31	136.5	136.5	–	–
32	137.6	137.5	–	–
33	123.4	123.4	–	–
34	127.7	127.7	–	–
35	124.2	124.2	–	–
36	–	–	129.7	–
37	–	–	108.1	–
38	–	–	106.7	–
39	–	–	117.6	–
40	–	–	–	159.1
41	–	–	–	122.4
42	–	–	–	136.6
43	–	–	–	122.2
44	–	–	–	149.3

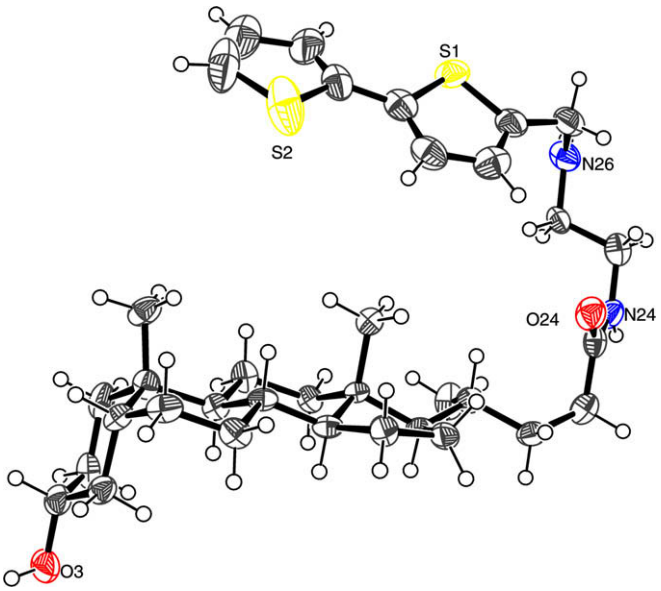


Fig. 2. Crystal structure of **1**, showing thermal ellipsoids drawn with 50% probability level.

(3H, s), 0.90 (3H, d), 0.92–1.96 (28H), 2.01–2.10 (1H, m), 2.19–2.27 (1H, m), 2.78 (2H, t), 3.35 (2H, q), 3.58 (1H, m), 3.89 (2H, s), 6.43 (1H, t), 7.17 (1H, m), 7.24 (1H, d), 7.63 (1H, dt), 8.54 (1H, qd). MS: m/z = 510 $[M+H]^+$, 532 $[M+Na]^+$. M.W. ($C_{32}H_{51}N_3O_2$) = 509.77. Elemental analysis: calcd. (%) for $C_{32}H_{51}N_3O_2$: C, 75.40; H, 10.08; N, 8.24. Found C, 74.99; H, 10.02; N, 7.71.

3. Results and discussion

3.1. NMR spectroscopy

Structures and numbering of compounds **1–4** are presented in Fig. 1. ^{13}C NMR chemical shifts are collected in Table 2. The chemical shift assignments of the steroidal part of **1–4** are based on ^{13}C NMR reference data of bile acids [19], ^{13}C DEPT-135, PFG ^{1}H,^{13}C HMQC [20], and PFG ^{1}H,^{13}C HMBC [21] spectra.

Steroidal parts in **1, 3**, and **4**, which all contain a lithocholamide fragment, show very similar ^{13}C NMR chemical shifts whereas those in **2** being a cholamide derivative differ owing to two additional hydroxyls at carbons 7 and 12. The ^{13}C shifts of these steroidal parts are in agreement with those reported previously [19]. Carbon-27 bearing in both **1** and **2** a bithiophenyl moiety possesses very similar chemical shift (48.2 and 48.0 ppm), whereas in **3** and **4** the chemical shift of C-27 differs significantly due to the presence of pyrrole (45.8 ppm) and pyridine (54.4 ppm) substituent, respectively. The effect of different substituents on the shifts of more distal carbons 25 and 26 is minimal.

3.2. X-ray crystallography

The quality of single crystal X-ray data of **1** is only moderate (see Table 1), due to weak crystallinity and scattering effects of the compound. The absolute structure parameter (Flack parameter) [22] of this chiral compound in chiral space group was meaningless (~0.5) after last refinement and was removed from the results. There is also small disorder in the second thiophene ring, which can be seen from the thermal ellipsoids of C32–C35 and S2 (Fig. 2). The use of weak restraints (SIMU 0.01) gave better result than finding the secondary possible positions of atoms in handling this disorder, most probably of static kind in low temperature data collection.

Three classical intermolecular hydrogen bonds were found from **1**, as presented in Fig. 3. Stacking interactions between thiophene rings were not observed. An infinite tail-to-head chains were found to be formed with O3–H3···N26 hydrogen bonds. Some geometric parameters are also collected in Table 3. The bile acid side chain lies on *anti* (*trans*) conformation, which can be deduced from C17–C20–C22–C23 dihedral angle value close to 180°. Overall side chain conformation can be expressed as a combination of the first four dihedral angles in Table 3, being *ttgi*, and the letters indicating the *trans* (*t*), *gauche* (*g*) and intermediate (i) conformation related angle values [23]. The angle between planes formed by thiophene rings is 13.7°.

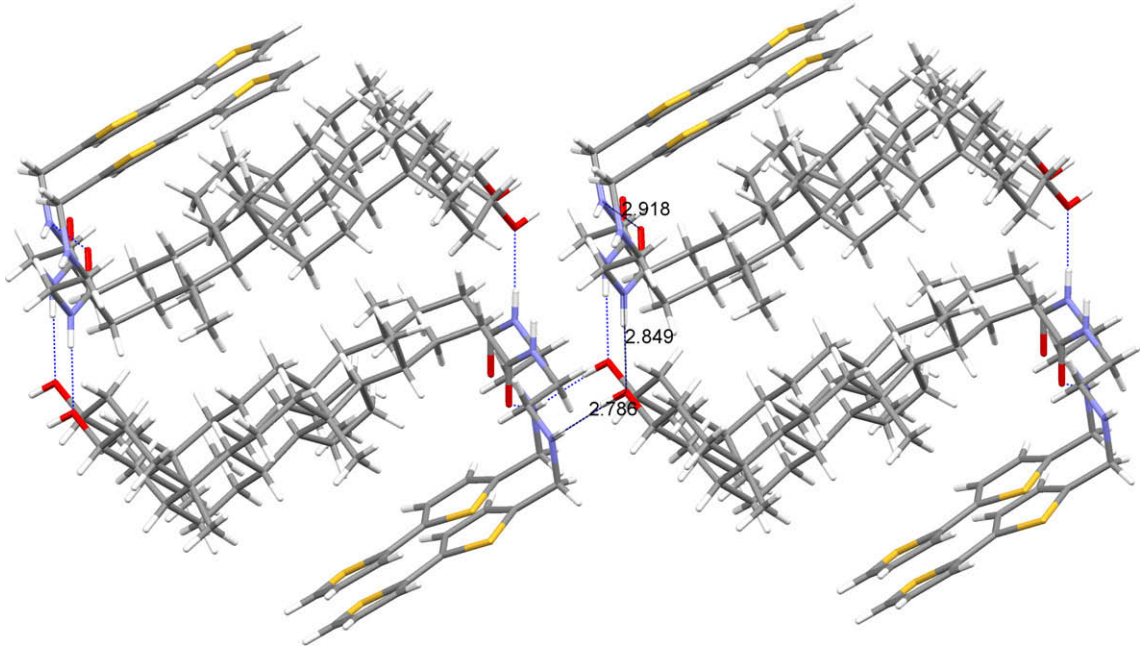


Fig. 3. A view of molecular packing of **1**.

Table 3
Some geometric parameters of **1**

X–Y	d(X–Y) [Å]	W–X–Y–Z	(WXYZ) [°]	D–H···A	d(D···A) [Å]	(DHA) [°]
S(1)–C(28)	1.720(8)	C13–C17–C20–C22	168.4(4)	O3–H3···N26	2.786(6)	174
S(1)–C(31)	1.725(7)	C17–C20–C22–C23	−176.7(5)	N24–H24···O3	2.849(6)	175
S(2)–C(32)	1.712(8)	C20–C22–C23–C24	54.0(7)	N26–H26···O24	2.918(8)	132
S(2)–C(35)	1.714(12)	C22–C23–C24–N24	−145.0(5)			
O(3)–C(3)	1.414(7)	C23–C24–N24–C25	175.3(5)			
O(24)–C(24)	1.245(6)	C24–N24–C25–C26	−85.8(7)			
N(24)–C(24)	1.327(8)	N24–C25–C26–N26	−179.8(5)			
N(24)–C(25)	1.452(8)	C25–C26–N26–C27	−78.6(6)			
N(26)–C(26)	1.453(7)	C26–N26–C27–C28	−66.6(8)			
N(26)–C(27)	1.467(7)	N26–C27–C28–S1	−83.3(7)			
		S1–C31–C32–S2	−170.8(4)			

Table 4
The glass transition temperatures, melting points, enthalpy and heat capacity changes of **1-4**

Compound	T_m, T_g	(ΔH); [ΔC_p]	
1	T_g 44.3	[0.57]	1st scan
	T_g 44.6	[0.59]	2nd scan
2	T_g 61.6	[0.30]	1st scan
	T_g 80.6	[0.59]	2nd scan
3	T_g 62.9	[0.32]	1st scan
	T_g 99.5	[0.49]	2nd scan
4	T_m 160.8	[99.56]	1st scan
	T_g 45.3	[0.37]	2nd scan

T_m = melting temperature (°C), ΔH = enthalpy change (J g^{-1}), T_g = glass transition temperature (°C), ΔC_p = heat capacity change (J g^{1} °C^{-1}).

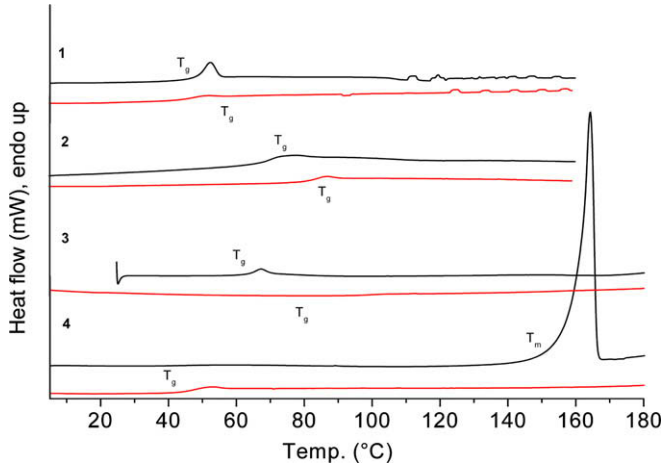


Fig. 4. DSC scans of compounds **1–4** heated at a rate of 10 °C/min.

3.3. Differential scanning calorimetry

For the compounds **1–3** only glass transitions (T_g) can be observed on both consecutive heating scans, indicating that the measured samples were initially in amorphous/glassy state. More characteristic (free of the effects of solvent/moisture residues) T_g values are been obtained from the second heating scans (Table 4). Compound **4** is crystalline showing clear melting transition at ~161 °C. On cooling, the sample enters to a glassy state, therefore showing only a glass transition on second heating scan at ~45 °C. DSC curves for **1–4** are presented in Fig. 4.

4. Conclusions

We have shown that lithocholyl and cholyl *N*-(2-aminoethyl)amides when reacted with various heteroaromatic carbaldehydes are useful starting compounds in preparation of bile acid–heteroaromatic conjugates. Reduction of the formed Schiff bases by $NaBH_4$ produced methylene linked heteroaryl derivatives in moderate to good yields. These conjugates are forwarded further for complex formation studies and for using as building blocks in bile acid derived receptors. Especially interesting is also their use in preparation of silver and other metal nanoparticles. These studies are in progress.

Acknowledgements

The authors acknowledge Spec. Lab. Tech. Mirja Lahtiperä for running ESI-TOF$^+$ mass spectra, Spec. Lab. Tech. Reijo Kauppinen for his help in running the NMR spectra, and Lab. Tech. Elina Hautakangas for elemental analysis.

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