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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia : Expediente No. **10123058**
Asunto : Solicitud de patente para. **"USO COMBINADO DE UN DERVIADO DE COLESTANOL"**
Solicitante : OTSUKA PHARMACEUTICAL CO., LTD. AND NATIONAL UNIVERSITY CORPORATION
Fecha de solicitud : 5 de Octubre de 2010

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad OTSUKA PHARMACEUTICAL CO., LTD. AND NATIONAL UNIVERSITY CORPORATION GUNMA UNIVERSITY solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **82288** del 20 de Octubre de 2015, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"USO COMBINADO DE UN DERVIADO DE COLESTANOL"** a favor de OTSUKA PHARMACEUTICAL CO., LTD. AND NATIONAL UNIVERSITY CORPORATION GUNMA UNIVERSITY

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución No. **82288** del 20 de Octubre de 2015, con fecha de publicación listado del 27 de Octubre de 2015, fecha de vencimiento del 27 de Noviembre de 2015, y fecha del término legal el 14 de Diciembre de 2015.

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III. LA DECISIÓN RECURRIDA

- 3.1 Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:
- 3.1.1 Denegar la patente de invención a la creación titulada: **"USO COMBINADO DE UN DERIVADO DE COLESTANOL"**
- 3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:
- 3.2.1 "Las nuevas reivindicaciones 1 a 5 no superan la objeción sobre la falta de unidad de invención, por cuanto el concepto común definido y que corresponde a composiciones farmacéuticas liposomales que comprenden compuestos derivados de glucósidos del colestanol útiles, se encuentra divulgado en el estado de la técnica, específicamente en el documento EP1647277 y no puede considerarse concepto común e inventivo de todas las combinaciones de principios activos que se reclaman. El capítulo reivindicatorio de la solicitud tal y como fue presentado o tal como se encuentra modificado, no cumple con el requisito de unidad de invención de conformidad con lo dispuesto en el artículo 25 de la referida decisión 486, en razón de que allí se establece que *"La solicitud de patente solo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conforme un único concepto inventivo"*. Lo anterior, por cuanto se encuentran 8 grupos inventivos definidos"
- 3.2.2 "La nueva reivindicación 1 no es clara ni concisa de acuerdo con lo establecido en el artículo 30 de la decisión 486 porque define los agentes contra el cáncer en términos del tipo de cáncer o funcionalidad mediante expresiones como *"cáncer texano"* y *"complejo de platino"*, se recuerda que los compuestos químicos deben ser identificados en términos de su estructura química, denominación común internacional DCI9 o número IUPAC"
- 3.2.3 "La solicitante argumenta que la solicitud guarda un único concepto común inventivo consistente en la combinación de un derivado de colestanol y un segundo agente anticancerígeno y que dicha combinación exhibe un efecto sinérgico. Al respecto, este despacho señala en primer lugar que el concepto común inventivo corresponde a composiciones liposomales que comprenden compuestos derivados de glucósidos esteroideos esta anticipado en el documento D2, el cual divulga composiciones liposomales que comprenden compuestos derivados de glucósidos del colestanol que corresponden al componente de fórmula (I) presente en las combinaciones entre principios activos reclamadas, en segundo lugar la yuxtaposición de agentes anticancerígenos en la composición

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reclamada no permite inferir un efecto técnico inesperado para la totalidad de la materia reclamada en la reivindicación independiente puesto que entre los segundos agentes anticancerígenos no existe ninguna cercanía estructural , sino que la relación es de tipo funcional y además solo existe evidencia cierta en el expediente administrativo de la combinación del compuesto de formula I con cisplatino, por lo que una persona de oficio normalmente versada en la materia concluiría sin dificultad que la materia reclamada en la reivindicación independiente no tiene sustento y además que a través de las pruebas técnicas presentadas no es posible inferir que la totalidad de las combinaciones reclamadas en la reivindicación independiente presente un efecto técnico inesperado. En conclusión, los argumentos de la solicitante carecen de validez. "

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

1. Revocar la Resolución No. **82288** del 20 de Octubre de 2015.
2. Conceder el privilegio de patente de invención para **"USO COMBINADO DE UN DERIVADO DE COLESTANOL"** a favor de **OTSUKA PHARMACEUTICAL CO., LTD. AND NATIONAL UNIVERSITY CORPORATION GUNMA UNIVERSITY**

V. MODIFICACIÓN DE UNA SOLICITUD EN TRÁMITE

A este respecto, en primer lugar mi representada desea poner de presente que en relación con la objeción del señor Examinador con respecto a la reivindicación 1, amablemente señalamos que la reivindicación 1 define claramente la estructura química del compuesto de formula (I) por lo tanto no es necesario que los otros agentes de la composición farmacéutica especifiquen de manera detallada su estructura química.

En cuanto a las objeciones de falta de claridad, el término "cáncer taxano" y "complejo de platino" corresponden a términos ampliamente conocidos por la persona versada en la materia. Por lo tanto, el eliminar estos términos y/o cambiarlos limitaría injustamente el alcance de la materia reclamada.

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Por otra parte, amablemente reiteramos nuestros argumentos presentados previamente en la respuesta a la Acción Oficial No. 19639 en cuanto a la falta de unidad de invención:

- "Por otro lado, respetuosamente ponemos de presente que las invenciones 1 a 7 forman un único concepto inventivo, que es, una combinación de un derivado de colestanol y un agente contra el cáncer, en el que dicha combinación exhibe un efecto sinérgico y hace una contribución frente al arte previo. Los agentes contra el cáncer de las invenciones 1 a 7 son aquellos que exhiben un efecto sinérgico cuando son usados en combinación con un derivado de colestanol como se prueba en la descripción y en los datos adicionales presentados previamente. Por lo tanto, mi representada respetuosamente manifiesta su desacuerdo con respecto a la objeción de falta de unidad de invención hacia las reivindicaciones 1 a 4 y 6 (nuevas 1 a 5). En consecuencia, las invenciones 1 a 7 de la presente invención cumplen con el requisito de unidad de invención en vista de lo anteriormente argumentado."

Finalmente, con respecto a la objeción de falta de unidad de invención atentamente señalamos que las reivindicaciones de la presente invención comparten el mismo concepto común inventivo ya que las reivindicaciones pendientes se encuentran dirigidas a combinaciones de un derivado de colestanol y un agente contra el cáncer, en el que dichas combinaciones exhiben un efecto sinérgico y hace una contribución frente al arte previo

Por lo tanto, los argumentos esgrimidos a continuación con respecto a la patentabilidad de la invención, en los términos del capítulo reivindicatorio modificado, resultan plenamente predicables del capítulo reivindicatorio sobre el cual la patente fue negada. En efecto, la no ampliación de la materia en el nuevo pliego es evidencia suficiente de que el presente recurso controvierte el análisis de patentabilidad efectuado por su Despacho, de tal manera que el presente recurso cumple con los requisitos de ley para su aceptación y trámite.

VI. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, toda vez que la presente solicitud sí cumple con los requerimientos de novedad y nivel inventivo exigidos en la Decisión 486, como se demostrará a continuación:

6.1 La presente solicitud sí tiene nivel inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

"Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

Respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha expuesto en la Interpretación Prejudicial del proceso 13-IP-2010:

"En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado".

[Señalado fuera del texto]

Por lo anterior, se entiende que para que una persona medianamente versada en la materia pudiera derivar de manera obvia una invención, requeriría simplemente aplicar sus conocimientos técnicos. En contraste, todo aquello que va más allá de la simple aplicación de los conocimientos técnicos y que no ha sido revelado en el estado de la técnica, debe ser considerado inventivo.

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Con base en lo anterior, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

En primer lugar, respetuosamente manifestamos que una persona normalmente versada en la materia nunca se vería motivada a combinar derivados de colestanol y los agentes anticancerígenos específicos reclamados (Paclitaxel, Docetaxcel, Alimta, 5-FU, Cisplatino y Oxaliplatino) esperando obtener un efecto sinérgico porque (i) existen muchos agentes anticancerígenos que pueden ser usados y (ii) no existen enseñanzas o sugerencia en D1 ni D2 que muestren un efecto sinérgico cuando se combinan los agentes anticancerígenos específicos reclamados (Paclitaxel, Docetaxcel, Alimta, 5-FU, Cisplatino y Oxaliplatino) y los derivados del colestanol. Los efectos sinérgicos de los derivados del colestanol y los agentes anticancerígenos específicos reclamados, están soportados en los ejemplos de la descripción y en la información adicional suministrada con el memorial de respuesta a la acción oficial No. 19639 del 6 de Marzo de 2013.

En segundo lugar, reiteramos los argumentos presentados anteriormente en la respuesta a la Acción Oficial No. 19639, en el que mi Representada señala que el problema resuelto por la presente invención es proporcionar una composición farmacéutica que comprende un derivado de colestanol y un agente contra el cáncer el cual muestra un efecto sinérgico. La presente invención es sobre la base del hallazgo que cuando el derivado de colestanol y un agente contra el cáncer son usados en combinación, la combinación exhibe un efecto sinérgico, el cual es mayor que un simple efecto aditivo de cada ingrediente por separado. Así, una persona del oficio normalmente versada en la materia no podría haber esperado tal efecto sinérgico a partir de las enseñanzas de D1 y D2.

Ahora bien, teniendo en cuenta lo anterior y que la composición acá reivindicada presenta un efecto anticancerígeno sinérgico, es decir el efecto técnico que produce la combinación es mayor que la suma de los efectos técnicos de los compuestos individuales, es claro que la presente invención se debe considerar patentable. Lo anterior, es evidente si se tiene en cuenta que de acuerdo con lo señalado por el "INSTRUCTIVO EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION Y MODELO DE UTILIDAD" de su Despacho con respecto a combinaciones no obvias, este mismo Instructivo en particular señala:

"Si las características técnicas combinadas producen un efecto técnico nuevo, es decir, si el efecto técnico que produce la combinación es mayor que la suma de los efectos técnicos de las características individuales, la invención tiene nivel inventivo. Es irrelevante si cada característica individual es total o parcialmente conocido".

Por lo tanto, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

En consecuencia de lo anterior, la invención de la presente solicitud tiene nivel inventivo en vista de los documentos D1 y D2 del estado de la técnica citados por el Examinador.

Conclusión

El documento D1, el documento D2, o su combinación no resulta anterioridad válida capaz de afectar la novedad y el nivel inventivo de la invención de la presente solicitud. Adicionalmente, la invención reivindicada cumple con los requisitos de unidad de invención y claridad.

6.2 Concesión de solicitudes equivalentes

El mérito investigativo de la presente invención ha sido reconocido por otras oficinas de patentes del mundo, las cuales han otorgado patentes para invenciones equivalentes. Tal es el caso de la Oficina de Patentes Europea, la cual ha emitido una notificación de aceptación que se adjunta a este recurso para la solicitud europea equivalente **EP 2251014**

A este respecto, deseamos poner de presente que si bien cada país es autónomo de conceder o negar una solicitud luego de la realización del estudio de fondo, es claro que el hecho de que la novedad y el nivel inventivo de una invención hayan sido reconocidos por varias oficinas a nivel mundial, es un indicio de la patentabilidad de la misma toda vez que (i) el estudio de novedad y nivel inventivo en todas las Oficinas de Patentes del mundo es realizado por personas con conocimientos técnicos en el área de interés que son consideradas personas idóneas para emitir conceptos sobre la patentabilidad de una invención y que (ii) los resultados de los exámenes de novedad o de patentabilidad efectuados respecto a solicitudes extranjeras pueden ser reconocidos como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención, tal como se señala en el artículo 46 de la Decisión 486:

"Artículo 46.- La oficina nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial.

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De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:

a) copia de la solicitud extranjera;

b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;

(...)

*La oficina nacional competente podrá **reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención*** (Negrilla fuera del texto).

Por todo lo anterior, consideramos que la presente solicitud cumple a cabalidad con los requerimientos de patentabilidad exigidos por la legislación actual, por lo que atentamente solicitamos en consideración lo siguiente:

VII. PETICIÓN

Por todo lo anterior, solicito a ese Despacho lo siguiente:

7.1 Que al considerar las razones precedentes se revoque la decisión contenida en la Resolución No. **82288** del 20 de Octubre de 2015, en cuanto resuelve negar el privilegio de patente de invención.

7.2. Que se otorgue el privilegio de patente de invención para **"USO COMBINADO DE UN DERIVADO DE COLESTANOL"** a favor de **OTSUKA PHARMACEUTICAL CO., LTD. AND NATIONAL UNIVERSITY CORPORATION GUNMA UNIVERSITY**

VIII. PRUEBAS

Solicito atentamente a ese Despacho se tengan como pruebas las siguientes:

8.1. Todos y cada uno de los documentos que obran en el expediente de la referencia y que reposan en las oficinas del Despacho a su cargo.

IX. NOMBRE Y DIRECCIÓN

El nombre y la dirección del solicitante recurrente son los siguientes:

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NATIONAL UNIVERSITY CORPORATION GUNMA UNIVERSITY

4-2 Aramaki-machi,
Maebashi-shi,
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Japon

X. ANEXOS

- Copia de la solicitud de patente en Europa en donde se reconoció la novedad y nivel inventivo como evidencia del nivel inventivo de la presente solicitud.

XI. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaría de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4º, de esta ciudad de Bogotá, D.C.

Señor Superintendente,



LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

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(12) EUROPEAN PATENT SPECIFICATION

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- (22) Date of filing: 04.03.2009
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A61K 33/24^(2006.01) A61K 45/06^(2006.01)
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C07J 9/00^(2006.01)
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(54) COMBINATIONS OF AN ANTI-CANCER AGENT AND A CHOLESTANOL DERIVATIVE
KOMBINATIONEN AUS EINEM ANTIKREBSMITTEL UND EINEM CHOLESTANOLDERIVAT
COMBINAISONS CONTENANT UN AGENT ANTI-CANCER ET UN DERIVÉ DU CHOLESTANOL

- (84) Designated Contracting States:
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HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO SE SI SK TR
- (30) Priority: 05.03.2008 JP 2008055284
- (43) Date of publication of application:
17.11.2010 Bulletin 2010/46
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- (56) References cited:
WO-A1-2005/007172 WO-A1-2007/026869
WO-A2-2005/118071 JP-A- 11 060 592
JP-A- 2000 191 685
- AHMAD FARIED ET AL: "Chemically synthesized sugar-cholestanols possess a preferential anticancer activity involving promising therapeutic potential against human esophageal cancer", CANCER SCIENCE, vol. 98, no. 9, 1 September 2007 (2007-09-01), pages 1358-1367, XP55024322, ISSN: 1347-9032, DOI: 10.1111/j.1349-7006.2007.00563.x
- Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

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Description

[0001] The present invention relates to a chemotherapeutic agent for cancer (hereinafter referred to as a "cancer chemotherapeutic agent") and, more particularly, to a cancer chemotherapeutic agent employing a cholestanol derivative and an anti-cancer agent in combination.

Background Art

[0002] Anticancer activity of chemically synthesized sugar-cholestanols is known from Faried A. et al. Cancer Science, 2007, 98(9), 1358-1367.

A variety of anti-cancer agents used in chemotherapy for cancer, which is one mode of cancer therapy, have hitherto been developed and classified based on structure, action mechanism, etc. However, the efficacy of such an anti-cancer agent employed as a single agent is unsatisfactory. Instead, multi-drug therapy employing a plurality of anti-cancer agents has been predominantly carried out in recent years from the viewpoint of suppressing adverse side effects, and the efficacy of multi-drug therapy has been recognized.

Under such circumstances, both of the development of new anti-cancer combination chemotherapy, which has fewer adverse side effect and higher efficacy than conventional chemotherapies, and the development of new chemotherapeutic agents for use in the chemotherapy are desired.

[0003] Meanwhile, a cholestanol derivative, in which a sugar chain such as GlcNAc-Gal-, GlcNAc-Gal-Glc-, Fuc-Gal-, Gal-Glc-, Gal-, or GlcNAc- is bonding to cholestanol (the compound that the double bond in the B ring of the cholesterol is saturated), were previously found to have excellent anti-tumor activity (Patent Documents 1 to 4).

However, no cases have been reported in which the aforementioned cholestanol derivatives and another anti-cancer agent are employed in combination.

[Patent Document 1] JP-A-2000-191685

[Patent Document 2] JP-A-1999-60592

[Patent Document 3] WO 2005/007172 (pamphlet)

[Patent Document 4] WO 2007/026869 (pamphlet)

Disclosure of the Invention

Problems to be Solved by the Invention

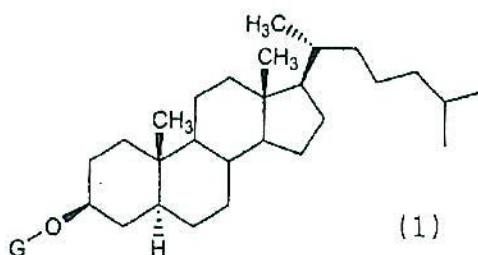
[0004] Thus, the present invention is directed to provision of a cancer chemotherapeutic agent which has fewer side effects and excellent efficacy.

Means for Solving the Problems

[0005] In view of the foregoing, the present inventors have carried out extensive studies, and have found that a remarkably potentiated anti-cancer effect can be attained through employment, in combination, of a cholestanol derivative represented by formula (1) or a cyclodextrin inclusion compound thereof and a known chemotherapeutic agent (anti-cancer agent), and thus the combined use of these pharmaceutical agents in cancer chemotherapy is very useful.

[0006] Accordingly, the present invention is directed to the following (1) to (10).

(1) A cancer chemotherapeutic agent comprising, in combination, a cholestanol derivative represented by formula (1):



(wherein G represents GlcNAc-Gal- or GlcNAc-) or a cyclodextrin inclusion compound thereof, and an anti-cancer

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agent.

(2) A cancer chemotherapeutic agent according to (1) above, wherein the anti-cancer agent is one or more species selected from the group consisting of a platinum complex anti-cancer agent.

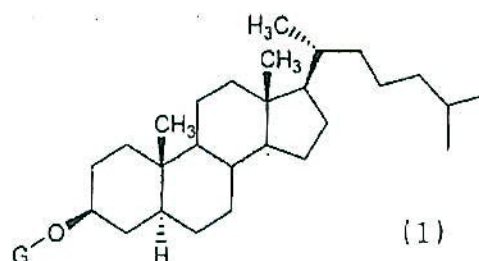
(3) A cancer chemotherapeutic agent according to (2) above, wherein the anti-cancer agent is one or more species selected from the group consisting of Cisplatin, and Oxaliplatin.

(4) A cancer chemotherapeutic agent according to any of (1) to (3) above, which is a compounding agent.

(5) A cancer chemotherapeutic agent according to any of (1) to (3) above, which is in the form of a kit including a drug containing a cholestanol derivative and a drug containing an anti-cancer agent.

(6) A cancer chemotherapeutic agent according to (5) above, wherein the drug containing a cholestanol derivative is a liposomal formulation.

(7) Use, in combination, of a cholestanol derivative represented by formula (1):



(wherein G represents GlcNAc-Gal- or GlcNAc-) or a cyclodextrin inclusion compound thereof and an anti-cancer agent, for producing a cancer chemotherapeutic agent.

Effects of the Invention

[0007] Through employment of the cancer chemotherapeutic agent and the cancer chemotherapy according to the present invention, prevention and treatment of cancer can be realized with safety and higher efficacy.

Brief Description of the Drawings

[0008]

Fig. 1 is a graph showing the cell proliferation inhibitory effects of CDDP, GC-CD, and CDDP + GC-CD on colon 26 cells;

Fig. 2 is a graph showing the cell proliferation inhibitory effects of CDDP, GC-CD, and CDDP + GC-CD on MKN45 cells, NCIH226 cells, or colo201 cells;

Fig. 3 is a graph showing the cell proliferation inhibitory effects of CDDP, GGC-CD, and CDDP + GGC-CD on colon26 cells, MKN45 cells, NCIH226 cells, or colo201 cells;

Fig. 4 is a graph showing the anti-tumor effect of single administration of CDDP, GC-CD, and CDDP + GC-CD against peritoneal dissemination caused by colon26 cells intraperitoneally inoculated in mice;

Fig. 5 is a graph showing the anti-tumor effect of multiple administration of CDDP, GC-CD, and CDDP + GC-CD against peritoneal dissemination caused by colon26 cells intraperitoneally inoculated in mice;

Fig. 6 is a graph showing the anti-tumor effect of single, delayed administration of CDDP, GC-CD, and CDDP + GC-CD against peritoneal dissemination caused by colon26 cells intraperitoneally inoculated in mice, after confirmation of peritoneal dissemination on the mesothelium of mice;

Fig. 7 is a graph showing the survival rate of mice to which colon26 cells were intraperitoneally inoculated, upon single administration of CDDP, GC-CD, or CDDP + GC-CD (single administration of CDDP and double administration of GC-CD, respectively);

Fig. 8 is a graph showing the effect of suppressing or reducing the tumor growth to which colon26 cells were subcutaneously inoculated in mice, upon single administration of CDDP, GGC-CD, or CDDP + GGC-CD ; and

Fig. 9 is a graph showing the effect of inhibiting metastasis of colon26 cells to the lung, upon single administration of CDDP, GC-CD, GGC-CD, CDDP + GC-CD, and CDDP + GGC-CD.

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Detailed Description of Preferred Embodiments

[0009] The specific cholestanol derivatives represented by formula (1) and employed in the present invention are all known compounds.

- 5 Among the cholestanol derivatives which are represented by formula (1) and in which G is GlcNAc-Gal-, G is preferably GlcNAc β 1,3-Gal β - or GlcNAc β 1,4-Gal β -. Among the cholestanol derivatives (1) in which G is GlcNAc-, G is preferably GlcNAc β -.

Of these, species in which G is GlcNAc-Gal- and GlcNAc- are essential, with those in which G is GlcNAc β 1,4-Gal β - and GlcNAc β - being more preferred.

- 10 The aforementioned cholestanol derivatives may be produced through a method, for example, disclosed in the aforementioned Patent Documents 1 to 4 or a similar method.

- [0010] The cholestanol derivative represented by (1) readily forms an inclusion complex with a cyclodextrin or a derivative thereof. Thus, the cholestanol derivative employed in the present invention may be a cyclodextrin inclusion compound thereof. In formation of such inclusion compounds, the size of the guest molecule to be included, Van der
15 Waals interaction between the guest molecule and cyclodextrin, and hydrogen bond between the hydroxyl groups of cyclodextrin and the guest molecule must be taken into consideration. Therefore, insoluble guest compounds do not always form the corresponding inclusion compounds. However, the cholestanol derivative of the present invention can form good inclusion complexes with cyclodextrin.

- [0011] Examples of the cyclodextrin forming the cyclodextrin inclusion compound of the present invention include
20 cyclodextrins such as α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin; and cyclodextrin derivatives such as methyl- β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin, monoacetyl- β -cyclodextrin, and 2-hydroxypropyl- γ -cyclodextrin. Of these, 2-hydroxypropyl- β -cyclodextrin is preferred for obtaining improved solubility.

- [0012] The cyclodextrin inclusion compound may be prepared through, for example, the following procedure: an
25 aqueous solution of a cyclodextrin or a derivative thereof having an appropriate concentration (e.g., 20 to 40%) is prepared, and the cholestanol derivative of the present invention is added to the aqueous solution, followed by stirring of the resultant mixture.

[0013] No particular limitation is imposed on the concentration of the solution of the cholestanol derivative (1), so long as the cholestanol derivative can form an inclusion compound with cyclodextrin. Generally, the concentration is about 1 to about 50 mass%, preferably about 10 to about 30 mass%.

- 30 [0014] The thus-produced cyclodextrin inclusion compound is highly water-soluble and, therefore, effectively exhibits the effect of the guest in vivo. Another advantage of the cyclodextrin inclusion compound is to ensure consistent in vitro test results.

- [0015] Alternatively, the cholestanol derivative (1) may be prepared into a liposomal formulation, whereby the cholestanol derivative can be more effectively delivered to the action expression site. Another advantage of the cyclodextrin
35 inclusion compound is to ensure consistent in vitro test results.

Preferably, the liposomal formulation includes the cholestanol derivative of the present invention, a membrane component, and an aliphatic or aromatic amine.

The cholestanol derivative content in the liposomal formulation is preferably 0.3 to 2.0 mol, more preferably 0.8 to 1.5 mol, with respect to 1 mol of the membrane component.

- 40 [0016] The membrane component may be a phospholipid. Specific examples of preferably employed phospholipids include natural and synthetic phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidic acid; mixtures thereof; and modified natural phospholipids such as aqueous lecithin. Examples of more preferred species include phosphatidylcholine (1 α -dipalmitoylphosphatidylcholine (DPPC)).

- [0017] The aliphatic or aromatic amine is employed mainly for positively charging the surface of lipid membrane.
45 Examples of such amines include aliphatic amines such as stearylamine and oleylamine; and aromatic amines such as fluorenylamine. Among them, stearylamine is particularly preferably employed.

Preferably, the amine is contained in an amount of 0.04 to 0.15 mol, more preferably 0.1 to 0.15 mol, with respect to 1 mol of membrane component (phospholipid).

- 50 [0018] In addition to the aforementioned components, if required, the liposome may further contain a membrane structure stabilizer such as cholesterol fatty acid or diacetyl phosphate.

[0019] The aqueous solution employing for dispersing the membrane component is preferably water, physiological saline, buffer, aqueous sugar solution, or a mixture thereof. Either an organic or an inorganic buffer may be used, so long as the buffer has a buffering action in the vicinity of the hydrogen ion concentration of body fluid. Examples of such buffers include a phosphate buffer.

- 55 [0020] No particular limitation is imposed on the method of preparing the liposomal formulation, and generally employed methods may be selected. Examples of the employable method include methods disclosed in JP-A-1982-82310, JP-A-1985-12127, JP-A-1985-58915, JP-A-1989-117824, JP-A-1989-167218, JP-A-1992-29925, and JP-A-1997-87168; a method disclosed in Methods of Biochemical Analysis (1988) 33, p.337; or a method disclosed in "Liposome" (published

by Nankodo).

[0021] No particular limitation is imposed on the anti-cancer agent which is used in combination with the cholestanol derivative represented by formula (1) or a cyclodextrin inclusion compound thereof, and known cancer chemotherapeutic agents may be used. Standard therapeutic agents which have been established with respect to the cancer of therapy target are preferably employed.

Specific examples include alkylating agents such as Cyclophosphamide, Ifosfamide, Melphalan (L-PAM), Busulfan, and Carboquione; metabolism antagonists such as 6-Mercaptopurine (6-MP), Methotrexate (MTX), 5-Fluorouracil (5-FU), Tegafur, Enocitabine (BHAC), and folic acid metabolism antagonists (pemetrexed compounds (Alimta, MTA)); carcinostatic antibiotics such as Actinomycin D, Daunorubicin, Bleomycin, Peplomycin, Mitomycin C, Aclarubicin, and Neocarzinostatin (NCS); plant alkaloids such as Vincristine, Vindesine, Vinblastine, and taxane anti-cancer agents (Taxotere (Docetaxel) and Taxol (Paclitaxel, TXL)); and platinum compounds such as Cisplatin (CDDP), and Carboplatin, Oxaliplatin (L-OHP). These anti-cancer agents may be used singly or in combination of two or more species.

[0022] As shown in the Examples described hereinbelow, when the cholestanol derivative represented by formula (1) or a cyclodextrin inclusion compound thereof is used in combination with an anti-cancer agent, proliferation of cancer cells of various types are strongly suppressed, as compared with the case of administration of only each agent. Therefore, this combined chemotherapy can drastically enhance therapeutic efficacy and mitigation of adverse side effects, and a pharmaceutical product containing these ingredients is a useful cancer chemotherapeutic agent.

No particular limitation is imposed on the cancer which can be effectively treated by administering the cancer chemotherapeutic agent of the present invention. Examples of the target cancer include malignant tumors such as gastric cancer, large bowel cancer, pancreatic cancer, uterus cancer, ovarian cancer, lung cancer, gallbladder cancer, esophageal cancer, liver cancer, breast cancer, mesothelioma, and prostatic cancer.

[0023] The form of the cancer chemotherapeutic agent of the present invention may be a compounding agent in which the aforementioned ingredients are mixed at an appropriate ratio, each at an effective amount, to form a single dosage form (single-formulation type), or may be a kit that consists of the respective dosage form of the aforementioned ingredients, each of which is formed independently including each effective amount, and that enables the dosage forms to be administered simultaneously or separately at intervals (double-formulation type).

[0024] Similar to general pharmaceutical formulations, no particular limitation is imposed on the dosage form of the above-described formulation, and the form may be any of the solid form such as tablet, liquid form such as injection, dry powder dissolving before use, etc.

No particular limitation is imposed on the administration route of the formulation, and an appropriate route may be determined depending on the dosage form of the agents. For example, an injection solution may be administered intravenously, intramuscularly, subcutaneously, intradermally, or interperitoneally, and a solid form may be administered orally or enterally.

[0025] The formulation may be prepared through a known method in the art. All pharmaceutically acceptable carriers (excipients or diluents such as a filler, a bulking agent, and a binder) generally employed in the art may also be employed. For example, a peroral solid form may be prepared through mixing the drug ingredients of the present invention with a excipient, and with an optional binder, disintegrant, lubricant, colorant, flavoring agent, deodorant, etc., and forming the mixture into tablets, coated-tablets, granules, powder, capsules, etc. through a method known in the art. These additive may be those generally employed in the art. Examples of the excipient include lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaolin, microcrystalline cellulose, and silicic acid. Examples of the binder include water, ethanol, propanol, simple syrup, liquid glucose, liquid starch, liquid gelatin, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, and polyvinylpyrrolidone. Examples of the disintegrant include dry starch, sodium alginate, agar powder, sodium hydrogencarbonate, calcium carbonate, sodium lauryl sulfate, monoglyceryl stearate, and lactose. Examples of the lubricant include purified talc, stearate salts, borax, and polyethylene glycol. Examples of the flavoring agent include sucrose, orange peel, citric acid, and tartaric acid.

[0026] An oral liquid formulation may be prepared by mixing the drug ingredients of the present invention with a flavoring agent, buffer, stabilizer, deodorant, etc., and forming the mixture into internal liquid agent, syrup, elixir, etc. through a method known in the art. The flavoring agent employed in the preparation may be any of the aforementioned members. Examples of the buffer include sodium citrate. Examples of the stabilizer include traganth, gum arabic, and gelatin.

[0027] Injection solutions may be prepared by mixing the drug ingredients of the present invention with additives such as a pH-regulator, buffer, stabilizer, tonicity agent, and local anesthetic agent, and forming the mixture through a method known in the art, to thereby provide subcutaneous, intramuscular, and intravenous injection liquids. Examples of the pH-regulator and buffer include sodium citrate, EDTA, thioglycolic acid, and thiolactic acid. Examples of the local anesthetic include procaine hydrochloride and lidocaine hydrochloride. Examples of the tonicity agent include sodium chloride and glucose.

[0028] Suppositories may be prepared by mixing the drug ingredients of the present invention with a carrier for

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mulation known in the art such as polyethylene glycol, lanolin, cacao butter, and fatty acid triglyceride, and with an optional surfactant such as Tween (registered trademark), and forming the mixture into suppositories through a method known in the art.

[0029] Ointments may be prepared by mixing the drug ingredients of the present invention with optional additives generally employed in the art such as a base, stabilizer, moisturizer, and preservatives, and forming the mixture into ointments through a method known in the art. Examples of the base include liquid paraffin, white petrolatum, white beeswax, octyldodecyl alcohol, and paraffin. Examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, and propyl p-hydroxybenzoate.

[0030] Cataplasms may be prepared by applying the aforementioned ointment, gel, cream, paste, etc. to a generally employed support through a routine method. Examples of appropriate supports include woven and nonwoven fabric made of cotton, staple fiber, or chemical fiber, and film and foamed sheet made of soft vinyl chloride, polyethylene or polyurethane.

[0031] Generally, the formulation is preferably prepared so as to have a cholestanol derivative content and an anti-cancer agent content of 0.0001 to 80 wt.% (as effective ingredient).

[0032] When the cancer chemotherapeutic agent of the present invention is provided as a kit, the kit may be designed to pack independently the respective dosage form including separately the cholestanol derivative represented by formula (1) or a cyclodextrin inclusion compound thereof and an anti-cancer agent, each of which have been prepared in the above manner, and to be used each pharmaceutical formulation taken separately from the corresponding respective package before use. Alternatively, each pharmaceutical formulation may be held in a package suitable for each time of combined administration.

[0033] The dose of the cancer chemotherapeutic agent of the present invention varies depending on the body weight, age, sex, symptoms of a patient in need thereof, route and frequency of administration to a patient in need thereof, etc. Generally, for example, the daily dose for an adult is about 0.1 to 30 mg/kg as the cholestanol derivative (1), preferably 3 to 10 mg/kg. The dose of the anti-cancer agent may fall within a range established with respect to the agent, or may be lower than that range.

No particular limitation is imposed on the frequency of administration, and the agent may be administered once or several times a day. Single administration a day is preferred. When the kit is used, each of the formulation including separated drug ingredients may be administered simultaneously or intermittently.

[0034] The present invention will next be described in more detail by way of examples.

Examples

Example 1

Effect of drug addition on inhibition of cancer cell proliferation

[0035] Colon26 cells (derived from mouse colon cancer) were inoculated to a 96-well plate (1×10^4 cells/50 μ L, 10%FCS-RPMI medium/well), and incubated at 37°C for 16 hours. To each well, cisplatin (abbreviated as "CDDP") and/or a cyclodextrin inclusion compound (abbreviated as "GC-CD") of a cholestanol derivative in which G in formula (1) is GlcNAc β - (abbreviated as "GC") was added (multi-fold dilution by FCS(-)-medium: final concentration: $\leq 500 \mu$ M, 50 μ L), followed by incubation at 37°C for two days. GC-CD was prepared in accordance with a method disclosed in Example 1(2) in Patent Document 4. Specifically, a 40% aqueous solution of hydroxypropyl- β -cyclodextrin was prepared, and GC was added to the solution, followed by mixing with stirring (80°C for 30 minutes), to thereby prepare GC-CD. As a control, wells to which only FCS(-)-medium had been added were employed. Viable count was performed by means of a cell counting kit (product of Dojin).

Cell proliferation inhibition (CPI) rate (%) was calculated by the following equation. Fig. 1 shows the results.

[0036]

$$\text{CPI rate (\%)} = \left(1 - \frac{\text{treated cells } OD_{450 - 650}}{\text{untreated cells } OD_{450 - 650}}\right) \times 100$$

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Example 2

Effect of inhibition of proliferation of various cancer cells

5 [0037] The procedure of Example 1 was repeated, except that colon26 cells were changed to MKN45 (derived from human gastric cancer), NCIH226 (derived from human lung cancer), and Colo201 (derived from human colon cancer). CPI rate (%) was determined in a similar manner. Fig. 2 shows the results.

In Example 2, a cyclodextrin inclusion compound (abbreviated as "GGC-CD") of a cholestanol derivative in which G in formula (1) is GlcNAc β 1, 4-Gal β -. (abbreviated as "GGC") was also used. GGC-CD was produced in a manner similar
10 to the method as the aforementioned GC-CD production method, except that the cholestanol compound was changed to GGC. CPI rate with respect to the cancer cells was determined. Fig. 3 shows the results.

Example 3

15 Effect of drug addition on inhibition of cancer cell proliferation in vivo

[0038] In the following Examples, Balb/c mice (6-weeks old, female) were employed as test animals.

(1) Colon26 cells (1×10^4 cells/mouse) were intraperitoneally inoculated to the mice (day 0). On the following day
20 after inoculation (day 1), CDDP and/or GC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration of interest, and CDDP, GC-CD, or CDDP + GC-CD (500 μ L) was intraperitoneally administered to the mice, followed by breeding. On day 19, mice were dissected, and the weight of the mesentery and the greater omentum was measured. To the control group, only physiological saline (500 μ L) was administered (n=10; 10 mice/group).

25 Fig. 4 shows the results.

(2) Colon26 cells (1×10^4 cells/mouse) were intraperitoneally inoculated to the mice (day 0). On day 1, day 2, day 3, day 6, day 7, and day 8, CDDP and/or GC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration of interest, and CDDP, GC-CD, or CDDP + GC-CD (500 μ L) was intraperitoneally administered to the mice, followed by breeding. On day 21, mice were dissected, and the weight of the mesentery and the greater
30 omentum was measured. To the control group, only physiological saline (500 μ L) was administered (n=10; 10 mice/group).

Fig. 5 shows the results.

(3) Colon26 cells (1×10^4 cells/mouse) were intraperitoneally inoculated to the mice (day 0). On day 7, CDDP and/or GC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration of interest, and
35 CDDP, GC-CD, or CDDP + GC-CD (500 μ L) was intraperitoneally administered to the mice, followed by breeding. On day 18, mice were dissected, and the weight of the mesentery and the greater omentum was measured. To the control group, only physiological saline (500 μ L) was administered (n=10; 10 mice/group).

Fig. 6 shows the results.

40 Example 4

Anti-tumor effect by drug addition

[0039] Balb/c mice (6 weeks old, female) were employed as test animals. Colon26 cells (1×10^4 cells/mouse) were
45 intraperitoneally inoculated to the mice (day 0). On day 2 and/or day 3, CDDP and/or GC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration of interest, and CDDP (once, on day 2), GC-CD (twice, on day 2 and 3), or CDDP (once, on day 2) + GC-CD (twice, day 2 and 3) (500 μ L) was intraperitoneally administered to the mice, followed by breeding. The survival duration (days) was counted to day 43. To the control group, only physiological saline (500 μ L) was administered (n=10; 10 mice/group).

50 Fig. 7 shows the results.

Example 5

Anti-tumor effect by drug addition

55 [0040] Balb/c mice (6 weeks old, female) were employed as test animals. Colon26 cells (5×10^4 cells/mouse) were subcutaneously inoculated to the mice (day 0). After confirmation that the tumor size reached about 4 mm (day 7 to 10 after inoculation), CDDP and/or GGC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration

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of interest, and CDDP, GGC-CD, or CDDP + GGC-CD (200 μ L) was administered to the mice through the tail vein, followed by breeding. Time-dependent change in tumor size was monitored to day 21, and the corresponding tumor volume was determined. To the control group, only physiological saline (200 μ L) was administered (n=7; 7 mice/group). Fig. 8 shows the results.

Example 6

Cancer metastasis inhibitory effect by drug addition

[0041] Balb/c mice (6 weeks old, female) were employed as test animals. Colon26 cells (5×10^4 cells/mouse) were intraperitoneally inoculated to the mice (day 0). Immediately after inoculation, CDDP and/or GC-CD or GGC-CD was adjusted with physiological saline (Otsuka normal saline) to a concentration of interest, and CDDP, GC-CD (or GGC-CD), or CDDP + GC-CD (or GGC-CD) (200 μ L) was administered to the mice through the caudal vein, followed by breeding. On day 14, mice were dissected, and the tumor nodes in the lungs were counted. To the control group, no substance was administered (n=10; 10 mice/group).

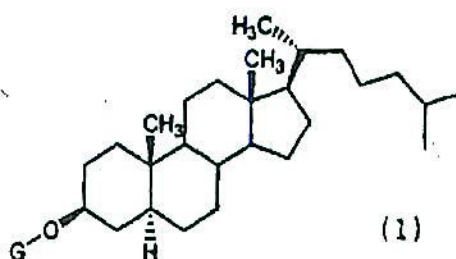
Fig. 9 shows the results.

[0042] As described hereinabove, through employment, in combination, of the cholestanol derivative of the present invention or a cyclodextrin inclusion compound thereof and an anti-cancer agent, proliferation of various cancer cells is strongly inhibited, and synergistic effect and/or effect of potentiating anti-tumor action of a known anti-cancer agent can be obtained.

Claims

1. A cancer chemotherapeutic agent comprising, in combination,

(a) a cholestanol derivative represented by formula (1) :



(wherein G is GlcNAc-Gal- or GlcNAc-) or a cyclodextrin inclusion compound thereof, and
(b) an anti-cancer agent.

2. A cancer chemotherapeutic agent according to claim 1, wherein the anti-cancer agent is one or more species selected from the group consisting of a platinum complex anti-cancer agent.

3. A cancer chemotherapeutic agent according to claim 2, wherein the anti-cancer agent is one or more species selected from the group consisting of Cisplatin and Oxaliplatin.

4. A cancer chemotherapeutic agent according to any of claims 1 to 3, which is a compounding agent.

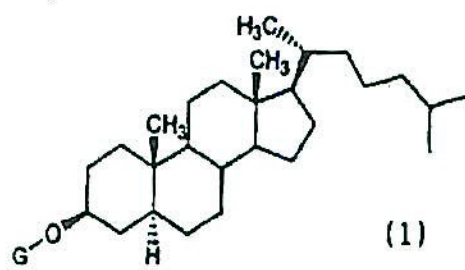
5. A cancer chemotherapeutic agent according to any of claims 1 to 3, which is in the form of a kit including a drug containing a cholestanol derivative and a drug containing an anti-cancer agent.

6. A cancer chemotherapeutic agent according to claim 5, wherein the drug containing a cholestanol derivative is a liposomal formulation.

7. Use, in combination, of a cholestanol derivative represented by formula (1):

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(wherein G is GlcNAc-Gal- or GlcNAc-) or a cyclodextrin inclusion compound thereof and an anti-cancer agent, for producing a cancer chemotherapeutic agent.

Patentansprüche

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1. Chemotherapeutisches Krebsmittel, umfassend in Kombination,

(a) ein Cholestanolderivat der Formel (1):

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(wobei G für GlcNAc-Gal- oder GlcNAc- steht) oder eine Cyclodextrininklusionsverbindung davon, sowie (b) ein Antikrebsmittel.

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2. Chemotherapeutisches Krebsmittel nach Anspruch 1, wobei das Antikrebsmittel eine oder mehrere sind, die ausgewählt werden aus der Gruppe, bestehend aus Platinkomplex-Antikrebsmitteln.

3. Chemotherapeutisches Krebsmittel nach Anspruch 2, wobei das Antikrebsmittel eines oder mehrere sind, die ausgewählt werden aus der Gruppe bestehend aus Cisplatin und Oxaliplatin.

4. Chemotherapeutisches Krebsmittel nach einem der Ansprüche 1 bis 3, das ein Mischungszubereitung ist.

45

5. Chemotherapeutisches Krebsmittel nach einem der Ansprüche 1 bis 3, das in Form eines Kils vorliegt, enthaltend ein Arzneimittel, enthaltend ein Cholestanolderivat sowie ein Arzneimittel, enthaltend ein Antikrebsmittel.

6. Chemotherapeutisches Krebsmittel nach Anspruch 5, wobei das Arzneimittel, das ein Cholestanolderivat enthält, eine liposomale Formulierung ist.

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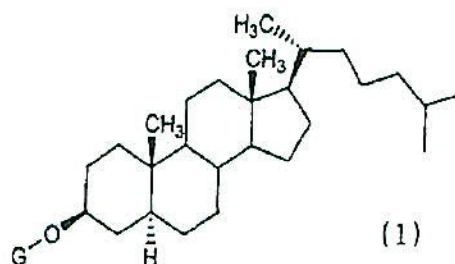
7. Verwendung, in Kombination, eines Cholestanolderivats der Formel (1):

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(wobei G für GlcNAc-Gal- oder GlcNAc- steht) oder eine Cyclodextrininkusionsverbindung davon, sowie ein Antikrebsmittel, zur Herstellung eines chemotherapeutischen Krebsmittels.

Revendications

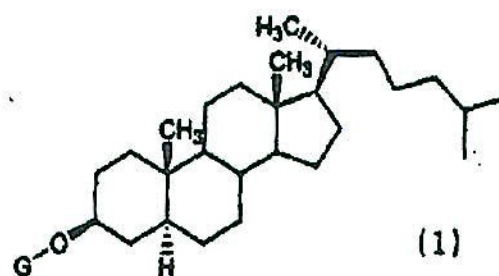
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1. Agent chimiothérapeutique anticancéreux comprenant, en combinaison,

(a) un dérivé de cholestanol représenté par la formule (1) :

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(dans laquelle G est GlcNAc-Gal- ou GlcNAc-) ou un composé d'inclusion de cyclodextrine de celui-ci, et
(b) un agent anticancéreux.

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2. Agent chimiothérapeutique anticancéreux selon la revendication 1, dans lequel l'agent anticancéreux est constitué d'une ou plusieurs espèce(s) choisie(s) dans l'ensemble constitué par les agents anticancéreux à base de complexes du platine.

3. Agent chimiothérapeutique anticancéreux selon la revendication 2, dans lequel l'agent anticancéreux est constitué d'une ou plusieurs espèce(s) choisie(s) dans l'ensemble constitué par le cisplatine et l'oxaliplatine.

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4. Agent chimiothérapeutique anticancéreux selon l'une quelconque des revendications 1 à 3, qui est un agent de malaxage.

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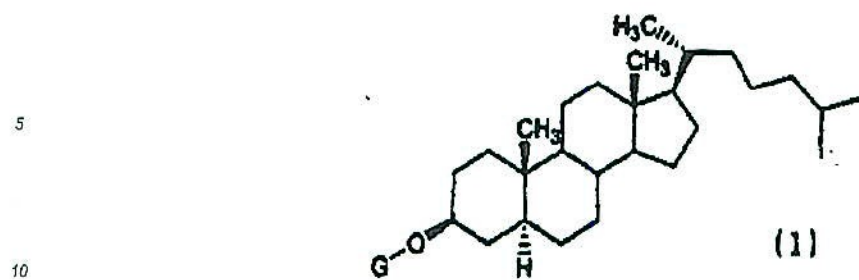
5. Agent chimiothérapeutique anticancéreux selon l'une quelconque des revendications 1 à 3, qui est sous la forme d'un kit comprenant un médicament contenant un dérivé de cholestanol et un médicament contenant un agent anticancéreux.

6. Agent chimiothérapeutique anticancéreux selon la revendication 5, dans lequel le médicament contenant un dérivé de cholestanol est une formulation de liposomes.

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7. Utilisation en combinaison d'un dérivé de cholestanol représenté par la formule (1) :

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(dans laquelle G est GlcNAc-Gal- ou GlcNAc-) ou d'un composé d'inclusion de cyclodextrine de celui-ci, et d'un agent anticancéreux, pour la production d'un agent chimiothérapeutique anticancéreux.

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Fig. 1

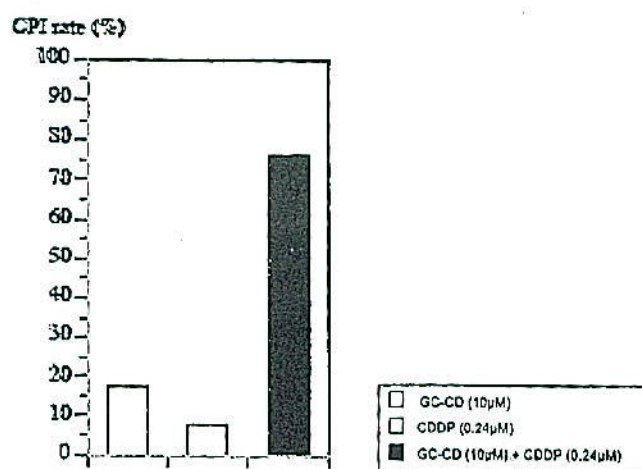


Fig. 2

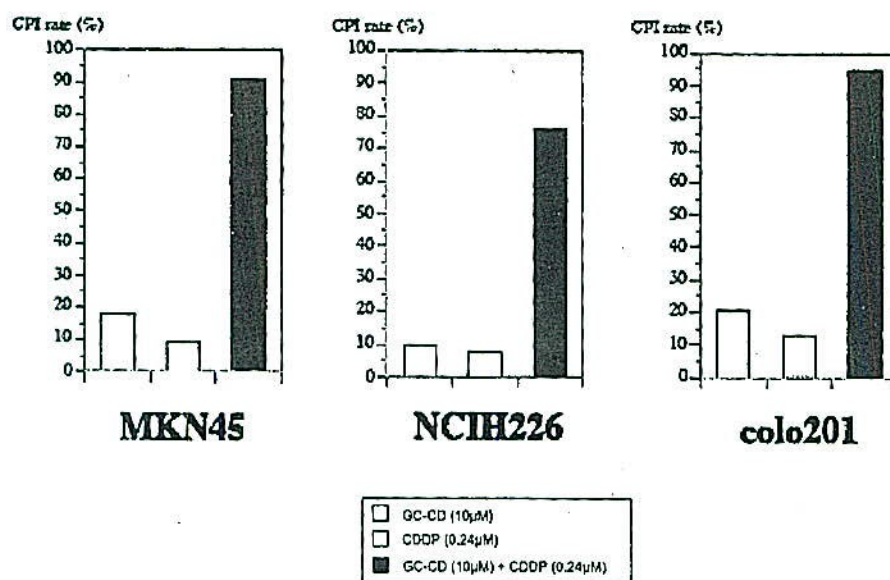


Fig. 3

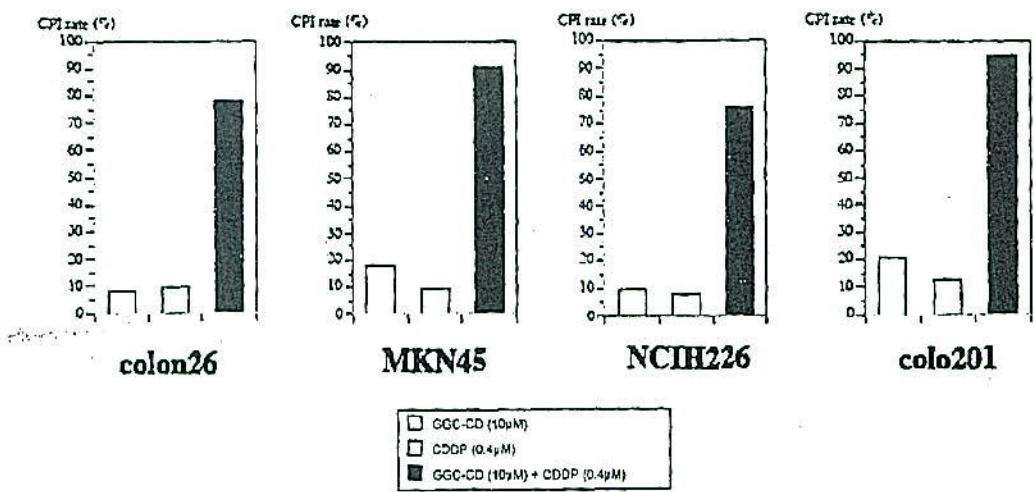


Fig. 4

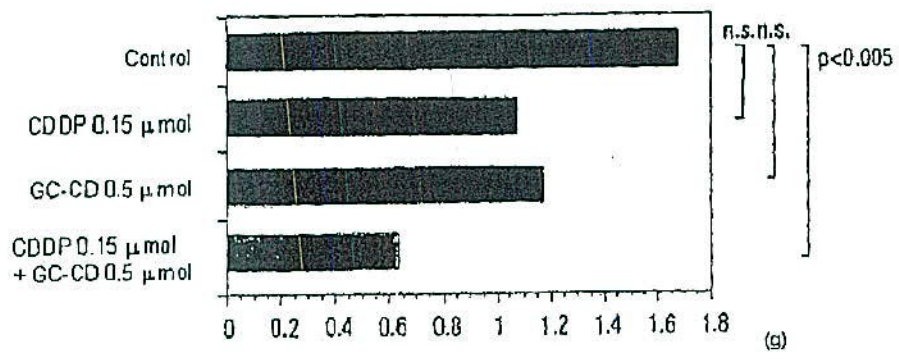


Fig. 5

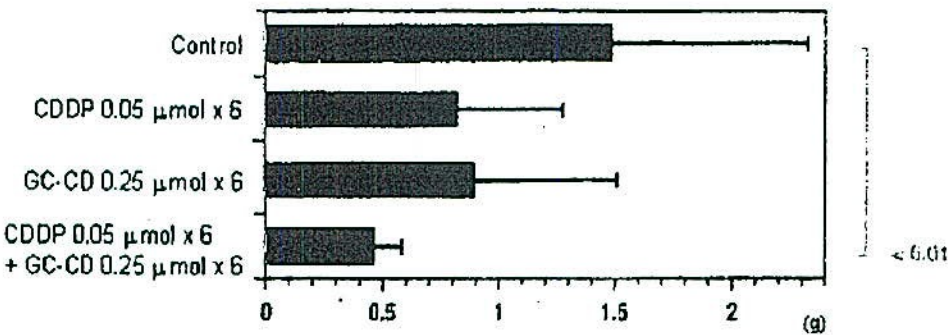


Fig. 6

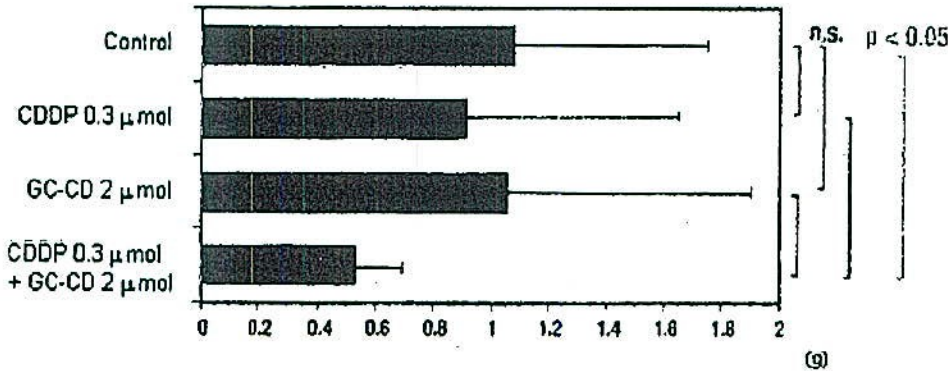
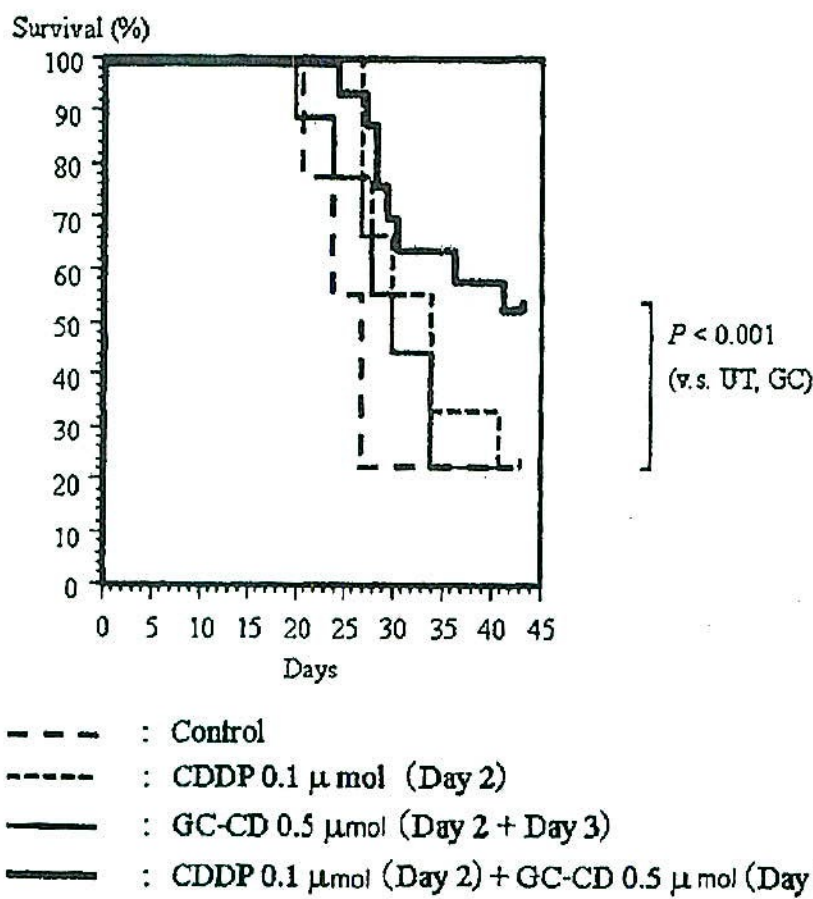
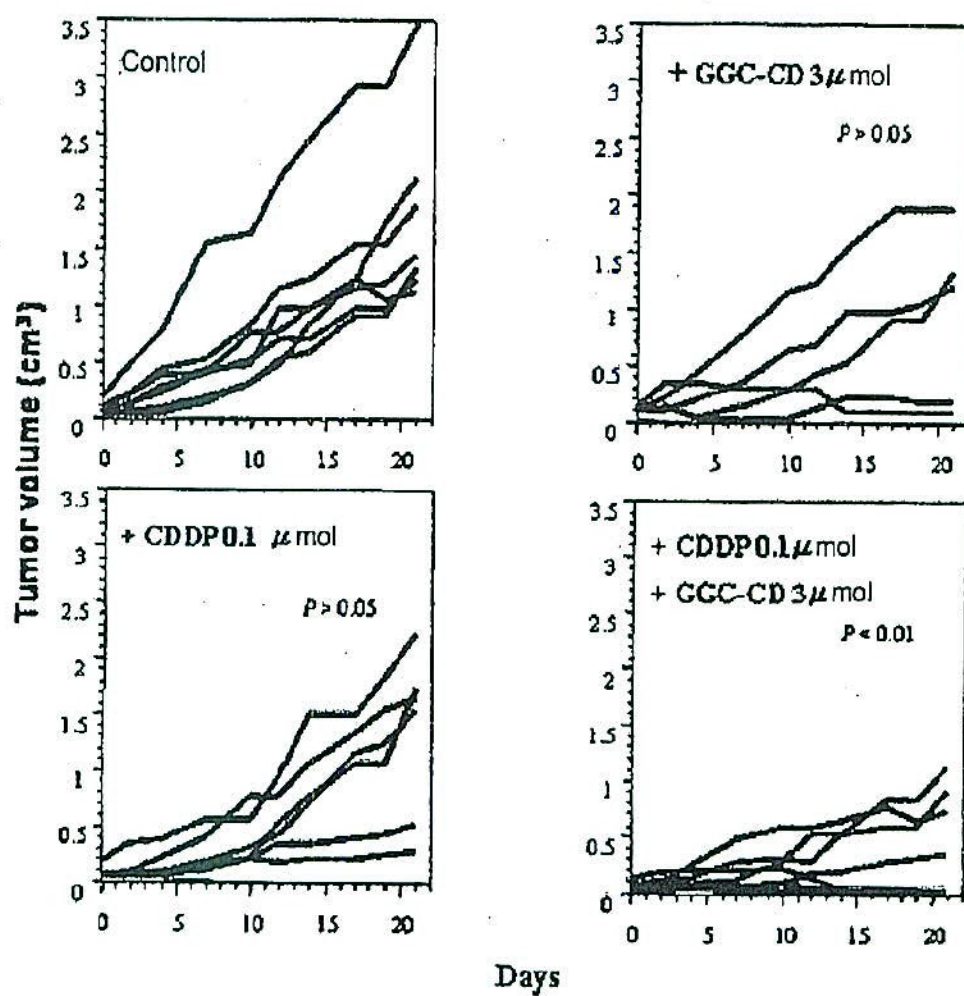


Fig. 7



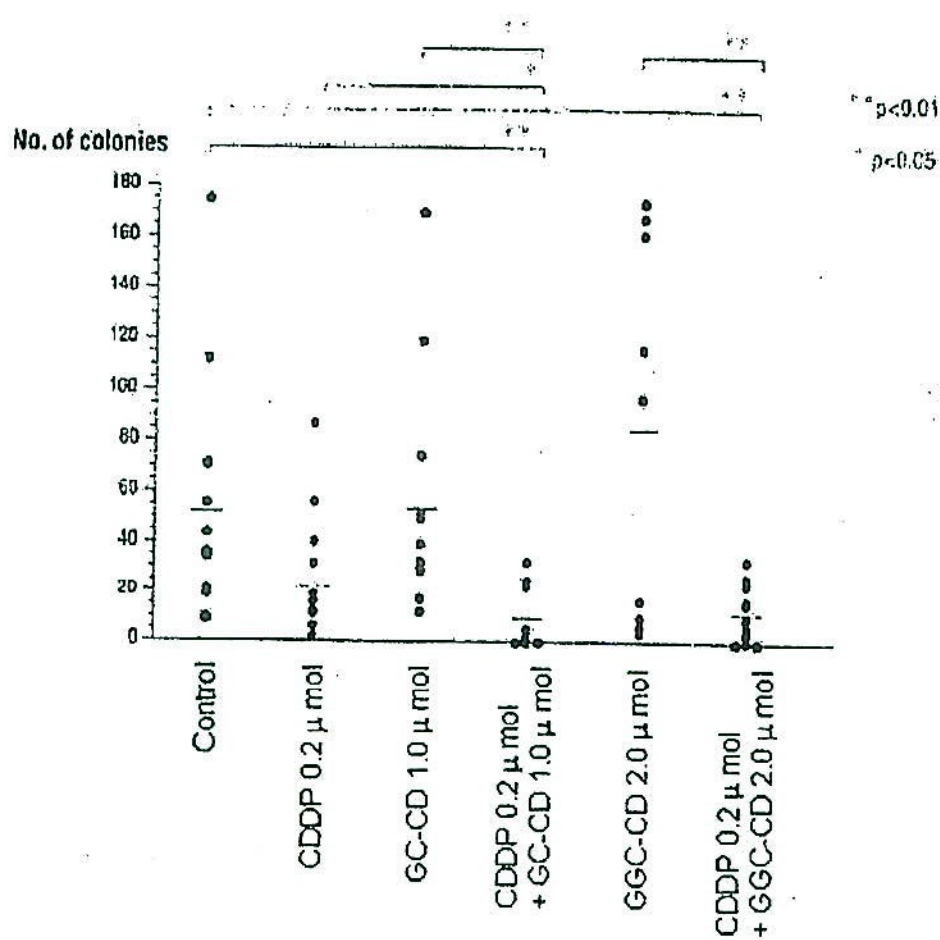
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Fig. 8



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Fig. 9



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REFERENCES CITED IN THE DESCRIPTION

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