

AUSTRALIA **653658**
Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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- [54] Invention Title: POLYMERS AND OLIGOMERS OF BILE ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS
- [72] Name(s) of actual inventor(s): WERNER KRAMER, STEFAN MULLNER, MATTHIAS GUTWEILER AND MATTHIAS KROGGEL

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BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
P41 42 379.8	GERMANY	DE	20TH DECEMBER 1991

Drawing number recommended to accompany the abstract

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Darryl B. Mischlewski
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NO 41010 111292

DATED this 17th day of December 1992.

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NOTICE OF ENTITLEMENT

(To be filed before acceptance)

We, HOECHST AKTIENGESELLSCHAFT of Building F 821, D-65926 Frankfurt am Main, Germany, being the applicant in respect of Application No. 30209/92 state the following:-

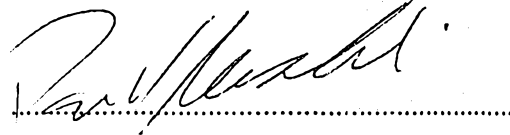
The person nominated for the grant of the patent has entitlement from the actual inventors by virtue of an employment contract between the nominated person and the inventors.

The person nominated for the grant of the patent is the applicant of the basic application listed on the Request Form.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

HOECHST AKTIENGESELLSCHAFT

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS


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4 August, 1994.

Darryl B. Mischlewski
Registered Patent Attorney



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(12) PATENT ABRIDGMENT (11) Document No. AU-B-30209/92
 (19) AUSTRALIA PATENT OFFICE (10) Acceptance No. 653658

(54) Title
 POLYMERS AND OLIGOMERS OF BILE ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION
 AND THEIR USE AS PHARMACEUTICALS

(51)⁵ International Patent Classification(s)

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(56) Prior Art Documents
 US 4104285

(57) Claim

1. A polymeric or oligomeric bile acid, which can be prepared by polymerization of a monomeric bile acid of the formula I



in which

G is a bile acid radical or derivative,

X is a bridge group of the formula II



in which

Y is adjacent to G and is $-O-$, $-NR'-$, $-O-C(=O)-$ or $-NR'-C(=O)-$,

Z is (C_1-C_{12}) -alkylene or (C_7-C_{13}) -aralkylene, where individual methylene groups in the alkylene or aralkylene radical can be replaced by groups such as $-O-$, $-NR'-$, $-NR'-C(=O)-$, $-O-C(=O)-$ or



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(10) 653658

-2-

o and p independently of one another are zero or 1, where

o and p are not simultaneously zero,

R' and R'' independently of one another are hydrogen or (C₁-C₆)-alkyl

A is a polymerizable, ethylenically unsaturated group, or by copolymerization with a monomer containing a polymerizable, ethylenically unsaturated double bond, in particular by copolymerization with a monomer of the formula IV



in which

R⁹ is hydrogen or methyl and

R¹⁰ is $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{R}^{11}$, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{12}\text{R}^{13}$, $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{14}$, $-\text{CN}$, $-\text{O}-\text{R}^{15}$, hydrogen, halogen, in particular chlorine, bromine or iodine, $-\text{SO}_3\text{H}$ or $-\text{O}-(\text{CH}_2-\text{CH}_2\text{O})_n\text{R}^{16}$,

in which

R¹¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₁-C₁₀)-mono-hydroxyalkyl or $-(\text{CH}_2\text{CH}_2-\text{O})_n\text{R}^{16}$,

R¹², R¹³, R¹⁵ and R¹⁶ are identical or different and are (C₁-C₁₀)-alkyl,

R¹⁴ is (C₁-C₁₈)-alkyl and

n is 1 to 50,

or by copolymerization with N-vinylpyrrolidone or its derivatives,

and/or by copolymerization with ethylenically unsaturated dicarboxylic anhydrides and ethylenically unsaturated dicarboxylic acids each having 2 to 6 carbon atoms; their esters or half esters, esters being understood as alkyl esters having 1-6 carbon atoms, cycloalkyl esters having 5 to 8 carbon atoms, benzyl esters or phenyl esters.

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**ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title:

POLYMERS AND OLIGOMERS OF BILE ACID DERIVATIVES, PROCESS
FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS

The following statement is a full description of this invention, including the
best method of performing it known to :-US

Description

Polymers and oligomers of bile acid derivatives, process for their preparation and their use as pharmaceuticals

- 5 The invention relates to polymers and oligomers of bile acids, a process for their preparation and their use as pharmaceuticals.

10 Bile acids and their salts are natural detergents and have an important physiological function in fat digestion, for example as cofactors of pancreatic lipases and in fat absorption. As the end products of cholesterol metabolism, they are synthesized in the liver, stored in the gall bladder and excreted from this by contraction into the small intestine, where they display their
15 physiological action. The major part of the secreted bile acids is recovered again via the enterohepatic circulation. They pass back to the liver again via the mesenterial veins of the small intestine and the portal vein system.

- 20 In reabsorption in the intestine, both active and passive transport processes are important. In the terminal ileum, a specific Na^+ -dependent transport system is responsible for bile acid reabsorption. In the enterohepatic circulation, the bile acids appear both as free acids,
25 but also in the form of amino acid conjugates, such as glycine and taurine conjugates.

Non-absorbable, insoluble, basic and crosslinked polymers (resins) have been used for some time for the binding of bile acids and have been used therapeutically on account
30 of these properties. The subject of treatment is regarded as being all diseases in which an inhibition of bile acid reabsorption in the intestine, in particular in the small

intestine, appears desirable. For example, chologenic diarrhea after resection of the ileum or alternatively increased cholesterol blood levels are treated in this manner. If the cholesterol blood level is increased, a
5 reduction of this level can be achieved by intervention in the enterohepatic circulation.

By means of reduction of the bile acid pool found in the enterohepatic circulation, the corresponding de novo
10 synthesis of bile acids from cholesterol in the liver is induced. To cover the cholesterol demand of the liver, resort is then had to the LDL-cholesterol (low density lipoprotein) found in the blood circulation, the hepatic
LDL receptors acting in increased numbers. The acceleration of LDL catabolism thus effected acts through the
15 reduction of the atherogenic cholesterol content in the blood.

Until now, the polymeric, basic insoluble and crosslinked ion exchange resins were the only possibility of influencing the enterohepatic circulation with respect to
20 increased bile acid secretion and subsequent reduction in the cholesterol level (US-A-3,383,281).

It was therefore the object of the present invention to seek further possibilities of influencing the enterohepatic circulation with respect to increased bile acid
25 secretion without continuing the disadvantages of the resins employed hitherto.

The object is achieved by making available polymeric or oligomeric bile acids which can be prepared by polymerization of monomeric bile acids of the formula I

30

G-X-A

(I)

in which

G is a bile acid radical or derivative,

X is a bridge group and

A is a polymerizable, ethylenically unsaturated group,
or by copolymerization with a monomer containing a
polymerizable, ethylenically unsaturated double bond, in
5 particular by copolymerization with a monomer of the
formula IV



10 in which

R⁹ is hydrogen or methyl and

R¹⁰ is $\overset{\text{O}}{\parallel}\text{-C-O-R}^{11}$, $\overset{\text{O}}{\parallel}\text{-C-NR}^{12}\text{R}^{13}$, $\overset{\text{O}}{\parallel}\text{-O-C-R}^{14}$, -CN, -O-R¹⁵,
15 hydrogen, halogen, in particular chlorine, bromine or
iodine, -SO₃H or -O-(CH₂-CH₂O)_nR¹⁶,

in which

R¹¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₁-C₁₀)-monohydroxy-
alkyl or -(CH₂CH₂-O)_nR¹⁶,
20 R¹², R¹³, R¹⁵ and R¹⁶ are identical or different and
are (C₁-C₁₀)-alkyl,
R¹⁴ is (C₁-C₁₈)-alkyl and
n is 1 to 50,

or by copolymerization with N-vinylpyrrolidone or its
25 derivatives,

and/or by copolymerization with ethylenically unsaturated
dicarboxylic anhydrides and ethylenically unsaturated
dicarboxylic acids each having 2 to 6 carbon atoms; their
esters or half esters, esters being understood as meaning
30 alkyl esters having 1-6 carbon atoms, cycloalkyl esters
having 5 to 8 carbon atoms, benzyl esters or phenyl
esters.

The term oligomers stands for homo-oligomers and co-
oligomers. The term polymers stands for homo-polymers
and copolymers.

The compounds are crosslinked or non-crosslinked. Polymerization and copolymerization stand also for oligomerization and cooligomerization.

Among the compounds of the formula I, the following are preferred:

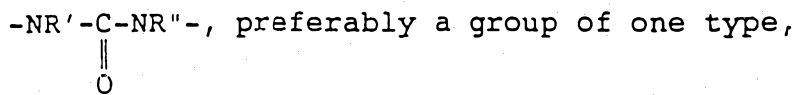
compounds in which

- G is a free bile acid or its alkali metal or alkaline earth metal salt or a bile acid esterified on ring D and which is bonded via its ring A or B, preferably via ring A, to the group
- X, to which the formula II preferably applies



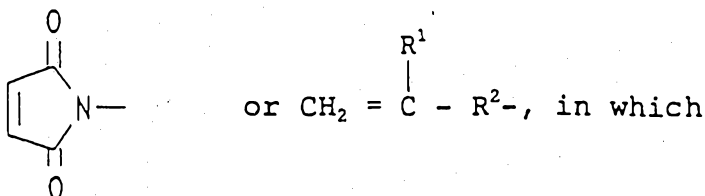
in which

- Y is adjacent to G and is $-O-$, $-NR'-$, $-O-\overset{\overset{O}{\parallel}}{C}-$ or $-NR'-\overset{\overset{O}{\parallel}}{C}-$,
- Z is (C_1-C_{12}) -alkylene or (C_7-C_{13}) -aralkylene, where individual methylene groups, preferably 1 to 4, in the alkylene chain of the alkylene or aralkylene radical can be replaced by groups such as $-O-$, $-NR'-$, $-NR'-\overset{\overset{O}{\parallel}}{C}-$, $-O-\overset{\overset{O}{\parallel}}{C}-$ or



o and p independently of one another are zero or 1, where o and p are not simultaneously zero,

A is an ethylenically unsaturated group of the formula

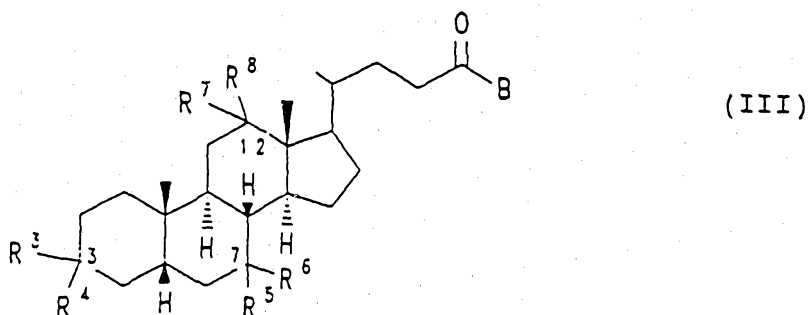


R^1 is hydrogen or CH_3 , and

R^2 is $-NR'-C(=O)-$, $-O-C(=O)-$, $-O-$, $-NR'-$ or a single bond, where the carbonyl groups are adjacent to the C-C double bond,

R' and R'' independently of one another are hydrogen or (C_1-C_6) -alkyl, preferably (C_1-C_3) -alkyl.

Among these, preferred polymers and oligomers are those in which G corresponds to the formula III



in which

R^3 to R^6 independently of one another are hydrogen, OH, NH_2 or an OH group protected by an OH protective group and one of the radicals R^3 to R^6 is a bond to the group X, where this bond starts from the positions 3 (R^3 or R^4) or 7 (R^5 or R^6), preferably the β -position, and the other position 7 or 3 in each case carries an OH group or a protected OH group,

B is $-OH$, $-O$ -alkali metal, $-O$ -alkaline earth metal, $-O$ - (C_1-C_{12}) -alkyl, $-O$ -allyl or $-O$ -benzyl, preferably $-OH$, $-O$ -alkali metal, $-O$ - (C_1-C_6) -alkyl, $-O$ -allyl or $-O$ -benzyl, where alkyl is either n-alkyl or iso-alkyl and where the ester group formed

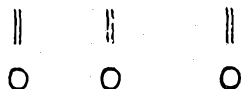


is esters which can be hydrolyzed both by acid and by base,

Y is $-O-$, $-NR'-$, $-O-C(=O)-$, $-NR'-C(=O)-$,

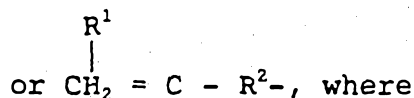
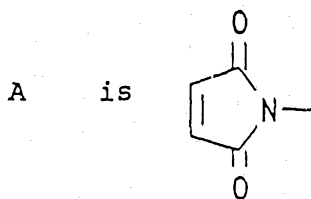
Z is (C₁-C₁₂)-alkylene, (C₇-C₁₃)-aralkylene, where 1 to 3 methylene groups in the alkylene chain are replaced by the groups -O-, -NR'-,

-NR'-C-, -O-C-, -NR'-C-NR''-



and

o and p independently of one another are zero or 1, where o and p are not simultaneously zero,



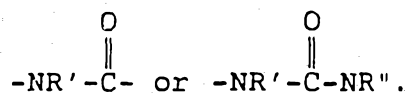
R¹ is hydrogen or CH₃, and

R² is -NR'-C-, -NR'- or a single bond, in which R' and R'' independently of one another are hydrogen or (C₁-C₆)-alkyl.

If p = zero and o = 1, Y is preferably $-\overset{\text{O}}{\parallel}{\text{C}}-$ or $-\text{NR}'-\overset{\text{O}}{\parallel}{\text{C}}-$.

If p = 1 and o = zero, Z is preferably (C₁-C₁₂)-alkylene, where 1-3 methylene groups, preferably one methylene group, are replaced by $-\text{NR}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}''$.

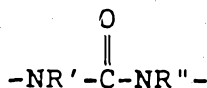
If p = 1 and o = 1, Y is preferably -O-. It is preferred here that Z is (C₁-C₁₂)-alkylene or (C₇-C₁₃)-aralkylene, where 1 or 2 methylene groups, preferably one methylene group, are replaced by



It is furthermore preferred here that one methylene group

of Z is $\text{-NR}'\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-NR}''\text{-}$ when Z itself is an aralkyl radical, in which the aryl radical is meta-linked, and Z on the

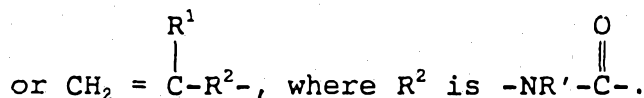
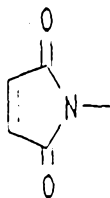
one hand as the radical A carries a group $\text{CH}_2\text{=}\overset{\text{R}^1}{\text{C}}\text{-R}^2\text{-}$ in which R² is a single bond and on the other hand carries a



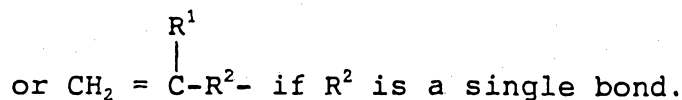
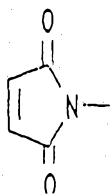
group which is meta-linked to the aralkylene radical via a methylene group.

It is also preferred here that, if Z is a (C₁-C₁₂)-alkylene group,

at most one methylene group is replaced by $\text{-NR}'\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-}$ and the radical A is



It is furthermore particularly preferred that Y is not directly adjacent to the group replacing a methylene group of Z and also is not adjacent to



The compounds of the formula I are the subject of German Patent Application P 4142323.2 filed at the same time.

OH protective groups are understood as meaning an alkyl radical having 1-10 carbon atoms or an alkenyl radical having 2-10 carbon atoms, where the rings are branched or unbranched, a cycloalkyl radical having 3-8 carbon atoms,

a phenyl radical which is unsubstituted or substituted 1-3 times by F, Cl, Br, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy, a benzyl radical which is unsubstituted or substituted 1-3 times by F, Cl, Br, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy or

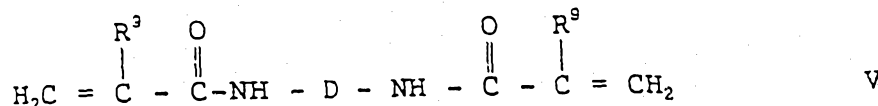
a R'''-C(=O)- radical, where R''' is hydrogen or (C₁-C₄)-alkyl.

Preferred comonomers of the formula IV are:

(meth)acrylic acid, (meth)acrylic acid esters, acrylamide or acrylamide derivatives. Carboxylic acid vinyl esters having 3-20 carbon atoms and N-vinylpyrrolidone and its derivatives are particularly preferred. The monomers are optionally employed in a mixture.

The described polymers or copolymers of bile acid derivatives can additionally be crosslinked by copolymerization with ethylenically polyunsaturated monomers. Ethylenically diunsaturated or triunsaturated acrylic and methacrylic acid derivatives are preferably mentioned. The polymeric and oligomeric bile acids according to the invention can also be crosslinked by polymer-analogous reactions with bifunctional reagents generally used.

Suitable crosslinking agents are in particular the acid amides of the compounds mentioned and among these, in turn, acid amides of the formula V



in which

R³ is hydrogen or methyl and

D is -(CHE)_m-,

where

m is 1 to 10, preferably 2 to 4 and

E is hydrogen or OH, preferably hydrogen for m = 2.

The invention furthermore relates to a process for the preparation of the polymeric bile acids.

The free radical polymerization or copolymerization is carried out in suspension or emulsion, or in substance, but preferably in solution using free radical initiators at temperatures below 250°C, preferably at temperatures from 40 to 100°C.

Suitable free radical initiators are inorganic or organic peroxides, percarbonates and azo compounds, which are preferably employed in amounts from 0.01 to 30 mol% with respect to that of monomers to be polymerized. The use of potassium peroxodisulfate, hydrogen peroxide, dilauryl peroxide is preferred or azobisisobutyronitrile, tert-butylperoxydiethyl acetate, dibenzoyl peroxide or tert-butoxy-2-ethyl hexanoate is particularly preferred.

The following can furthermore be employed:

tert-butyl peroxyisobutyrate, tert-butyl peroxyisopropyl carbonate, tert-butylperoxy-3,5,5-trimethylhexanoate, 2,2-bis(tert-butyl)peroxybutane, tert-butyl peroxy-stearyl carbonates, tert-butyl peroxyacetates, tert-butyl peroxybenzoate, dicumyl peroxide, 2,5-dimethyl-2,5-bis(tert-butylperoxy)hexane, tert-butyl cumyl peroxide, 1,3-bis(tert-butylperoxyisopropyl)benzene, di-tert-butyl peroxide, bis(2-methylbenzoyl) peroxide, bis(3,5,5-trimethylhexanoyl) peroxide, tert-butyl peroxy-pivalate, tert-amyl peroxy-pivalate, tert-butyl peroxyneodecanoate, tert-amyl peroxyneodecanoate, diisopropyl peroxydicarbonate, bis(2-ethylhexyl) peroxydicarbonate, di-n-butyl peroxydicarbonate, di-sec-butyl peroxydicarbonate and others.

The type of solvents employed depends on the solubility of the monomers employed. Water-soluble monomers are polymerized in aqueous solution. Monomers soluble in organic solvents can in principle be polymerized in all organic solvents in which free radical polymerizations

are customarily carried out. Those employed are, for example, dimethyl sulfoxide, dimethylformamide, chloroform, methylene chloride, esters having up to 10 carbon atoms, for example ethyl acetate or methyl acetate or hydrocarbons such as benzene, toluene or xylene. Alcohols having up to 6 carbon atoms, for example methanol, ethanol, isopropanol, propanol and others as well as ethers such as, for example, tetrahydrofuran or dioxane are preferred. The solvents can optionally also be employed in a mixture or possibly in combination with water.

The molecular weight of the polymeric products can be controlled by the type and amount of the solvents employed and the free radical initiators used, by the reaction time and by the reaction temperature. Moreover, molecular weight control is possible by the use of regulators, preferably in amounts of up to 2 mol% with respect to the monomers employed, such as, for example, alkyl and aryl mercaptans, aldehydes, phenols and amines.

The polymers can be synthesized both by generally known metering methods and by the batch reaction.

The polymeric bile acids according to the invention have weight-average molecular weights of, preferably, up to 250,000 g/mol. Particularly preferred products are those having weight-average molecular weights between 2,000 and 100,000 g/mol, particularly preferred compounds are those whose molecular weight is between 3,000 and 60,000 g/mol.

In copolymeric compounds, the molar ratio of bile acid units to copolymerized monomer units should preferably be between 300:1 and 1:300, molar ratios of 150:1 to 1:150 are particularly preferred.

Polymeric bile acids of the type according to the invention containing hydrolyzable or transesterifiable units can be transesterified or hydrolyzed in solution to give

the corresponding compounds. Suitable solvents here are preferably alcohols having up to 6 carbon atoms, ethers such as diethyl ether, tetrahydrofuran, dioxane, halo-hydrocarbons such as chloroform, methylene chloride, and moreover dimethyl sulfoxide or dimethylformamide.

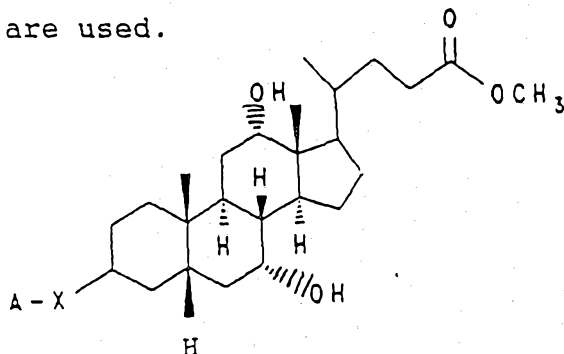
Water-miscible solvents which can be employed in combination with water are particularly preferred. The hydrolyses are carried out with the addition of inorganic acids such as, for example, hydrochloric acid, sulfuric acid, or organic acids such as, for example, p-toluenesulfonic acid. However, the use of bases such as, for example, NaOH, KOH, prim. amines, sec. amines, tert. amines, alkali metal and alkaline earth metal alkoxides and others is preferred.

The hydrolyses are as a rule carried out at temperatures from 15 to 100°C.

The hydrolyzed polymers can be isolated and purified by chromatographic processes such as, for example, HPLC or GPC, by dialysis and subsequent lyophilization or by precipitation of the products from the reaction mixture.

The synthesis and properties of the polymeric bile acids according to the invention are illustrated in greater detail by the following examples. The examples shown do not restrict the subject matter of the invention in the slightest, but are to be understood as being a choice from the subject matter of the invention.

In the following examples, bile acid methyl esters of the formula VI are used.



The group A-X is in each case defined in the examples.

For dialysis, Spectra/Por No. 3 dialysis tubing with an exclusion limit of 3,500 g/mol from Spectrum Medical Industries, INC. was employed.

The determination of the weight-average molecular weights was carried out by means of GPC in comparison with polystyrene standards.

Chromatograph: ALC/GPC 244 Waters chromatography
Column set: 4 ultrastyrigel columns
Solvent: THF
Flow rate: 1 ml/min
Sample amount: 0.4 ml sample solution of $c = 0.2$ g/dl
Detector: RI + 4X

Examples

Example 1

In a reaction vessel, 1,000 mg of a bile acid methyl

ester in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_2-\text{O}-$ are dissolved under nitrogen in 4 ml of tetrahydrofuran and treated with 10 g of vinyl acetate and 300 mg of 75% strength dibenzoyl peroxide. The reaction mixture is heated at 80°C with stirring for 6 hours. The reaction mixture is then treated with 15 ml of THF and the mixture is concentrated to dryness on a rotary evaporator. The residue is taken up in 25 ml of THF and treated under stirring with 2 ml of 10% strength methanolic sodium hydroxide solution and heated at 40°C for 2 hours. The reaction mixture is then diluted with 50 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Molar ratio of bile acid units to vinyl alcohol units:
1:80 (determined by NMR),
weight-average molecular weight of the unhydrolyzed
substance:
 $M_w = 34,000$ g/mol (determined using GPC).

Example 2

In a reaction vessel, 3,000 mg of a bile acid methyl

ester in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_2-\text{O}-$ are dissolved under nitrogen in 4 ml of tetrahydrofuran and treated with 7 g of vinyl acetate and 300 mg of 75% strength dibenzoyl peroxide. The reaction mixture is heated at 80°C with stirring for 6 hours. The reaction mixture is then treated with 15 ml of THF and the mixture is concentrated to dryness on a rotary evaporator. The residue is taken up in 25 ml of THF and treated under stirring with 2 ml of 10% strength methanolic sodium hydroxide solution and heated at 40°C for 2 hours. The reaction mixture is then diluted with 50 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Molar ratio of bile acid units to vinyl alcohol units:
1:12.5 (determined by NMR),
weight-average molecular weight of the unhydrolyzed
substance:
 $M_w = 8,000$ g/mol (determined using GPC).

Example 3

In a reaction vessel, 4,920 mg of a bile acid methyl

ester, where A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_2-\text{O}-$ are dissolved in 4 ml of tetrahydrofuran under nitrogen and treated

with 220 mg of 75% strength dibenzoyl peroxide, dissolved in 0.3 ml of THF and 0.2 ml of methanol. The reaction mixture is heated at 80°C with stirring. 17.01 g of N-vinylpyrrolidone are continuously metered into the reaction mixture in the course of 4 hours, after 2 and after 4 hours reaction time in each case 220 mg of 75% strength dibenzoyl peroxide, dissolved in 0.3 ml of THF and 0.2 ml of methanol, being added. After metering in of the N-vinylpyrrolidone has taken place, the mixture is allowed to react at 80°C for 7 hours. The reaction mixture is then diluted with 15 ml of THF and treated with 0.5 ml of 20% strength aqueous sodium hydroxide solution. After about 10 minutes, the turbidity of the reaction mixture which occurs is removed by addition of water, and this process is repeated until turbidity of the mixture no longer occurs. The reaction mixture is then diluted with 50 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Molar ratio of bile acid units to N-vinylpyrrolidone units: 1:1 (determined by NMR),
weight-average molecular weight of the unhydrolyzed substance:
 $M_w = 38,000$ g/mol (determined using GPC).

Example 4

In a reaction vessel, 3,000 mg of a bile acid methyl

ester, where A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_6-\text{O}-$ are dissolved in 4 ml of tetrahydrofuran under nitrogen and treated with 120 mg of 75% strength dibenzoyl peroxide, dissolved in 0.4 ml of toluene. The reaction mixture is heated at 80°C with stirring. 17.01 g of N-vinylpyrrolidone are continuously metered into the reaction mixture in the course of 4 hours, after 2 and after 4 hours reaction time in each case 120 mg of 75% strength dibenzoyl peroxide, dissolved in 0.4 ml of toluene, being added.

After metering in of the N-vinylpyrrolidone has taken place, the mixture is allowed to react at 80°C for 2 hours. The reaction mixture is then diluted with 15 ml of THF and treated with 0.5 ml of 20% strength aqueous sodium hydroxide solution. After about 10 minutes, the turbidity of the reaction mixture which occurs is removed by addition of water, and this process is repeated until turbidity of the mixture no longer occurs. The reaction mixture is then diluted with 50 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Molar ratio of bile acid units to N-vinylpyrrolidone units: 2:3 (determined by NMR),
weight-average molecular weight of the unhydrolyzed substance:
 $M_w = 16,000$ g/mol (determined using GPC).

Example 5

In a reaction vessel, 1,110 mg of a bile acid methyl

ester, in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_6-\text{O}-$ are dissolved in 8 ml of tetrahydrofuran under nitrogen and treated with 150 mg of 75% strength dibenzoyl peroxide, dissolved in 0.75 ml of toluene. The reaction mixture is heated at 75°C with stirring for 18 hours. The reaction mixture is then diluted with 10 ml of THF and treated with 0.5 ml of 20% strength aqueous sodium hydroxide solution. After about 10 minutes, the turbidity of the reaction mixture which occurs is removed by addition of water. This process is repeated until turbidity of the mixture no longer occurs. The reaction mixture is then diluted with 30 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Weight-average molecular weight of the unhydrolyzed substance:
 $M_w = 10,000$ g/mol (determined using GPC).

Example 6

In a reaction vessel, 386.8 mg of a bile acid methyl

5 ester, in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_2-\text{O}-$ are dissolved
in 2.78 ml of tetrahydrofuran under nitrogen and treated
with 52 mg of 75% strength dibenzoyl peroxide, dissolved
in 0.5 ml of toluene. The reaction mixture is heated at
10 75°C with stirring for 18 hours. The reaction mixture is
then diluted with 10 ml of THF and treated with 0.5 ml of
20% strength aqueous sodium hydroxide solution. After
about 10 minutes, the turbidity of the reaction mixture
which occurs is removed by addition of water. This
process is repeated until turbidity of the mixture no
15 longer occurs. The reaction mixture is then diluted with
30 ml of water, dialyzed against deionized water for 24
hours (cut-off: 3,500 g/mol) and lyophilized.

Weight-average molecular weight of the unhydrolyzed
substance:

20 $M_w = 11,000$ g/mol (determined using GPC).

Example 7

In a reaction vessel, 340 mg of a bile acid methyl

25 ester, in which A-X is $\text{H}_2\text{C}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}_2-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-(\text{CH}_2)_2-\text{O}-$
are dissolved in 2.4 ml of tetrahydrofuran under nitrogen
and treated with 45 mg of 75% strength dibenzoyl
peroxide, dissolved in 0.5 ml of toluene. The reaction
mixture is heated at 75°C with stirring for 18 hours. The
30 reaction mixture is then diluted with 10 ml of THF and
treated with 0.5 ml of 20% strength aqueous sodium
hydroxide solution. After about 10 minutes, the turbidity
of the reaction mixture which occurs is removed by
addition of water. This process is repeated until
35 turbidity of the mixture no longer occurs. The reaction

mixture is then diluted with 30 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Example 8

5 In a reaction vessel, 558.8 mg of a bile acid methyl

10 ester, in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2)_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{CH}_2-\text{O}-$ are dissolved in 4 ml of tetrahydrofuran under nitrogen and treated with 74.5 mg of 75% strength dibenzoyl peroxide, dissolved in 0.8 ml of toluene. The reaction mixture is heated at 75°C for 18 hours with stirring. The reaction mixture is then diluted with 10 ml of THF and treated with 0.5 ml of 20% strength aqueous sodium hydroxide
15 solution. After about 10 minutes, the turbidity of the reaction mixture which occurs is removed by addition of water. This process is repeated until turbidity of the mixture no longer occurs. The reaction mixture is then diluted with 30 ml of water, dialyzed against deionized
20 water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Weight-average molecular weight of the unhydrolyzed substance:

$M_w = 14,000$ g/mol (determined using GPC).

25 Example 9

In a reaction vessel, 437.4 mg of a bile acid methyl

30 ester, in which A-X is $\text{H}_2\text{C}=\text{CH}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2)_2-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-(\text{CH}_2)_2-\text{O}-$ are dissolved in 3.2 ml of tetrahydrofuran under nitrogen and treated with 62.7 mg of 75% strength dibenzoyl peroxide, dissolved in 0.7 ml of toluene. The reaction mixture is heated at 75°C for 18 hours with stirring. The reaction mixture is then diluted with 10 ml of THF and

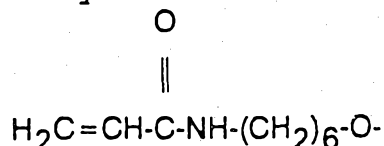
treated with 0.5 ml of 20% strength aqueous sodium hydroxide solution. After about 10 minutes, the turbidity of the reaction mixture which occurs is removed by addition of water. This process is repeated until
5 turbidity of the mixture no longer occurs. The reaction mixture is then diluted with 30 ml of water, dialyzed against deionized water for 24 hours (cut-off: 3,500 g/mol) and lyophilized.

Weight-average molecular weight of the unhydrolyzed
10 substance:
 $M_w = 13,000$ g/mol (determined using GPC).

Example 10

The example is carried out in accordance with Example 9, but the following compounds are employed:

15 424 mg of bile acid methyl ester in 3 ml of THF, in which A-X is



0.424 mg of dodecyl mercaptan in 50 μ l of THF as a regulator and

56.52 mg of dibenzoyl peroxide (BSO), 75% strength, in
20 563.7 μ l of toluene.

The product obtained has a weight-average molecular weight of the unhydrolyzed substance of $M_w = 6,900$ g/mol (determined using GPC).

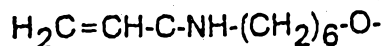
Example 11

25 The example is carried out in accordance with Example 9, but the following compounds are employed:

400 mg of bile acid methyl ester in 2.9 ml of THF, in which A-X is



and



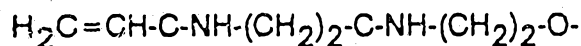
5.39 mg of BSO, 75% strength, in 53.8 μl of toluene.

The product obtained has a weight-average molecular weight of the unhydrolyzed substance of $M_w = 8,800\text{g/mol}$ (determined using GPC).

Example 12

The example is carried out in accordance with Example 9, but the following compounds are employed:

407.3 mg of bile acid methyl ester in 2.95 ml of THF, in which A-X is



1.53 mg of glyoxal bisacrylamide in 74.6 μl of methanol as crosslinking agent and
58.4 mg of BSO, 75% strength, in 582.4 μl of toluene.

The product obtained in each case has an average molecular weight of the unhydrolyzed substance of $M_w = 5,400\text{ g/mol}$ (determined using GPC).

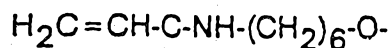
Example 13

The example is carried out in accordance with Example 9, but the following compounds are employed:

409 mg of bile acid methyl ester in 2.95 ml of THF, in which A-X is



and



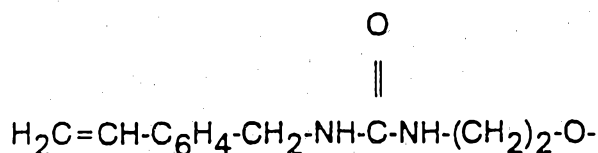
54.53 mg of BSO, 75% strength, in 543.8 μ l of toluene.

The product obtained has a weight-average molecular weight of the unhydrolyzed substance of $M_w = 7,500$ g/mol (determined using GPC).

5 Example 14

The example is carried out in accordance with Example 9, but the following compounds are employed:

400.7 mg of bile acid methyl ester in 2.9 ml of THF, in which A-X is

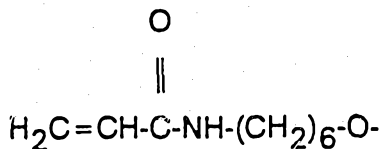


10 1.5 mg of glyoxal bisacrylamide as crosslinking agent in 70 μ l of methanol and 53.4 mg of BSO, 75% strength, in 529 μ l of toluene.

Example 15

15 The example is carried out in accordance with Example 9, but the following compounds are employed:

416.3 mg of bile acid methyl ester in 2.9 ml of THF, in which A-X is



20 0.81 mg of tert-butyl peroxydiethyl acetate as initiator in 15.5 μ l of THF, reaction time 21 h.

The product obtained has a weight-average molecular weight of the unhydrolyzed substance of $M_w = 10,700$ g/mol (determined using GPC).

In in-vitro and in-vivo investigations of the compounds of the polymeric bile acid type according to the invention, which have a high affinity for the bile acid transport system, it has surprisingly been found that these compounds inhibit bile acid absorption in a concentration-dependent manner. It was furthermore possible to show that the compounds according to the invention are not absorbed themselves and thus do not pass into the enterohepatic circulation. As a result of this knowledge, it is now possible to intervene in the enterohepatic circulation with greater efficiency than was hitherto possible using the resins.

In the case of the resins already obtainable as pharmaceuticals, for example colestyramine (contains quaternary ammonium groups) or colestipol (contains secondary or tertiary amino groups), the expedient daily dose is very high. For example, for colestyramine it is 12-24 g, highest daily dose 32 g. The recommended dose is 15-20 g. Furthermore, taste, odor and the high dosage make patient compliance difficult. The known side effects (for example avitaminoses) of the resins are attributed to lack of selectivity. These side effects must also be taken into account in the dosage of simultaneously administered medicaments, but also in the case of bile acid depletion, which is caused by various gastrointestinal disorders (obstipation, steatorrhea) to a differing degree.

For colestyramine and colestipol, therapeutic importance as a result of combination with other hypolipidemic pharmaceuticals such as fibrates, HMG-CoA reductase inhibitors, probucol (cf., for example, M.N. Cayen, Pharmac. Ther. 29, 187 (1985) and 8th International Symposium on Atherosclerosis, Rome, Oct. 9-13, 1988, Abstracts P. 544, 608, 710) was described, the effects obtained also making possible the therapy of severe hyperlipidemias. But the following features of said preparations and in particular of, for example, colestipol were to be regarded as worthy

of improvement:

1. The high daily doses, which can be attributed to a relatively low binding rate at neutral pH in isotonic medium and the (partial) re-release of the adsorbed bile acids.
2. The qualitative shift in the bile acid composition of the bile with a decrease in tendency for chenodeoxycholic acid and the increasing risk of cholelithiasis associated therewith.
3. The lack of a damping action on the cholesterol metabolism of the intestinal bacteria.
4. The excessively high binding rate of vitamins and pharmaceuticals makes a need for a substitute for these substances and blood level controls possibly necessary.
5. The current administration form is to be regarded as unsatisfactory.

By means of inhibition of bile acid re-absorption with the aid of the polymeric bile acids according to the invention in the small intestine, the bile acid concentration found in the enterohepatic circulation is reduced in an essentially more effective manner, so that a fall in the cholesterol level in the serum takes place. Avitaminoses are seen just as little when using the compounds according to the invention as is the effect on the absorption of other pharmaceuticals. Nor is there a negative effect on the intestinal flora, since the binding of the polymers according to the invention to the intestinal mucous membrane is extremely stable and persists very long after binding has taken place.

It is additionally to be expected that the known side effects (obstipation, steratorrhoea) are not observed.

Finally, the use of high doses does not lead to cell damage. The dose of the resins which is otherwise usual can therefore be considerably reduced by use of the compounds according to the invention. The recommended dose is appropriately up to 10 g per day, preferably 0,1 to 5,0 g/day, in particular 0,3 to 5,0 g/day.

The following methods were used:

HPLC with FLUORESCENCE DETECTION

Equipment: HPLC unit from Kontron, consisting of three pumps and mixing chamber, auto-sampler, UV detector and analysis unit with MT2 software.

Merck-Hitachi fluorescence detector.

Since the samples are light- and heat-sensitive, the autosampler is cooled to about 5°C.

Mobile phase: Eluent A: Millipore water (in-house unit)
Eluent B: acetonitrile/methanol 60:30

Column: LiChrospher 100 RP-18, 25 mm, 5 µm from Merck

Precolumn: LiChrospher 60 RP-select B, 4 mm, 5 µm from Merck

Flow rate: 1.3 ml/min

Detection: Excitation: 340 nm
 Emission: 410 nm

Gradient: 0.00 min 66% B
 7.50 min 66% B
5 8.00 min 76% B
 12.50 min 76% B
 13.00 min 83% B
 25.00 min 83% B
 25.50 min 91% B
10 40.00 min 91% B

Enzymatic determination of the total bile acid

- 900 μ l each of the following mixture are added to Eppendorf vessels:
 - 6 ml of tetrasodium diphosphate buffer 0.1 M, pH 8.9,
 - 2 ml of NAD solution (4 mg/ml water),
 - 20 ml of Millipore water
- 30 μ l of the sample and 30 μ l of enzyme solution are added to this by pipette.
- 20 - Enzyme solution: 3-alpha-hydroxysteroid dehydrogenase 0.5 units/ml
- The batches are mixed and incubated at room temperature for 2 h.
- Subsequently transfer to 1 ml disposable cuvettes and measurement in a photometer at 340 nm.
- 25 - Only of limited suitability for bile samples, since the green color interferes.

HPLC with UV DETECTION

Equipment: HPLC unit from Kontron, consisting of
30 three pumps and mixing chamber, auto-sampler, UV detector and analysis unit with MT2 software.

Mobile Phase: Eluent A: ammonium carbamate buffer
0.019 M, adjusted to pH 4.0
with phosphoric acid.

Eluent B: acetonitrile

5 Column: LiChrospher 100 RP-8, 25 mm, 5 μ m from
Merck

Precolumn: LiChrospher 60 RP-select B, 4 mm, 5 μ m
from Merck

10 Flow rate: Gradient: 0.00 min 0.8 ml/min
20.00 min 0.8 ml/min
23.00 min 1.3 ml/min
51.00 min 1.3 ml/min

Detection: 200 nm (for preparations additionally at
254 nm)

15 Gradient: 0.00 min 32% B
8.00 min 35% B
17.00 min 38% B
20.00 min 40% B
24.00 min 40% B
20 30.00 min 50% B
45.00 min 60% B

The in vivo investigation was carried out as described in
F.G.J. Poelma et al. (J. Pharm. Sci. 78 (4), 285-89,
1989) with some modifications.

25 In the investigations, taurocholate and taurocholic acid
or cholate and cholic acid are used synonymously.

Cannulation of the bile duct

The bile duct is dissected free and a catheter is tied in
(PE 50, Intramedic®). An adaptor for admitting 100 μ l

disposable pipette tips (Brandt) was attached to its end. The bile is collected in these pipettes and transferred to weighed Eppendorf reaction vessels after specific time intervals. After the end of the experiment, the bile, as well as the medium samples, is weighed and aliquots are measured in a scintillation counter. For this purpose, 10 μ l samples are pipetted into a Sarstedt sample vessel, 58 x 22 mm, mixed with 10 ml of Quickszint 212 (Zinsser GmbH, Frankfurt am Main, Germany) and counted in a Beckman 2800 β -counter after a 30 min decay period.

1. The compounds according to the invention, Examples 1 to 15, were instilled into the intestinal segment together with 10 mM taurocholate containing ^3H -taurocholate or ^{14}C -taurocholate as tracer and the perfusion solution was circulated for 2 h with the aid of a peristaltic pump. The decrease of the tracer in the intestine (medium) and the appearance of the tracer in the bile fluid (bile) was determined with the aid of scintillation measurements and HPLC. As a control, 10 ml taurocholate which tracer and without a compound of the invention was instilled and the change in the intestine and in the bile fluid was determined (Figures 1a-10a and 1b-10b).

2. In vivo perfused intestine

The experimental animals used are Wistar rats bred in-house (animal-holding Hoechst) having, on average, a body weight of 230-290 g. The experimental animals are not fasted before anesthesia (urethane 1 g/kg i.p.). After onset of anesthesia, the animals are immobilized on a temperature-adjustable (constant 37°C) OP bench (Medax), shaved on the ventral side and the abdominal wall of the animals is then opened using a cut about 7 cm long. A Luer adaptor (Hoechst Precision Engineering) is then tied into the lower small intestine about 8 cm from the ileocaecal valve, the secondary small intestine being tied off in this way. A further tying into and tying off of the small intestine

is then carried out 13-14 cm from the start of the small intestine. The contents of this intestinal segment are carefully washed out with 37°C isotonic saline solution. The test solution is later instilled into this segment,
5 the end part of the jejunum - start of the ileum.

The pump tubing is first filled from the 2 ml of instillation solution (10 mM taurocholate, preparation in the given concentration, tracer: 3.5 μ Ci [3 H(G)]-taurocholic acid, NET-322, lot 2533-081, DuPont de Nemour GmbH, Dreieich, Germany) dissolved in phosphate-buffered
10 isotonic saline solution (silicone tubing A, 0.5 mm Desaga, Heidelberg, Germany, Order No. 132020). The pump tubing is then attached to the intestinal segment using two Luer adaptors and the remaining solution is added by
15 means of a three-way valve (Pharmaseal 75a) and a 2 ml disposable syringe (Chirana). Immediately after this, the peristaltic pump (LKB Multiperpex 2115) is switched on, and the medium is circulated at 0.25 ml/min. At regular
20 intervals, a sample for measurement of the activity (decrease in radioactivity in the intestine = absorption rate) is removed from an infusion tube integrated in the circulation by means of a Hamilton syringe and a cannula (Termo 0.4 x 20).

To detect the prolonged effect of the oligomeric or
25 polymeric bile acids (Figures 11a + b), in this special test design the outflow (intestine) and the filling (bile) of the radioactive tracer were tested during the first (inst. I) instillation with inhibitor and during the second instillation (inst. II) without the inhibitor.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A polymeric or oligomeric bile acid, which can be prepared by polymerization of a monomeric bile acid of the formula I



in which

G is a bile acid radical or derivative,

X is a bridge group of the formula II



in which

Y is adjacent to G and is -O-, -NR'-, $\begin{array}{c} \text{O} \\ \parallel \\ \text{-O-C-} \end{array}$ or $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NR'-C-} \end{array}$,

Z is (C₁-C₁₂)-alkylene or (C₇-C₁₃)-aralkylene, where individual methylene groups in the alkylene or aralkylene radical can be replaced by groups such as -O-, -NR'-, -NR'-C-, -O-C- or



o and p independently of one another are zero or 1, where

o and p are not simultaneously zero,

R' and R'' independently of one another are hydrogen or (C₁-C₆)-alkyl



~~THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:~~

~~By the following~~

1. A polymeric or oligomeric bile acid, which can be prepared by polymerization of a monomeric bile acid of the formula I

5



in which

G is a bile acid radical or derivative,

~~X is a bridge group and~~

10

A is a polymerizable, ethylenically unsaturated group, or by copolymerization with a monomer containing a polymerizable, ethylenically unsaturated double bond, in particular by copolymerization with a monomer of the formula IV

15



in which

R⁹ is hydrogen or methyl and

20

R¹⁰ is $-\overset{O}{\parallel}C-O-R^{11}$, $-\overset{O}{\parallel}C-NR^{12}R^{13}$, $-\overset{O}{\parallel}C-O-R^{14}$, $-\text{CN}$, $-\text{O}-R^{15}$, hydrogen, halogen, in particular chlorine, bromine or iodine, $-\text{SO}_3\text{H}$ or $-\text{O}-(\text{CH}_2-\text{CH}_2\text{O})_nR^{16}$,

25

in which

R¹¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₁-C₁₀)-mono-hydroxyalkyl or $-(\text{CH}_2\text{CH}_2-\text{O})_nR^{16}$,

30

R¹², R¹³, R¹⁵ and R¹⁶ are identical or different and are (C₁-C₁₀)-alkyl,

R¹⁴ is (C₁-C₁₈)-alkyl and

n is 1 to 50,

or by copolymerization with N-vinylpyrrolidone or its derivatives,

35

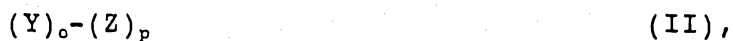
and/or by copolymerization with ethylenically

unsaturated dicarboxylic anhydrides and ethylenically unsaturated dicarboxylic acids each having 2 to 6 carbon atoms; their esters or half esters, esters being understood as alkyl esters having 1-6 carbon atoms, cycloalkyl esters having 5 to 8 carbon atoms, benzyl esters or phenyl esters.

5

2. A polymer or oligomer as claimed in claim 1, wherein G is a free bile acid or its alkali metal salt or a bile acid esterified on ring D and which is bonded via its ring A, B or C, preferably via ring A, to the group X, to which the formula II preferably applies

10



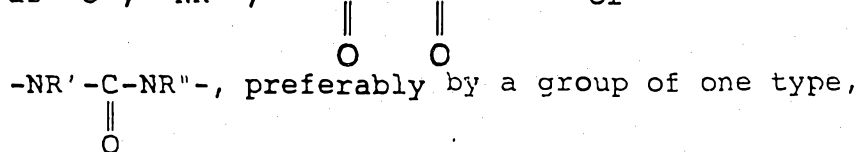
in which



15

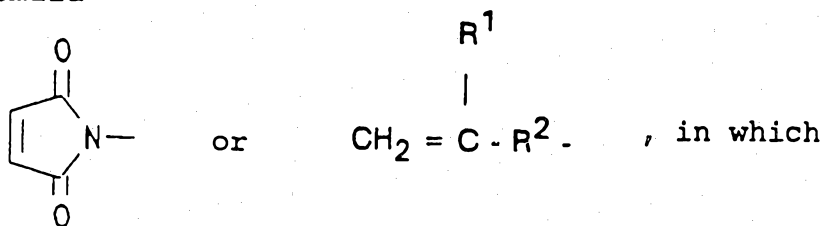
Y is adjacent to G and is -O-, -NR'-, -O-C-, -NR'-C-, Z is (C₁-C₁₂)-alkylene or (C₇-C₁₃)-aralkylene, where individual methylene groups, preferably 1 to 4, in the alkylene chain of the alkylene or aralkylene radical can be replaced by groups such as -O-, -NR'-, -NR'-C-, -O-C- or

20



o and p independently of one another are zero or 1, where o and p are not simultaneously zero, A is an ethylenically unsaturated group of the formula

25



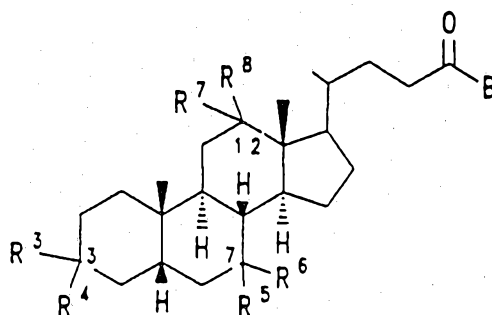
R¹ is hydrogen or CH₃ and

R² is $\text{-NR}'\text{-C}(=\text{O})\text{-O-C}(=\text{O})\text{-}$, $\text{-O-C}(=\text{O})\text{-}$, -O- , $\text{-NR}'\text{-}$ or a single bond, where the carbonyl groups are adjacent to the C-C double bond,

R' and R'' independently of one another are hydrogen or (C₁-C₆)-alkyl, preferably (C₁-C₃)-alkyl.

3. A polymer or oligomer as claimed in claim 1 or 2, wherein

G corresponds to the formula III



(III)

10

in which

R³ to R⁶ independently of one another are hydrogen, OH, NH₂ or an OH group protected by an OH protective group and one of the radicals R³ to R⁶ is a bond to the group X, where this bond starts from the positions 3 (R³ or R⁴) or 7 (R⁵ or R⁶), preferably the β-position, and the other position 7 or 3 in each case carries an OH group or a protected OH group,

15

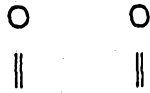
B is -OH, -O-alkali metal, -O-alkaline earth metal, -O-(C₁-C₁₂)-alkyl, -O-allyl or -O-benzyl, preferably -OH, -O-alkali metal, -O-(C₁-C₆)-alkyl, -O-allyl or -O-benzyl, where alkyl is either n-alkyl or iso-alkyl and where the ester group formed

20

25

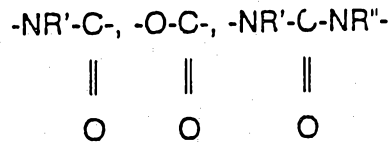


is esters which can be saponified both by acid and by base,



Y is -O-, -NR'-, -O-C-, -NR'-C-,

Z is (C₁-C₁₂)-alkylene, (C₇-C₁₃)-aralkylene, where 1 to 3 methylene groups in the alkylene chain are replaced by the groups -O-, -NR'-,



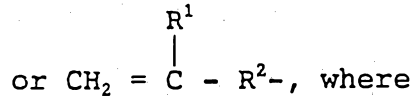
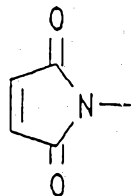
5

and

o and p independently of one another are zero or 1, where o and p are not simultaneously zero,

A is

10



R¹ is hydrogen or CH₃ and



R² is -NR'-C-, -NR'- or a single bond, in which R and R'' independently of one another are hydrogen or (C₁-C₆)-alkyl.

15

4. A polymer or oligomer as claimed in any one of claims 1 to 3, wherein the monomers are compounds according to the formula IV (meth)acrylic acid, (meth)acrylic acid esters, acrylamide and its derivatives, carboxylic acid vinyl esters having 3-20 carbon atoms or N-vinylpyrrolidone and its derivatives.

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5. A polymer or oligomer as claimed in any one of claims 1 to 4, wherein the weight-average molecular weight is up to 250,000 g/mol, particularly preferably between 2,000 and 100,000 g/mol, very particularly preferably between 3,000 and

25

and/or N-vinylpyrrolidone or its derivatives and/or an ethylenically unsaturated dicarboxylic acid having 2 to 6 carbon atoms and/or an ethylenically unsaturated dicarboxylic anhydride having 2 to 6 carbon atoms, and/or an ethylenically unsaturated dicarboxylic acid half ester having 2 to 6 carbon atoms using at least one free radical initiator.

11. The process as claimed in claim 10, wherein the polymerization is carried out in suspension, in substance or in solution.
12. The process as claimed in claim 10, wherein the polymerization is carried out in a solvent in which the monomer or monomers are soluble.
13. The process as claimed in any one of claims 10 to 12, wherein the esterified polymeric and oligomeric bile acids are dissolved in suitable solvents, preferably water-miscible solvents, and completely or partially hydrolyzed with the addition of inorganic acids or organic acids or of bases.
14. The process as claimed in claim 10, wherein the temperature is in the range from 15 to 100°C.
- ~~15. The use of the polymeric and oligomeric bile acids as claimed in claims 1 to 9 as pharmaceuticals, and as pharmaceutical preparations, foodstuff additives, formulation auxiliaries and detergents.~~
- ~~16. The use of the polymeric and oligomeric bile acids for affecting the enterohepatic circulation, the bile acids, the lipid-resorption and the serumcholesterol level.~~



15. A pharmaceutical composition comprising one or more polymeric and/or oligomeric bile acids as claimed in any one of claims 1-9 in adjunct with acceptable carriers and/or excipients.

16. A foodstuff additive comprising a pharmaceutical composition comprising one or more polymeric and/or oligomeric bile acids as claimed in any one of claims 1-9 in adjunct with acceptable carriers and/or excipients.

17. A formulation auxiliary comprising a pharmaceutical composition comprising one or more polymeric and/or oligomeric bile acids as claimed in any one of claims 1-9 in adjunct with acceptable carriers and/or excipients.

18. A detergent comprising a pharmaceutical composition comprising one or more polymeric and/or oligomeric bile acids as claimed in any one of claims 1-9 in adjunct with acceptable carriers and/or excipients.

19. A pharmaceutical composition comprising one or more polymeric and/or oligomeric bile acids as claimed in any one of claims 1 to 6 in adjunct with systemically acting active compounds which affect lipid metabolism and suitable pharmaceutically acceptable carriers and/or excipients.

20. A method of affecting the enterohepatic circulation, the bile acids, the lipid-resorption and the serumcholesterol level comprising administering to a patient requiring such treatment an effective amount of a polymeric and/or oligomeric bile acid as claimed in any one of claims 1-9.

21. A method of concentration-dependent inhibition of bile acid absorption in the gastrointestinal tract comprising administering to a patient requiring such treatment an effective amount of a polymeric and/or oligomeric bile acid as claimed in any one of claims 1-9.



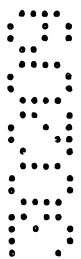
22. A method of non-systemic reduction of elevated serum cholesterol or blood lipid values for the prevention of arteriosclerotic phenomena comprising administering to a patient requiring such treatment an effective amount of polymeric and/or oligomeric bile acid as claimed in any one of claims 1-6.

DATED this 4th day of August, 1994.

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Abstract

Polymeric and oligomeric bile acids are described which can be prepared by polymerization of monomeric bile acids of the formula I



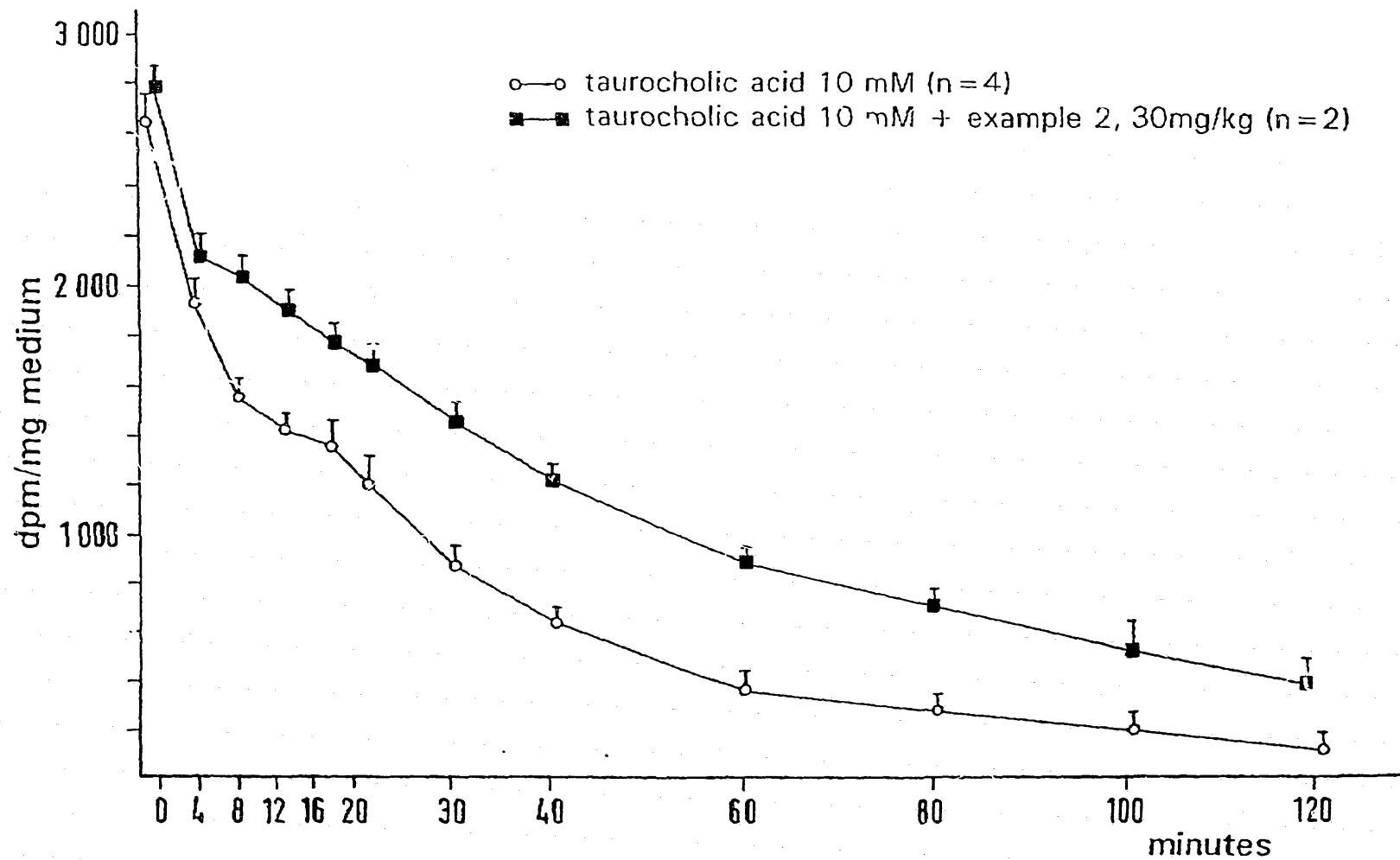
in which G, X and A have the given meanings or by copolymerization with a monomer of the formula IV



in which R⁹ and R¹⁰ have the given meanings, or by copolymerization with N-vinylpyrrolidone or its derivatives,

and/or by copolymerization with ethylenically unsaturated dicarboxylic anhydrides and ethylenically unsaturated dicarboxylic acids each having 2 to 6 carbon atoms; their esters or half esters, alkyl esters having 1-6 carbon atoms, cycloalkyl esters having 5 to 8 carbon atoms, benzyl esters or phenyl esters being understood as esters. They can be used as pharmaceuticals, foodstuff additives, formulation auxiliaries and detergents.

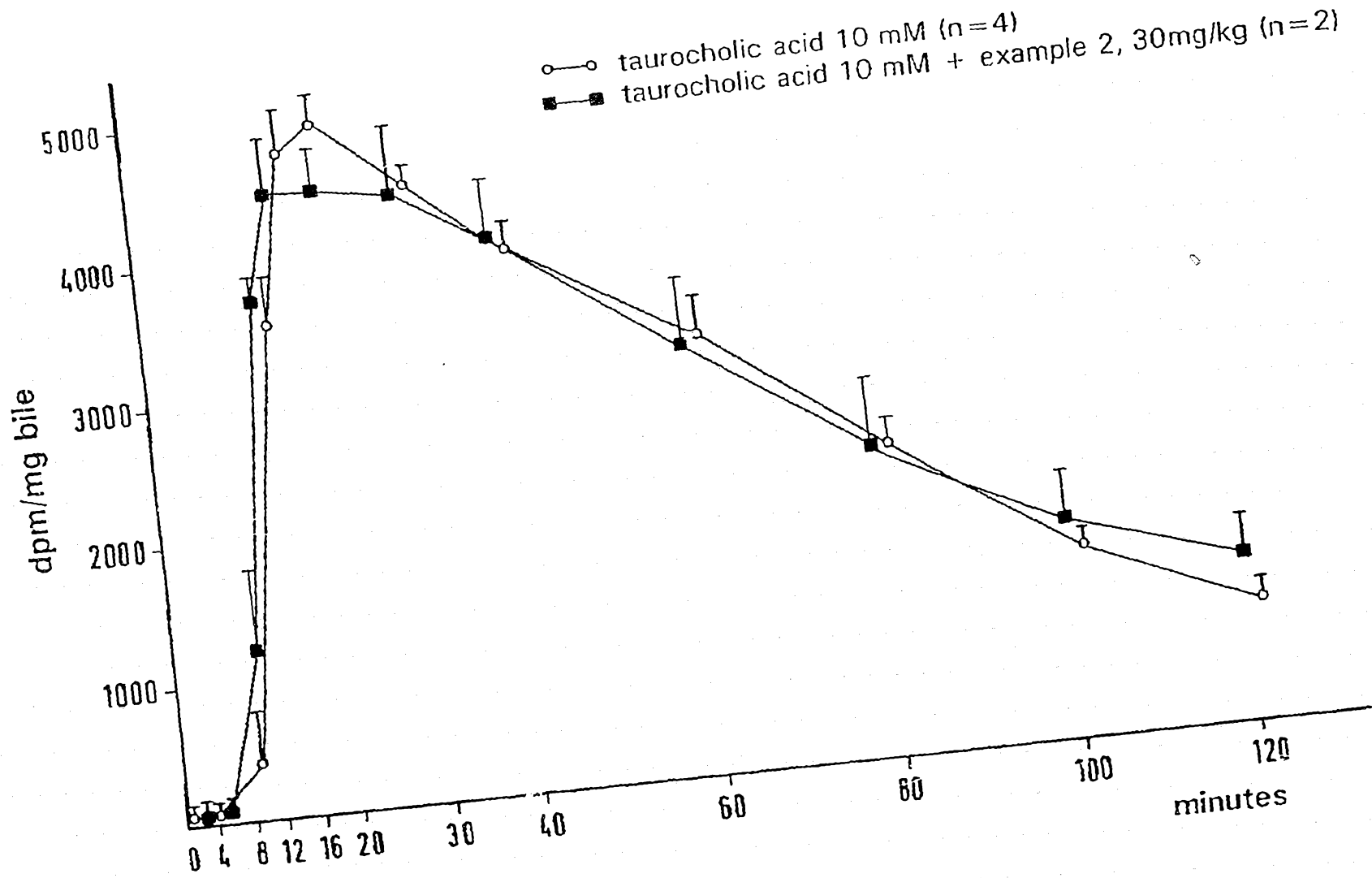
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Fig. 1a

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Fig. 1 b

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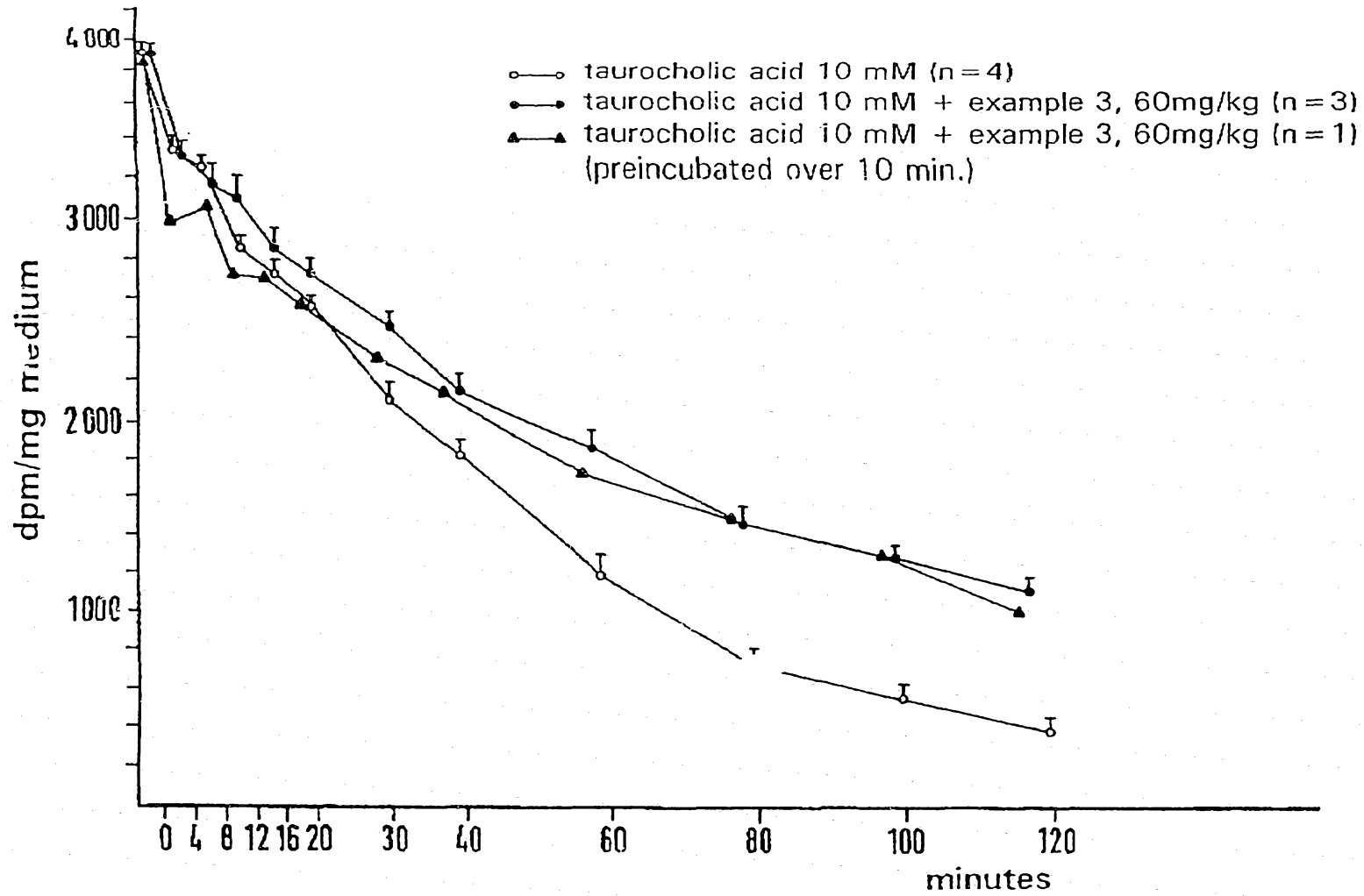


Fig. 2a

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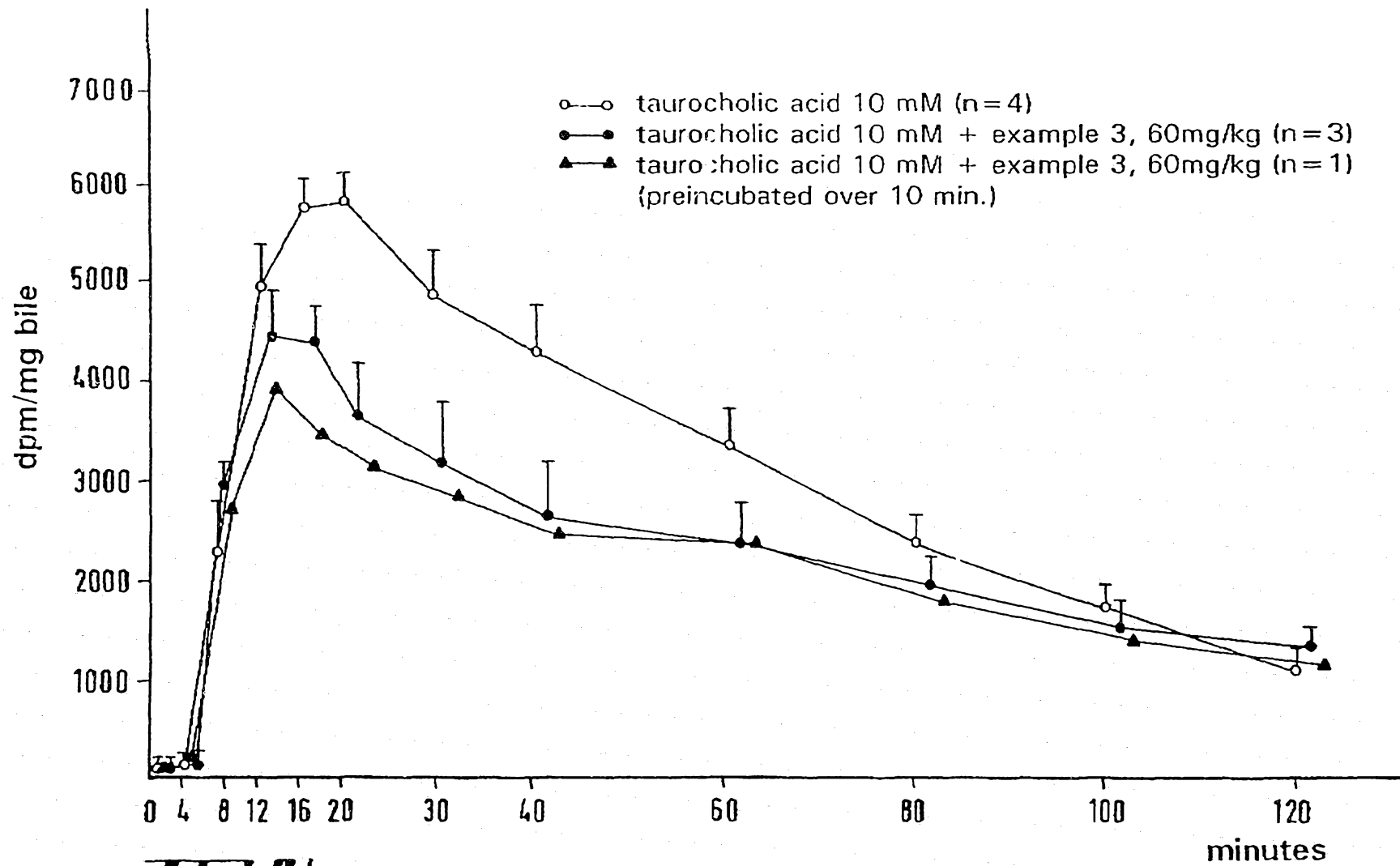


Fig. 2b

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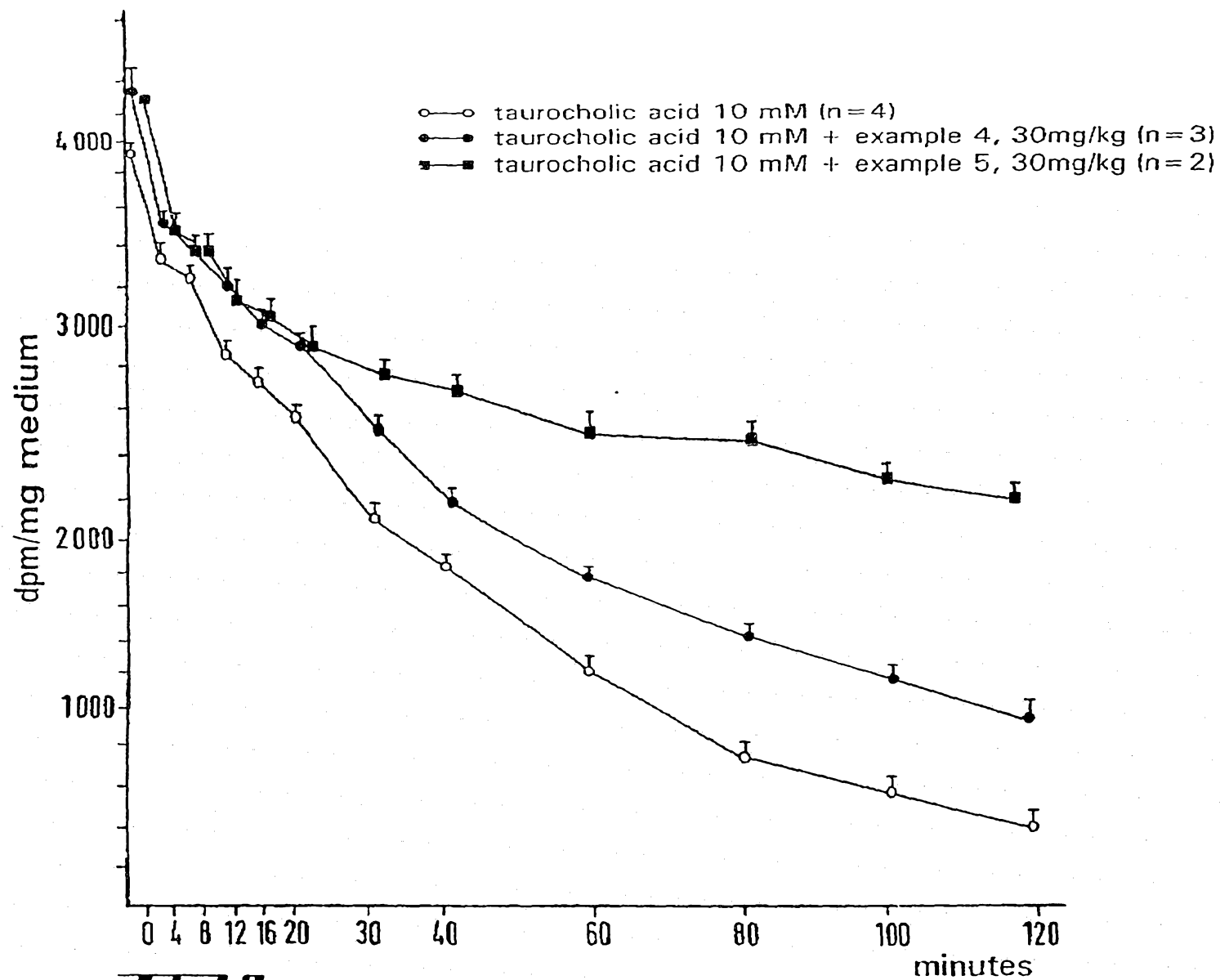


Fig. 3a

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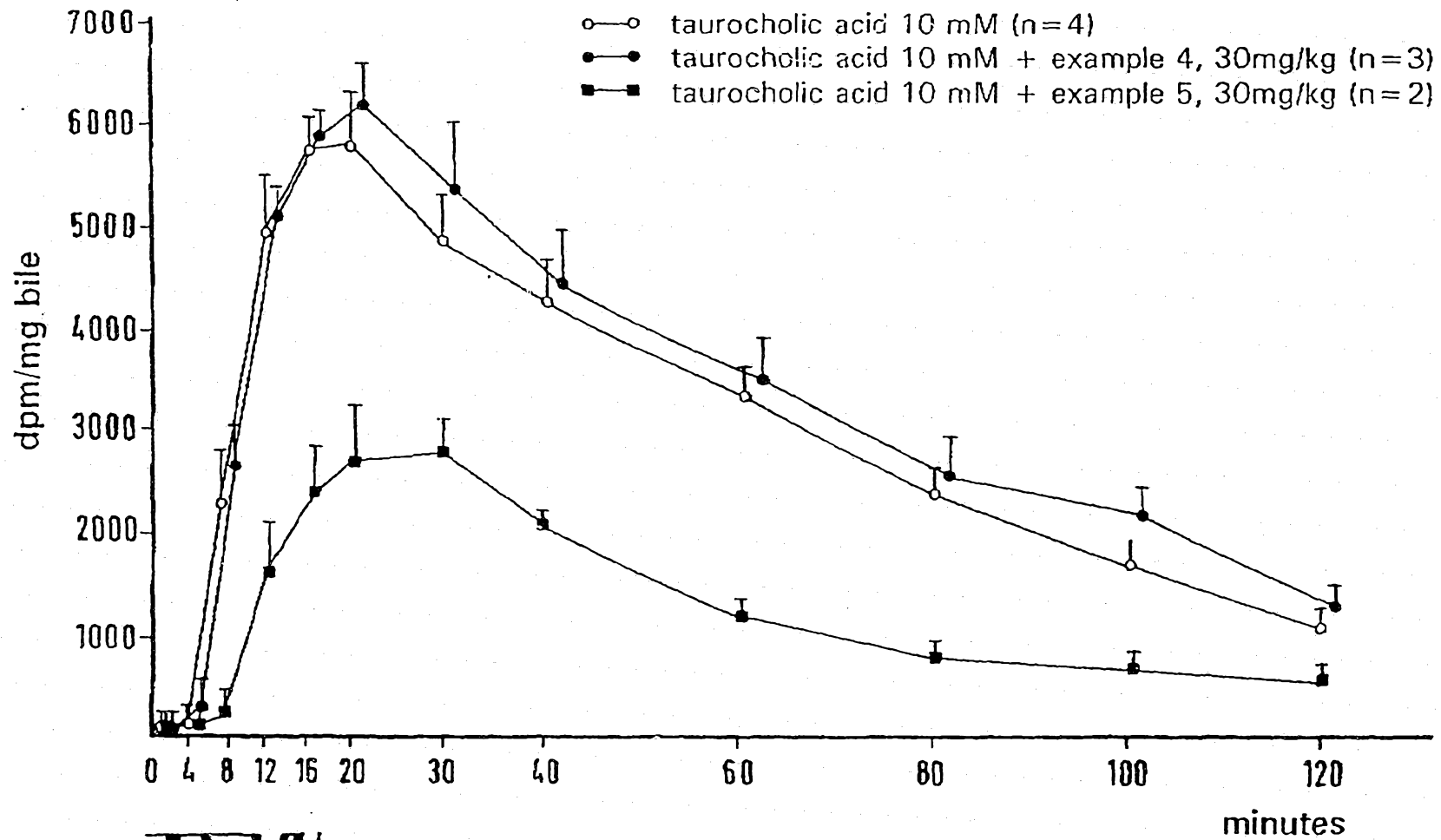


Fig. 3b

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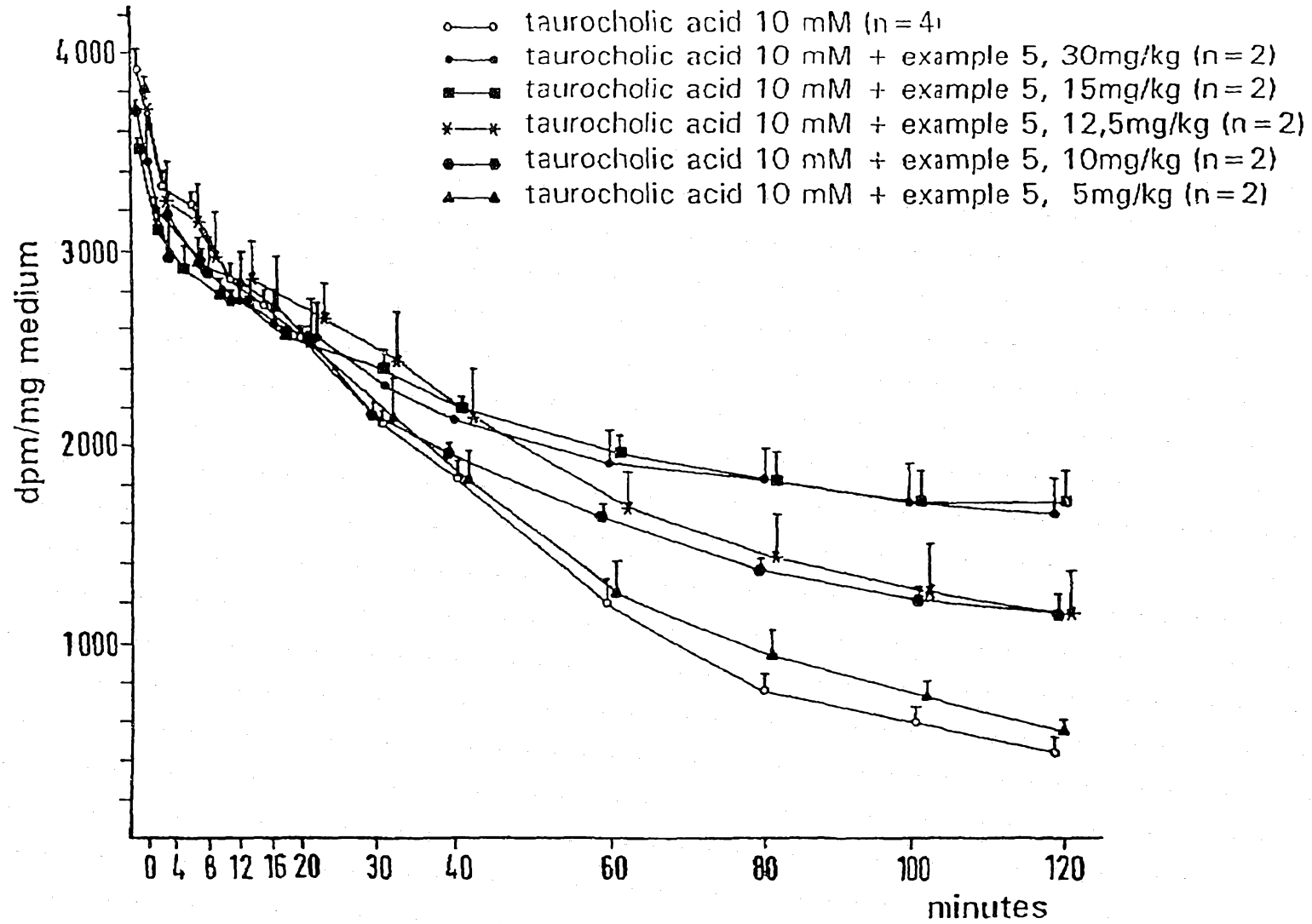


Fig. 4a

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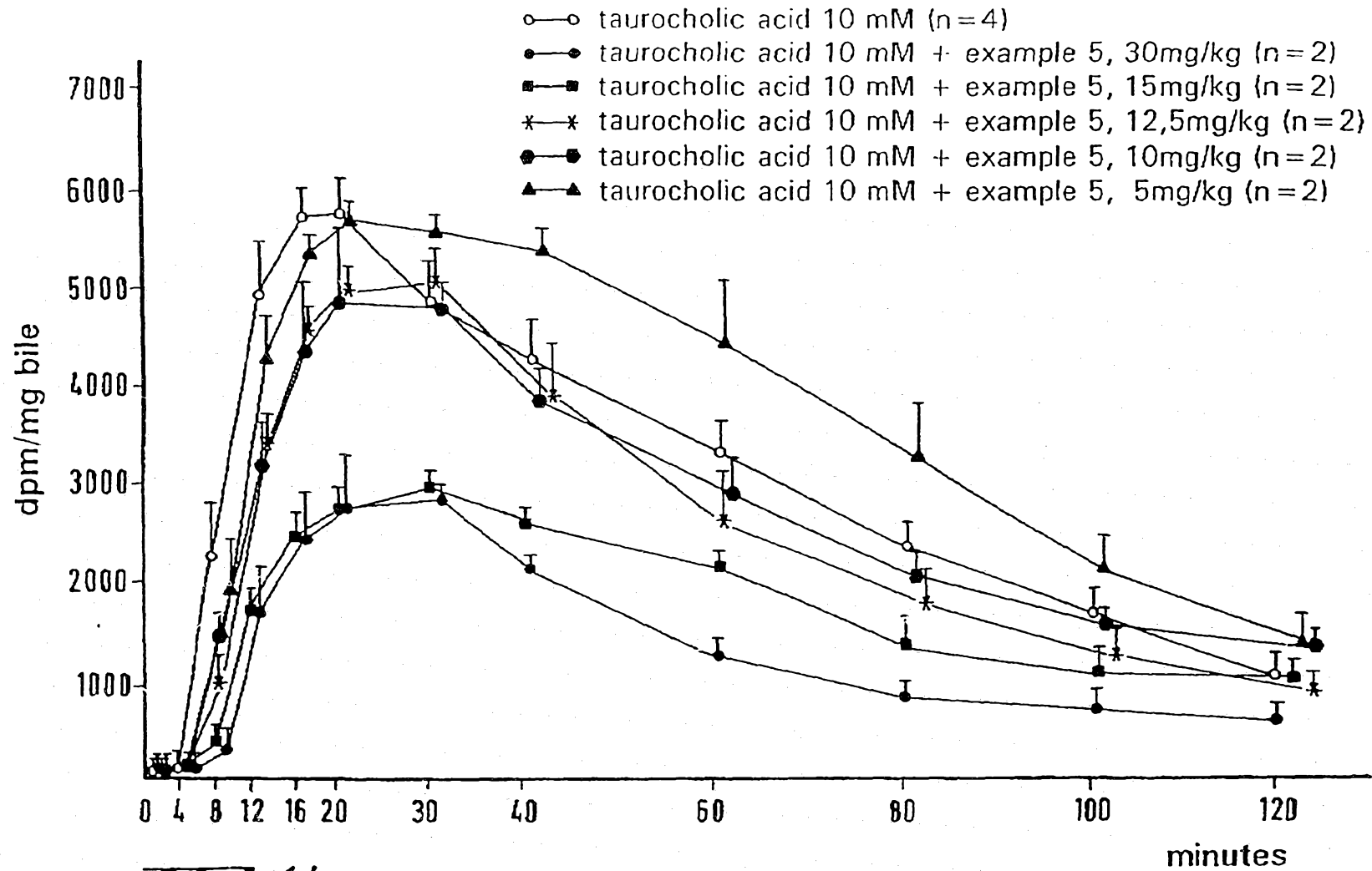
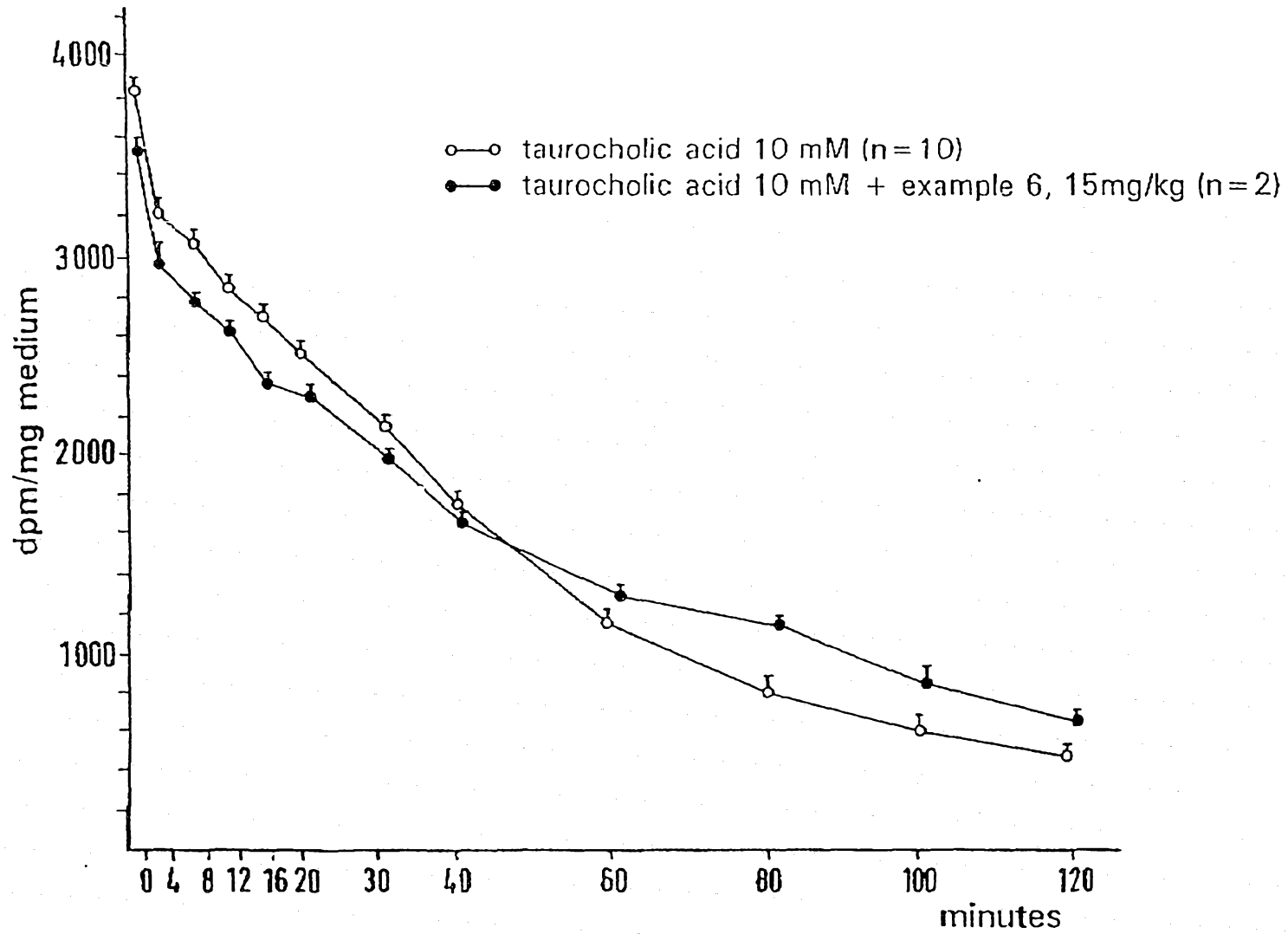


Fig. 4b

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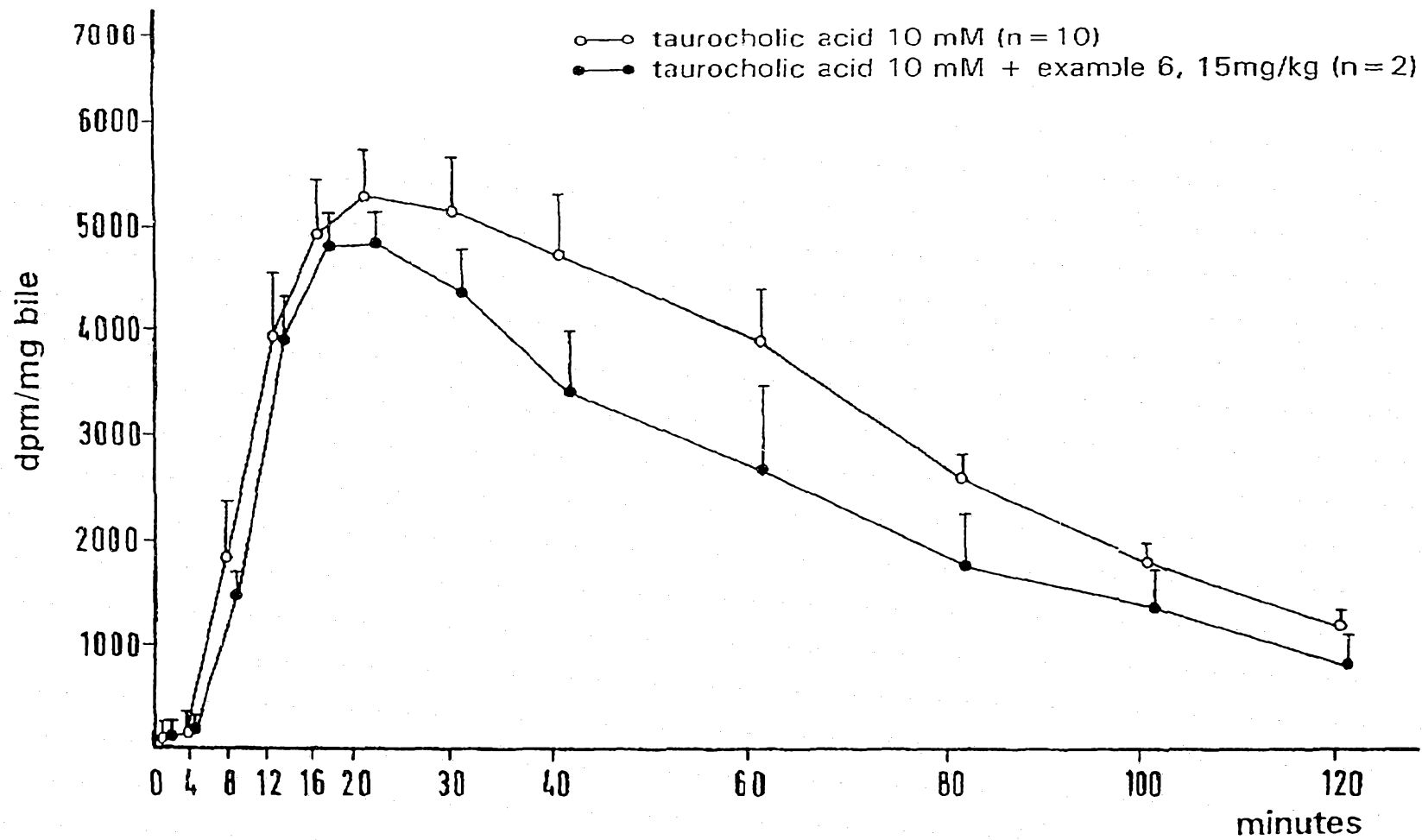
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Fig. 5a

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Fig. 5b

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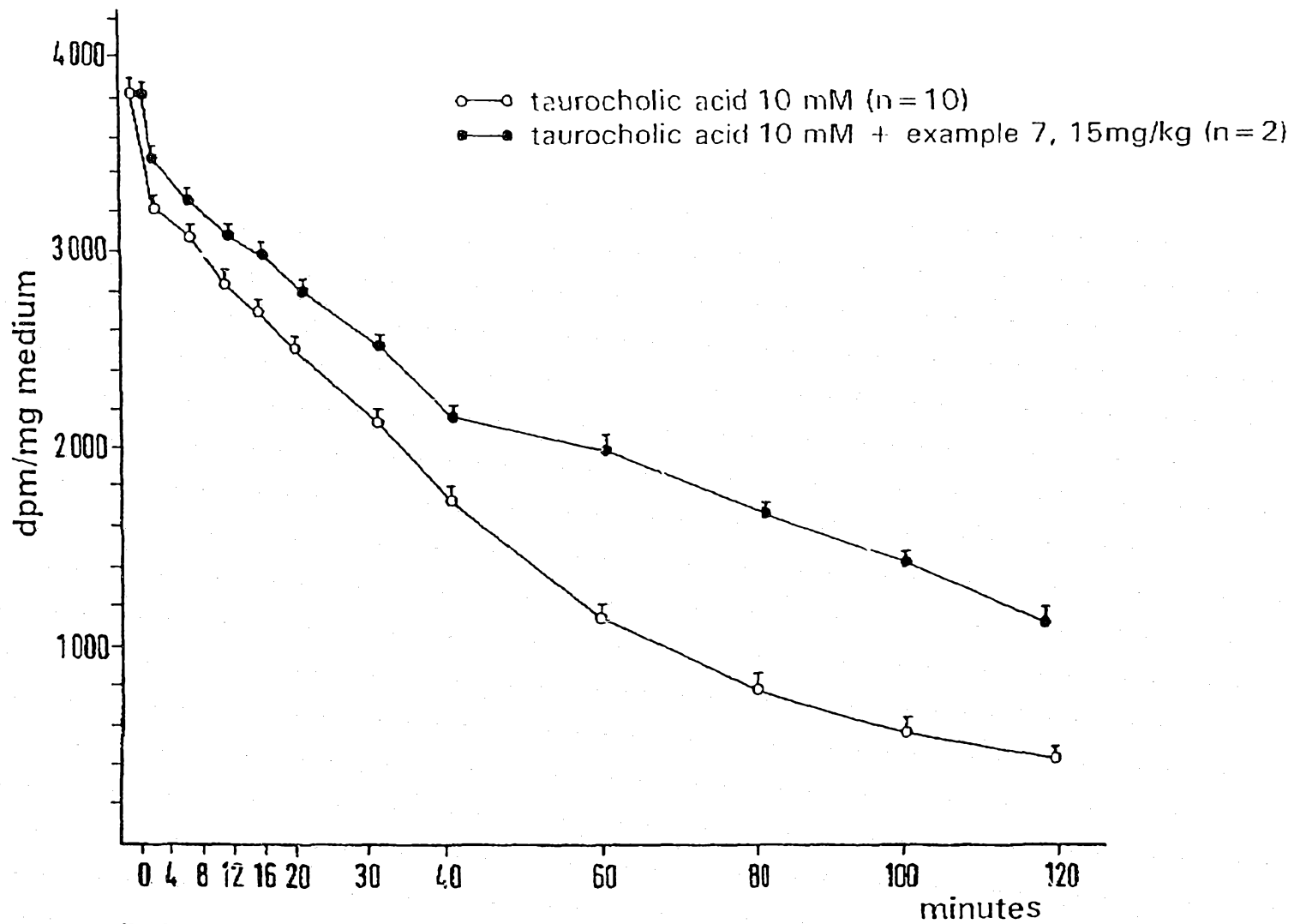


Fig. 6a

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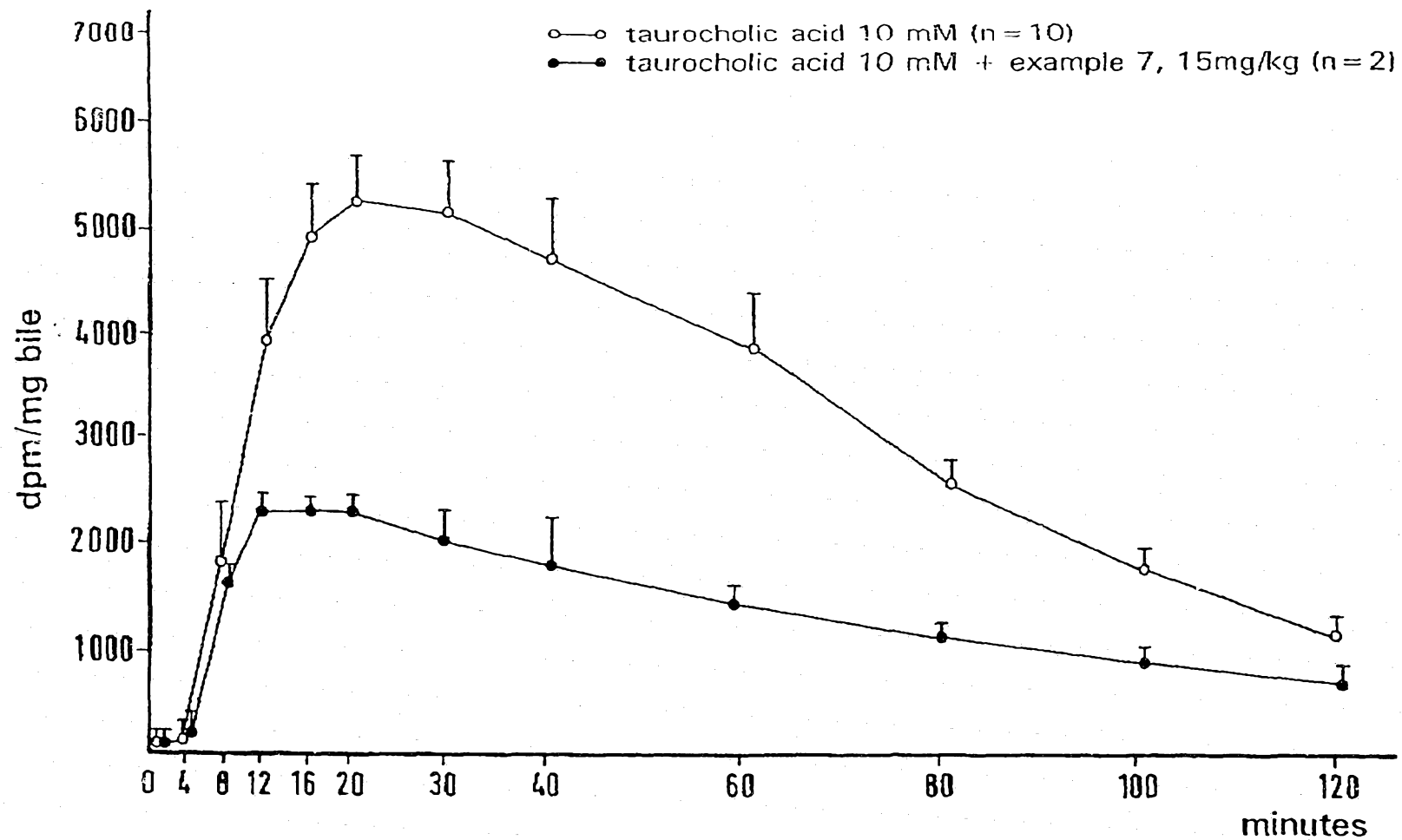
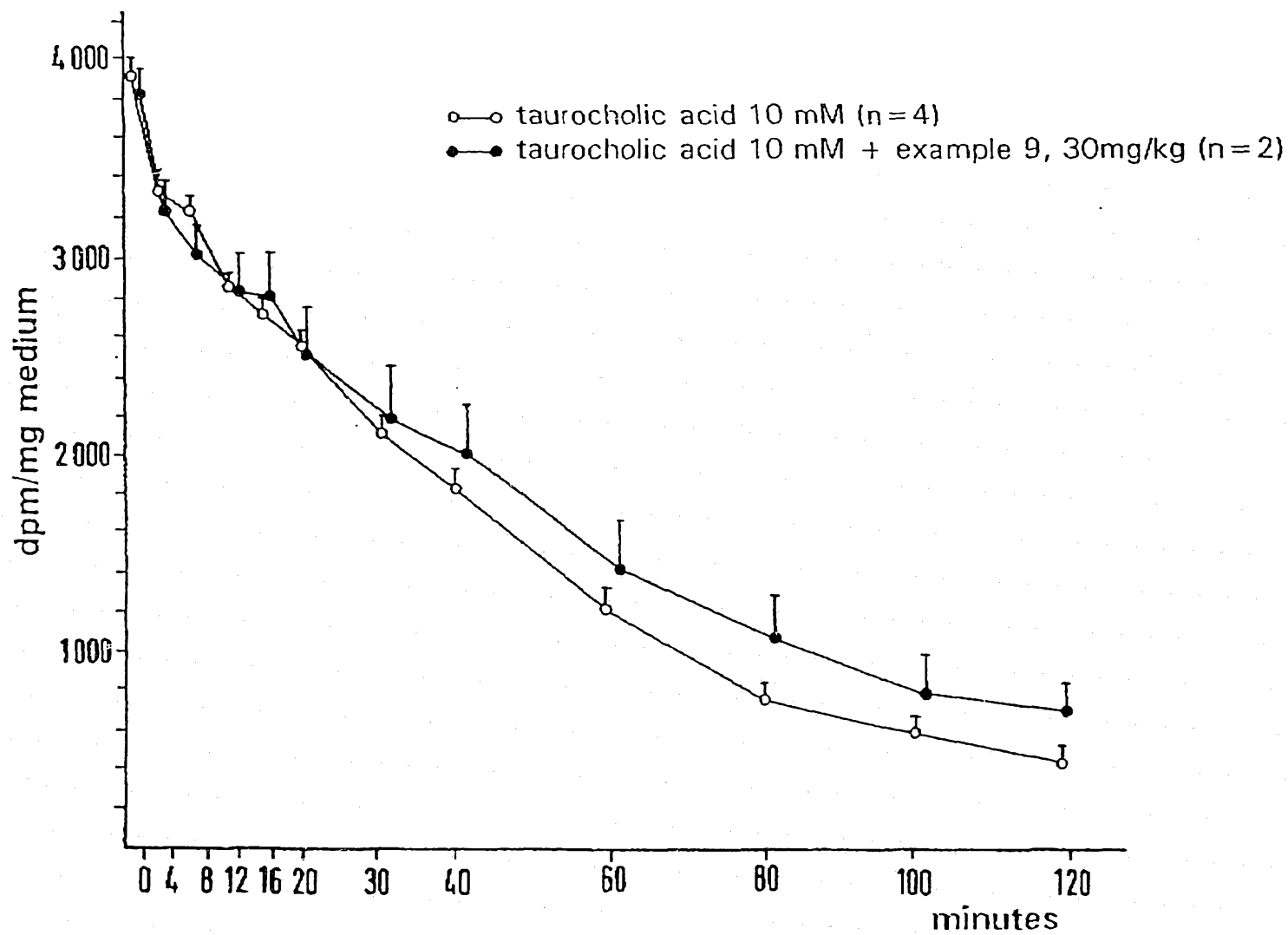


Fig. 6b

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Fig. 7a

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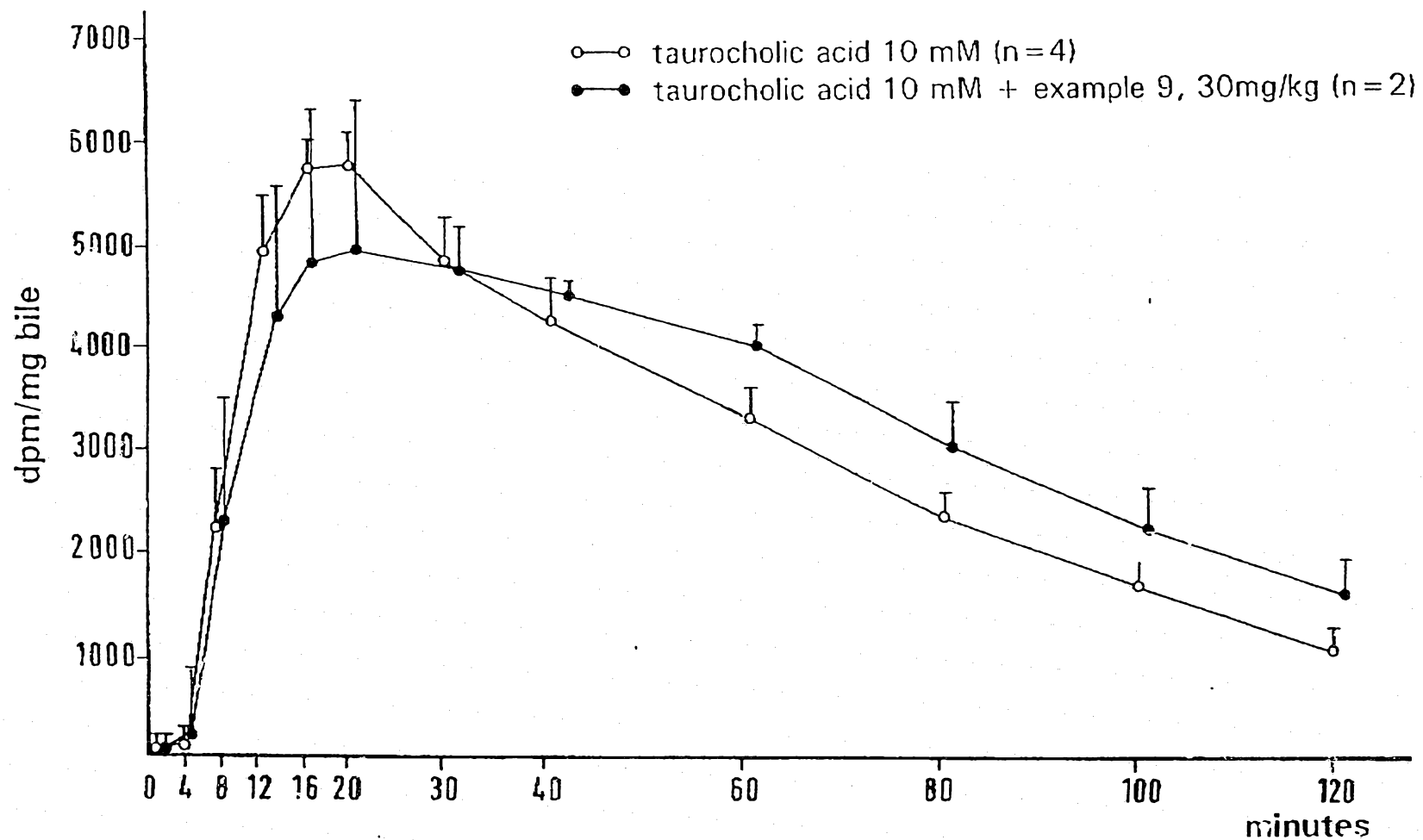


Fig: 7 b

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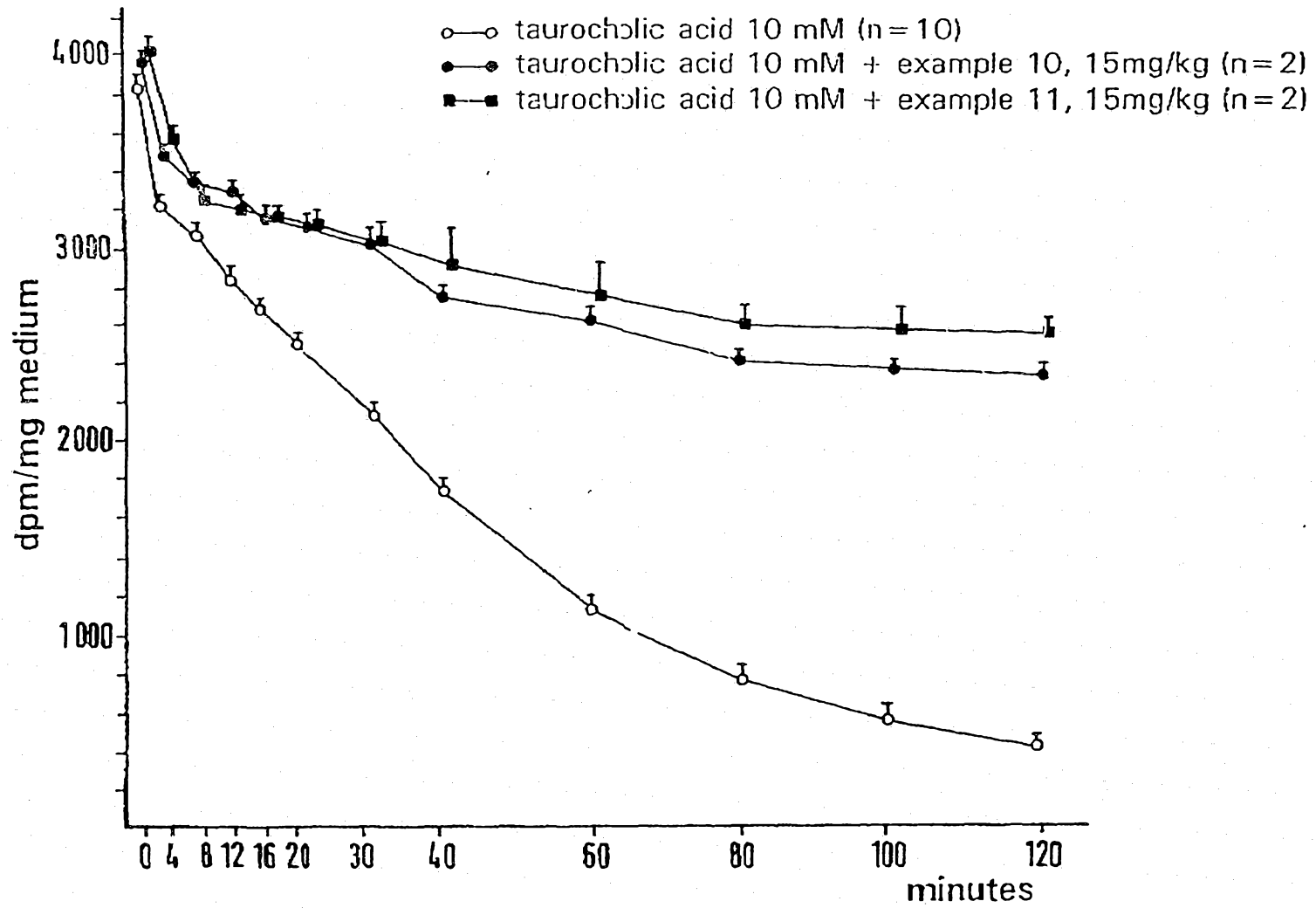


Fig. Ba

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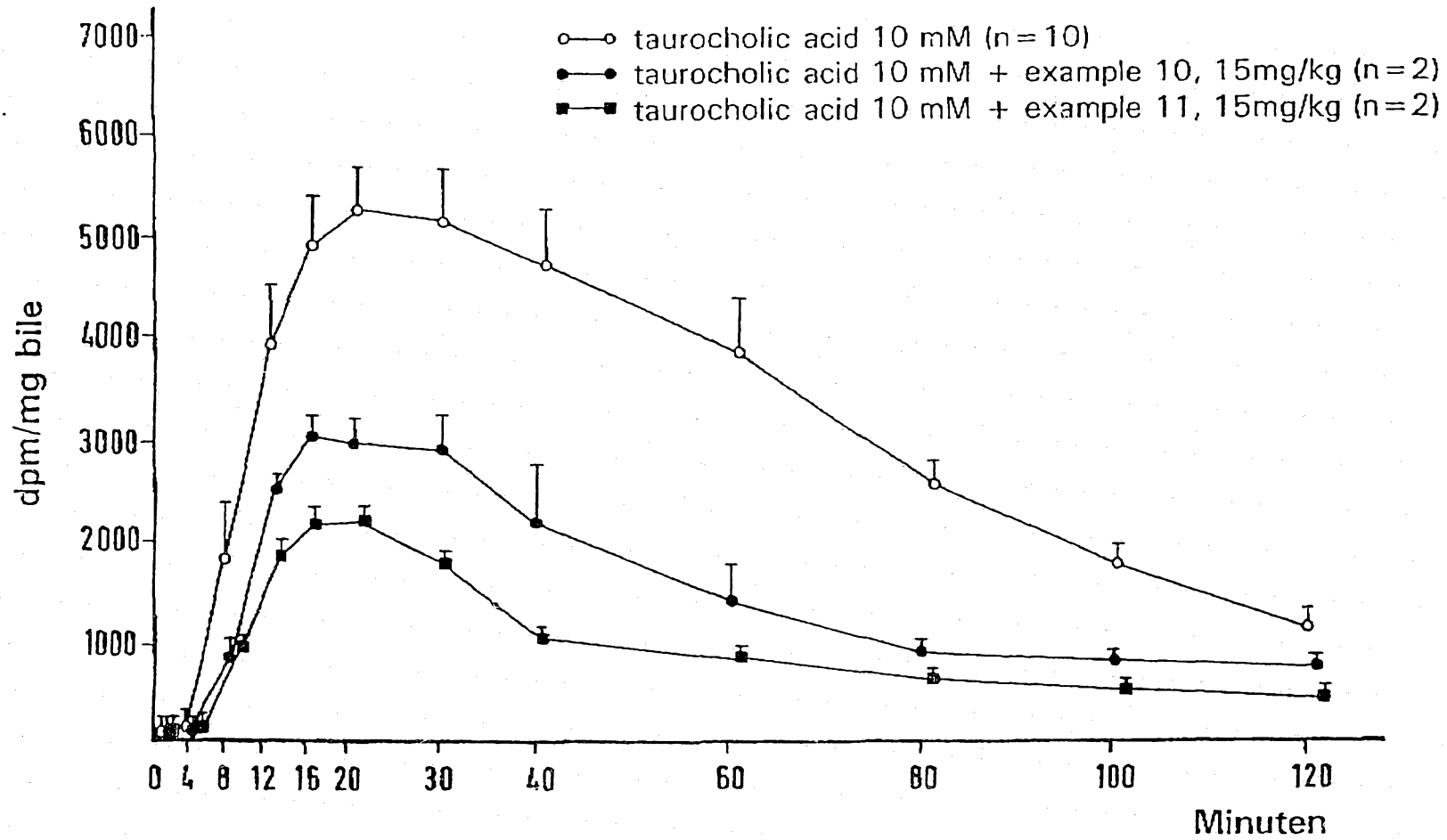


Fig. 8b

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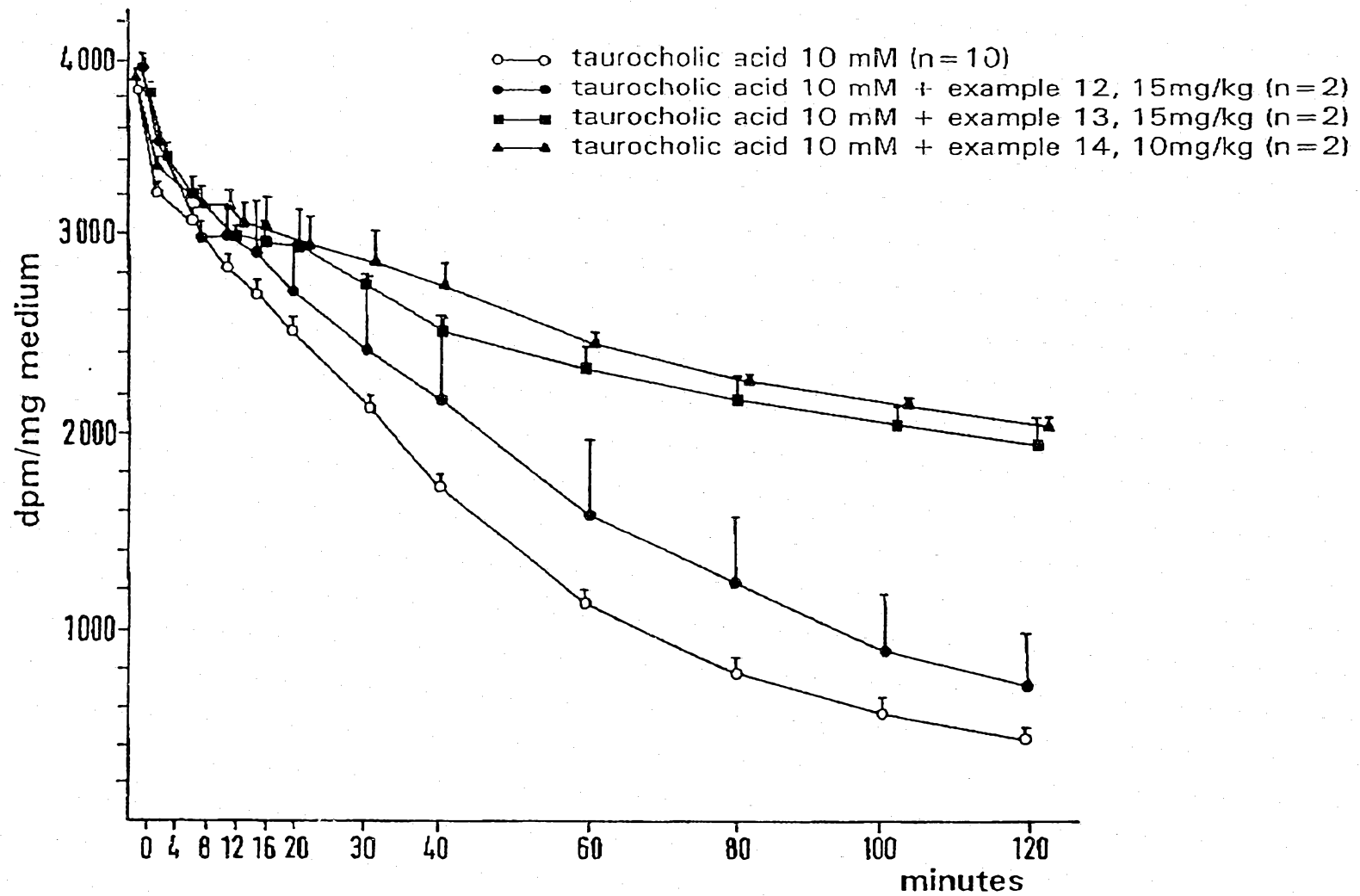


Fig. 9a

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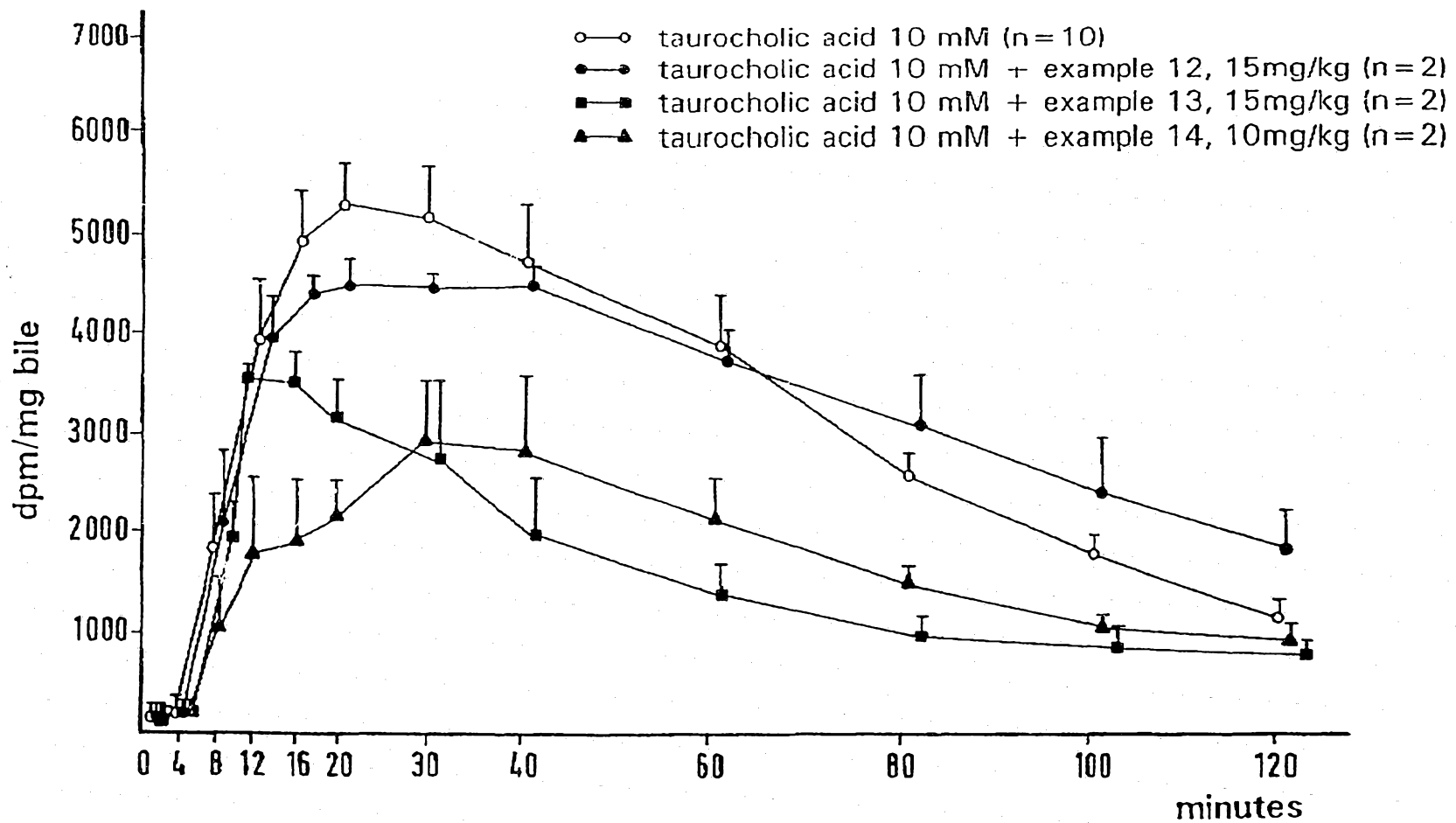


Fig. 9b

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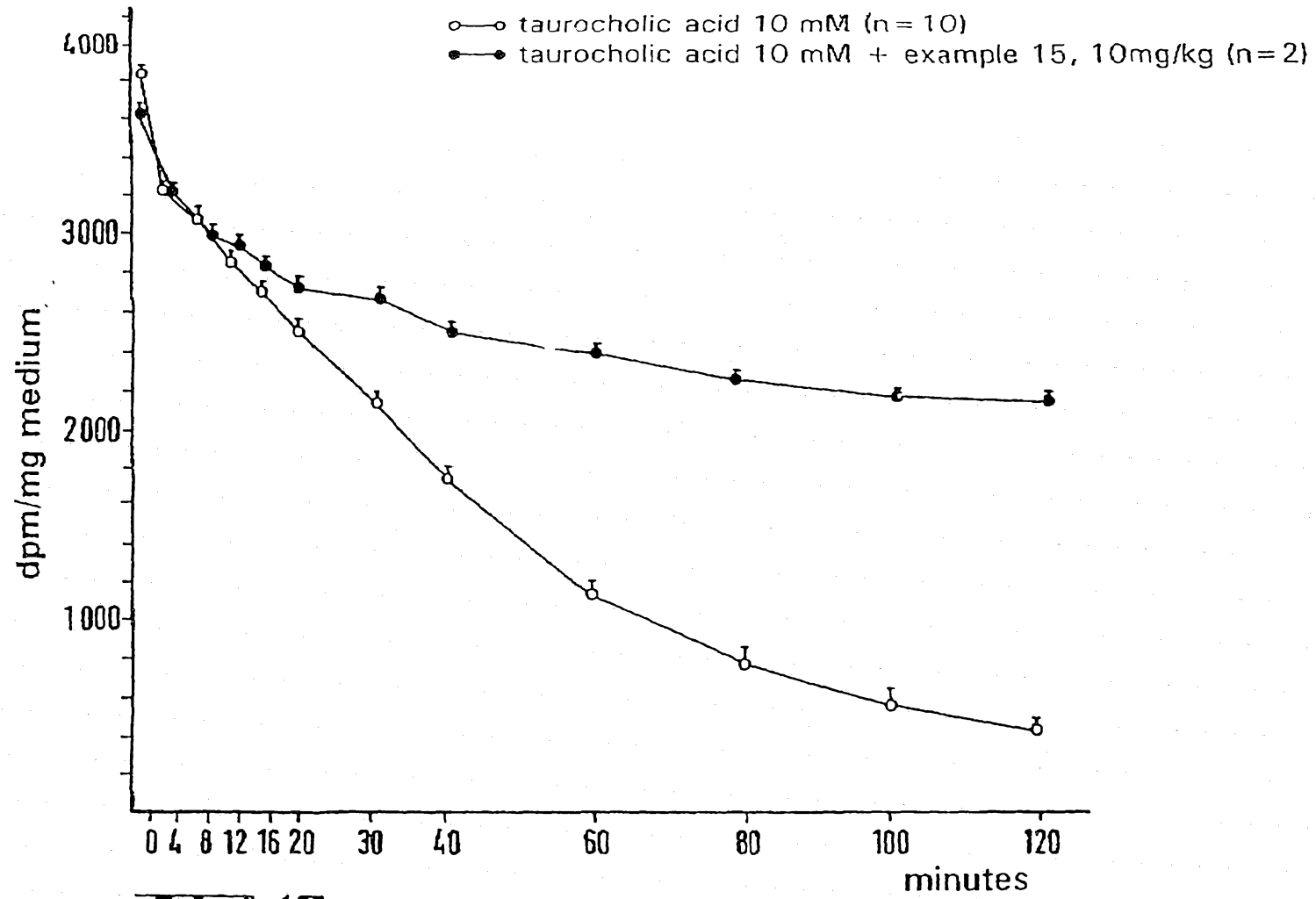
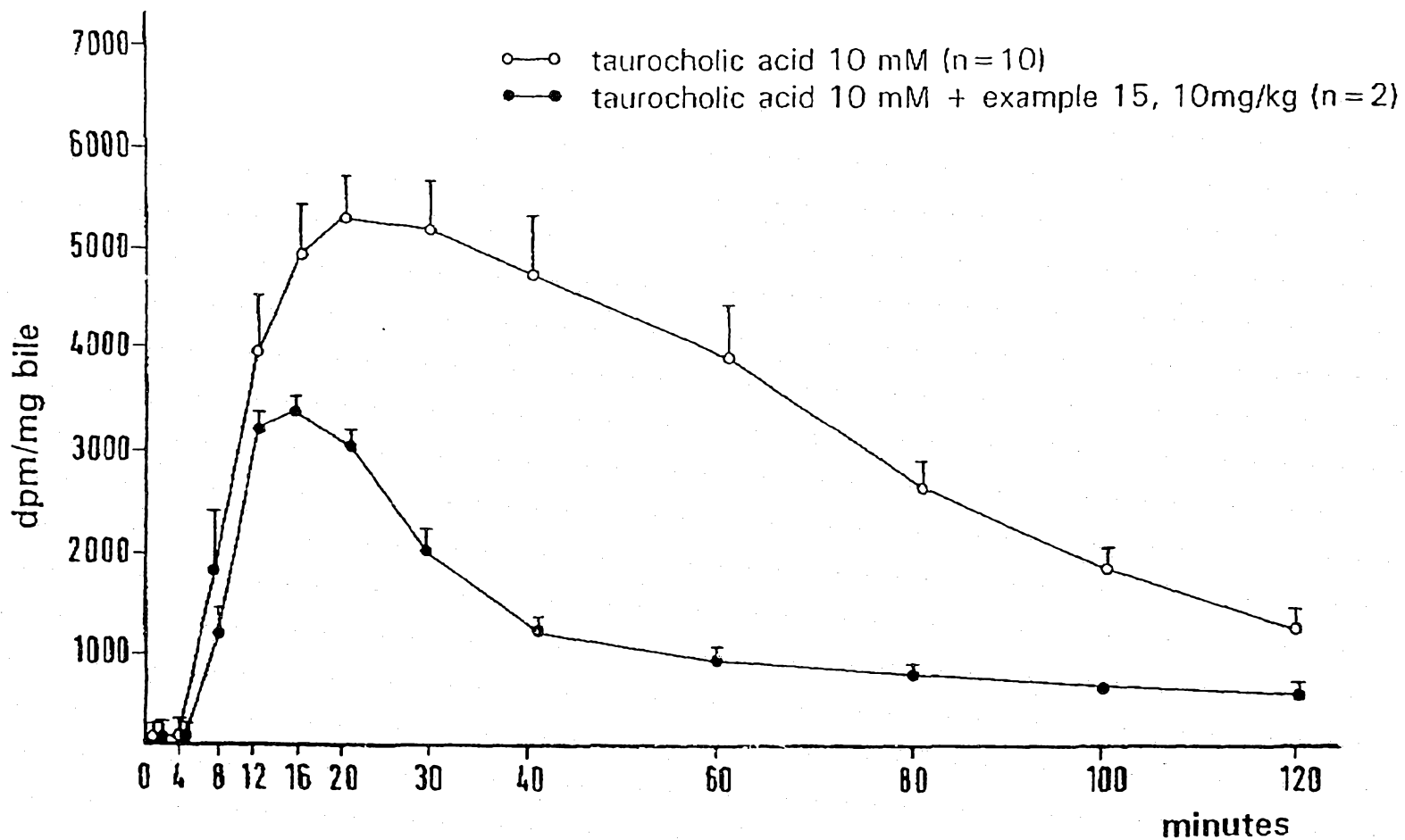


Fig. 10a

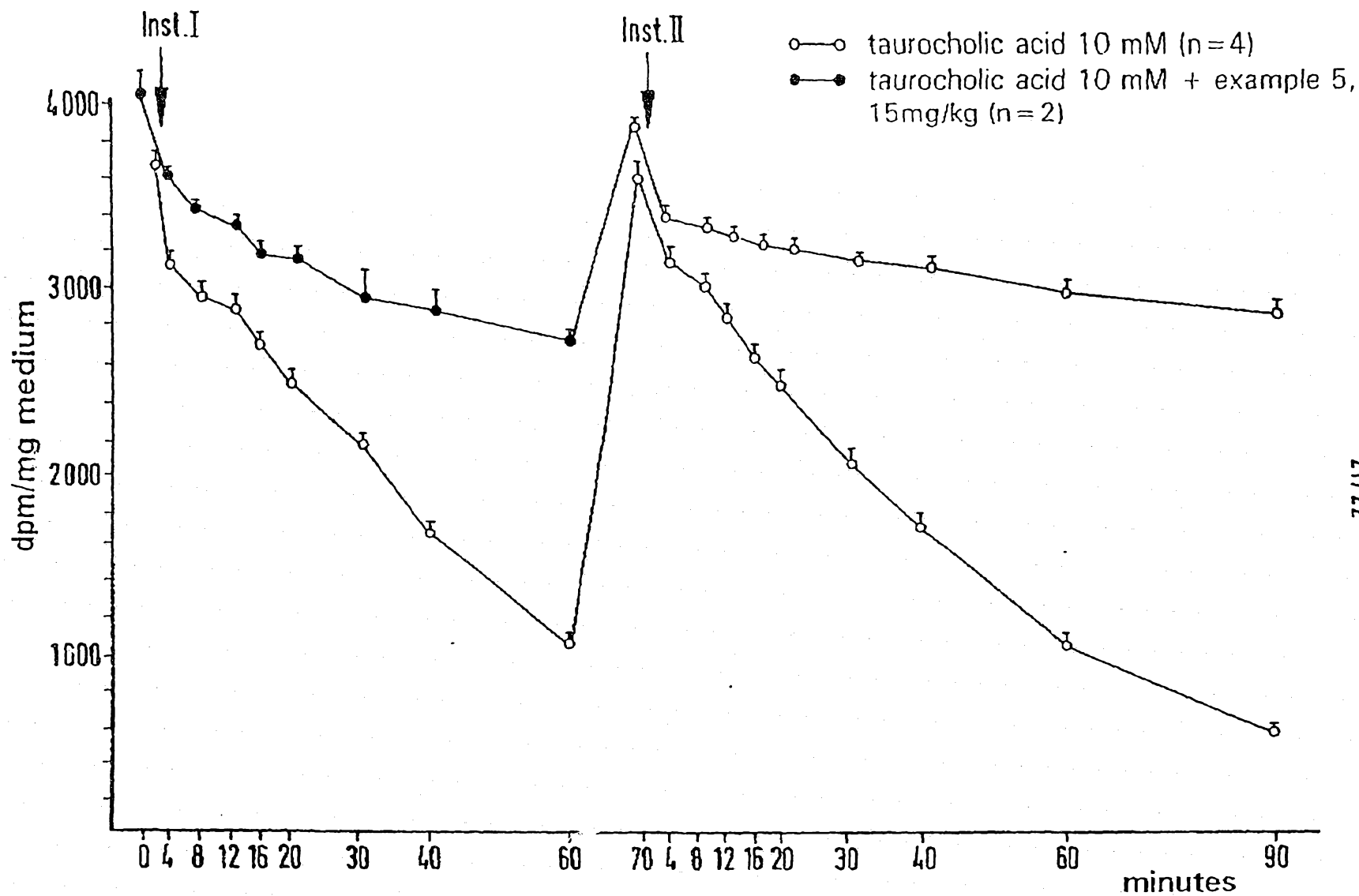
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Fig. 10b

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Fig. 11a

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○-○ taurocholic acid 10 mM (n=4)
●-● taurocholic acid 10 mM + example 5, 15mg/kg (n=2)

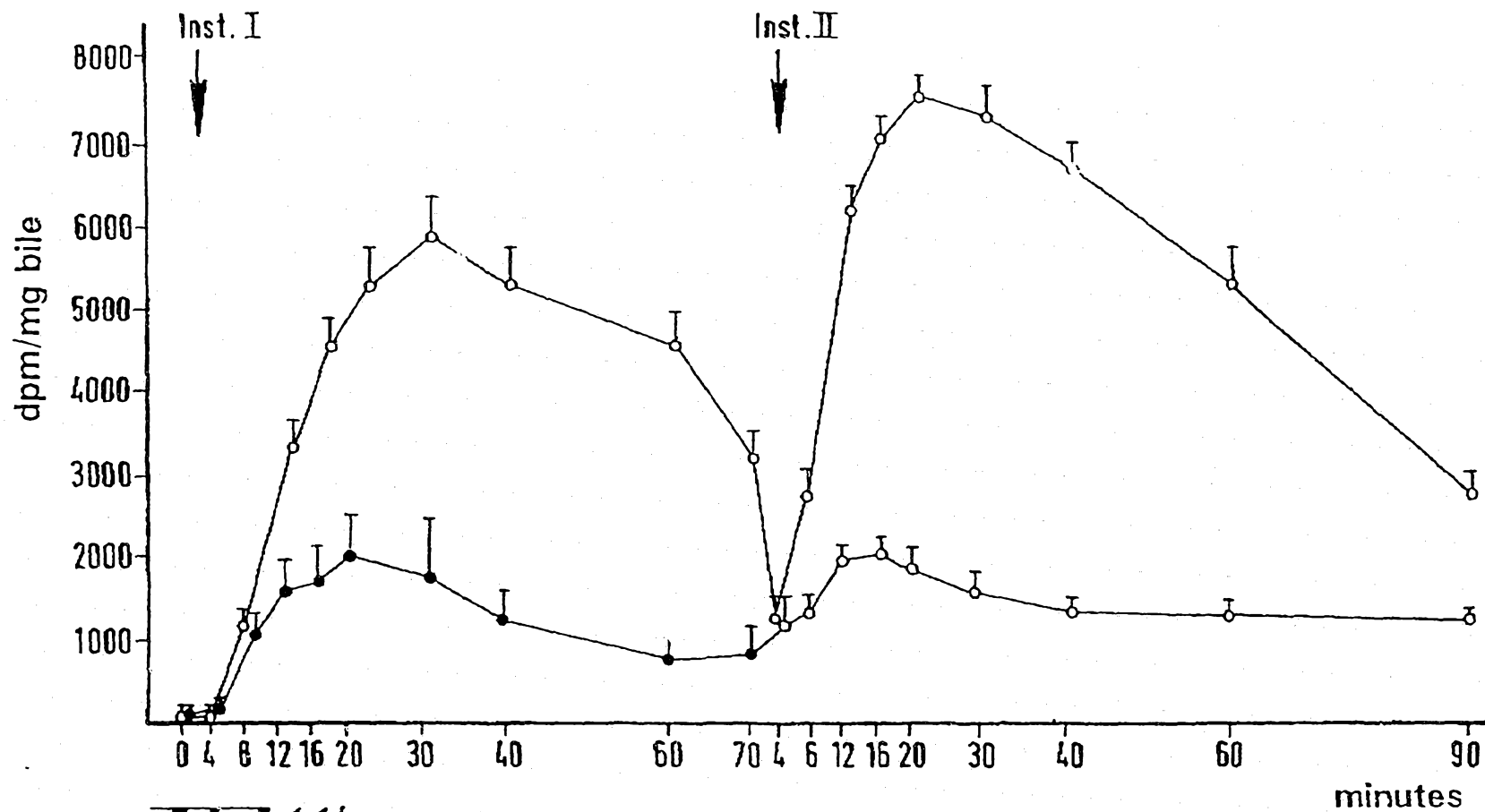


Fig. 11b

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