Synthesis of C-24 β-Lactams of Bile Acids

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Methyl 3α-hydroxy-5β-cholan-24-oate **III** and methyl 3α,12α-dihydroxy-5β-cholan-24-oate **IV** were converted into the respective hydrazides **V** and **VI** by reaction with hydrazine. These hydrazides were reacted with aryl aldehyde **VII** to give the corresponding 24-arylidene-hydrazides **VIII** and **IX**. The reaction of Schiff bases **VIII** and **IX** with monochloroacetyl chloride in the presence of triethylamine afforded β-lactams **X-XI**.

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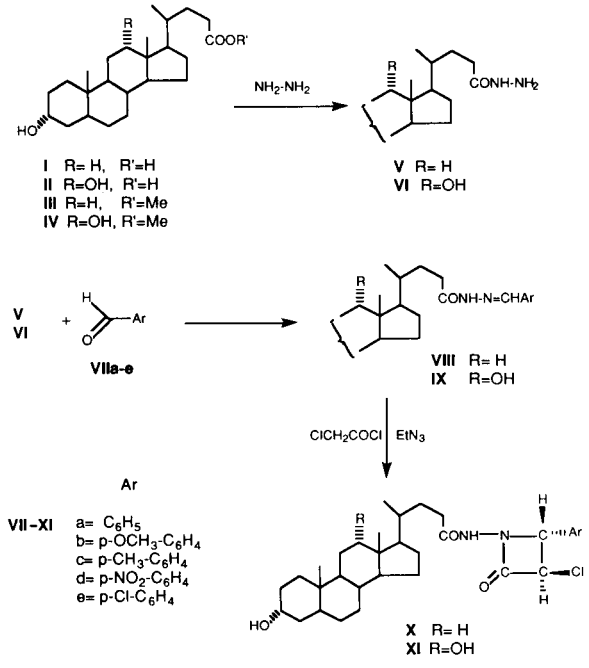
The discovery of β-lactam antibiotics has stimulated a lot of interest in the synthesis of β-lactams and their derivatives [2]. The reaction of an imine and an acid chloride in the presence of an amine base has been extensively used in the preparation of β-lactams [3,4]. This paper describes the synthesis of C-24 β-lactams of bile acids, lithocholic acid (**I**) and deoxycholic acid (**II**). The present work was stimulated by reports that C-24 derivatives of bile acids possess useful biological activities [5,6].

The methyl ester of bile acids, methyl 3α-hydroxy-5β-cholan-24-oate **III** and methyl 3α,12α-dihydroxy-5β-cholan-24-oate **IV** on reaction with hydrazine afforded hydrazides **V** and **VI**. The infrared spectra showed absorption bands at 3250, 3100 (NH_2, NH) and 1660 (CONH) cm^{-1}. The nmr spectrum of **V** and **VI** gave broad singlets at δ 5.9 (NH_2) and at δ 8.1 (CON*H*) which disappeared upon treatment with deuterium oxide. The hydrazides **V** and **VI** were reacted with aromatic aldehydes **VIIa-e** to give the corresponding 24-arylidene-hydrazides **VIIIa-e** and **IXa-e**. The infrared spectra showed absorption bands at 3250 (NH), 1660 (CONH), 1600 (C=C) and 1560 (C=N) cm^{-1}. The nmr spectra further supported their structures and showed a doublet at δ 8.5 for N=CH proton and multiplets in the region of δ 7.2-7.8 for aromatic protons.

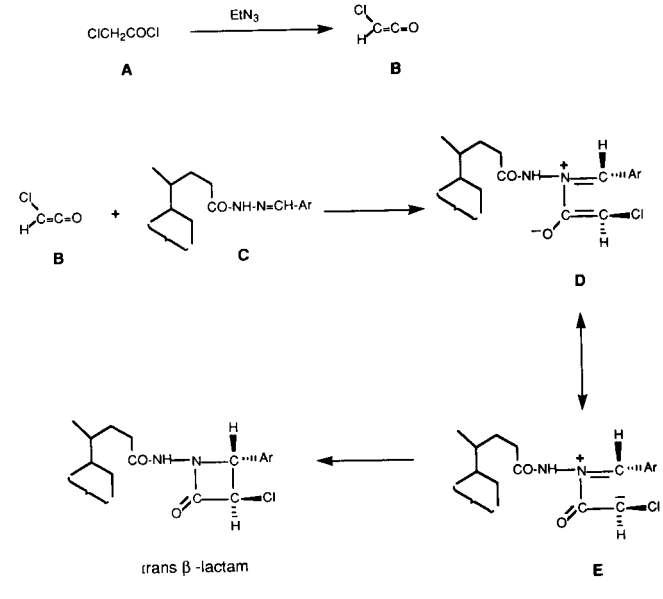
The reaction of Schiff bases **VIIIa-e** and **IXa-e** with monochloroacetyl chloride in the presence of triethylamine afforded β-lactams **Xa-e** and **XIa-e**. The infrared spectra showed absorption bands at 1750 (C=O), 1660 (CONH) and 600 cm^{-1} (C-Cl). The nmr spectra revealed a doublet at δ 6.4 for C'_3-H (J = 2 Hz), doublet at δ 4.3 for C'_4-H (J = 2 Hz) and other signals are attributed to CON*H* and aromatic protons. The stereochemistry at C'_3 and C'_4 of the β-lactam ring was established by ^1H nmr and was found to be *trans* on the basis of coupling constant (J_{trans} = 1-2 Hz) [7].

The β-lactam formation occurs through a ketene intermediate [8]. The dehydrohalogenation of the acid halide by an amine base is a reliable method to generate ketenes. However, the stereochemistry of β-lactams formed by the

Scheme I



Scheme II



reaction of acid halides with imines in the presence of triethylamine is difficult to predict [9]. Generally, the β-lactams formed from the reactions between chloroacetyl chloride, phenylacetyl chloride or phthaloylacetyl chloride with an imine in the presence of triethylamine are *trans* isomers [10]. The formation of β-lactams **Xa-e** and **XIa-e** (Scheme II) seems to proceed by prior formation of ketene **B** by reaction of acid chloride with triethylamine and subsequent cycloaddition with Schiff's base **C** gives zwitterion intermediate **D**. If the substituent on ketene is a good carbanion-stabilizing group, resonance structure **E** of the dipolar intermediate could be expected to be a major contributor to the resonance hybrid. It is well known that chlorine, sulfur, phenyl, phthaloyl [11] are good carbanion stabilizing groups, thus ring closure of **E** results in the formation of the *trans* isomer which has been shown to be the more stable isomer by epimerization studies [12].

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 283B spectrometer in solid phase potassium bromide. The nmr spectra were determined with a JEOL FX-90 Q FT instrument using deuteriochloroform-deuteriomethanol-d_4 4:1 (v/v) as a solvent and tetramethylsilane as internal standard. Lithocholic acid (**I**) and deoxycholic acid (**II**) were purchased from Sigma Chemical Company (St. Louis, MO, USA). Methyl esters **III** and **IV** were prepared by treatment of bile acids **I** and **II** with diazomethane.

General Procedure for the Preparation of Hydrazides **V** and **VI**.

To a solution of methyl ester of bile acids **III** or **IV** (5 mmoles) in ethanol (100 ml) was added hydrazine monohydrochloride (5 mmoles) and hydrazine hydrate (20 mmoles) and the mixture was refluxed for 4-5 hours. The mixture was concentrated under reduced pressure and then poured onto ice. The product formed was filtered, washed with water and recrystallized from ethanol.

3α-Hydroxy-5β-cholan-24-hydrazide (**V**).

This compound was obtained as colorless needles from ethanol (85%), mp 210-211°; ir: ν max 3450 (OH), 3250, 3080 (NH_2, NH), 1660 (CONH) cm^{-1}; ^1H nmr: δ 8.10 (br s, 1H, CON*H*), 5.90 (br s, 2H, NH_2), 3.52 (m, 1H, C_3-βH), 2.22 (m, 2H, C_{23}-H_2), 1.35 (m, 1H, C_5-βH), 0.95 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{24}H_{42}N_2O_2$: C, 73.84; H, 10.76; N, 7.17. Found: C, 73.72; H, 10.68; N, 7.13.

3α,12α-Dihydroxy-5β-cholan-24-hydrazide (**VI**).

This compound was obtained as a colorless solid from methanol (84%), mp 262-264°; ir: ν max 3480 (OH), 3260, 3100 (NH_2, NH), 1660 (CONH) cm^{-1}; ^1H nmr: δ 8.15 (br s, 1H, CON*H*), 5.94 (br s, 2H, NH_2), 4.02 (m, 1H, C_{12}-βH), 3.58 (m, 1H, C_3-βH), 2.30 (m, 2H, C_{23}-H_2), 1.39 (m, 1H, C_5-βH), 1.05 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.73 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{24}H_{42}N_2O_3$: C, 70.93; H, 10.34; N, 6.89. Found: C, 70.85; H, 10.30; N, 6.85.

General Procedure for the Preparation of 24-Arylidene-hydrazides **VIIIa-e** and **IXa-e**.

To a solution of hydrazide of bile acids **V** or **VI** (2.5 mmoles) in benzene (30 ml) was added aromatic aldehyde **VII** (5 mmoles) with a few drops of piperidine. The mixture was refluxed for 4-5 hours. The solid obtained was recrystallized from methanol.

3α-Hydroxy-5β-cholan-24-benzylidene-hydrazide (**VIIIa**).

This compound was obtained as colorless needles from methanol (72%), mp 206-207°; ir: ν max 3460 (OH), 3225 (NH), 1650 (CONH), 1610 (C=C), 1560 (C=N) cm^{-1}; ^1H nmr: δ 8.46 (d, 1H, J = 1.5 Hz, CH=N), 8.12 (br s, 1H, CON*H*), 7.2-7.6 (m, 5H, Ar-H), 3.50 (m, 1H, C_3-βH), 2.24 (m, 2H, C_{23}-H_2), 1.35 (m, 1H, C_5-βH), 0.96 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.90 (s, 3H, C_{19}-H_3), 0.66 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{46}N_2O_2$: C, 77.82; H, 9.62; N, 5.85. Found: C, 77.78; H, 9.60; N, 5.82.

3α-Hydroxy-5β-cholan-24-(*p*-methoxybenzylidene)-hydrazide (**VIIIb**).

This compound was obtained as colorless needles from ethanol (76%), mp 165-167°; ir: ν max 3450 (OH), 3210 (NH), 1655 (CONH), 1610 (C=C), 1560 (C=N) cm^{-1}; ^1H nmr: δ 8.50 (d, 1H, J = 1.5 Hz, CH=N), 8.15 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 3.55 (s, 3H, Ar-OCH_3), 3.48 (m, 1H, C_3-βH), 2.25 (m, 2H, C_{23}-H_2), 1.36 (m, 1H, C_5-βH), 0.96 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.90 (s, 3H, C_{19}-H_3), 0.65 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{32}H_{48}N_2O_3$: C, 75.59; H, 9.44; N, 5.51. Found: C, 75.55; H, 9.40; N, 5.58.

3α-Hydroxy-5β-cholan-24-(*p*-methylbenzylidene)-hydrazide (**VIIIc**).

This compound was obtained as colorless needles from methanol (75%), mp 238-240°; ir: ν max 3460 (OH), 3210 (NH), 1660 (CONH), 1600 (C=C), 1565 (C=N) cm^{-1}; ^1H nmr: δ 8.53 (d, 1H, J = 1.5 Hz, CH=N), 8.14 (br s, 1H, CON*H*), 7.2-7.6 (m, 4H, Ar-H), 3.45 (m, 1H, C_3-βH), 2.28 (s, 3H, Ar-CH_3), 2.22 (m, 2H, C_{23}-H_2), 1.35 (m, 1H, C_5-βH), 0.95 (d, 3H, J = 6.2 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{32}H_{48}N_2O_2$: C, 78.04; H, 9.75; N, 5.69. Found: C, 77.98; H, 9.78; N, 5.66.

3α-Hydroxy-5β-cholan-24-(*p*-nitrobenzylidene)-hydrazide (**VIIId**).

This compound was obtained as a pale yellow solid from methanol (74%), mp 202-204°; ir: ν max 3455 (OH), 3215 (NH), 1670 (CONH), 1600 (C=C), 1570 (C=N) cm^{-1}; ^1H nmr: δ 8.58 (d, 1H, J = 2 Hz, CH=N), 8.12 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 3.52 (m, 1H, C_3-βH), 2.23 (m, 2H, C_{23}-H_2), 1.37 (m, 1H, C_5-βH), 0.95 (d, 3H, J = 6.1 Hz, C_{21}-H_3), 0.90 (s, 3H, C_{19}-H_3), 0.66 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{45}N_3O_4$: C, 71.12; H, 8.60; N, 8.03. Found: C, 71.08; H, 8.68; N, 7.95.

3α-Hydroxy-5β-cholan-(*p*-chlorobenzylidene)-hydrazide (**VIIIe**).

This compound was obtained as a pale yellow solid from methanol (72%), mp 140-142°; ir: ν max 3450 (OH), 3210 (NH), 1660 (CONH), 1610 (C=C), 1560 (C=N), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.55 (d, 1H, J = 1.8 Hz, CH=N), 8.18 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 3.53 (m, 1H, C_3-βH), 2.22 (m, 2H, C_{23}-H_2), 1.36 (m, 1H, C_5-βH), 0.96 (d, 3H, J = 6.2 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.67 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{45}N_2O_2Cl$: C, 72.58; H, 8.78; N, 5.46. Found: C, 72.55; H, 8.72; N, 5.45.

3α,12α-Dihydroxy-5β-cholan-24-benzylidene-hydrazide (**IXa**).

This compound was obtained as a colorless solid from methanol (73%), mp 160-162°; ir: ν max 3470 (OH), 3250 (NH), 1660 (CONH), 1610 (C=C), 1570 (C=N) cm^{-1}; ^1H nmr: δ 8.52 (d, 1H, J = 1.5 Hz, CH=N), 8.15 (br s, 1H, CON*H*), 7.2-7.6 (m, 5H, Ar-H), 4.01 (m, 1H, C_{12}-βH), 3.58 (m, 1H, C_3-βH), 2.30 (m, 2H, C_{23}-H_2), 1.39 (m, 1H, C_5-βH), 1.05 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.97 (s, 3H, C_{19}-H_3), 0.72 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{46}N_2O_3$: C, 75.30; H, 9.31; N, 5.66. Found: C, 75.24; H, 9.25; N, 5.68.

3α,12α-Dihydroxy-5β-cholan-24-(*p*-methoxybenzylidene)-hydrazide (**IXb**).

This compound was obtained as colorless needles from methanol (75%), mp 138-140°; ir: ν max 3470 (OH), 3240 (NH), 1665 (CONH), 1610 (C=C), 1570 (C=N) cm^{-1}; ^1H nmr: δ 8.51 (d, 1H, J = 1.5 Hz, CH=N), 8.12 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 3.98 (m, 1H, C_{12}-βH), 3.60 (s, 3H, Ar-OCH_3), 3.54 (m, 1H, C_3-βH), 2.28 (m, 2H, C_{23}-H_2), 1.40 (m, 1H, C_5-βH), 1.03 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.73 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{32}H_{48}N_2O_4$: C, 73.28; H, 9.16; N, 5.34. Found: C, 73.20; H, 9.12; N, 5.28.

3α,12α-Dihydroxy-5β-cholan-24-(*p*-methylbenzylidene)-hydrazide (**IXc**).

This compound was obtained as a colorless solid from methanol (74%), mp 181-183°; ir: ν max 3470 (OH), 3220 (NH), 1660 (CONH), 1605 (C=C), 1565 (C=N) cm^{-1}; ^1H nmr: δ 8.54 (d, 1H, J = 1.8 Hz, CH=N), 8.15 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 4.0 (m, 1H, C_{12}-βH), 3.55 (m, 1H, C_3-βH), 2.32 (m, 2H, C_{23}-H_2), 2.26 (s, 3H, Ar-CH_3), 1.41 (m, 1H, C_5-βH), 1.04 (d, 3H, J = 6.2 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.72 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{32}H_{48}N_2O_3$: C, 75.59; H, 9.44; N, 5.51. Found: C, 75.62; H, 9.40; N, 5.45.

3α,12α-Dihydroxy-5β-cholan-24-(*p*-nitrobenzylidene)-hydrazide (**IXd**).

This compound was obtained as a pale yellow solid from methanol (72%), mp 168-170°; ir: ν max 3460 (OH), 3220 (NH), 1655 (CONH), 1600 (C=C), 1560 (C=N) cm^{-1}; ^1H nmr: δ 8.58 (d, 1H, J = 2 Hz, CH=N), 8.18 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 4.01 (m, 1H, C_{12}-βH), 3.52 (m, 1H, C_3-βH), 2.30 (m, 2H, C_{23}-H_2), 1.40 (m, 1H, C_5-βH), 1.06 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.73 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{45}N_3O_5$: C, 69.0; H, 8.34; N, 7.79. Found: C, 68.95; H, 8.30; N, 7.84.

3α,12α-Dihydroxy-5β-cholan-24-(*p*-chlorobenzylidene)-hydrazide (**IXe**).

This compound was obtained as a pale yellow solid from methanol (71%), mp 133-135°; ir: ν max 3470 (OH), 3215 (NH), 1660 (CONH), 1610 (C=C), 1550 (C=N), 590 (C-Cl) cm^{-1}; ^1H nmr: δ 8.56 (d, 1H, J = 1.8 Hz, CH=N), 8.15 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 4.02 (m, 1H, C_{12}-βH), 3.58 (m, 1H, C_3-βH), 2.32 (m, 2H, C_{23}-H_2), 1.42 (m, 1H, C_5-βH), 1.05 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.93 (s, 3H, C_{19}-H_3), 0.74 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{45}N_2O_3Cl$: C, 70.38; H, 8.51; N, 5.29. Found: C, 70.43; H, 8.45; N, 5.32.

General Procedure for the Preparation of β-Lactams **Xa-e** and **XIa-e**.

All of these reactions were carried out under a nitrogen atmosphere. To a stirred and cooled (0-5°) solution of Schiff bases **VIIIa-e** or **IXa-e** (1 mmole) and triethylamine (2 mmoles) in dry methylene chloride (5 ml) a solution of monochloroacetyl chloride (2 mmoles) in dry methylene chloride (3 ml) was added drop by drop for ten minutes. After being warmed to room temperature gradually, the mixture was stirred for 3 hours. The resultant triethylamine hydrochloride was filtered and the filtrate was evaporated *in vacuo* to give an oily residue. The residue was subjected to column chromatography (silica gel; 70-230 mesh) using petroleum ether-ether 4:1 for compounds **Xa-e** and petroleum ether-ether 1:1 for compounds **XIa-e** as the eluting solvent. After the evaporation of the eluting solvent, a solid was obtained which was recrystallized from methanol.

3α-Hydroxy-5β-cholan-24-(3'-chloro-2'-oxo-4'-phenylazetidin)-amide (**Xa**).

This compound was obtained as a colorless solid from methanol (48%), mp 170-172°; ir: ν max 3460 (OH), 3220 (NH), 1750 (C=O), 1660 (CONH), 1600 (C=C), 590 (C-Cl) cm^{-1}; ^1H nmr: δ 8.15 (br s, 1H, CON*H*), 7.2-7.6 (m, 5H, Ar-H), 6.35 (d, 1H, J = 1.8 Hz, C'_3-αH), 4.32 (d, 1H, J = 1.8 Hz, C'_4-βH), 3.55 (m, 1H, C_3-βH), 2.23 (m, 2H, C_{23}-H_2), 1.38 (m, 1H, C_5-βH), 0.95 (d, 3H, J = 6.2 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{33}H_{47}N_2O_3Cl$: C, 71.41; H, 8.47; N, 5.05. Found: C, 71.40; H, 8.45; N, 5.10.

3α-Hydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-methoxyphenyl)-azetidin]amide (**Xb**).

This compound was obtained as colorless needles from methanol (50%), mp 151-153°; ir: ν max 3450 (OH), 3210 (NH), 1755 (C=O), 1650 (CONH), 1610 (C=C), 590 (C-Cl) cm^{-1}; ^1H nmr: δ 8.14 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 6.32 (d, 1H, J = 1.8 Hz, C'_3-αH), 4.36 (d, 1H, J = 1.9 Hz, C'_4-βH), 3.60 (s, 3H, Ar-OCH_3), 3.50 (m, 1H, C_3-βH), 2.22 (m, 2H, C_{23}-H_2), 1.35 (m, 1H, C_5-βH), 0.94 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.90 (s, 3H, C_{19}-H_3), 0.65 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{34}H_{49}N_2O_4Cl$: C, 69.80; H, 8.38; N, 4.79. Found: C, 69.76; H, 8.40; N, 4.80.

3α-Hydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-methylphenyl)-azetidin]amide (**Xc**).

This compound was obtained as colorless needles from methanol (51%), mp 140-142°; ir: ν max 3460 (OH), 3210 (NH), 1752 (C=O), 1660 (CONH), 1600 (C=C), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.12 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 6.35 (d, 1H, J = 2 Hz, C'_3-αH), 4.35 (d, 1H, J = 2 Hz, C'_4-βH), 3.48 (m, 1H, C_3-βH), 2.35 (s, 3H, Ar-CH_3), 2.23 (m, 2H, C_{23}-H_2), 1.36 (m, 1H, C_5-βH), 0.96 (d, 3H, J = 6.3 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.65 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{34}H_{49}N_2O_3Cl$: C, 71.76; H, 8.61; N, 4.92. Found: C, 71.72; H, 8.58; N, 4.93.

3α-Hydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-nitrophenyl)-azetidin]amide (**Xd**).

This compound was obtained as a colorless solid from methanol (48%), mp 136-138°; ir: ν max 3450 (OH), 3220 (NH), 1750 (C=O), 1660 (CONH), 1600 (C=C), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.15 (br s, 1H, CON*H*), 7.3-7.7 (m, 4H, Ar-H), 6.40 (d, 1H, J = 2 Hz, C'_3-αH), 4.38 (d, 1H, J = 2 Hz, C'_4-βH), 3.56 (m, 1H, C_3-βH), 2.25 (m, 2H, C_{23}-H_2), 1.37 (m, 1H, C_5-βH), 0.94 (d, 3H, J = 6.2 Hz, C_{21}-H_3), 0.92 (s, 3H, C_{19}-H_3), 0.67 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{33}H_{46}N_3O_5Cl$: C, 66.05; H, 7.67; N, 7.0. Found: C, 66.0; H, 7.62; N, 6.95.

3α-Hydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-chlorophenyl)-azetidin]amide (**Xe**).

This compound was obtained as a colorless solid from ethanol (48%), mp 121-123°; ir: ν max 3455 (OH), 3210 (NH), 1750 (C=O), 1655 (CONH), 1610 (C=C), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.14 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.38 (d, 1H, J = 1.8 Hz, C'$_3$-αH), 4.35 (d, 1H, J = 1.8 Hz, C'$_4$-βH), 3.55 (m, 1H, C$_3$-βH), 2.25 (m, 2H, C$_{23}$-H$_2$), 1.38 (m, 1H, C$_5$-βH), 0.96 (d, 3H, J = 6.2 Hz, C$_{21}$-H$_3$), 0.92 (s, 3H, C$_{19}$-H$_3$), 0.66 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{33}H_{46}N_2O_3Cl_2$: C, 67.22; H, 7.86; N, 4.75. Found: C, 67.28; H, 7.92; N, 4.82.

3α,12α-Dihydroxy-5β-cholan-24-(3'-chloro-2'-oxo-4'-phenylazetidin)amide (**XIa**).

This compound was obtained as a colorless solid from methanol (49%), mp 141-143°; ir: ν max 3470 (OH), 3240 (NH), 1750 (C=O), 1660 (CONH), 1610 (C=C), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.15 (br s, 1H, CONH), 7.3-7.7 (m, 5H, Ar-H), 6.38 (d, 1H, J = 1.9 Hz, C'$_3$-αH), 4.36 (d, 1H, J = 1.8 Hz, C'$_4$-βH), 4.02 (m, 1H, C$_{12}$-βH), 3.52 (m, 1H, C$_3$-βH), 2.30 (m, 2H, C$_{23}$-H$_2$), 1.40 (m, 1H, C$_5$-βH), 1.04 (d, 3H, J = 6.2 Hz, C$_{21}$-H$_3$), 0.92 (s, 3H, C$_{19}$-H$_3$), 0.74 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{33}H_{47}N_2O_4Cl$: C, 69.41; H, 8.23; N, 4.90. Found: C, 69.36; H, 8.20; N, 4.92.

3α,12α-Dihydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-methoxyphenyl)azetidin]amide (**XIb**).

This compound was obtained as colorless needles from ethanol (51%), mp 118-120°; ir: ν max 3460 (OH), 3240 (NH), 1750 (C=O), 1660 (CONH), 1610 (C=C), 600 (C-Cl) cm^{-1}; ^1H nmr: δ 8.16 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.40 (d, 1H, J = 1.8 Hz, C'$_3$-αH), 4.32 (d, 1H, J = 1.8 Hz, C'$_4$-βH), 4.02 (m, 1H, C$_{12}$-βH), 3.69 (s, 3H, Ar-OCH$_3$), 3.56 (m, 1H, C$_3$-βH), 2.32 (m, 2H, C$_{23}$-H$_2$), 1.41 (m, 1H, C$_5$-βH), 1.02 (d, 3H, J = 6.3 Hz, C$_{21}$-H$_3$), 0.91 (s, 3H, C$_{19}$-H$_3$), 0.72 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{34}H_{49}N_2O_5Cl$: C, 67.94; H, 8.15; N, 4.66. Found: C, 67.90; H, 8.10; N, 4.65.

3α,12α-Dihydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-methylphenyl)azetidin]amide (**XIc**).

This compound was obtained as a colorless solid from methanol (51%), mp 158-160°; ir: ν max 3465 (OH), 3210 (NH), 1750 (C=O), 1660 (CONH), 1610 (C=C), 610 (C-Cl) cm^{-1}; ^1H nmr: δ 8.18 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.40 (d, 1H, J = 2 Hz, C'$_3$-αH), 4.28 (d, 1H, J = 1.9 Hz, C'$_4$-βH), 4.0 (m, 1H, C$_{12}$-βH), 3.58 (m, 1H, C$_3$-βH), 2.38 (s, 3H, Ar-CH$_3$), 2.30 (m, 2H, C$_{23}$-H$_2$), 1.42 (m, 1H, C$_5$-βH), 1.03 (d, 3H, J = 6.4 Hz, C$_{21}$-H$_3$), 0.90 (s, 3H, C$_{19}$-H$_3$), 0.74 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{34}H_{49}N_2O_4Cl$: C, 69.80; H, 8.38; N, 4.79. Found: C, 69.84; H, 8.35; N, 4.86.

3α,12α-Dihydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-nitrophenyl)azetidin]amide (**XId**).

This compound was obtained as a colorless solid from methanol (49%), mp 147-148°; ir: ν max 3460 (OH), 3220 (NH), 1755 (C=O), 1655 (CONH), 1600 (C=C), 610 (C-Cl) cm^{-1}; ^1H nmr: δ 8.15 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.38 (d, 1H, J = 2.1 Hz, C'$_3$-αH), 4.28 (d, 1H, J = 2.1 Hz, C'$_4$-βH), 4.01 (m, 1H, C$_{12}$-βH), 3.60 (m, 1H, C$_3$-βH), 2.32 (m, 2H, C$_{23}$-H$_2$), 1.43 (m, 1H, C$_5$-βH), 1.04 (d, 3H, J = 6.3 Hz, C$_{21}$-H$_3$), 0.93 (s, 3H, C$_{19}$-H$_3$), 0.72 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{33}H_{46}N_3O_6Cl$: C, 64.33; H, 7.47; N, 6.82. Found: C, 64.35; H, 7.50; N, 6.80.

3α,12α-Dihydroxy-5β-cholan-24-[3'-chloro-2'-oxo-4'-(*p*-chlorophenyl)azetidin]amide (**XIe**).

This compound was obtained as a colorless solid from methanol (48%), mp 106-107°; ir: ν max 3470 (OH), 3220 (NH), 1755 (C=O), 1660 (CONH), 1610 (C=C), 605 (C-Cl) cm^{-1}; ^1H nmr: δ 8.16 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.38 (d, 1H, J = 2 Hz, C'$_3$-αH), 4.30 (d, 1H, J = 2.1 Hz, C'$_4$-βH), 4.02 (m, 1H, C$_{12}$-βH), 3.58 (m, 1H, C$_3$-βH), 2.34 (m, 2H, C$_{23}$-H$_2$), 1.43 (m, 1H, C$_5$-βH), 1.05 (d, 3H, J = 6.3 Hz, C$_{21}$-H$_3$), 0.95 (s, 3H, C$_{19}$-H$_3$), 0.73 ppm (s, 3H, C$_{18}$-H$_3$).

Anal. Calcd. for $C_{33}H_{46}N_2O_4Cl_2$: C, 65.45; H, 7.66; N, 4.63. Found: C, 65.42; H, 7.62; N, 4.58.

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