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Act. 400 OPOSIOBSERVTER Folios: 34

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

☒ Patente de invención

☐ Registro de Diseño Industrial

☐ Patente de Modelo de Utilidad

Esquema de Trazado de Circuitos Integrados

Número de expediente: 12-029-986

Solicitante: SANOFL

Apoderado: LUZ CLEMENCIA DE PAEZ

Título de la Nueva Creación: CONJUGADOS DE DIMEROS DE PIRROLO (1,4) BENZODIAZEPINA COMO AGENTES ANTICANCEROSOS

Gaceta: 661 de 01 de febrero de 2013, No. de publicación 2210

2. Datos del Opositor

Persona Natural

☐ Persona Jurídica

☒

TECNOQUIMICAS S.A.

Nombre o denominación /Razón social completa

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐ Cuál

Número 890 300 466-5

Dirección Calle 23 No. 7-39 Ciudad Cali

Teléfono (092) 882.55.55 Fax: (092) 883.88.59 E-mail: _____



Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

79 152.473

44655

Apellidos y Nombre

Documento de identificación

T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica

info@reyes-abogados.com

No. Fax

621.25.42

Número telefónico

621.26.31

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

2

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga:

SI

☒

NO

☐

7. Anexos

☒

Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____

☒

Poder, si fuera el caso con el que se acredita la representación.

☒

Pruebas de los fundamentos de la oposición

☒

Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR



Nombre y apellidos

Firma

79.152.473

44655

C.C.

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 12-029-986

**TÍTULO SOLICITADO: “CONJUGADOS DE DIMEROS DE PIRROLO(1.4)
BENZODIAZEPINA COMO AGENTES
ANTICANCEROSOS”**

**PUBLICACIÓN: Gaceta 661 de 01 de febrero de 2013, N° de
publicación 2210.**

**PRIORIDAD: FR 0904043 25/08/2009
FR 0904368 11/09/2009**

SOLICITANTE: SANOFI

APODERADO: LUZ CLEMENCIA DE PAEZ

TRÁMITE: PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 12-029-986, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

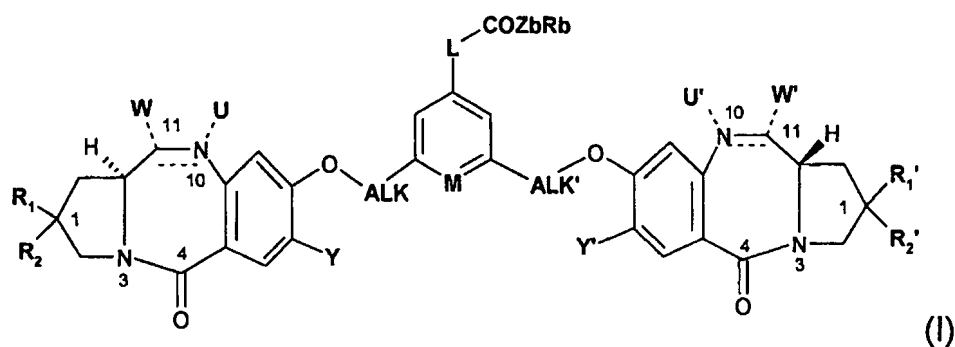
Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 12-029-986, que revela conjugados de dímeros pirrolo [1,4] benzodiazepina (PBD), composiciones que los contienen y su aplicación terapéutica, no cumple los requisitos materiales para otorgársele el privilegio de patente de invención, tal y como puede determinarse al valor de los siguientes argumentos:

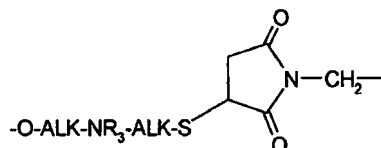
Falta de Claridad y Soporte en la descripción

La reivindicación principal busca protección para el siguiente conjugado:

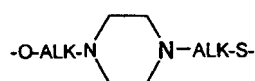
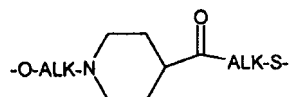
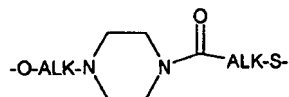


Se observa que dicha reivindicación carece de claridad y soporte en la descripción pues cubre materia que no se encuentra divulgada allí; un ejemplo de lo anterior se observa en la definición del radical L que representa el grupo L1-L2, de los cuales el grupo L1 está unido al ciclo aromático que comprende M y representa los siguientes sustituyentes:

-ALK-S-



-O-ALK-NR₃-ALK-S-



En este caso, las sustituciones varían en estructura y grupo funcional con diversidad de cadenas, grupos alqueno, ciclos aromáticos y demás sustituyentes como R y R'. Así mismo, la longitud de las cadenas varía considerablemente sin tener en cuenta una extrapolación razonable de lo descrito y sin demostrar el efecto técnico que las variaciones ejercen en el conjugado.

Por lo tanto, se llama la atención del Despacho sobre el hecho que la materia incluida en el capítulo reivindicatorio es muy amplia y cobija una gran variedad de conjugados posibles que no han sido completamente desarrollados en la descripción.

Por otro lado, la inclusión de anticuerpos en el conjugado cambia diametralmente el enfoque de la solicitud ya que dichos compuestos presentan una estructura y función diferentes a las reclamadas por el conjugado, en consecuencia, su inclusión hace que todo el efecto técnico demostrable varíe.

Así mismo, la definición dada en la reivindicación 17 (por ejemplo) no puede ser aceptable ya que no se realiza mediante la estructura química o secuencial del anticuerpo sino por parámetros de absorbancia que no permiten definir los límites técnicos del conjugado.

Usos

La presente solicitud en sus reivindicaciones 18 a 21 revelan el uso o utilización de los conjugados para la preparación de dímeros:

18. Utilización de un compuesto según una de las reivindicaciones 1 a 9 para la preparación de un agente de selección al que esté unido de forma covalente, en la posición para- de M, el dímero de fórmula:

si tenemos en cuenta que el artículo 14 de la Decisión 486 dice: *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*; Por lo tanto, las reivindicaciones 18 a 21 contienen materia que no se considera un elemento que pueda ser patentado.

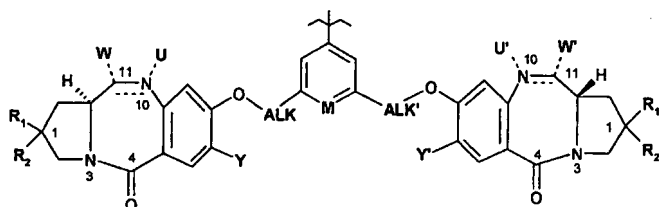
También se reclama en las reivindicaciones 30 a 34 el uso de intermediarios en la preparación de un compuesto de fórmula I, lo que evidentemente contraviene la Decisión 486, en especial lo relacionado con el art 14, tal como se demostró en el párrafo anterior.

Carencia de unidad de invención.

La solicitud 12-029-986 en trámite, más específicamente a partir de la reivindicación 10, revela un agente de selección (el cual es un ligando, una proteína un anticuerpo, un fragmento de proteína o de un anticuerpo, un péptido, un oligonucleótido o un oligosacárido) y que forma parte del dímero reclamado por la reivindicación principal.

Más específicamente, en las reivindicaciones 22 – 25 se reclaman los agentes de selección (anticuerpos) que se han unido de forma covalente al dímero reivindicado, por tanto, es importante destacar aquí que existen dos invenciones completamente diferentes las cuales has sido reclamadas de forma arbitraria como si obedecieran a un único concepto inventivo. Adicionalmente, es necesario resaltar que se pretende cobijar cualquier anticuerpo, sin importar su estructura, función, selectividad, actividad, inmunogenicidad, con la única condición de unirse al dímero:

22. Agente de selección al que se ha unido de forma covalente en la posición para- de M el dímero de fórmula:



después de la reacción de un compuesto tal como se ha definido en una de las reivindicaciones 1 a 9 con el agente de selección.

23. Agente de selección según la reivindicación 22 en la que el dímero es tal como se ha definido en una de las reivindicaciones 20 ó 21.

24. Agente de selección según la reivindicación 23 que presenta afinidad por un antígeno o grupo de antígenos localizado en células cancerosas o células estromales asociadas a un tumor.

25. Agente de selección según las reivindicaciones 22 a 24 que es un anticuerpo, preferentemente monoclonal.

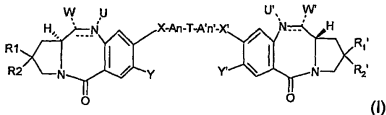
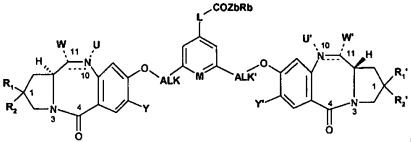
Adicional a los múltiples conceptos inventivos hasta aquí señalados, la solicitud posee el agravante de no definir al anticuerpo por una caracterización técnica, sino por su unión covalente al grupo pirrolo Benzodiazepínico definido, lo cual incluye materia reclamada mediante un resultado a alcanzar, una inexistente definición técnica y una amplitud que excede lo desarrollado, abarcando materia no sustentada ni definida en la misma solicitud en trámite.

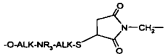
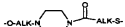
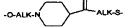
Por su parte, la reivindicación 25 hace énfasis en que el agente de selección es un anticuerpo, preferiblemente monoclonal, lo que demuestra una vez más que la materia expuesta NO es clara ni concisa ya que no se puede identificar fielmente de qué tipo de anticuerpo se trata; llamamos de manera especial la atención de éste Despacho en la cantidad de anticuerpos susceptibles a unirse a una molécula como la descrita y que quedarían cubiertos por la solicitud, evaluados o no por la misma y que pertenecerían incluso al estado de la técnica, lo que evidentemente demuestra la falta de claridad y sustento en la descripción de las reivindicaciones.

Ahora bien, con el ánimo de profundizar en cuanto a la falta de requisitos para la patentabilidad total o parcial de la solicitud, se ha observado lo siguiente:

La solicitud no cumple con el requisito de nivel inventivo.

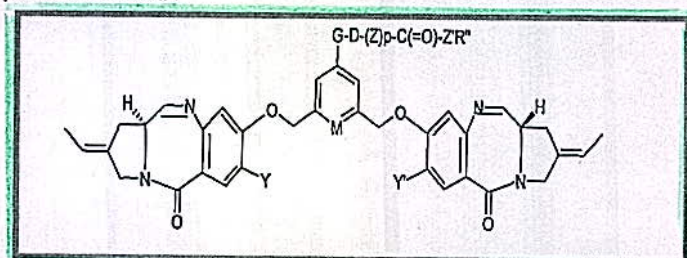
Pese a la flagrante violación a la D. 486 en cuanto a claridad, soporte, unidad de invención y amplitud se refiere, la materia reclamada ha sido descrita en el arte anterior, de forma que se resuelve el problema técnico según la publicación internacional **WO 2009/016516** de Herve et al., de 5 de febrero de 2009, en la cual se encuentran derivados de tomaymicina de formula (I) (ver página 8 y 9), y que corresponden a los compuestos derivados de pirrolo benzodíacepina similares a los revelados en la solicitud en trámite, veamos:

Publicación Internacional WO 2009/016516	Solicitud colombiana 12-029-986
Pág 8 Derivados de tomamicina de fórmula (I)  (I)	Reiv 1 Un compuesto de fórmula (I)  (I)
wherein : — represents an optional single bond ; — represents either a single bond or a double bond ; provided that when — represents a single bond, U and U', the same or different, independently represent H, and W and W', the same or different, are independently selected from the group consisting of OH, an ether such as -OR, an ester (e.g. an acetate), such as -OCOR or -COOR, a carbonate such as -OCOOR, a carbamate such as -OCONRR', a cyclic carbamate, such that N10 and C11 are a part of the cycle, a urea such as -NRCONRR', a thiocarbamate such as -OCSNHR, a cyclic thiocarbamate such that N10 and C11 are a part of the cycle, -SH, a sulfide such as -SR, a sulfoxide such as -SOR, a sulfone such as -SOOR, a sulphonate such as -SO₃, a sulfonamide such as -NRSOOR', an amine such as -NRR', optionally cyclic amine such that N10 and C11 are a part of the cycle, a hydroxylamine derivative such as -NROR', an amide such as -NRCOR', an azido such as -N₃, a cyano -CN, a halide (Hal), a trialkyl or triarylphosphonium ; Preferably W and W' are the same or different and are -OH, -OMe, -OEt, -NHCONH₂, -SMe;	en la que: — representa un enlace sencillo o un enlace doble con la condición de que si — representa un enlace sencillo, entonces: — representa un enlace sencillo; - U y/o U', idénticos o diferentes, representan independientemente el uno del otro, H; - W y/o W', idénticos o diferentes, representan independientemente el uno del otro, OH, -OR, -OCOR, -COOR, -OCOOR, -OCONRR', un carbamato cíclico tal que N10 y C11 estén incluidos en un ciclo, -NRCONRR', -OCSNHR, un tiocarbamato cíclico tal que N10 y C11 estén incluidos en un ciclo, -SH, -SR, -SOR, -SOOR, -SO₃, -NRSOOR', -NRR', una amina cíclica tal que N10 y C11 estén incluidos en un ciclo, -NROR', -NRCOR', -N₃, -CN, Hal, un grupo trialkilfosfonio o triarilfosfonio; - R₁, R₂, R₁', R₂', idénticos o diferentes, representan independientemente uno del otro: H, Hal o un grupo alquilo (C₁-C₆) opcionalmente sustituido con uno o varios sustituyentes elegidos entre: Hal, CN, NRR', CF₃, OR, un grupo arilo o heteroarilo, S(O)_qR siendo q = 0,1 ó 2;

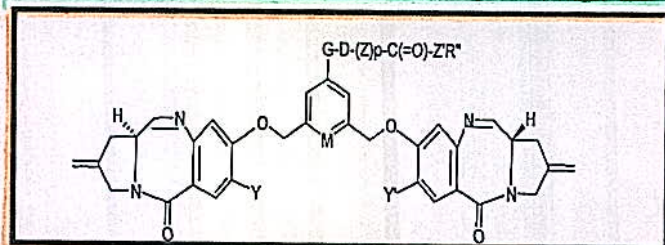
Publicación Internacional WO 2009/016516	Solicitud colombiana 12-029-986
and when  represents a double bond, U and U' are absent and W and W' represent H. • R1, R2, R1', R2' are the same or different and independently chosen from H, Halide or Alkyl optionally substituted by one or more Hal, CN, NRR', CF₃, OR, Aryl, Het, S(O)_aR, or R1 and R2 and R1' and R2' form together a double bond containing group =B and =B' respectively. Preferably, R1 and R2 and R1' and R2' form together a double bond containing group =B and =B' respectively. • B and B' are the same or different and independently chosen from Alkenyl being optionally substituted by one or more Hal, CN, NRR', CF₃, OR, SR, SOR, SO₂R, Aryl, Het, or B and B' represent an oxygen atom. Preferably, B=B'. More preferably, B=B'=CH₂ or =CH-CH₃. • X, X' are the same or different and independently chosen from one or more -O-, -S-, -NR-, -(C=O)-, -SO-, -SO₂-; Preferably, X=X'. More preferably, X=X'=O. • A, A' are the same or different and independently chosen from Alkyl or Alkenyl, each being optionally substituted by one or more Hal, CN, NRR', CF₃, OR, SR, SOR, SO₂R, Aryl, Het, Alkyl, Alkenyl. Preferably, A=A'. More preferably, A=A'=linear unsubstituted alkyl. • Y, Y' are the same or different and independently chosen from H, OR; Preferably, Y=Y'. More preferably, Y=Y'=OAlkyl, more preferably OMethyl. • T is -NR- or a 4 to 10-membered aryl, cycloalkyl, heterocyclic, heteroaryl or a linear or branched alkyl, each being substituted by one or more non-cleavable linker(s) and optionally substituted by one or more of Hal, CN, NRR', CF₃, R, OR, SOR or SO₂R.	o bien: • R₁ y R₂ y/o R₁' y R₂' forman juntos respectivamente un enlace doble =CH₂ o =CH-CH₃; • Y e Y', idénticos o diferentes, representan independientemente uno del otro H u OR; • M representa CH o N; • ALK y ALK', idénticos o diferentes, representan independientemente uno del otro un grupo alquileo (C₁-C₆); • R y R' representan, independientemente uno del otro, H o un grupo alquilo (C₁-C₆) o arilo opcionalmente sustituido con uno o varios sustituyentes elegidos entre: Hal, CN, NRR', CF₃, OR, un grupo arilo o heteroarilo; • L representa: ❖ el grupo -L₁-L₂- en el que L₁ está unido al ciclo aromático que comprende M por el grupo ALK u OALK y representa uno de los grupos siguientes: -ALK-S-  -O-ALK-NR₂-ALK-S- -O-ALK-NR₂-ALK-S-  -O-ALK-N-ALK-S-  -O-ALK-N-ALK-S- y L₂ representa el grupo -CH₂C(=O)-NR₂-(CH₂CH₂O)_n-ALK- unido a L₁ por -CH₂C(=O)- o bien: ❖ el grupo -O-ALK-NR₂-ALK-S-(CH₂CH₂O)_n-ALK- unido al ciclo aromático que comprende M por el grupo OALK; R₃ representa H o un grupo alquilo (C₁-C₆); i representa un número entero que va de 1 a 40, mejor de 1 a 20, preferentemente de 1 a 10; Z_a representa un enlace sencillo, -O- o -NH-, representando R_b H o un grupo alquilo (C₁-C₆), cicloalquilo (C₂-C₇), arilo, heteroarilo o heterocicloalquilo (C₂-C₇) o bien Z_a representa un enlace sencillo y R_b representa Hal.

En dicha estructura principal, es decir sobre el anillo de pirrolo (1,4) Benzodiazepina es posible hacer distintas sustituciones, tal como se reclama en dicha anterioridad (ver reivindicación 29) y como se observa en la reivindicación 3 de la solicitud en trámite:

29. Compound of formula :



or

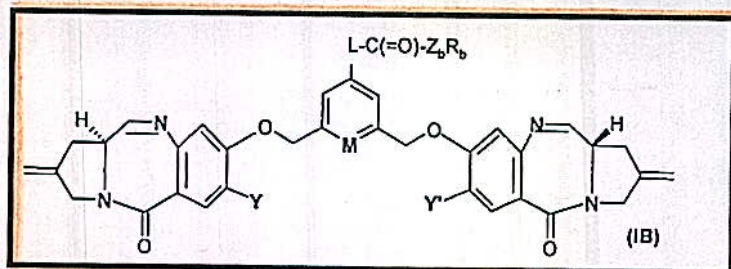
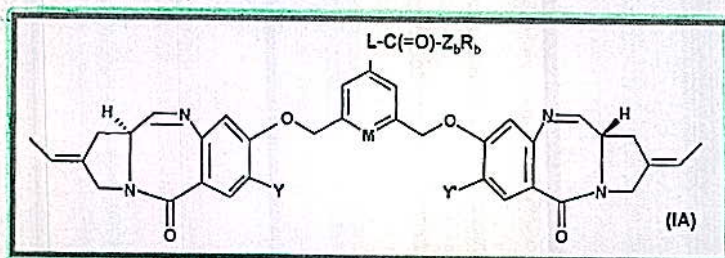


wherein :

- $-G-D-(Z)_p-C(=O)-Z'R''$ is as defined in claims 2 or 14 to 28 ;
- M represents CH or N.

WO 2009/016516

3. Compuesto según la reivindicación 1 de fórmula (IA) o (IB):



CO 12-029-986

No siendo suficiente con los argumentos anteriores en donde se describe en esencia la misma molécula con variaciones mínimas en los grupos pertenecientes a "G", la anterioridad tantas veces mencionada revela un conjugado de la molécula con un anticuerpo o cadenas del mismo de igual forma que la solicitud en estudio veamos:

33. A conjugate molecule according to claim 31 or 32 wherein said cell binding agent is chosen from antibodies or a fragment of an antibody that contains at least one binding site, lymphokines, hormones, growth factors, nutrient-transport molecules, or any other cell binding molecule or substance.
34. A conjugate molecule according to claim 31 to 33 wherein said cell binding agent is chosen from monoclonal antibodies; chimeric antibodies; humanized antibodies; fully human antibodies; single chain antibodies; fragments of antibodies such as Fab, Fab', F(ab')₂ and F_v, interferons; peptides; lymphokines such as IL-2, IL-3, IL-4, IL-6; hormones such as insulin, TRH (thyrotropin releasing hormones), MSH (melanocyte-stimulating hormone), steroid hormones, such as androgens and estrogens; growth factors and colony-stimulating factors such as EGF, TGF α , insulin like growth factor (IGF-I, IGF-II) G-CSF, M-CSF and GM-CSF; vitamins, such as folate and transferrin.

En este caso las moléculas así compuestas, los conjugados, los sustituyentes, los grupos de unión y los efectos técnicos tanto en la solicitud como en la anterioridad son los mismos.

De esta forma, queda demostrado que es evidente para cualquier técnico medio versado en la materia resolver el problema técnico de encontrar alternativas supuestamente novedosas de conjugados de dímeros de pirrolo (1,4) benzodiazepina bajo una selección arbitraria y reemplazo de diferentes sustituyentes y verificar su conjugación con biomoléculas como anticuerpos, entre otros.

Por lo tanto, con los argumentos dados en el presente escrito y dada la ausencia de un efecto técnico demostrable para todos los conjugados posibles con respecto al arte previo, se concluye que la solicitud colombiana en trámite carece al menos de nivel inventivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

IV PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación internacional WO 2009/016516 de Herve et al., "*Cytotoxic agents comprising new tomaymycin derivatives and their therapeutic use*" publicado el 5 de febrero de 2009. Portada, página 1 – 5, 8 y reivindicaciones.

VI. ANEXOS

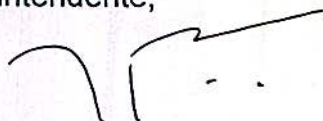
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. Las mencionadas en el acápite de pruebas

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.

AA 3286875 NOTARIA TERCERA ENCOPIA



ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----
En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----.

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
por escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO

Como Notario Veintitres de este Círculo
hago constar que esta fotocopia coincide
con su fotocopia auténtica que se tiene
a la vista
13 AGO 2007
WILLY VALENZUELA
NOTARIO VEINTITRES
Bogotá D.C. Colombia

4539
05-23

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaria 3ª de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

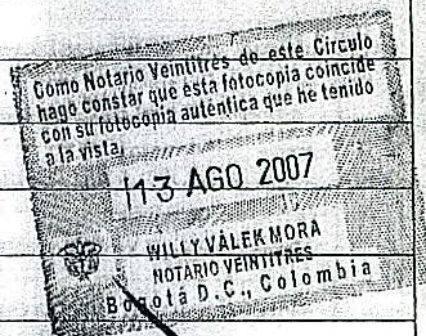
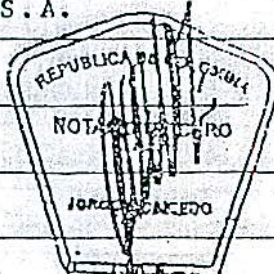
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

91 *Juan m Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

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(74) Agents: SENNINGER, Thierry et al.; Sanofi-aventis,
Département Brevets, 174 avenue de France, F-75013 Paris
(FR).

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(71) Applicant (for all designated States except US): SANOFI-
AVENTIS [FR/FR]; 174 avenue de France, F-75013 Paris
(FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOUCHARD,
Hervé [FR/FR]; Patent Department, 174 avenue de
France, F-75013 Paris (FR). CHARI, Ravi V.J [US/US];
128 Sidney Street, Cambridge, Massachusetts 02139 (US).
COMMERÇON, Alain [FR/FR]; Patent Department, 174
avenue de France, F-75013 Paris (FR). DENG, Yonghong
[CN/US]; 128 Sidney Street, Cambridge, Massachusetts
02139 (US).

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(54) Title: CYTOTOXIC AGENTS COMPRISING NEW TOMAYMYCIN DERIVATIVES AND THEIR THERAPEUTIC USE

(57) Abstract: The invention relates to novel tomaymicine derivatives comprising a linker. It also relates to the conjugate molecules that comprise one or more of said tomaymicine derivatives covalently linked to a cell binding agent through a linking group that is present on the linker of the tomaymycin derivative. It also relates to the preparation of the tomaymicine derivatives and of the conjugate molecules.

**CYTOTOXIC AGENTS COMPRISING NEW TOMAYMYCIN DERIVATIVES
AND THEIR THERAPEUTIC USE**

FIELD OF THE INVENTION

5 The present invention relates to novel tomaymycin derivatives and their therapeutic use as cytotoxic agents. The therapeutic use is the result of delivering the tomaymycin derivatives to a specific cell population in a targeted fashion by chemically linking the tomaymycin derivative to a cell binding agent. The invention relates also to conjugate molecules comprising one or more of said tomaymycin derivatives chemically linked to a cell binding agent, optionally modified.

BACKGROUND OF THE INVENTION

10 Many reports have appeared on the attempted specific targeting of tumor cells with monoclonal antibody-drug conjugates (Sela et al, in *Immuno-conjugates*, 189-216 (C. Vogel, ed. 1987); Ghose et al, in *Targeted Drugs* 1-22 (E. Goldberg, ed. 1983); Diener et al, in *Antibody mediated delivery systems*,

15 1-23 (J. Rodwell, ed. 1988); Pietersz et al, in *Antibody mediated delivery systems*, 25-53 (J. Rodwell, ed. 1988); Bumol et al, in *Antibody mediated delivery systems*, 55-79 (J. Rodwell, ed. 1988); G.A. Pietersz & K. Krauer, 2, *J. Drug Targeting*, 183-215 (1994); R.V.J. Chari, 31 *Adv. Drug Delivery Revs.*, 89-104 (1998); W.A. Blattler & R.V.J. Chari, in *Anticancer Agents, Frontiers in Cancer Chemotherapy*, 317-338, ACS Symposium Series 796; Ojima et al eds, *American Chemical Society* 2001; J.M. Lambert, 5 *Current Opinion in Pharmacology*, 543-549 (2005); P.R. Hamann, 15 *Expert Opinion on Therapeutics Patents*, 1087-1103 (2005)). All references and patents cited herein are incorporated by reference.

25 Cytotoxic drugs such as methotrexate, daunorubicin, doxorubicin, vincristine, vinblastine, melphalan, mitomycin C, and chlorambucil have been conjugated to a variety of murine monoclonal antibodies. In some cases, the drug molecules were linked to the antibody molecules through an intermediary carrier molecule such as serum albumin (Garnett et al, 46, *Cancer Res.* 2407-2412 (1986); Ohkawa et al 23, *Cancer Immunol. Immunother.* 81-86 (1986); Endo et al, 47 *Cancer Res.* 1076-1080 (1980), dextran (Hurwitz et al, 2 *Appl. Biochem.* 25-35 (1980); Manabi et al, 34 *Biochem. Pharmacol.* 289-291 (1985); Dillman et al, 46 *Cancer Res.*, 4886-4891 (1986); Shoval et al, 85, *Proc. Natl. Acad. Sci.*, 8276-8280 (1988)), or polyglutamic acid (Tsukada et al, 73, *J. Natl. Canc. Inst.*, 721-729 (1984); Kato et al, 27 *J. Med. Chem.*, 1602-1607 (1984); Tsukada et al, 52, *Br. J. Cancer*, 111-116 (1985)).

35 A wide array of linker technologies has been employed for the preparation of such immunoconjugates and both cleavable and non-cleavable linkers have been investigated. In most cases, the high cytotoxic potential of the drugs could only be observed, however, if the drug

molecules could be released from the conjugates in unmodified form at the target site using a cleavable linker.

In vitro cytotoxicity tests, however, have revealed that antibody-drug conjugates could kill not only antigen-positive cells, but also other cells in the vicinity, irrespective of the antigen expression on their surface. This phenomenon is called the bystander effect. This effect was observed in conjugates of the anti-CanAg antibody, huC242, with maytansinoids and with a CC1065 analog (Erickson et al, 66 *Cancer Res.*, 4426-4433 (2006); Kovtun et al, 66 *Cancer Res.*, 3214-3221 (2006)). So far only conjugates linked via a cleavable bond such as reducible disulfide bond demonstrated bystander cytotoxicity, while conjugates linked via a non-reducible thioether link exhibited no bystander effect.

Highly potent cytotoxic effector molecules linked to targeting agents such as antibodies could generate potent drug derivatives after intra-cellular processing of the conjugate. This could be an issue if generated cellular metabolites display undesired or not easily manageable side effects. In order to control the toxicity of antibody-drug conjugates, it could be very beneficial to use non-cleavable linkers.

Another major drawback with most antibody-drug conjugates is their inability to deliver a sufficient concentration of drug to the target site because of the limited number of targeted antigens and the relatively moderate cytotoxicity of cancerostatic drugs like methotrexate, daunorubicin, and vincristine. In order to achieve significant cytotoxicity, linkage of a large number of drug molecules, either directly to the antibody or through a polymeric carrier molecule, becomes necessary. However, such heavily modified antibodies often display impaired binding to the target antigen and fast *in vivo* clearance from the blood stream. So an alternative is to use much more potent drug molecules such as the ones disclosed herebelow.

Non cleavable linkers have been also used in conjugation. They have an interest in radioimmunotherapeutic applications in particular. This has been also utilized in the attachment of toxins to monoclonal antibodies, as for *Pseudomonas* exotoxin with MAb 9.2.27 using heterobifunctional maleimide succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) (EP 306943). The MAb toxin conjugate turned out to be of greater specificity *in vitro* against positive cell lines than the corresponding disulfide bond conjugate and thus less toxic in mouse models. Nonspecific toxicity is significantly decreased when a noncleavable linker is used. This non-cleavable linker has been used in the case of trastuzumab (Herceptin) which target HER2 (ErbB) HERR2 is a key target and methods are being investigated to maximize the effect of using MAb to inhibit this receptor. One approach aims to augment the efficacy of trastuzumab (Herceptin) by

coupling it to a chemotherapeutic agent, thus enabling the delivery of cytotoxic therapy at a cellular level (Ranson and Sliwowski, 63 (Suppl. 1) *Oncology*, 17-24 (2002)).

Other versions of the SMCC reagent exist, for instance water soluble sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC), has been also used in conjugation reaction. Other non-cleavable linkers include in particular N-succinimidyl-S-acetylthioacetate (SATA), SATA-SMCC, 2-iminothiazole (2IT) and 2IT-SMCC (Foulon et al, 10, *Bioconjugate Chem.*, 867-876 (1999)). Crosslinking reagents comprising a haloacetyl-based moiety have also been used and include N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB), N-succinimidyl iodoacetate (SIA), N-succinimidyl bromoacetate (SBA) and N-succinimidyl 3-(bromo-acetamido)propionate (SBAP). These crosslinking reagents form non-cleavable linkers derived from haloacetyl-based moieties.

In spite of the above-reported difficulties because of the drug molecules, useful cytotoxic agents comprising cell binding moieties and the group of cytotoxic drugs known as maytansinoids have been reported (USP 5,208,020, USP 5,416,064, and R. V. J. Chari, 31 *Advanced Drug Delivery Reviews* 89-104 (1998)). Similarly, useful cytotoxic agents comprising cell binding moieties and analogues and derivatives of the potent antitumor antibiotic CC-1065 have also been reported (USP 5,475,092, USP 5,585,499 and USP 6,756,397).

Tomaymycin derivatives are pyrrolo[1,4]benzodiazepines (PBDs), a known class of compounds exerting their biological properties by covalently binding to the N2 of guanine in the minor groove of DNA. PBDs include a number of minor groove binders such as anthramycin, neothramycin and DC-81. Tomaymycin antitumor activity is however limited because of its non-specific toxicity towards normal cells. Thus there is a need to increase the therapeutic activity, and diminish the non-specific toxic effects of tomaymycin compounds. The present inventors have shown that this need can be met by targeted delivery of tomaymycin compounds by linking them to cell binding agents. Additionally, there is a need to develop tomaymycin derivatives that are soluble and stable in aqueous solutions. Further, tomaymycin is not sufficiently potent to be used in conjugates of cell binding agents.

Recently, a few new PBD derivatives and their anti-tumour activity in preclinical models have been disclosed (WO 00/12508 and WO 2005/085260). However, initial clinical trials in humans indicate that compounds of this class are severely toxic, based on the very low dose that can be administered to humans (I. Puzanov, Proc. AACR-NCI-EORTC International Conference, Philadelphia, USA 2005, Abstract #B117). Thus, it is desired to provide alternative derivatives showing lesser side effects without compromising the cytotoxic activity.

PRIOR ART

International applications WO 2007/085930 and WO 2008/010101 describe tomaymicin derivatives that can be linked to a cell binding agent through a linker, but the linker is not a linker as defined for the compounds of the invention.

Article "Tetrahedron Letters, Vol.29, N°40, pp.5105-5108" describes tomaymicin derivatives ref. (13)-(15) without any linker.

International application WO 2005/085250 describes dimers of PBDs of general formula $\text{PBD-A-Y-X-(Het)}_{n_a}\text{-L-(Het)}_{n_b}\text{-L-(Het)}_{n_c}\text{-T-(Het')}_{n_d}\text{-L-(Het')}_{n_e}\text{-L-(Het')}_{n_f}\text{-X'-Y'-A'-PBD'}$ wherein Het and Het' are amino-heteroarylene-groups of formulae -J-G-J' or J'-G-J where G is an optionally substituted heteroarylene, n_a - n_f are integers between 0 and 5, L can be β -alanine, glycine, 4-aminobutanoic acid or a single bond. X and X' are both either -NH- or -C(=O)- and Y and Y' are divalent groups such that HY is an alkyl, heterocyclic or aryl group or a single bond. A and A' are selected from O, S, NH or a single bond. T is a divalent linker of the form -NH-Q-NH- or -C(=O)-Q-C(=O)- where Q is divalent group such that QH is an alkyl, heterocyclic or aryl group (optionally substituted). The compounds according to the general formula all comprise -NH- or -C(=O)- as X and X' and -NH-Q-NH- or -C(=O)-Q-C(=O)- which is not the case for the compounds of the invention.

International application WO 2005/023814 describes dimers of PBDs protected on the nitrogen atom N10 by $\text{R}_{10}\text{-COO-}$ comprising a bridge -X-R''-X- wherein R'' is an alkylene group optionally interrupted by one or more heteroatoms NH, O or S and/or aromatic rings and X is O, S or NH. There is no mention of a linker on the bridge -X-R''-X- . Moreover, the compounds of the invention are not protected on N10.

Article "European Journal of Medicinal Chemistry Vol.40, N°7, pp. 641-654" describes dimers of PBDs ref. (38)-(40) that do not comprise any linker as for the compounds of the invention.

Article "Expert opinion ; Monoclonal antibody-drug conjugates", Ashley publications, Vol.15, N°9, 2005, pp. 1087-1103, ISSN:1354-3774 does not describe the compounds of the invention and article "Cancer Res. 2006, 66(8), pp. 4426-4433" describes maytansinoid linked to cell binding agents.

SUMMARY OF THE INVENTION

The invention relates to novel tomaymicine derivatives of claims 1 to 30 comprising a linker. It also relates to the conjugate molecules that comprise one or more of said tomaymicine derivatives covalently linked to a cell binding agent through a linking group that is present on the linker of the

tomaymycin derivative. It also relates to the preparation of the tomaymicine derivatives and of the conjugate molecules.

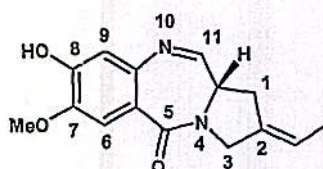
DETAILED DESCRIPTION OF THE INVENTION

Definitions

- Alk represents alkyl, alkene or alkyne ;
- "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having 1 to 20 carbon atoms in the chain or cyclic having 3 to 10 carbon atom. Preferred alkyl groups have 1 to 12 carbon atoms in the chain. "Branched" means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. Exemplary alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, octyl, nonyl, decyl, cyclopentyl and cyclohexyl ;
- "Alkene" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having 2 to 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to 12 carbon atoms in the chain; and more preferably about 2 to 4 carbon atoms in the chain. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, nonenyl, decenyl ;
- "Alkyne" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having 2 to 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to 12 carbon atoms in the chain; and more preferably 2 to 4 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl ;
- "Halogen atom" refers to fluorine, chlorine, bromine or iodine atom; preferably fluorine and chlorine atom ;
- "Aryl" means an aromatic monocyclic or multicyclic hydrocarbon ring system of 6 to 14 carbon atoms, preferably of 6 to 10 carbon atoms. Exemplary aryl groups include phenyl or naphthyl ;
- "Het" means heterocycle or heteroaryl ;
- the terms "heterocycle" or "heterocyclic" refer to a saturated, partially unsaturated or unsaturated, non aromatic stable 3 to 14, preferably 5 to 10 membered mono, bi or multicyclic rings wherein at least one member of the ring is a hetero atom. Typically, heteroatoms include, but are not limited to, oxygen, nitrogen, sulfur, selenium, and phosphorus atoms. Preferable heteroatoms are oxygen, nitrogen and sulfur. Suitable heterocycles are also disclosed in *The Handbook of Chemistry and Physics*, 76th Edition, CRC Press, Inc., 1995-1996, p. 2-25 to 2-26, the disclosure of which is hereby incorporated by reference.
- Preferred non aromatic heterocyclic include, but are not limited to pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxiranyl, tetrahydrofuranyl, dioxolanyl, tetrahydro-pyranyl, dioxanyl, dioxolanyl, piperidyl, piperazinyl, morpholinyl, pyranyl, imidazolinyl, pyrrolinyl, pyrazolinyl, thiazolidinyl, tetrahydrothiopyranyl,

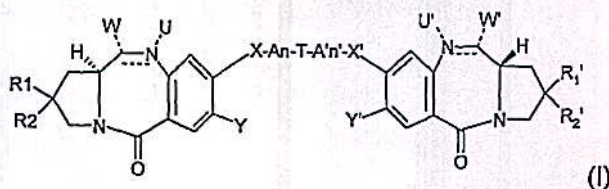
Tomaymycin derivatives

The invention is based on the synthesis of novel tomaymycin derivatives that retain high cytotoxicity and that can be effectively linked to cell binding agents with non-cleavable linkers, such conjugates demonstrating high potency in killing tumor cells. It has previously been shown that the linkage of highly cytotoxic drugs to antibodies using a cleavable link, such as a disulfide bond, ensures the release of fully active drugs inside the cell, and such conjugates are cytotoxic in an antigen specific manner (US 6,340,701; US 6,372,738; US 6,436,931). However, the art reveals that it is extremely difficult to modify existing drugs without diminishing their cytotoxic potential. The disclosed invention overcomes this problem by modifying the disclosed tomaymycin derivatives with chemical moieties. As a result, the disclosed novel tomaymycin derivatives preserve, and in some cases could even enhance the cytotoxic potency of tomaymycin derivatives. The cell binding agent-tomaymycin derivative complexes permit the full measure of the cytotoxic action of the tomaymycin derivatives to be applied in a targeted fashion against unwanted cells only, therefore, avoiding side effects due to damage to non-targeted healthy cells. Thus, the invention provides useful agents for the elimination of diseased or abnormal cells that are to be killed or lysed such as tumor cells (particularly solid tumor cells).

**Tomaymycin**

The cytotoxic agent according to the present invention comprises one or more tomaymycin derivatives, optionally linkable or linked to a cell binding agent via a non-cleavable linking group. The linking group is part of a chemical moiety that is covalently bound to a tomaymycin derivative through conventional methods.

According to one aspect, the invention relates to tomaymycin derivatives of formula (I) :



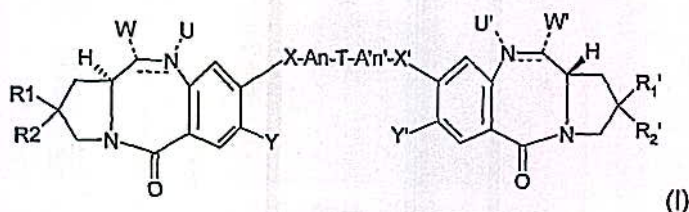
wherein :

— represents an optional single bond ;

— represents either a single bond or a double bond ;

CLAIMS

1. Compound of formula (I) :



wherein :

— represents an optional single bond;

— represents either a single bond or a double bond ;

provided that when — represents a single bond, U and U', the same or different, independently represent H, and W and W', the same or different, are independently selected from the group consisting of -OH, -OR, -OCOR, -COOR, -OCOOR, -OCONRR', a cyclic carbamate such that N10 and C11 are a part of the cycle,

-OCSNHR, a cyclic thiocarbamate such that N10 and C11 are a part of the cycle, -SH, -SR, -SOR, -SOOR, -SO₃⁻, -NRSOOR', -NRR', a cyclic amine such that N10 and C11 are a part of the cycle, -NROR', -NRCOR', -N₃, -CN, Hal, a trialkyl or triarylphosphonium ;

and when — represents a double bond, U and U' are absent and W and W' represent H ;

• R₁, R₂, R₁', R₂' are the same or different and independently chosen from H, halide or alkyl optionally substituted by one or more Hal, CN, NRR', CF₃, OR, aryl, Het, S(O)₆R, or R₁ and R₂ and R₁' and R₂' form together a double bond containing group =B and =B' respectively ;

• B and B' are the same or different and independently chosen from Alkenyl being optionally substituted by one or more Hal, CN, NRR', CF₃, OR, SR, SOR, SO₂R, Aryl, Het, or B and B' represent an oxygen atom.;

• X, X' are the same or different and independently chosen from one or more -O-, -S-, -NR-, -(C=O)-, -SO-, -SO₂- ;

• A, A' are the same or different and independently chosen from Alkyl or Alkenyl, each being optionally substituted by one or more Hal, CN, NRR', CF₃, OR, SR, SOR, SO₂R, Aryl, Het, Alkyl, Alkenyl ;

• Y, Y' are the same or different and independently chosen from H, OR ;

▪ T is -NR- or a 4 to 10-membered aryl, cycloalkyl, heterocyclic, heteroaryl or a linear or branched alkyl, each being substituted by one or more non-cleavable linker(s) and optionally substituted by one or more of Hal, CN, NRR', CF₃, R, OR, SOR or SO₂R ;

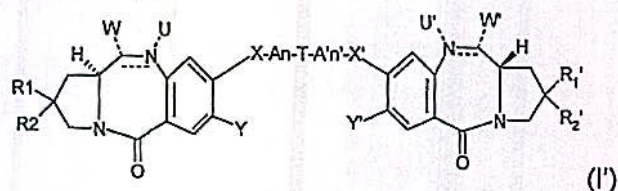
▪ n, n', equal or different, are 0 or 1 ;

▪ q is 0, 1 or 2 ;

▪ R, R' are equal or different and independently chosen from H, Alkyl, Aryl, each being optionally substituted by Hal, CN, COOH, COOR, CONHR, CONRR', NRR', CF₃, R, OR, SOR, SO₂R, Aryl, Het.

or the pharmaceutically acceptable salts, hydrates or hydrated salts, the polymorphic crystalline structures or optical isomers, racemates, diastereomers or enantiomers of said compound.

2. Compound of formula (I') :



wherein :

▪ T is -NR- or a 4 to 10-membered aryl, cycloalkyl, heterocyclic, heteroaryl or a linear or branched alkyl, each being substituted by one or more linker(s) of formula -G-D-(Z)_pC(=O)-Z'R'' and optionally substituted by one or more of Hal, CN, NRR', CF₃, R, OR, SOR or SO₂R. ;

▪ G is a single, a double or a triple bond, -O-, -S- or -NR-;

▪ D is a single bond or -E-, -E-NR-, -E-NR-F-, -E-O-, -E-O-F-, -E-NR-CO-, -E-CONR-, -E-NR-CO-F-, -E-CO-NR-F-, -E-CO-, -CO-E-, -E-CO-F-, -E-S-, -E-S-F-, -E-NR-CS-, -E-CS-NR-, -E-NR-CS-F-, -E-CS-NR-F- ;

▪ E and F are the same or different and are independently chosen from linear or branched -(OCH₂CH₂)_iAlkyl(OCH₂CH₂)_j-, -Alkyl(OCH₂CH₂)_i-Alkyl-, -(OCH₂CH₂)_j-, -(OCH₂CH₂)_iCycloalkyl(OCH₂CH₂)_j-, -(OCH₂CH₂)_iHeterocyclic(OCH₂CH₂)_j-, -(OCH₂CH₂)_iAryl(OCH₂CH₂)_j-, -(OCH₂CH₂)_iHeteroaryl(OCH₂CH₂)_j-, -Alkyl-(OCH₂CH₂)_iAlkyl(OCH₂CH₂)_j-, -Alkyl-(OCH₂CH₂)_j-, -Alkyl-(OCH₂CH₂)_iCycloalkyl(OCH₂CH₂)_j-, -Alkyl(OCH₂CH₂)_iHeterocyclic(OCH₂CH₂)_j-, -Alkyl-(OCH₂CH₂)_iAryl(OCH₂CH₂)_j-, -Alkyl(OCH₂CH₂)_iHeteroaryl(OCH₂CH₂)_j-, -Cycloalkyl-Alkyl-, -Alkyl-Cycloalkyl-, -Heterocyclic-Alkyl-, -Alkyl-Heterocyclic-, -Alkyl-Aryl-, -Aryl-Alkyl-,

-Alkyl-Heteroaryl-, -Heteroaryl-Alkyl-;

▪ i and j, identical or different are integers and independently chosen from 0, 1 to 2000;

▪ Z is a linear or branched Alkyl, cycloalkyl, Aryl, heteroaryl, heterocyclyl, aralkyl, cycloalkyl, heteroaralkyl, or heterocyclalkyl, optionally substituted by solubilizing functions such as amino, ether, sulfonic and carboxylic groups;

▪ p is 0 or 1;

▪ -C(=O)-Z'R'' is a carbonyl containing function wherein:

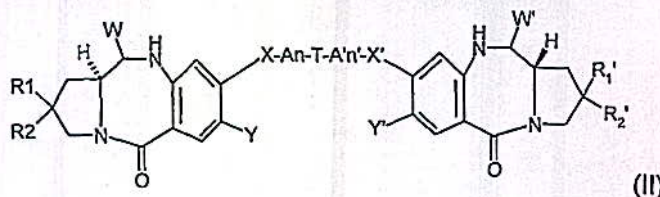
- Z' represents a single bond or -O-, -S-, -NR- and

- R'' represents H, Alkyl, Cycloalkyl, Aryl, heteroaryl or heterocyclic, each being optionally substituted by one or more Hal, CN, NRR', CF₃, R, OR, SOR, SO₂R, Aryl, Het;

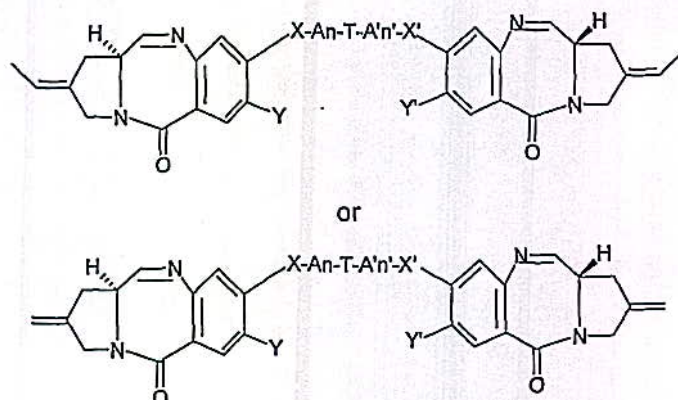
▪ R₁, R₁', R₂, R₂', W, W', U, U', Y, Y', X, X', A, A', n, n', R and R' are as defined in claim 1.

3. Compound according to claims 1 or 2 wherein W and W' are the same or different and are -OH, -OMe, -OEt, -NHCONH₂, -SMe.

4. Compound according to claims 1 to 3 having the following formula (II):



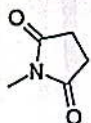
5. Compound of formula:



wherein X, X', A, A', Y, Y', T, n, n' are as defined as in claim 1 or 2.

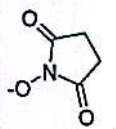
- 26
6. Compound according to any one of the preceding claims wherein $X=X'$.
 7. Compound according to any one of the preceding claims wherein $X=X'=O$.
 - 5 8. Compound according to any one of the preceding claims wherein $A=A'$.
 9. Compound according to any one of the preceding claims wherein $A=A'$ =linear unsubstituted alkyl.
 - 10 10. Compound according to any one of the preceding claims wherein $Y=Y'$.
 11. Compound according to any one of the preceding claims wherein $Y=Y'=O$ Alkyl.
 12. Compounds according to any one of the preceding claims wherein T is a 4 to 10-
15 membered aryl or heteroaryl substituted by one or more of said linker(s) and optionally substituted by one or more of Hal, CN, NRR', CF₃, R, OR, SOR or SO₂R.
 13. Compound according to claim 12 wherein T is a phenyl or pyridyl group.
 - 20 14. Compound according to any one of the preceding claims wherein the linker is of formula $-G-D-(Z)_p-C(=O)-Z'R''$ as defined in claim 2.
 15. Compound according to claim 14 wherein G is a single, a double or a triple bond or $-O-$, $-S-$ or $-NR-$.
 - 25 16. Compound according to claim 14 or 15, wherein - G is a single bond or $-O-$.
 17. Compound according to claim 14, 15 or 16, wherein D is a single bond or $-E-$ or $-E-O-$.
 - 30 18. Compound according to any one of claims 14 to 17, wherein D is $-E-$.
 19. Compounds according to any one of claims 14 to 18 wherein E is linear or branched $-Alkyl-$ or $-Alk(OCH_2CH_2)_i-$.
 - 35 20. Compound according to any one of claims 14 to 19, wherein Z is linear or branched $-Alkyl-$.

21. Compound according to any one of claims 14 to 20 wherein p is 0.
22. Compound according to anyone of claims 14 to 21 wherein Z' is a single bond or O.
23. Compound according to any one of claims 14 to 22 wherein Z' is O.
24. Compound according to any one of claims 14 to 23 wherein R" is H or linear or branched -Alkyl- or optionally substituted heterocyclic.
25. Compound according to any one of claims 14 to 24 wherein R" is H or alkyl or a



succinimide group

26. Compound according to any one of claims 14 to 25 wherein -Z'R" is -OH, -Oalkyl



or

27. Compound according to any one of the preceding claims wherein the linker is chosen from:

- (CR₁₃R₁₄)_i(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i(OCH₂CH₂)_yO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i(NR₁₉CO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i(OCO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i(CO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i(CONR₁₉)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 - (CR₁₃R₁₄)_i-phenyl-CO(CR₁₅R₁₆)_uCOZ'R", - (CR₁₃R₁₄)_i-furyl-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i-oxazolyl-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i-thiazolyl-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i-thienyl-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i-imidazolyl-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_ipiperazino-CO(CR₁₅R₁₆)_uCOZ'R",
 - (CR₁₃R₁₄)_i-phenyl-QCOZ'R",

- (CR₁₃R₁₄)_t-furyl-QCOZ'R", -(CR₁₃R₁₄)_t-oxazolyl-QCOZ'R",
 -(CR₁₃R₁₄)_t-thiazolyl-QCOZ'R", -(CR₁₃R₁₄)_t-thienyl-QCOZ'R",
 -(CR₁₃R₁₄)_t-imidazolyl-QCOZ'R", -(CR₁₃R₁₄)_t-piperazino-QCOZ'R",
 5 -(C≡C)-(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -O(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -O(CR₁₃R₁₄)_t(NR₁₉CO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -O(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -O-phenyl-QCOZ'R", -O-furyl-QCOZ'R", -O-oxazolyl-QCOZ'R",
 10 -O-thiazolyl-QCOZ'R", -O-thienyl-QCOZ'R", -O-imidazolyl-QCOZ'R",
 -O-morpholino-QCOZ'R", -O-piperazino-QCOZ'R",
 -OCO(CR₁₃R₁₄)_t(NR₁₉CO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -OCO-(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 15 -OCONR₁₂(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -OCO-phenyl-QCOZ'R", -OCO-furyl-QCOZ'R", -OCO-oxazolyl-QCOZ'R",
 -OCO-thiazolyl-QCOZ'R", -OCO-thienyl-QCOZ'R", -OCO-imidazolyl-QCOZ'R",
 -OCO-piperazino-QCOZ'R", or
 20 -CO(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -CO-(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -CONR₁₂(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -CO-phenyl-QCOZ'R", -CO-furyl-QCOZ'R", -CO-oxazolyl-QCOZ'R",
 -CO-thiazolyl-QCOZ'R", -CO-thienyl-QCOZ'R", -CO-imidazolyl-QCOZ'R",
 25 -CO-piperazino-QCOZ'R", -CO-piperidino-QCOZ'R",
 -NR₁₉(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -NR₁₉CO(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -NR₁₉(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 30 -NR₁₉CO(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -NR₁₉CONR₁₂(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -NR₁₉CO NR₁₂(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -NR₁₉CO-phenyl-QCOZ'R", -NR₁₉CO-furyl-QCOZ'R", -NR₁₉CO-oxazolyl-QCOZ'R",
 -NR₁₉CO-thiazolyl-QCOZ'R", -NR₁₉CO-thienyl-QCOZ'R",
 35 -NR₁₉CO-imidazolyl-QCOZ'R", -NR₁₉CO-morpholino-QCOZ'R",
 -NR₁₉CO-piperazino-QCOZ'R", -NR₁₉CO-piperidino-QCOZ'R",
 -NR₁₉-phenyl-QCOZ'R", -NR₁₉-furyl-QCOZ'R", -NR₁₉-oxazolyl-QCOZ'R",

-NR₁₉-thiazolyl-QCOZ'R", -NR₁₉-thienyl-QCOZ'R", -NR₁₉-imidazolyl-QCOZ'R",
 -NR₁₉-piperazino-QCOZ'R", -NR₁₉-piperidino-QCOZ'R",
 -NR₁₉CO-NR₁₂-phenyl-QCOZ'R", -NR₁₉CO-NR₁₂-oxazolyl-QCOZ'R",
 -NR₁₉CO-NR₁₂-thiazolyl-QCOZ'R", -NR₁₉CO-NR₁₂-thienyl-QCOZ'R",
 -NR₁₉CO-NR₁₂-piperidino-QCOZ'R",

-S(O)_q(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -S(O)_q(CR₁₃R₁₄)_t(CR₁₇=CR₁₈)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R",
 -SCONR₁₂(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R", -SCO-piperazino-QCOZ'R",
 and -SCO-piperidino-QCOZ'R",

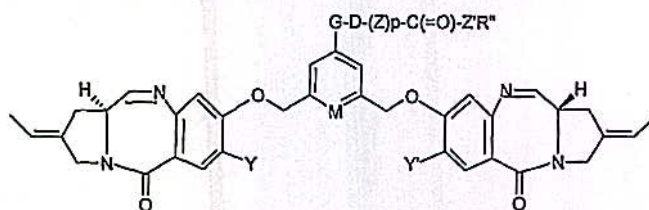
wherein :

- Q is a direct link or a linear alkyl or branched alkyl having from 1-10 carbon atoms or a polyethylene glycol spacer with 2 to 20 repeating ethyleneoxy units;
- R₁₉ and R₁₂ are the same or different and are linear alkyl, branched alkyl or cyclic alkyl having from 1 to 10 carbon atoms, or simple or substituted aryl or heterocyclic, and R₁₂ can in addition be H ;
- R₁₃, R₁₄, R₁₅ and R₁₆ are the same or different and are H or a linear or branched alkyl having from 1 to 4 carbon atoms ;
- R₁₇ and R₁₈ are H or alkyl ;
- q is 0, 1 or 2 ;
- u is an integer from 1 to 10 and can also be 0 ;
- t is an integer from 1 to 10 and can also be 0 ;
- y is an integer from 1 to 20 and can also be 0.

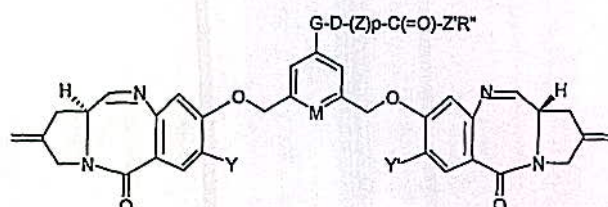
28. Compound according to claim 27 wherein said linker is chosen from:

- -(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R" ;
- -(CR₁₃R₁₄)_t(OCH₂CH₂)_yO(CR₁₅R₁₆)_uCOZ'R" ;
- -O(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R" ;
- -O(CR₁₃R₁₄)_t(NR₁₉CO)(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R" ;
- -(C≡C)-(CR₁₃R₁₄)_t(CR₁₅R₁₆)_u(OCH₂CH₂)_yCOZ'R" ;
- -O(CR₁₃R₁₄)_tCOZ'R" ;
- -(OCH₂CH₂)_yCOZ'R" ;
- -(C≡C)-(CR₁₃R₁₄)_tCOZ'R" ;
- -O(CR₁₃R₁₄)_t(NR₁₉CO)(CR₁₅R₁₆)_uCOZ'R" ;
- -(CR₁₃R₁₄)_t(OCH₂CH₂)_yCOZ'R".

29. Compound of formula :



or



wherein :

- $-G-D-(Z)_p-C(=O)-Z'R''$ is as defined in claims 2 or 14 to 28 ;
- M represents CH or N.

30. Compound selected in the group consisting of :

- 4-(3,5-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenoxy)-butyric acid ;
- 4-(3,5-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenoxy)-acetic acid ;
- 3-(2-[2-[2-(3,5-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenoxy)-ethoxy]-ethoxy)-ethoxy)-propionic acid ;
- 6-(3,5-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenyl)-hex-5-ynoic acid ; [1,4]
- 3-(2-[2-[2-(2,6-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-pyridin-4-yloxy)-ethoxy]-ethoxy)-ethoxy)-propionic acid ;
- 4-(2,6-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-pyridin-4-yloxy)-butyric acid ;
- N-[2-(3,5-Bis-[(S)-2-eth-(E)-ylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenoxy)-ethyl]-N-methyl-succinamic acid ;
- 4-(3,5-Bis-[(S)-2-methylidene-7-methoxy-1,2,3,11a-tetrahydro-pyrrolo[2,1c][1,4]benzodiazepin-5-one-8-yloxymethyl]-phenyl)-propanoic acid ;

- (2-{2-[2-(2-{3-[3,5-Bis-(7-methoxy-2-methylene-5-oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-8-yloxymethyl)-phenyl]-propoxy}-ethoxy)ethoxy]-ethoxy}-ethoxy)-acetic acid ;
- (3-{2-[2-(2-{3-[3,5-Bis-(7-methoxy-2-methylene-5-oxo-2,3,5,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-8-yloxymethyl)-phenyl]-propoxy}-ethoxy)ethoxy]-ethoxy}-ethoxy)-propanoic acid ;

as well as the corresponding N-hydroxysuccinimidyl esters,

or their pharmaceutically acceptable salts, hydrates, or hydrated salts, or the polymorphic crystalline structures of these compounds or their optical isomers, racemates, diastereomers or enantiomers.

31. A conjugate molecule comprising one or more tomaymycin derivative(s) according to any one of claims 1 to 30 chemically linked to a cell binding agent, optionally modified, through the linker.

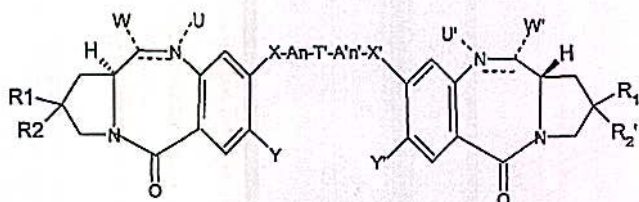
32. A conjugate molecule comprising one or more tomaymycin derivative(s) according to one of claims 1 to 30 covalently linked to a cell binding agent through the linking group of the linker of the tomaymycin derivative.

33. A conjugate molecule according to claim 31 or 32 wherein said cell binding agent is chosen from antibodies or a fragment of an antibody that contains at least one binding site, lymphokines, hormones, growth factors, nutrient-transport molecules, or any other cell binding molecule or substance.

34. A conjugate molecule according to claim 31 to 33 wherein said cell binding agent is chosen from monoclonal antibodies; chimeric antibodies; humanized antibodies; fully human antibodies; single chain antibodies; fragments of antibodies such as Fab, Fab', F(ab')₂ and F_v, interferons; peptides; lymphokines such as IL-2, IL-3, IL-4, IL-6; hormones such as insulin, TRH (thyrotropin releasing hormones), MSH (melanocyte-stimulating hormone), steroid hormones, such as androgens and estrogens; growth factors and colony-stimulating factors such as EGF, TGF α , insulin like growth factor (IGF-I, IGF-II) G-CSF, M-CSF and GM-CSF; vitamins, such as folate and transferrin.

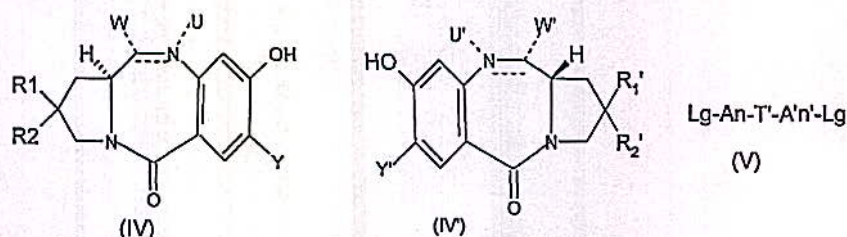
35. A conjugate molecule according to any one of claims 31 to 34 wherein cell binding agent and said derivative(s) are linked through an amide group.

36. Process of preparation of a compound according to anyone of claims 1 to 30, comprising the step of hydrolysing or deprotecting a corresponding compound of formula :



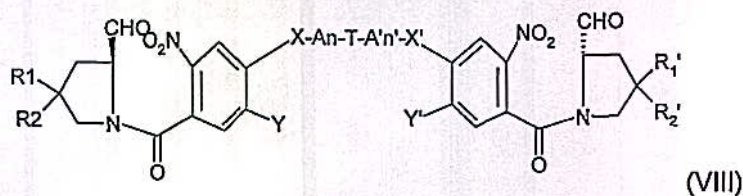
wherein T' corresponds to T wherein the terminal carboxy group is esterified or protected, and optionally isolating the desired compound.

37. Process according to claim 36 wherein the compound to be hydrolyzed or deprotected is obtained from coupling corresponding compounds of formulae (IV), (IV') and (V):



wherein Lg is a leaving group.

38. Process of preparation of a compound according to anyone of claims 1 to 30 comprising the step of cyclizing the corresponding compound of formula (VIII):



39. Process of preparation of a conjugate molecule comprising the step where a compound as defined in claim 1 to 30 wherein the linker comprises a terminal carboxy group, said carboxy group being optionally activated as an amide group, or a precursor thereof, is reacted with a cell binding agent so that the compound and the cell binding agent are linked together via an amide bond.

40. A pharmaceutical composition comprising a conjugate molecule as defined in any one of claims 31 to 35, or a compound as defined in anyone of claims 1 to 30 together with a pharmaceutically acceptable carrier.
- 5
41. Use of an effective amount of a conjugate molecule as defined in any one of claims 31 to 35 or a compound as defined in any one of claims 1 to 30 for the preparation of a medicament for the treatment of cancer.
- 10

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