

JOSE LLORED A CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 8069700 Fax 8069701

314
317

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 00-077374-00010-0000

Fec: 2008-06-21 11:58:30 Dep. 2020 NUECREACIONES

Tra. 2 PATENTES

Eve: 1 REGDEPOSITO

Act 444 RESPUESTAREQUE Folios: 68

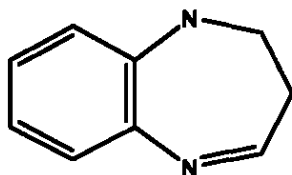
Re: P1.-F.HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención para "DERIVADOS AROMÁTICOS Y HETEROAROMÁTICOS DE BENZO[B][1,4]DIAZEPIN-2-ONAS".-Clase A.61.-Expediente número 00-077.374.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 29 de Junio de 2006.

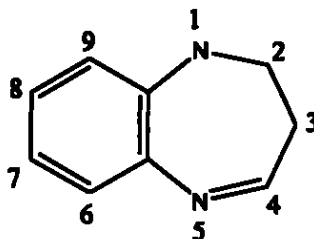
2. De acuerdo con el Concepto Técnico número 0969, el señor Examinador objeta la claridad de la solicitud teniendo en cuenta los siguientes argumentos:

- Aún cuando de acuerdo con la fórmula I, reivindicada por la cláusula Independiente 1, es claro que se reclama protección para **benzo[b][1,5]diazepin-2-onas**, las reivindicaciones 3 y 5 están dirigidas a proteger un núcleo de **benzo[b]diazepin-2-onas** de tipo [1,4], por lo cual no existe una relación estrecha con el concepto inventivo definido entorno a la fórmula (I).
- Sustituciones tan diversas como las que se definen para -R₁, el cual fluctúa entre halógeno, alquilo, cicloalquilo, benzilo, fenilo opcionalmente sustituido con halógeno, hidroxilo, alquilo (C₁-C₇), alcoxilo, halo-alcoxilo o ciano, estírenilo, naftilo, bifenilo, benzofuranilo entre otros lo cual indetermina el objeto central de la Invención.
- No es lo mismo tener un sustituyente de tipo halógeno a tener en la misma posición un sustituyente de tipo aromático: fenilo, naftilo o bifenilo, o heteroaromático como tiofenilo, furanilo, piridinilo.

En respuesta a todo lo anterior, me permito manifestar como primera medida que los compuestos de la presente Invención **se encuentran correctamente nombrados** ya que según las reglas de nomenclatura de la IUPAC, el anillo que presento a continuación puede ser nombrado con base en dos enfoques diferentes, a saber A y B:



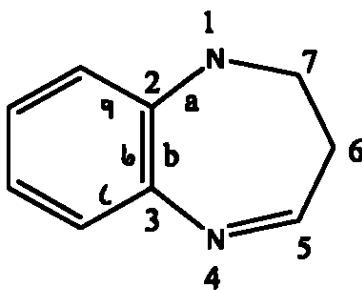
ENFOQUE A: Nombrar el bíciclo como un núcleo de acuerdo con la regla IUPAC FR-2.2.8 -Componentes heterobíclicos con un anillo de benceno- (de la cual anexo copia), de tal manera que la numeración del anillo correspondería a la siguiente:



Para este caso, el nombre correcto del anillo-sistema sería:

4,5-dihidro-1H-1,5-benzodiazepina (sin incluir paréntesis cuadrados en el nombre), teniendo en cuenta que la existencia de la numeración "1,5" en el nombre del compuesto hace referencia a la posición de los átomos de nitrógeno en el anillo de benzodiazepina, siendo necesario que dicha numeración se coloque antes del anillo de benzodiazepina.

ENFOQUE B: Nombrar los anillos por separado y la forma en que se encuentran unidos uno al otro, de acuerdo con las reglas IUPAC FR-3 -Construcción de los nombres de fusión- y FR-4 -Descriptores de fusión- de las cuales anexo copia, de tal manera que la numeración del anillo sería la siguiente:



Numeraçión anillo diazepina
Letras anillo benceno
lectura en igual sentido

Para este caso, el nombre correcto del anillo sería

4,5-dihidro-1H-benzo[b][1,4]diazepina (Incluyendo paréntesis cuadrados en el nombre), teniendo en cuenta que el descriptor de enlace "[b]" y la numeración de los átomos de nitrógeno "[1,4]" hacen referencia a monociclos (el anillo de diazepina), que los números 1 y 4 indican que los átomos de nitrógeno se encuentran en las posiciones 1 y 4 del anillo de diazepina y que la letra "b" indica que el anillo de diazepina se enlaza al anillo de benceno en el lado b (esto es, el lado siguiente al lado "a" que inicia con la posición 1). Al usar este

Puente. localización

1) benzo [2,3-b][1,4] diazepina

2) 1,5 benzo[2,3b] diazepina.
-2 0179.

enfoque, es necesario tener en cuenta que las expresiones "[b]" y "[1,4]" deben ubicarse, dentro del nombre, **entre** los monociclos y además que el uso de los paréntesis cuadrados es **obligatorio**.

Ahora bien, si lo anterior se aplica a los compuestos de la invención, es claro que al emplear la regla **FR-2.2.8-** de la IUPAC, los compuestos de la invención se nombran teniendo en cuenta el núcleo **4,5-dihidro-1H-1,5-benzodiazepina**, mientras que si se siguen en combinación, las reglas **FR-3** y **FR-4** de la IUPAC, los compuestos de la invención corresponden a **4,5-dihidro-1H-benzo[b][1,4]diazepin derivados**.

De esta manera, no es **posible en ningún momento** que los compuestos de la invención sean nombrados como **4,5-dihidro-1H-benzo[b][1,5]diazepin derivados** de acuerdo con las reglas de la nomenclatura IUPAC, tal como lo sugirió el señor Examinador. Las anteriores reglas de nomenclatura de la IUPAC fueron extraídas de la siguiente página Web: <http://www.chem.qmul.ac.uk/iupac/fusedring/>. En esta no solo se encuentran las tres reglas mencionadas en este memorial sino también todas las reglas de nomenclatura de la IUPAC.

Por otro lado, en cuanto a los argumentos del Examinador dirigidos a que las diversas posibilidades contempladas para los sustituyentes de los compuestos de la presente invención no permiten definir con claridad los compuestos reclamados, me permito llamar la atención de ese Despacho al hecho de que una persona versada en la materia reconocería que un núcleo como el anillo de benzodiazepina, es una estructura básica que permite agrupar los compuestos reclamados por la presente solicitud, toda vez que están **caracterizados** por tener en común dicho núcleo.

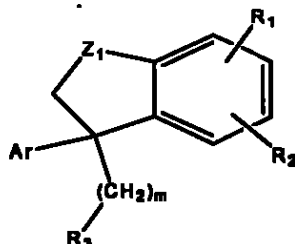
Adicionalmente, el hecho de que los sustituyentes de los compuestos en mención estén definidos con una serie de posibilidades que comprende desde un grupo halógeno hasta un grupo aromático o heteroaromático (como es el caso de la definición para el sustituyente del anillo de benzodiazepina R₁), no implica **en ningún momento** que una persona versada en la materia **no se encuentre en la capacidad de comprender** que los compuestos reclamados por la presente, en efecto pertenecen a la familia de las benzodiazepinas, específicamente la familia de las benzo[b][1,4]diazepinas, tal como se demostró anteriormente, mediante la utilización del enfoque B previamente enseñado. Por lo tanto, es claro que una persona versada en la materia se encuentra en la capacidad de construir los compuestos de la presente invención con las diferentes posibilidades para los sustituyentes y aún así continuar reconociendo que estos pueden ser agrupados en una misma familia conformada por un núcleo básico definido.

317
320

Por otro lado, me permito manifestar que el solicitante no entiende por qué, el hecho de que existan varias posibilidades diferentes para la definición de los sustituyentes de los compuestos que tienen en su estructura el anillo reclamado por la presente invención así como el hecho de que en algunos casos dichas posibilidades comprendan un sustituyente voluminoso, son considerados por ese Despacho como fundamentos para objetar la falta de claridad de la solicitud, toda vez que es ampliamente conocido que en el campo de la Propiedad Industrial el hecho de que se tengan múltiples posibilidades para la definición de los sustituyentes de un compuesto reclamado y que esto **no constituye** un impedimento para que se conceda el beneficio de patente para una solicitud. De hecho, en la práctica es muy común encontrar solicitudes que comprenden varias posibilidades diversas para la definición de sustituyentes sin que esto implique que no se cumpla con el requisito de claridad para la obtención del beneficio de patente, pues es reconocido y practicado en este campo que una familia de compuestos pueda agruparse con base en un núcleo básico común, que incluso en algunos casos puede ser bastante simple, a partir del cual se puede llegar a estructuras particulares más complejas mediante las diversas sustituciones que se pueden realizar sobre las posiciones con diferentes posibilidades de identidad, sin que ello implique ambigüedad en la materia reivindicada.

En efecto, es bastante común encontrar documentos de patente, otorgados por Oficinas reconocidas por su rigurosidad al momento de realizar el examen de patentabilidad, que presentan esta característica. Con el fin de reforzar mi argumento anterior, me permito remitir a ese Despacho copia de la portada y las páginas correspondientes a la reivindicación 1 de los documentos de patente **WO97/29100** (en adelante referenciado como **P1**), **WO 2005/060692 A2** (en adelante referenciado como **P2**) y **WO 2005/058884** (en adelante referenciado como **P3**), los cuales reclaman compuestos con esqueletos principales sencillos y sustituyentes que comprenden diversas posibilidades tal como me permito enseñar a continuación:

- El documento **P1** publicado el 19 de Agosto de 1997 reclama compuestos "diarilo heterocíclicos" con el siguiente núcleo básico:

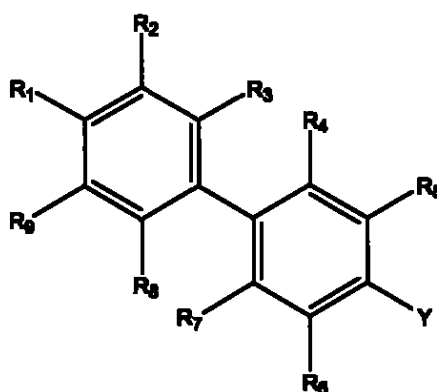


4

318
321

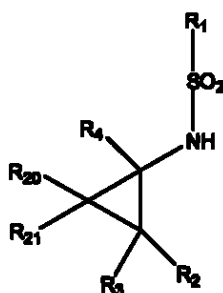
En donde, tal como puede apreciarse en la página 45, líneas 14-30 de dicho documento, el sustituyente Ar puede tener tres posibilidades diferentes en la cual la primera corresponde a un anillo de benceno con 4 posibles sustituyentes (R_4 , R_5 , R_6 y R_7) los cuales a su vez puede ser definidos con varias posibilidades, siendo más compleja la segunda posibilidad para el sustituyente Ar y aún más compleja la tercera posibilidad para dicho sustituyente. Puede evidenciarse que para los demás sustituyentes sucede lo mismo, claro está, en mayor o menor proporción. Sin embargo, el hecho de que los sustituyentes definidos tengan a su vez más sustituyentes, no implica en ningún momento que para la persona versada en la materia no sea perfectamente claro y entendible que los compuestos allí reclamados pueden construirse de manera sencilla haciendo uso de nociones básicas de química y que además dichos compuestos pueden agruparse en la familia de compuestos diarilos heterocíclicos reclamados en tal documento de patente.

- Por otro lado, el documento P2 publicado el 7 de Julio de 2005 reclama compuestos bifenilo como los siguientes:



Para los cuales, por citar apenas un ejemplo puede verificarse que uno de los sustituyentes R_1 o R_2 está definido por un grupo de posibilidades que comprende desde un átomo de Hidrógeno hasta un heteroarilo opcionalmente sustituido. Adicionalmente, R_{12} varía entre un alquilo inferior opcionalmente sustituido hasta un heteroarilo opcionalmente sustituido, y sucede lo mismo con los demás sustituyentes en mayor o menor proporción.

- Por último, el documento P3 publicado el 30 de Junio de 2005 reclama compuestos de ciclopropano con un núcleo básico muy sencillo tal como se muestra a continuación:



2

Compuesto en el cual, citando solo un ejemplo, la segunda opción para R_1 comprende un grupo $-(CH_2)_m-X-(CH_2)_n-A^1$, donde X tiene varias posibilidades para su definición incluyendo un enlace sencillo y un grupo $-N(R^5)COO-$. Lo mismo sucede con los demás sustituyentes, permitiendo observar que se parte de un núcleo básico pequeño a partir del cual se pueden obtener compuestos voluminosos, sin que la persona versada en la materia pierda la capacidad de comprender el alcance de la invención, teniendo en cuenta de lo que enseñan las reivindicaciones y las nociones básicas de química, permitiéndole sin mayor dificultad construir las estructuras de los compuestos reclamados.

Aunque el solicitante reconoce que ese Despacho es independiente en sus decisiones y que la legislación que se aplica en los países donde se presentaron los documentos de patente citados como ejemplo, son comunes en el campo de la Propiedad Industrial puede ser diferente a la legislación que se aplica para la presente solicitud en este proceso, es claro que en el campo de las Invenciones relacionadas con la química, específicamente con el desarrollo de nuevos compuestos, es comúnmente aceptado que entre las posibilidades de un mismo sustituyente se pueden encontrar opciones relativamente amplias para los grupos químicos cobijados por dicho sustituyente, sin que esta situación afecte la claridad de la materia a proteger.

En conexión con lo anterior y como un indicio claro no solo de que la presente solicitud cumple con el requisito de claridad, sino además de que la misma ha sido reconocida bajo las disposiciones de la Decisión 486, me permito nuevamente llamar la atención del señor Examinador al hecho de que tal como mencioné en mi memorial de 25 de Mayo de 2006, el capítulo reivindicatorio de la solicitud en estudio corresponde al mismo presentado ante la Oficina de Patentes Peruana, con la única diferencia de que en el capítulo reivindicatorio de la solicitud en estudio, se definieron las condiciones de reacción de las reivindicaciones que hacen referencia al proceso de obtención de los compuestos reclamados con el fin de superar una objeción previamente realizada por el señor Examinador.

En este sentido, me permito resaltar que la solicitud presentada ante la Oficina Peruana fue concedida con el número de patente 3645 (de la cual anexo copia) y como se sabe, Perú es uno de los países que conforman la Comunidad Andina de Naciones, a la cual también pertenece Colombia y ambos deben cumplir con los lineamientos consignados en la Decisión 486 - la cual es el Régimen Común sobre Propiedad Industrial. Por lo tanto, en el campo de la Propiedad Industrial es claro que ambos países se rigen por la

misma legislación, y aunque es vidente que tanto la Peruana como la Colombiana son Oficinas Independientes, y que la concesión de una patente en alguno de los países no obliga a los demás a actuar de la misma manera, también resulta válido señalar que al aplicar los mismos criterios de evaluación, el hecho de que la claridad de la solicitud haya sido reconocida por alguno de los miembros de la CAN, resulta relevante, ya que al encontrarse regidos por las mismas leyes, utilizan las mismas bases y conceptos al momento de realizar el examen de patentabilidad por lo que el reconocimiento de la patentabilidad por parte de alguno de ellos constituye un indicio claro y evidente de que la solicitud cumple con los requisitos establecidos en la Decisión 486 para gozar del privilegio solicitado.

3. El señor Examinador en su Concepto Técnico número 0969 objeta la Unidad de Invención de la solicitud presentada argumentando que la familia a la que pertenecían los compuestos reclamados de manera específica no era la misma familia que agrupaba de manera general los compuestos de la Invención.

Sobre este particular, me permito manifestar que habiendo demostrado que la nomenclatura empelada para el núcleo básico reclamado es correcta, y que en consecuencia los compuestos específicos reclamados **sí pertenecen a la familia** descrita por el núcleo básico reclamado por la presente solicitud, es decir **benzo[b][1,4]diazepin-2-onas**, sí existe un concepto común Inventivo para la solicitud en estudio y por ende se supera la objeción realizada por el señor Examinador a este respecto.

Para concluir, teniendo claro que los compuestos reclamados de manera general a través de su núcleo básico y de manera específica en las listas de compuestos contenidas en el capítulo reivindicatorio y además de que el hecho en el campo de la Propiedad Industrial sean ampliamente empleadas múltiples posibilidades para definir los sustituyentes en un anillo, se entiende que la presente solicitud sí cumple con los requisitos de patentabilidad, y por lo tanto se entienden superadas las objeciones de **CLARIDAD y NIVEL INVENTIVO** realizadas por el señor Examinador.

4. Anexo me permito presentar:

- (1) Copia de las reglas FR-2.2.8, FR-3 y FR-4 de la IUPAC;
- (2) Copia de la portada y las páginas correspondientes a la reivindicación 1 de los documentos de patente Nos. **WO 97/29100, WO 2005/060692 A2 y WO 2005/058884 A2**; y

JOSE LLORED A CAMACHO & CO.

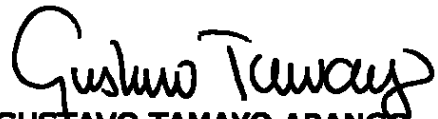
Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

324³²⁴

(3) Copia del título y de las reivindicaciones de la Patente No. 3645 concedida en el Perú.

5. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y conceder el privilegio de patente solicitado.

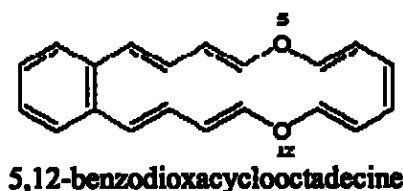
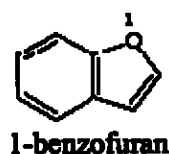
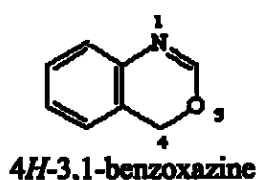
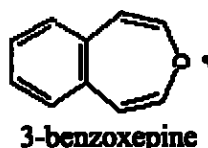
Señor Superintendente,


GUSTAVO TAMAYO ARANGO
T.P. 37.172

FR-2.2.8 Heterobicyclic components with a benzene ring

Unless listed as a trivially named heterobicyclic component in Appendix 2 a benzene ring fused to a heteromonocycle of five or more members (a benzoheterocycle) is named by prefixing number locants indicating the position(s) of the heteroatom(s) to benzo followed by the trivial, Hantzsch-Widman, or modified replacement name (see FR-2.2.1) of the heteromonocycle without locants. The locants quoted correspond to the numbering of the bicyclic structure, which follows FR-5.4. Locants are not needed if their omission does not result in ambiguity, e.g. benzimidazole, benzotriazole. As an exception to FR-4.7 the 'o' of benzo is elided if followed by a vowel. See FR-3.5 for the use of this type of name as a component and FR-4.8 for the use of square brackets around locants. Brackets are not used for the unmodified ring system.

Examples:



Names of this type are only used as components under certain conditions; see FR-3.5 for the details. *Beilstein* does not use this type of name.

Notes

1. 1-Benzofuran and 2-benzofuran were formerly called benzofuran and isobenzofuran (ref 3) and may still be used for the isolated ring system. *CAS* still uses benzofuran and isobenzofuran as fusion components.

2. 1,2-Benzoxazole and its 2,1- and 1,3-isomers and chalcogen analogues were called 1,2- benzisoxazole, 2,1-benzisoxazole, benzoxazole, *etc.* These are still used by *CAS* for the isolated ring system and as fusion components.

References for this Section

3. *IUPAC Nomenclature of Organic Chemistry, Sections A and B*, 1st edition, 1958; 2nd edition, 1966; 3rd edition (combined with section C), 1971; 4th edition (combined with sections C, D, E, F and H), 1979.

3a. *A Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993*, Blackwell Scientific Publications, 1993.

9. IUPAC, Revision of the extended Hantzsch-Widman system of nomenclature for heteromonocycles, *Pure Appl. Chem.* 55, 409-416 (1983), see also ref 3a, pp. 40-44.

Continue with FR-2.3 Priority order of Component Ring Systems.

Return to home page for Fused Ring Nomenclature.

Fused Ring and Bridged Fused Ring Nomenclature
(IUPAC Recommendations 1998)327
324**FR-3. Construction of Fusion Names**Continued from FR-2.3 Priority order of component ring systems**Contents of Section**FR-3. Construction of Fusion NamesFR-3.1 *Ortho-* or *ortho-* and *peri-*fused systemsFR-3.2 Selection of componentsFR-3.3 Selection of parent component(s)FR-3.3.1 Order of preference between locations for parent componentsReference for this SectionContinue with FR-3.4 Selection of Attached Components.

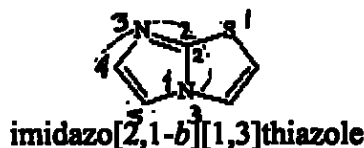
FR-3 Construction of Fusion Names**FR-3.1 *Ortho-*, or *ortho-* and *peri-*fused systems**

Before naming a polycyclic parent hydride containing a fused ring system it is necessary to identify the bridges (if any) which are treated separately from the *ortho-* or *ortho-* and *peri-*fused system (see FR-8).

FR-3.2 Selection of components

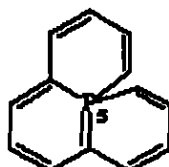
Each ring and/or combination of rings in a fused ring system is considered in order to select the parent component(s) (see FR-3.3). The first-order attached component(s) is then selected (if necessary) followed by second-order attached component(s) and higher-order attached components (see FR-3.4). It should be noted that when a heteroatom is common to two components it must be indicated in the name of each component.

Example:



If an atom is in a non-standard valence state this is indicated using the λ -convention (ref 17). The bonding number n is cited as a superscript *i.e.* λ^n , together with the locant of the atom with a non-standard valence state, in front of the name of the fused ring system (see FR-9.1).

Example:

5λ⁵-phosphininino[2,1-*d*]phosphinolizine325
328**Note**

Fusion nomenclature provides no means of describing the fusion of one component to two other components which are themselves fused together. If this problem arises see [FR-7](#) for examples and how to name them.

FR-3.3 Selection of parent component(s)

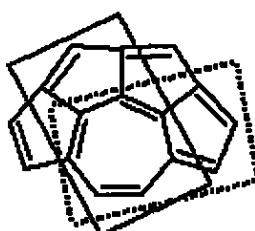
The ring or rings selected as the parent component are those most preferred by the criteria of [FR-2.3](#) (see examples therein). The parent component may be identified in more than one location in a fused ring system by using different rings or combinations of rings. Such alternative locations of the parent component may be overlapping; or directly fused together; or separated by one or more components. When there are alternative locations for the parent component(s) the criteria of [FR-3.3.1](#) are used to select the preferred location(s).

FR-3.3.1 Order of preference between locations for parent components

If there are two or more potential locations for a parent component the following criteria apply in order until a distinction is obtained. If a partial distinction is obtained the following criteria are only applied to distinguish between remaining choices. In the examples below the preferred location(s) is identified by a complete box and other locations with a dashed line. In the examples below second-order components are in bold type.

a. The location that enables the whole ring system to be named by fusion nomenclature is preferred to one where alternative approaches are required (see [FR-7](#)).

Example:



cyclopenta[*ij*]pentaleno[2,1,6-*cde*]azulene
not 1,9-methenopentaleno[1,6-*ef*]azulene
nor 1,9-methenodicyclopenta[*cd,f*]azulene

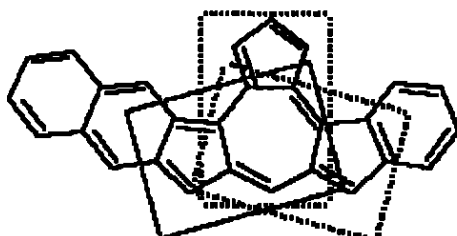
Note

With this criterion *CAS* and *Beilstein* permit the use of a less preferred parent component or attached component if that enables the whole system to be named by fusion nomenclature

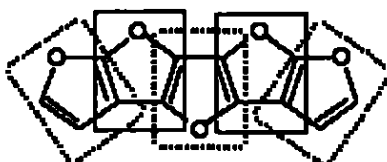
(See however FR- 7.1 and FR-7.1.1).

b. The location that results in a name which does not require higher-order attached components. Second order component names are shown in bold below.

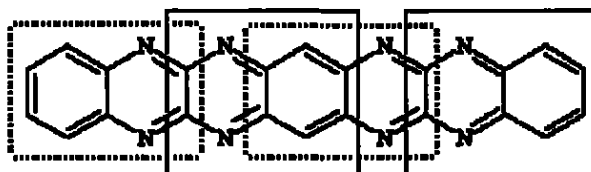
Examples:



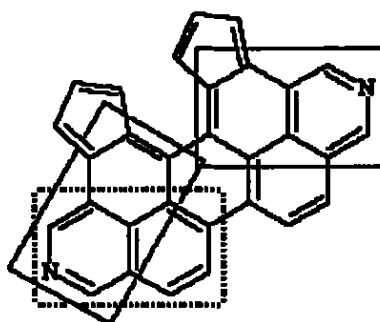
cyclopenta[*h*]indeno[2,1-*f*]naphtho[2,3-*a*]azulene
not benzo[*a*]benzo[5,6]indeno[2,1-*f*]cyclopenta[*h*]azulene
nor benzo[5,6]indeno[1,2-*e*]indeno[2,1-*h*]azulene
(no second-order components in preferred name)



difuro[3,2-*d*:3',2'-*d'*]furo[3,2-*b*:4,5-*b'*]difuran
not bis(furo[3',2':4,5]furo)[3,2-*b*:2',3'-*d*]furan
nor furo[2'',3'':4,5;5'',4'':4',5']difuro[2,3-*b*:2',3'-*b'*]difuran
(no second-order components in preferred name)



quinoxalino[2,3-*b*]pyrazino[2,3-*g*:5,6-*b'*]diquinoxaline
not quinoxalino[2,3-*b*]quinoxalino[2',3':5,6]pyrazino[2,3-*g*]quinoxaline
nor quinoxalino[2'',3'':5',6']pyrazino[2',3':6,7]quinoxalino[2,3-*b*]quinoxaline
(no second-order components in preferred name)

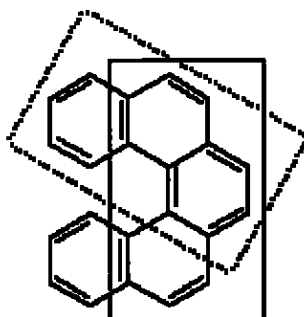


dicyclopenta[*h,h'*]phenanthro[2,1,10-*def*:7,8,9-*d'e'f'*]diisoquinoline
not cyclopenta[*h*]cyclopenta[7,8]anthra[2,1,9-*def*:6,5,10-*d'e'f'*]diisoquinoline
(no second-order components in preferred name)

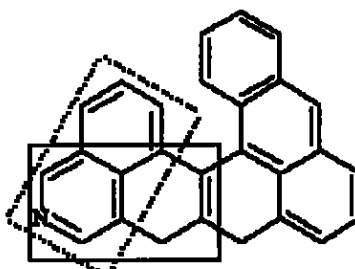
329
326

c. The location that results in the maximum number of first-order attached components (then second-order *etc.*).

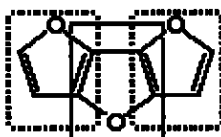
Examples:



dibenzo[c,g]phenanthrene
not naphtho[2,1-c]phenanthrene
(2 attached components preferred to 1)



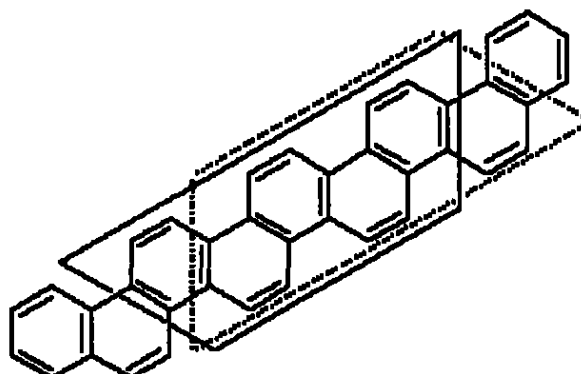
benzo[de]benzo[1,10]phenanthro[4,3-g]isoquinoline
not naphtho[3',2',1':8,9]anthra[3,2,1-de]isoquinoline
nor dibenzo[5,6:8,9]phenanthro[2,3,4-de]isoquinoline
(2 first-order attached components preferred to 1)



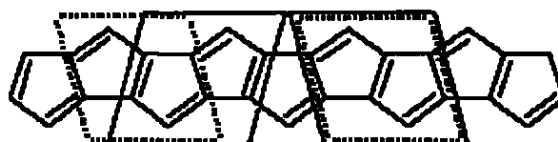
difuro[3,2-b:2',3'-d]furan
not furo[3,2-b:4,5-b']difuran
(2 attached components preferred to 1)
(multiplicative name preferred to multiparent name)

d. A location that permits the expression of the maximum number of identical attached components with multiplicative prefixes.

Example:

331
328

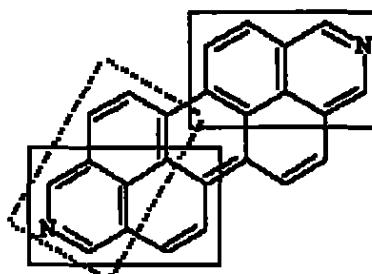
dinaphtho[1,2-*c*:2',1'-*m*]picene
not benzo[*c*]phenanthro[2,1-*m*]picene



1*H*-dipentaleno[2,1-*e*:2',1'-*e'*]cyclopenta[1,2-*a*:4,3-*a'*]dipentalene
not 1*H*-cyclopenta[*e*]pentaleno[2,1-*e'*]pentaleno[2,1-*a*:5,4*a'*]dipentalene

e. A location that uses a preferred interparent component.

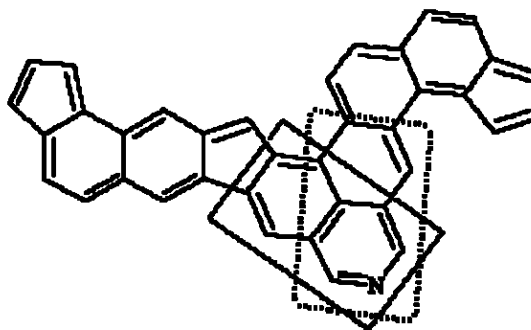
Example:



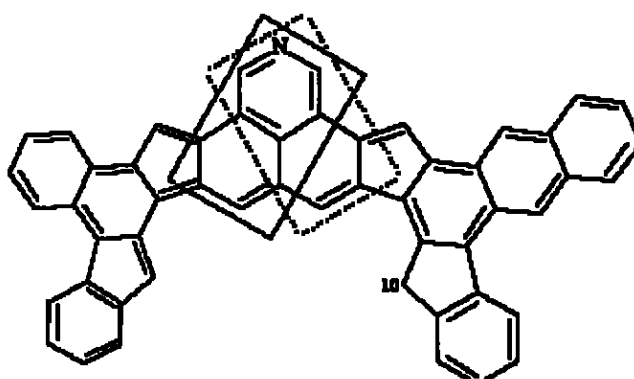
anthra[2,1,9-*def*:6,5,10-*d'ef'*]diisoquinoline
not phenanthro[2,1,10-*def*:7,8,9-*d'ef'*]diisoquinoline
(anthracene preferred to phenanthrene)

f. A location that results in preferred attached components (see FR-3.4) comparing first-order attached components, then their attachment locants (see FR-4.5), then comparing the preferred second-order attached components in order of the priority of the first-order components to which they are attached, then their attachment locants (see FR-4.5), then third-order components, *etc.*

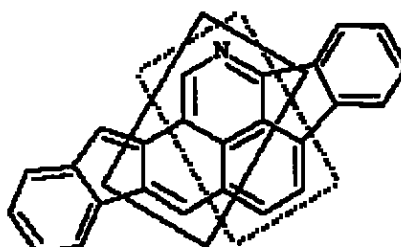
Examples:

332
329

cyclopenta[5,6]phenanthro[3,2,1-*de*]indeno[4',5':5,6]indeno[2,1-*g*]isoquinoline
not cyclopenta[7,8]naphtho[2,1-*g*]indeno[5',4':6,7]fluoreno[3,2,1-*de*]isoquinoline
(phenanthrene preferred to fluorene)



10*H*-dibenzo[4,5:6,7]-*as*-indaceno[1,2-*h*]indeno2',1':5,6]naphtho[2',3':7,8]fluoreno[1,2,3-*de*]isoquinoline
not 10*H*-benzo[7,8]indeno[2',1':5,6]fluoreno[1,2,3-*de*]enzo[6,7]naphtho[2',3':4,5]-*as*-indaceno[1,2-*h*]isoquinoline
[at first-order level both names have fluorene[1,2,3-*de*] and *as*-indacene[1,2-*h*] with the same attachment locants, however fluorene is preferred to *as*-indacene;
comparing the preferred second-order component attached to fluorene in each case naphthalene (preferred to indene) is preferred to indene (preferred to benzene)]



fluoreno[9,1,2-*cde*]indeno[1,2-*h*]isoquinoline
not fluoreno[1,2,3-*de*]indeno[1,2,3-*ij*]isoquinoline
(*cdeh* preferred to *deij*)

Reference for this Section

17. IUPAC, Treatment of variable valence in organic nomenclature (lambda convention), *Pure Appl. Chem.* **56**, 769-778 (1984).

Continue with FR-3.4 Selection of Attached Components.

Return to home page for Fused Ring Nomenclature.

~~333~~
330

Fused Ring and Bridged Fused Ring Nomenclature
(IUPAC Recommendations 1998)

32/31

FR-3.4 Selection of attached component(s)

Continued from FR-3 Construction of Fusion Names

Contents of Section

FR-3.4 Selection of attached component(s)

FR-3.4.1 Order of preference between attached components

FR-3.5 Heterobicyclic compounds with a benzene ring as a component

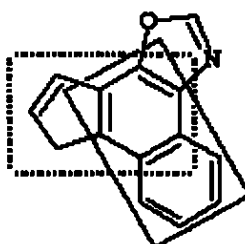
FR-3.6 Order of citation of fusion prefixes

Continue with FR-4 Fusion Descriptors.

FR-3.4 Selection of attached component(s)

After selection of the parent component (or parent components and interparent component(s) if a multiparent name is selected - see FR-6) other rings are identified as far as possible as attached components. If there are alternative first-order attached components FR-2.3 is used to select the preferred component.

Example:



8H-cyclopenta[3,4]naphtho[1,2-*d*][1,3]oxazole
not *8H*-benzo[6,7]indeno[5,4-*d*][1,3]oxazole
(naphthalene preferred to indene)

If there are alternative locations for the first-order attached components, the criteria of FR-3.4.1 are used to select the preferred arrangement. After selection of the first-order attached components remaining rings are considered for second-order attached components and so on to higher-order attached components.

If there are alternative names which only differ in their fusion locants see FR-4.5 for the criteria to select the preferred name.

Note

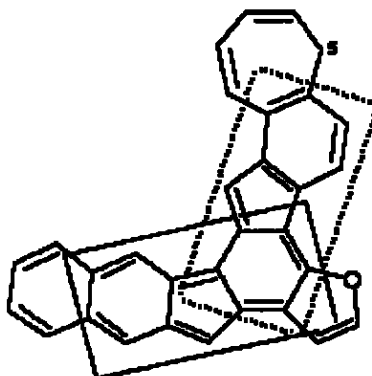
Heterobicyclic components with a benzene ring named by FR-2.2.8 are only identified after this stage (see FR-3.5).

335
332FR-3.4.1 *Order of preference between attached components*

If after consideration of the parent component there are two or more potential attached components, or two or more locations for an attached component, the following criteria are applied in order until a distinction is obtained. If a partial distinction is obtained the following criteria are only applied to distinguish between remaining choices. In the examples below the preferred attached component is marked with a complete box and the other location(s) with a dashed line.

a. The location that has preferred locants for fusion to the parent component as a set.

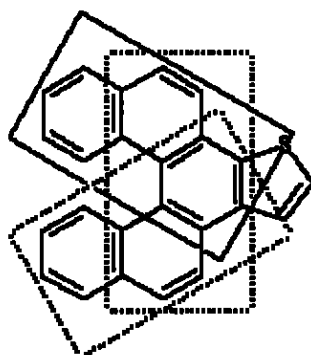
Example:



5H-benzo[6,7]cyclohepta[4',5']indeno[1',2':3,4]fluoreno[2,1-*b*]furan
not *5H*-benzo[5',6']indeno[1',2':1,2]cyclohepta[7,8]fluoreno[4,3-*b*]furan
(1,2 preferred to 3,4)

b. The location that has preferred locants for fusion to the parent component in the order of citation.

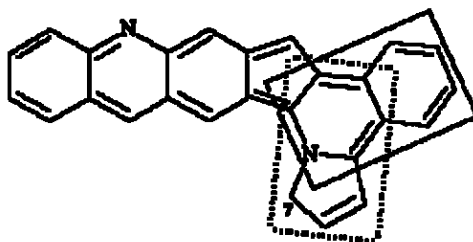
Example:



naphtho[2',1':3,4]phenanthro[1,2-*b*]thiophene
not naphtho[2',1':3,4]phenanthro[2,1-*b*]thiophene
nor dibenzo[3,4:5,6]phenanthro[9,10-*b*]thiophene
(1,2 preferred to 2,1 and both preferred to 9,10)

c. The above procedure is continued exploring outwards to the preferred second-order attached components; preferred fusion locants between the first and second-order attached components; *etc.*

Example:



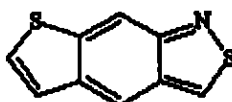
336
333

7H-pyrrolo[2'',1'':1',2']isoquinolino[4',3':4,5]cyclopenta[1,2-b]acridine
 not 7H-benzo[7',8']indolizino[6',5':4,5]cyclopenta[1,2-b]acridine
 (isoquinoline preferred to indolizine)

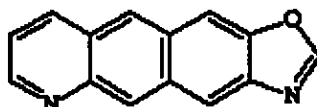
FR-3.5 Heterobicyclic compounds with a benzene ring as a component

If the initially identified preferred components for naming the fused ring system include an isolated benzo component (*i.e.* not forming part of a component such as quinoline or naphthalene) *ortho*-fused to a heteromonocyclic component, these two components are treated together as a one-component unit (a 'benzoheterocycle'; see FR-2.2.8). However this approach should not be used if it disrupts a multiparent name (see FR-6) or the use of multiplicative prefixes (FR-4.9). The other initially identified preferred components should not be changed in any other way except in so far as the 'benzoheterocycle' may change the preference between components *i.e.* the use of a 'benzoheterocycle' component may change the order of attached components and may affect the choice of the preferred parent and/or attached component.

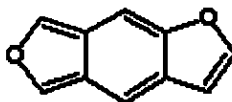
Examples:



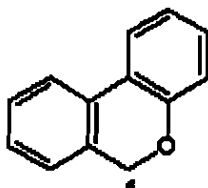
thieno[3,2-f][2,1]benzothiazole
 (2,1-benzothiazole is preferred to 1-benzothiophene)
CAS name thieno[3,2-f]-2,1-benzisothiazole
Beilstein name thieno[3',2':4,5]benzo[1,2-c]isothiazole



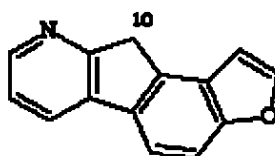
[1,3]benzoxazolo[6,5-g]quinoline
 (quinoline preferred to benzoxazole)
CAS name benzoxazolo[6,5-g]quinoline
Beilstein name oxazolo[4',5':4,5]benzo[1,2-g]quinoline



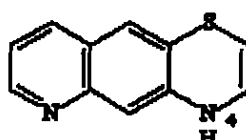
benzo[1,2-b:4,5-c']difuran
 not furo [3,4-f][1]benzofuran
 (multiparent name preferred)

337
334

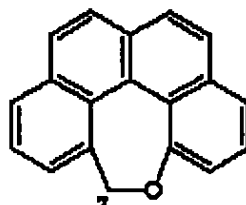
6H-benzo[c]chromene
CAS name 6H-dibenzo[b,d]pyran



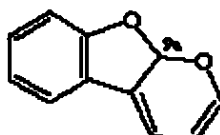
10H-furo[3',2':4,5]indeno[2,1-b]pyridine
 not [1]benzofuro[5',4':3,4]cyclopenta[1,2-b]pyridine
 (pyridine preferred to benzofuran)
 (indene must be used as a component)



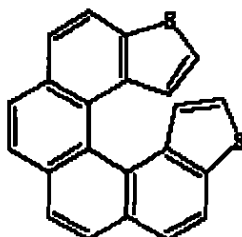
4H-[1,4]thiazino[2,3-g]quinoline
 not 4H-pyrido[2,3-g][1,4]benzothiazine
 (quinoline must be used as a component)



7H-phenanthro[5,4,3-cde][1]benzoxepine
Beilstein name 8H-1,12-etheno-benzo[e]naptho[1,8-bc]oxepine



9aH-pyrano[2,3-b][1]benzofuran
 (pyran preferred to furan but benzofuran preferred to pyran)
CAS name 9aH-pyrano[2,3-b]benzofuran
Beilstein name 9aH-benzo[4,5]furo[2,3-b]pyran



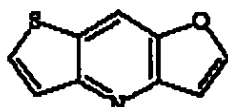
thieno[3',2':5,6]phenanthro[4,3-*e*][1]benzothiophene
 CAS name naphtho[1,2-*e*:8,7-*e'*]bis[1]benzothiophene
 Beilstein name thieno[2'',3'';5',6']benzo[1',2';5,6]phenanthro[3,4-*b*]thiophene

338
335

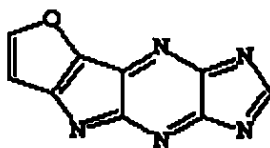
FR-3.6 Order of citation of fusion prefixes

Fusion between two components is indicated by the technique described in [FR-4](#). All attached components are cited in front of the parent component(s). Each second-order attached component is cited in front of the first-order attached component to which it is fused and so on to higher-order attached components. If there are two or more different components, or sets of components, attached to a lower-order component they are cited in alphabetical order.

Examples:



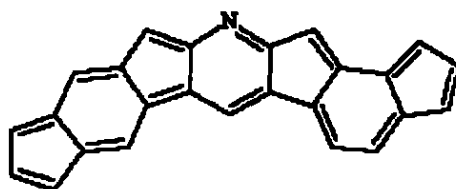
furo[3,2-*b*]thieno[2,3-*e*]pyridine
 (furo is before thieno)



furo[2',3':4,5]pyrrolo[2,3-*b*]imidazo[4,5-*e*]pyrazine
 (fur-pyrrolo is before imidazo)

If the only distinction is between *as*-indacene and *s*-indacene then the italic characters are considered; otherwise they are treated as indacene for consideration of alphabetical order.

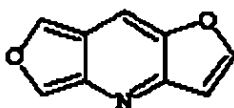
Example:



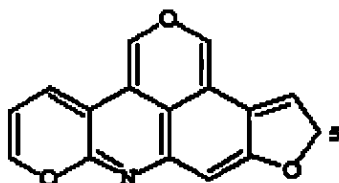
as-indaceno[2,3-*b*]-*s*-indaceno[1,2-*e*]pyridine

If two (or more) identical components are fused to a third they are cited together by the use of di- (or tri-, etc.) or bis- (or tris-, etc.) as described in [FR-4.9](#). Use of a multiplicative prefix does not affect the alphabetical order of citation of components attached at the same level.

Examples:

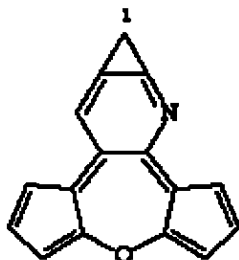


difuro[3,2-*b*:3',4'-*e*]pyridine



5H-furo[3,2-g]dipyrano[2,3-b:3',4',5'-de]quinoline
(furo before dipyrano)

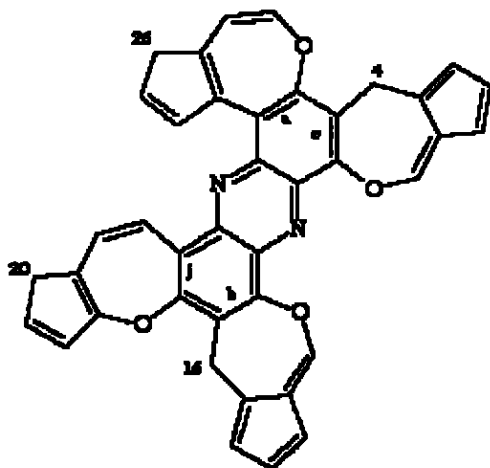
339
336



1H-cyclopropa[b]dicyclopenta[2,3:6,7]oxepino[4,5-e]pyridine
not **1H-dicyclopenta[2,3:6,7]oxepino[4,5-b]cyclopropa[e]pyridine**
[cyclopropa is before dicyclopentaoxepino (treated as a unit)]

If two or more groups of components only differ by virtue of the fusion locants within the group then these are used to determine the order.

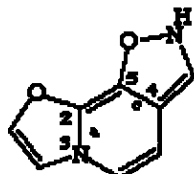
Example:



4H,16H,20H,26H-cyclopenta[4,5]oxepino[3,2-a]bis(cyclopenta[5,6]oxepino)-
[3',2'-c:2'',3''-h]cyclopenta[6''',7'''-i]oxepino[2''',3'''-j]phenazine

If two or more groups of components only differ by virtue of the heteroatom locants these are used to determine the order.

Example:



2H-[1,2]oxazolo[5,4-c][1,3]oxazolo[3,2-a]pyridine

340
337

Continue with FR-4 Fusion Descriptors.

Return to home page for Fused Ring Nomenclature.

Fused Ring and Bridged Fused Ring Nomenclature
(IUPAC Recommendations 1998)

341
338

FR-4. Fusion Descriptors

Continued from FR-3.4 Selection of attached component(s)

Contents of Section

FR-4. Fusion Descriptors

FR-4.1 Identification of sides of parent components

FR-4.2 Identification of sides of attached components

FR-4.3 Fusion of a first-order attached component to the parent component

FR-4.4 Fusion of a higher-order attached component to an attached component

FR-4.5 Choice of locants

Continue with FR-4.6 Omission of Locants.

FR-4 Fusion Descriptors

After identification of components the fusion name can be constructed. Details of how the common bonds are specified are given below. Examples are labelled, where appropriate, with the relevant letters or locants of components within the rings, and with the numbering of the whole ring system (see FR-5) outside the structure.

FR-4.1 Identification of sides of parent components

The sides around the periphery of the parent component are identified by italic letters *a*, *b*, *c*, etc. with *a* for the side 1,2; *b* for the side 2,3 (or in certain cases 2,2a e.g. acenaphthylene); etc. following continuously round the periphery, ignoring non-standard numbering (see Appendices 1 and 2). If there are more than twenty-six sides the additional sides are identified by subscript numbers *a*₁, *b*₁, *c*₁, etc. then *a*₂, *b*₂, *c*₂, etc. (Contrast the use of *a'*, *b'*, *c'*, etc. in FR-6.1) Each letter locant implies also a direction for the specified bond, i.e. the direction of the side *a* is from the atom with locant 1 to the atom with the next higher locant (see arrows on the structures below).

FR-4.2 Identification of sides of attached components

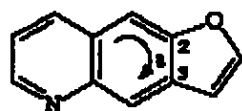
The sides of attached components are identified by the appropriate pairs of number locants.

FR-4.3 Fusion of a first-order attached component to the parent component

Those bonds that are common to each component are indicated by the appropriate numerical locants for the attached components and letter locants for the parent component separated by a hyphen and cited within square brackets. Numerical locants are separated by commas, while letter locants are quoted together if there is more than one. Letter locants are cited in the same direction as they were assigned (i.e. clockwise when considered as in Appendices 1 and 2). The numerical locants are cited in the same direction as the letter locants. The first-order attached component is quoted before the locant set to

which it applies and in front of the parent component name. If there is more than one first-order attached component they are quoted in alphabetical order unless second-order attached components modify this order (see FR-3.6 and FR-4.4). See FR-4.6 for the omission of locants.

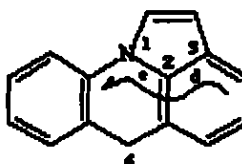
Examples:



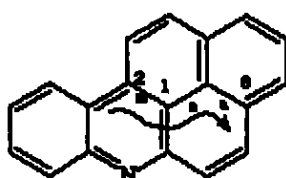
furo[2,3-*g*]quinoline



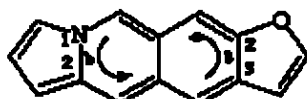
furo[3,2-*g*]quinoline



6*H*-pyrrolo[3,2,1-*de*]acridine



naphtho[2,1,8-*mna*]acridine

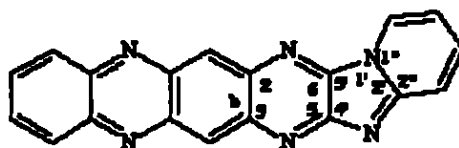


furo[3,2-*g*]pyrrolo[1,2-*b*]isoquinoline

FR-4.4 Fusion of a higher-order component to an attached component

The procedure for indicating the common bond(s) between a higher-order attached component and an attached component follows that for the attachment of the first-order attached component to the parent component (see FR-4.3) except that only numerical locants are used instead of letters and the two sets of locants are separated by a colon. The locants of second-order attached components are primed to contrast with those of first-order attached components. The locants of third-order (fourth-order, *etc.*) attached components are double (triple, *etc.*) primed.

Example:

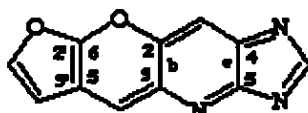


pyrido[1'',2'':1',2']imidazo[4',5':5,6]pyrazino[2,3-*b*]phenazine

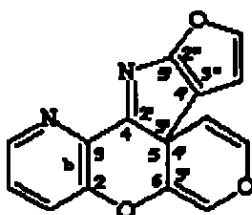
343
340

If more than one component is fused to the same lower-order component they are cited in alphabetical order unless higher-order components alter this order (see FR-3.6).

Example:



furo[3',2':5,6]pyrano[3,2-*b*]imidazo[4,5-*e*]pyridine
(furo-pyrano before imidazo)



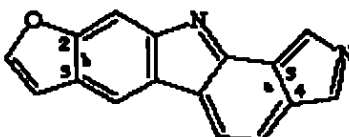
furo[3'',2'':4',5']pyrrolo[2',3':4,5]pyrano[4',3':5,6]pyrano[3,2-*b*]pyridine
(furo-pyrrolo before pyrano)

FR-4.5 Choice of locants

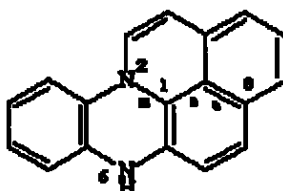
If there is a choice of numerical or letter locants (consistent with the numbering of the component) then the lower numbers or letters are selected. Preference is given in the following order:

a. Parent component letters as a set.

Examples:



furo[3,2-*h*]pyrrolo[3,4-*a*]carbazole
not furo[2,3-*b*]pyrrolo[3,4-*i*]carbazole
(*a, h* preferred to *b, i*)



6*H*-isoquinolino[2,1,8-*mna*]phenazine
not 6*H*-isoquinolino[8,1,2-*cde*]phenazine
(*a, m, n* preferred to *c, d, e*)

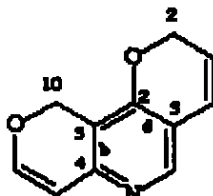
b. Parent component letters in order of citation.

344
341

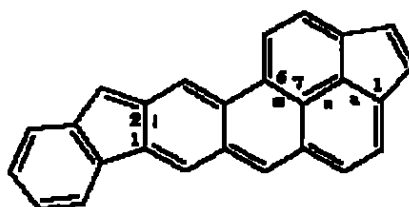
Examples:



furo[3,4-*b*]thieno[2,3-*e*]pyrazine
not furo[3,4-*e*]thieno[2,3-*b*]pyrazine
(*b...e* preferred to *e....b*)



2*H*,10*H*-dipyrano[4,3-*b*:2',3'-*d*]pyridine
not 2*H*,10*H*-dipyrano[2,3-*d*:4',3'-*b*]pyridine
(*b....d* preferred to *d....b*)



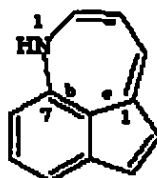
diindeno[1,2-*i*:6',7',1'-*mna*]anthracene
not diindeno[6,7,1-*mna*:1',2'-*i*]anthracene
(*i ...mna* preferred to *mna...i*)

Note

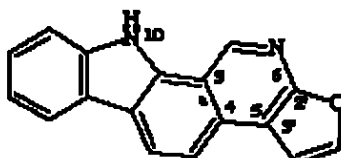
Both names for this example have the letters *a,i,m,n* when compared in alphabetic order (see FR- 4.5.a), but when compared in the order of citation *i ...mna* is preferred to *mna...i*.

c. Set of locants for the first-order attached components for fusion to the parent component.

Examples:



1*H*-indeno[7,1-*bc*]azepine
not 1*H*-indeno[4,3-*bc*]azepine
(1,7 preferred to 3,4)

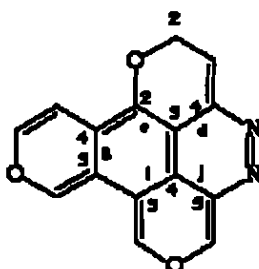


10*H*-furo[3',2':5,6]pyrido[3,4-*a*]carbazole
 10*H*-furo[2',3':2,3]pyrido[5,4-*a*]carbazole
 (3,4 preferred to 4,5)

345
342



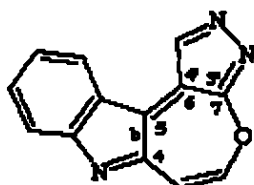
cyclopenta[1,2-*b*:5,1-*b'*]difuran
 not cyclopenta[1,2-*b*:2,3-*b'*]difuran
 (1,1,2,5 preferred to 1,2,2,3)



2*H*-tripyrano[4,3,2-*de*:4',3'-*g*:3'',4'',5''-*ij*]phthalazin
 not 2*H*-tripyrano[3,4,5-*de*:3',4'-*g*:2'',3'',4''-*ij*]phthalazin
 (2,3,3',3'',4,4',4'',5'' preferred to 2'',3,3',3'',4,4',4'',5)

d. First-order attached component locants for fusion to the parent component in order of citation.

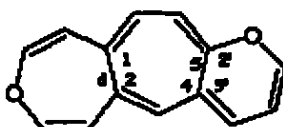
Example:



pyrazolo[4',3':6,7]oxepino[4,5-*b*]indole
 not pyrazolo[3',4':2,3]oxepino[5,4-*b*]indole
 (4,5 preferred to 5,4)

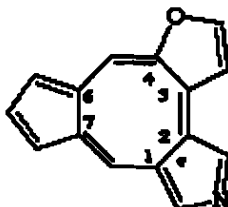
e. Locants for lower-order attached components as a set for fusion to higher-order attached components.

Examples:

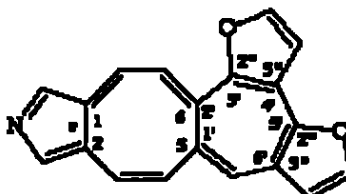


pyrano[3',2':4,5]cyclohepta[1,2-*d*]oxepine

not pyrano[2',3':5,6]cyclohepta[1,2-*d*]oxepine
(4,5 preferred to 5,6)



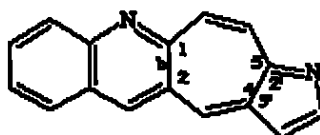
cyclopenta[6,7]furo[3',2':3,4]cycloocta[1,2-*c*]pyrrole
not cyclopenta[4,5]furo[2',3':7,8]cycloocta[1,2-*c*]pyrrole
(3,4,6,7 preferred to 4,5,7,8)



difuro[2'',3'':3',4';2''',3''':5',6']cyclohepta[1',2':5,6]cycloocta[1,2-*c*]pyrrole
not difuro[3'',2'':4',5';3''',2''':6',7']cyclohepta[1',2':5,6]cycloocta[1,2-*c*]pyrrole
(3',4',5',6' preferred to 4',5',6',7')

f. Locants for lower-order attached components for fusion to higher-order attached components in order of citation.

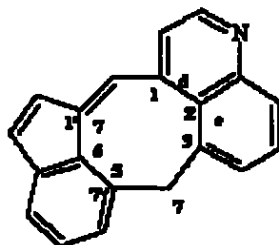
Example:



pyrrolo[3',2':4,5]cyclohepta[1,2-*b*]quinoline
not pyrrolo[2',3':5,4]cyclohepta[1,2-*b*]quinoline
(4,5 preferred to 5,4)

g. Locants for higher-order attached components as a set for fusion to the lower-order attached component.

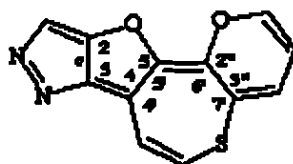
Example:



7*H*-indeno[7',1':5,6,7]cycloocta[1,2,3-*de*]quinoline
not 7*H*-indeno[3',4':5,6,7]cycloocta[1,2,3-*de*]quinoline
(1',7' preferred to 3',4')

h. Locants for higher-order components for fusion to lower-order components in order of citation.

Example:



pyrano[2'',3'':6',7']thiepino[4',5':4,5]furo[3,2-c]pyrazole
 not pyrano[3'',2'':2',3']thiepino[5',4':4,5]furo[3,2-c]pyrazole
 (4',5' preferred to 5',4')

347
344

Continue with FR-4.6 Omission of Locants.

Return to home page for Fused Ring Nomenclature.

Fused Ring and Bridged Fused Ring Nomenclature
(IUPAC Recommendations 1998)

348
345

FR-4.6 Omission of Locants

Continued from FR-4.5 Choice of Locants

Contents of Section

FR-4.6 Omission of locants

FR-4.6.1 Unnecessary locants

FR-4.6.2 Locants of peripheral fusion carbon atoms of a component

FR-4.7 Elision

FR-4.8 Heteroatom locants of components

FR-4.9 Treatment of identical attached components

FR-4.9.1 Additional components attached to a system with a multiplicative prefix

FR-4.9.2 Groups of identical components with identical fusion

Reference for this Section

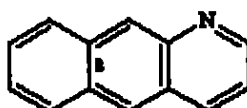
Continue with FR-5 Numbering.

FR-4.6 Omission of locants

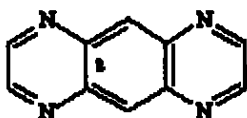
FR-4.6.1 Unnecessary locants

If there is no ambiguity the numerical and/or letter locants may be omitted for a system with only first-order attached components.

Examples:

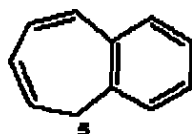


benzo[g]quinoline



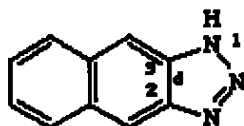
pyrazino[g]quinoxaline

CAS and Beilstein name pyrazino[2,3-g]quinoxaline



5H-benzo[7]annulene

CAS and Beilstein name 5H-benzocycloheptene

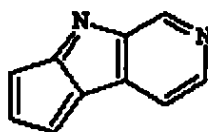


1H-naphtho[2,3][1,2,3]triazole
CAS name *1H*-naphtho[2,3-*d*]triazole
Bestein name *1H*-naphtho[2,3-*d*][1,2,3]triazole

349
346

Locants are also omitted when there is no ambiguity for the fusion of terminal attached components.

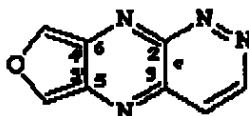
Example:



cyclopenta[4,5]pyrrolo[2,3-*c*]pyridine

When locants are required for the fusion of a higher-order component then all locants for the linking component must be cited.

Example:

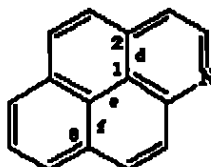


furo[3',4':5,6]pyrazino[2,3-*c*]pyridazine

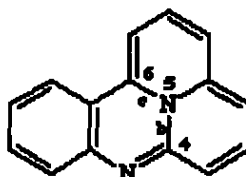
FR-4.6.2 Locants of peripheral fusion carbon atoms of a component

The numerical locants of peripheral fusion carbon atoms of a component are omitted with an *ortho*- and *peri*-fused system.

Examples:



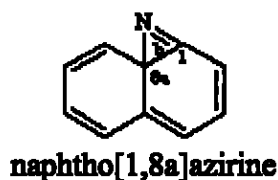
naphtho[2,1,8-*def*]quinoline



quinolizino[4,5,6-*bc*]quinazoline

Both terminal fusion atom locants for *ortho*-fusion must be cited even if one is a fusion atom.

Example:



350
347

FR-4.7 Elision

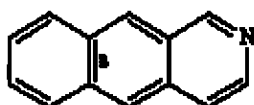
Vowels are not elided in fusion names, however see [FR-2.2.8](#).

Note

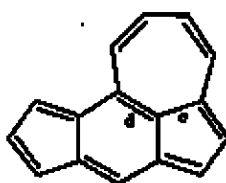
The previous edition of these rules included elision (see footnote to A-21.4 [ref 3](#)) which is still used by *CAS*. in the following way.

When acenaphtho-, benzo-, or naphtho- is followed by a component which starts with a vowel the 'o' is elided. Similarly the 'a' of cycloalka- is elided under these conditions. In all other cases the 'o' or 'a' is retained.

Examples:



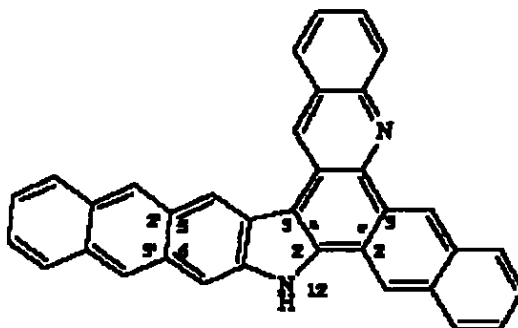
CAS name benz[*g*]isoquinoline
IUPAC name benzo[*g*]isoquinoline



CAS name cyclohept[*cd*]-s-indacene
IUPAC name cyclohepta[*cd*]-s-indacene

If there is more than one first-order attached component, and at least one second-order attached component, elision between the second-order and the first-order attached component is applied after determination of the alphabetical order of the components (see [FR-3.6](#)).

Example:



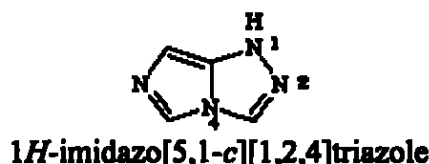
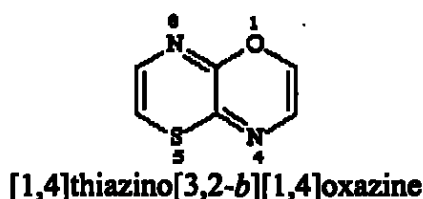
CAS name 12*H*-naphtho[2,3-*c*]naphth[2',3':5,6]indolo[3,2-*a*]acridine
even though naphthindolo is alphabetically before naphtho
IUPAC name 12*H*-naphtho[2,3-*c*]naphtho[2',3':5,6]indolo[3,2-*a*]acridine

351
348

FR-4.8 Heteroatom locants of components

When a component requires the citation of locants (*e.g.* in a Hantzsch-Widman name) these are always quoted in square brackets. Note that these numbers in brackets only refer to the numbering of the component and have no significance in the final numbering of the complete fused ring system.

Examples:



Note

In the previous version of these rules (See B-3.1, [ref 3](#)) any locants of a component which are cited in the name and are the same as that of the final system (see [FR-5.3](#) and [FR-5.4](#)) are not enclosed in brackets.

CAS still does not use brackets when the locants of the heteroatoms of the component correspond to those of the whole fused ring system. Thus the CAS index names for the above examples are [1,4]thiazino[3,2-*b*]-1,4-oxazine and 1*H*-imidazo[5,1-*c*]-1,2,4-triazole although in the latter case the triazole was numbered anticlockwise to derive the fusion locants and clockwise afterwards to assign the system locants.

FR-4.9 Treatment of identical attached components

When there are two or more components which are identical and both fused to a parent or attached component this is indicated by the use of the prefix di-, tri-, *etc.* (or bis-, tris-, *etc.* to avoid ambiguity). This multiplicative prefix is not considered in deciding the alphabetical order of components attached at

352

the same level (see FR-3.6).

If a complete set of locants are used for first-order attached components fused to the parent component these are cited together separated by a colon. If abbreviated sets of locants are used the letters are separated by a comma. If complete sets of locant are used for second-order attached components fused to a first-order attached component, or for higher-order cases, the locants are cited together separated by a semicolon. If abbreviated sets are used they are separated by a colon. (See note 1)

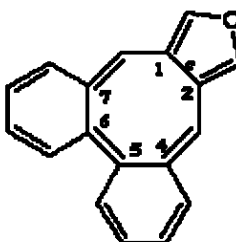
349

To distinguish between the two or more components of the same order the locants of the second component are primed (or double primed if the first is primed, *etc.*), the third double primed *etc.*

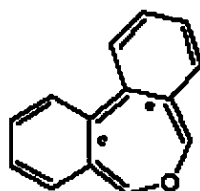
Examples:



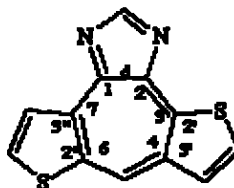
difuro[3,2-*b*:3',4'-*e*]pyridine



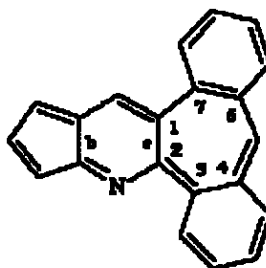
dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan



dibenzo[*c,e*]oxepine



dithieno[2',3':3,4;2'',3'':6,7]cyclohepta[1,2-*d*]imidazole



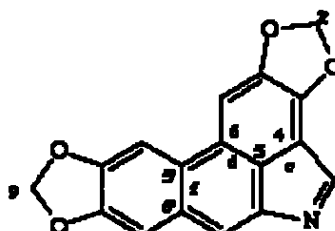
cyclopenta[*b*]dibenzo[3,4:6,7]cyclohepta[1,2-*e*]pyridine

353

350

If the use of di-, tri-, *etc.* might be ambiguous bis-, tris-, *etc.* are used. This applies when di-, tri-, *etc.* prefixes might be used to name the component (*e.g.* Hantzsch-Widman name).

Example:



2*H*,9*H*-bis[1,3]benzodioxolo[4,5,6-*cd*:5',6'-*f*]indole

Beilstein name [1,3]dioxolo[4',5':4,5]benzo[1,2-*f*][1,3]dioxolo[4',5':5,6]benzo[1,2,3-*cd*]indole

Note

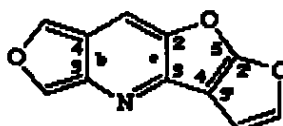
Apart from the use of a hyphen with a full set of locants for fusion of the first-order attached component to a parent component the punctuation is in the order comma, colon, semicolon. See examples above. The semicolon separates sets which use a colon; the colon separates sets which use a comma or hyphen; and the comma is used if only one punctuation mark is needed.

Beilstein uses the hyphen as above. A colon is used for fusion of attached components. A semicolon is used to separate fusion descriptors which already contain a colon or comma *e.g.* difuro[3,2-*b*;3',4'-*e*]pyridine and dibenzo[4,5;6,7]cycloocta[1,2-*c*]furan (*cf.* above).

FR-4.9.1 Additional components attached to a system with a multiplicative prefix

Fusion of a higher-order attached component to a system named with a multiplicative prefix requires each set of attached components to be specified separately.

Example:

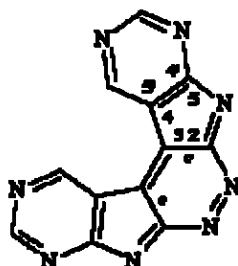


furo[3,4-*b*]furo[3',2':4,5]furo[2,3-*e*]pyridine

FR-4.9.2 Groups of identical components with identical fusion

When two or more groups of identical components (including identical fusion between these components) are fused to another component this is indicated by the use of bis-, tris-, *etc.* with the group of components in round brackets.

Example:

354
351

bis(pyrimido[5',4':4,5]pyrrolo)[2,3-c:3',2'-e]pyridazine
CAS name bispyrimido[5',4':4,5]pyrrolo[2,3-c:3',2'-e]pyridazine

Reference for this Section

3. *IUPAC Nomenclature of Organic Chemistry, Sections A and B*, 1st edition, 1958; 2nd edition, 1966; 3rd edition (combined with section C), 1971; 4th edition (combined with sections C, D, E, F and H), 1979.

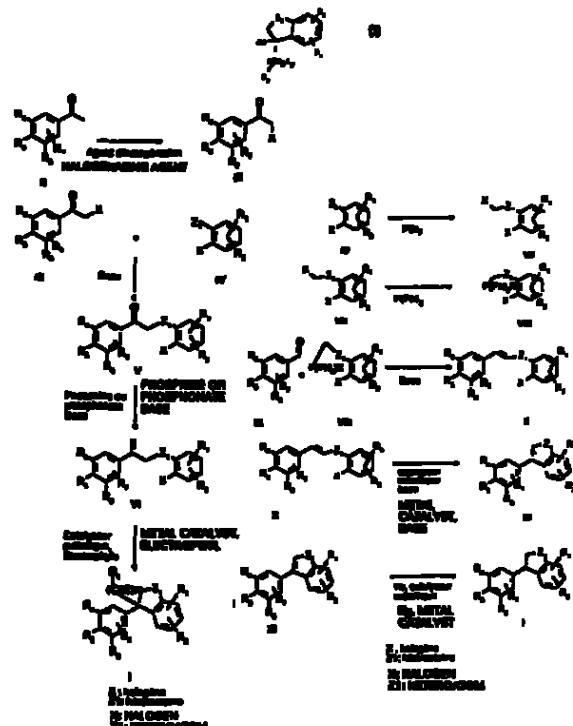
Continue with FR-5 Numbering.

Return to home page for Fused Ring Nomenclature.

PCT

ORGANISATION MONDIALE DE LA PROPRIÉTÉ INTELLECTUELLE
Bureau International

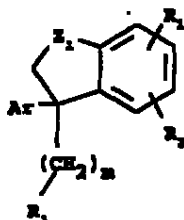
DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(51) Classification internationale des brevets ⁶ : C07D 307/80, 307/79, 307/93, A61K 31/34		(11) Numéro de publication internationale: WO 97/29100
A1		(43) Date de publication internationale: 14 août 1997 (14.08.97)
(21) Numéro de la demande internationale: PCT/FR97/00217		(51) États désignés: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, UA, UG, US, UZ, VN, brevet ARIPO (KE, LS, MW, SD, SZ, UG), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TO).
(22) Date de dépôt international: 4 février 1997 (04.02.97)		
(30) Données relatives à la priorité: 96/01424 6 février 1996 (06.02.96) FR		
(71) Déposant (pour tous les États désignés sauf US): CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES GALDERMA (C.I.R.D. GALDERMA) [FR/FR]; Sophia Antipolis, 635, route des Lucioles, F-06560 Valbonne (FR).		
(72) Inventeurs; et (75) Inventeurs/Déposants (US seulement): DIAZ, Philippe [FR/FR]; 4, avenue du Parc Robiony, F-06200 Nice (FR). CHARPENTIER, Bruno [FR/FR]; 252, chemin de la Gorgue, F-06410 Biot (FR).		
(74) Mandataire: TEZIER HERMAN, Béatrice; L'Oréal - D.P.I., 90, rue du Général-Roguet, F-92583 Clichy Cédex (FR).		Publiée Avec rapport de recherche internationale.
(54) Title: HETEROCYCLIC DIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING SAME, AND USES THEREOF		
(54) Titre: COMPOSÉS BIARYLES HÉTÉROCYCLIQUES, COMPOSITIONS PHARMACEUTIQUES ET COSMÉTIQUES LES CONTENANT ET UTILISATIONS		
(57) Abstract		
Novel heterocyclic diaryl compounds of general formula (I), and the use thereof in pharmaceutical compositions for use in human or veterinary medicine (particularly for dermatological, rheumatic, respiratory, cardiovascular and ophthalmological disorders), or in cosmetic compositions, are disclosed.		
(57) Abrégé		
L'invention concerne de nouveaux composés biaryles hétérocycliques qui présentent comme formule générale (I), ainsi que l'utilisation de ces derniers dans des compositions pharmaceutiques destinées à un usage en médecine humaine ou vétérinaire (affections dermatologiques, rhumatismales, respiratoires, cardiovasculaires et ophtalmologiques notamment), ou bien encore dans des compositions cosmétiques.		
		

REVENDICATIONS

5

1/ Composés biaryles hétérocycliques, caractérisés par le fait qu'ils répondent à la formule générale (I) suivante :



10

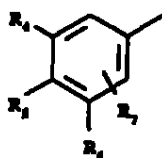
(I)

dans laquelle:

- Ar représente

15

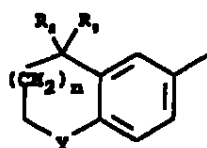
. soit le radical de formule (II) suivante :



20

(II)

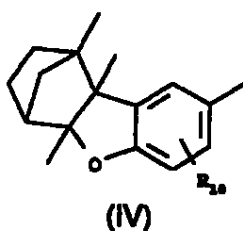
. soit le radical de formule (III) suivante :



25

(III)

. soit le radical de formule (IV) suivante :



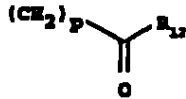
30

(IV)

357 354

- R₁ représente un atome ou un radical choisi parmi

- 5 (i) le radical -CH₃,
 (ii) le radical -(CH₂)_p-O-R₁₁,
 (iii) un radical -OR₁₁,
 (iv) un radical



(v) un radical -S(O)_tR₁₃.

R₁₁, R₁₂, R₁₃, p et t ayant les significations données ci-après,

10

- R₂ représente un atome d'hydrogène, un atome d'halogène, un radical alkyle ou le radical -OR₁₁,

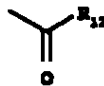
R₁₁ ayant la signification donnée ci-après,

15 - R₃ représente un atome ou un radical choisi parmi :

(i) un atome ou un radical choisi parmi l'atome d'hydrogène, un radical alkyle, un radical alkényle, un radical alkynyle, un radical aryle, un radical monohydroxyalkyle ou polyhydroxyalkyle, un radical polyéther, un radical cyano ou un radical -O-R₁₁.

20 R₁₁ ayant la signification donnée ci-après,

(ii) un radical



R₁₂ ayant la signification donnée ci-après,

(iii) un radical



25

r et r' ayant la signification donnée ci-après

- Z₁ représente O, S, NR',

30 - m est un nombre entier compris entre 0 et 10,

étant entendu que dans tout ce qui précède :

R₄, R₅, R₆, R₇, identiques ou différents, sont choisis parmi:

- 35 (i) un atome d'hydrogène,
 (ii) un radical alkyle présentant au moins 4 atomes de carbone, parmi lesquels le carbone attaché au radical phényl est au moins substitué par deux atomes de carbone,

- 40 (iii) un radical cycloalkyle,
 (iv) un radical -(Z₂)_n-(CH₂)_q-CO-R₁₂,
 (v) un radical -Z₃-R₁₁,

avec au moins un des radicaux R₄, R₅, R₆ et R₇ étant un radical alkyle tel que défini en (ii) ou un radical cycloalkyle (iii),

$Z_2, Z_3, R_{11}, R_{12}, n$ et q ayant la signification donnée ci-après,

R_8 et R_9 représentent des radicaux alkyles inférieur,

- 5 R_{10} représente un radical alkyle inférieur, un radical $-OR_{11}$ ou un radical polyéther,

- 10 R_{11} , identique ou différent, représente un atome d'hydrogène, un radical alkyle inférieur, un radical aryle, un radical aralkyle, un radical monohydroxyalkyle ou polyhydroxyalkyle ou un radical polyéther, un radical acyle inférieur,

R_{12} , identique ou différent, représente:

(a) un atome d'hydrogène, un radical alkynyle, un radical alkényle, un radical alkyle, un hétérocycle,

- 15 (b) un radical



r'' et r''' ayant la signification donnée ci-après

- (c) un radical $-OR_{13}$

- 20 R_{13} , identique ou différent, représente un atome d'hydrogène, un radical alkyle, un radical monohydroxyalkyle ou polyhydroxyalkyle, un radical aryle ou aralkyle éventuellement substitué(s) ou un reste de sucre, d'acide aminé ou de peptide.

- 25 R' , identique ou différent, représente un groupement protecteur de fonctions amines, un atome d'hydrogène, un radical alkyle inférieur, un radical polyéther ou un radical aryle éventuellement substitué ou un reste d'acide aminé, de peptide ou de sucre,

- 30 r et r' , identiques ou différents, représentent des groupements protecteurs de fonctions amines, un atome d'hydrogène, un radical alkyle inférieur, un radical polyéther ou un radical aryle éventuellement substitué ou un reste d'acide aminé, de peptide ou de sucre, ou encore pris ensemble, forment un hétérocycle,

- 35 r'' et r''' , identiques ou différents, un atome d'hydrogène, un radical alkyle inférieur, un radical polyéther ou un radical aryle éventuellement substitué ou un reste d'acide aminé, de peptide ou de sucre, ou encore pris ensemble, forment un hétérocycle,

Y représente $C(R_9)_2, O, S, NR', CHOH, CO, SO, SO_2$,

40

Z_2 représente O, S, NR' ,

Z_3 représente O ou S ,

- 45 n , identique ou différent, est égal à 0 ou 1; p , identique ou différent, est égal à 0, 1, 2 ou 3; t est égal à 0, 1, 2 ou 3; q est un entier compris entre 0 et 10,

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 July 2005 (07.07.2005)

PCT

(10) International Publication Number
WO 2005/060692 A2

(51) International Patent Classification: Not classified

(74) Agents: HENDERSON, Loretta, J. et al.; GlaxoSmithKline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(21) International Application Number:
PCT/US2004/042762

(22) International Filing Date:
17 December 2004 (17.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/531,569 19 December 2003 (19.12.2003) US

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AU, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicants (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US). CYTOKINETICS [US/US]; 280 East Grand Avenue, South San Francisco, CA 94080 (US).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KR, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and
(75) Inventors/Applicants (for US only): PARRISH, Cynthia, A. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). DHANAK, Dushyant [GB/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). KNIGHT, Steven, David [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). MORGANS, David, J., Jr. [US/US]; 781 Vista Grande Avenue, Los Altos, CA 94024 (US).

Published:
— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/060692 A2

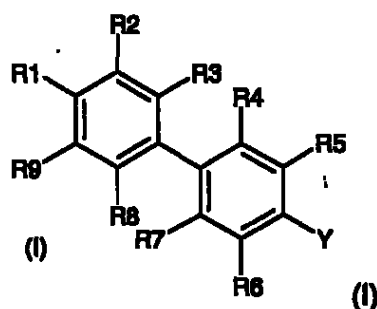
(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS

(57) Abstract: Compounds useful for treating cellular proliferative diseases and disorders by modulating the activity of KSP are disclosed.

360
357

We claim:

1. A compound having the structure shown by formula I



wherein:

one of R1 and R2 is $-NR^{17}S(O)_mR^{12}$ and the other is selected from the group consisting of hydrogen, halogen, hydroxy, optionally substituted lower alkoxy, cyano, nitro, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-NR^{13}R^{14}$, optionally substituted aminosulfonyl, and optionally substituted aminocarbonyl;

R¹² is selected from the group consisting of optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, and optionally substituted heteroaryl;

R¹⁷ is selected from hydrogen and lower alkyl;

m is 1 or 2;

R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from the group consisting of hydrogen, halogen, hydroxy, optionally substituted lower alkoxy, cyano, nitro, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-NR^{13}R^{14}$, optionally substituted aminosulfonyl, and optionally substituted

144

361
358

aminocarbonyl;

Y is selected from the group consisting of optionally substituted lower alkyl, halogen, trifluoromethoxy, $-S(O)_nCF_3$, $-CR_{15}R_{16}CF_3$, and $-C(X)CF_3$,

X is selected from the group consisting of oxygen and sulfur;

R15 and R16 taken together with the carbon to which they are attached form a saturated or unsaturated ring having 3 to 6 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, and oxygen, which ring is optionally substituted with halogen, hydroxy, optionally substituted lower alkoxy, cyano, or optionally substituted lower alkyl;

n is 0, 1, or 2;

or Y and R5, or Y and R6, taken together with the carbons to which they are attached form a 5 to 7 membered saturated or unsaturated ring optionally containing 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur, which ring is optionally substituted with halogen, hydroxy, cyano, $-NR_{13}R_{14}$, optionally substituted lower alkyl, or optionally substituted lower alkoxy, which ring may be aromatic or non-aromatic;

R13 and R14 are independently selected from the group consisting of hydrogen, hydroxy, optionally substituted lower alkoxy, optionally substituted lower alkyl, optionally substituted aryl, and optionally substituted heteroaryl, or R13 and R14 taken together with the nitrogen to which they are attached form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, and oxygen, which ring is optionally substituted with halogen, hydroxy, cyano, optionally substituted lower alkyl, or optionally substituted lower alkoxy;

or a pharmaceutically acceptable derivative or solvate thereof.

00-077.372
P3
362
359

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
30 June 2005 (30.06.2005)

PCT

(10) International Publication Number
WO 2005/058884 A2

(51) International Patent Classification⁷: C07D 409/00

(21) International Application Number:
PCT/US2004/041852

(22) International Filing Date:
14 December 2004 (14.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/529,116 15 December 2003 (15.12.2003) US

(71) Applicant (for all designated States except US): JAPAN
TOBACCO INC. [JP/JP]; 2-1, Toranomon 2-chome Mi-
nato-ku, Tokyo, 105-8422 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): INABA, Takashi
[JP/JP]; c/o Japan Tobacco Inc., Central Pharmaceuti-
cal Research Institute, Murasaki-cho Takatsuki, Osaka
569-1125 (JP). HAAS, Julia [DE/US]; 2775 Lee Hill
Drive, Boulder, CO 80302 (US). SHIOZAKI, Makoto
[JP/JP]; c/o Japan Tobacco Inc., Central Pharmaceuti-
cal Research Institute, Murasaki-cho Takatsuki, Osaka
569-1125 (JP). LITTMAN, Nicole, M. [CA/US]; 1659
Powell Street, Erie, CO 08516 (US). YASUE, Katsutaka
[JP/JP]; c/o Japan Tobacco Inc., Central Pharmaceuti-
cal Research Institute, Murasaki-cho Takatsuki, Osaka
569-1125 (JP). ANDREWS, Steven, W. [US/US]; 2020
Kentmere Drive, Longmont, CO 80501 (US). SAKAI,
Atsushi [JP/JP]; c/o Japan Tobacco Inc., Central Phar-
macological Research Institute, Murasaki-cho Takatsuki,
Osaka 569-1125 (JP). FRYER, Andrew, M. [GB/US];
1785 Wilson Circle, Erie, CO 80516 (US). MATSUO,
Takafumi [JP/JP]; c/o Japan Tobacco Inc., Central Phar-
macological Research Institute, Murasaki-cho Takatsuki,
Osaka 569-1125 (JP). LAIRD, Ellen, R. [US/US]; 2435
Mallard Circle, Longmont, CO 80504 (US). SUMA,
Akira [JP/JP]; c/o Japan Tobacco Inc., Central Phar-
macological Research Institute, Murasaki-cho Takatsuki,

Osaka 569-1125 (JP). SHINOZAKI, Yukihi [JP/JP]; c/o
Japan Tobacco Inc., Central Pharmaceutical Research
Institute, Murasaki-cho Takatsuki, Osaka 569-1125 (JP).
HORI, Yoshikazu [JP/JP]; c/o Japan Tobacco Inc.,
Central Pharmaceutical Research Institute, Murasaki-cho
Takatsuki, Osaka 569-1125 (JP). IMAI, Hiroto [JP/JP];
c/o Japan Tobacco Inc., Central Pharmaceutical Research
Institute, Murasaki-cho Takatsuki, Osaka 569-1125 (JP).
NEGORO, Tamotsu [JP/JP]; c/o Japan Tobacco Inc.,
Central Pharmaceutical Research Institute, Murasaki-cho
Takatsuki, Osaka 569-1125 (JP).

(74) Agent: GARRETT, Arthur, S.; Finnegan, Henderson,
Parabow, Garrett & Dummer, L.L.P., 901 New York Avenue,
NW, Washington, D.C. 20001-4413 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KR,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

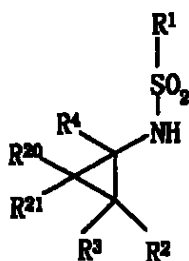
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NI, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CYCLOPROPANE COMPOUNDS AND PHARMACEUTICAL USE THEREOF



(1)

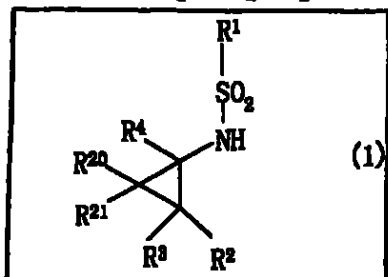
(57) Abstract: The present invention provides a compound having aggrecanase inhibitory activity and MMP-13 inhibitory activity, and useful as a therapeutic agent for osteoarthritis, rheumatoid arthritis and the like, more specifically, a cyclopropane compound of formula (1): wherein R¹ is - (CH₂)_m-X- (CH₂)_n-A¹ etc., wherein m and n are the same or different and each is 0 to 6, X is a single bond, etc. and A¹ is a substituted C₃₋₁₄ hydrocarbon ring group, etc.; R² and R³ are the same or different and each is a hydrogen atom, - (CH₂)_p-X₁-(CH₂)_q-A², etc., wherein p and q are the same or different and each is 0 to 6, X₁ is a single bond, etc. and A² is an optionally substituted C₃₋₁₄ hydrocarbon ring group, etc.; R⁴ is -CO₂R⁵, etc., wherein R⁵ is a hydrogen atom, etc.; and R²⁰ and R²¹ are the same or different and each is a hydrogen atom, - (CH₂)_{m12}-X₁₂-(CH₂)_{m12}-R²⁰, etc., wherein m12 and m12 are the same or different and each is 0 to 6, X₁₂ is a single bond, etc. and R²⁰ is a hydrogen atom, etc.; or a prodrug thereof or a pharmaceutically acceptable salt thereof.

WO 2005/058884 A2

363
360

WHAT IS CLAIMED IS:

1. A cyclopropane compound of formula (1):



wherein

5 R¹ is selected from(1) a substituted C₁₋₆ alkyl group

and

(2) -(CH₂)_m-X-(CH₂)_n-A¹,

wherein

10 m and n are the same or different and each is selected from 0 and an integer ranging from 1 to 6,X is a linker selected from the following group A,group A:

- (a) a single bond,
- 15 (b) a C₁₋₆ alkylene group,
- (c) a C₂₋₆ alkenylene group,
- (d) a C₂₋₆ alkynylene group,
- (e) -O-,
- (f) -N(R⁵)-,
- 20 (g) -S(O)_{m1}-,
- (h) -CO-,
- (i) -COO-,
- (j) -OCO-,
- (k) -CON(R⁵)-,
- 25 (l) -N(R⁵)CO-,
- (m) -SO₂N(R⁵)-,
- (n) -N(R⁵)SO₂-,
- (o) -N(R⁵)CON(R⁶)-,
- (p) -N(R⁵)SO₂N(R⁶)-,
- 30 (q) -OCON(R⁵)-,
- (r) -N(R⁵)COO-

and

(s) -S(O)_{m1}-(CH₂)_{m1}-CO-;

74

36A
361

wherein

- 5 R^5 and R^6 are the same or different and each is selected from a hydrogen atom, a C_{1-6} alkyl group optionally substituted by halogen atoms or hydroxyl groups, a C_{3-14} hydrocarbon ring group and a heterocyclic group, $m1$ is selected from 0 and an integer ranging from 1 to 2 and

$n1$ is selected from an integer ranging from 1 to 2, and

- 10 A^1 is selected from a substituted C_{3-14} hydrocarbon ring group and a substituted heterocyclic group;

R^2 and R^3 are the same or different and each is selected from (1) $-(CH_2)_p-X_1-(CH_2)_q-A^2$,

- 15 wherein

p and q are the same or different and each is selected from 0 and an integer ranging from 1 to 6,

X_1 is a linker selected from the above-mentioned group A and

- 20 A^2 is selected from an optionally substituted C_{3-14} hydrocarbon ring group and an optionally substituted heterocyclic group, and

 (2) $-(CH_2)_{m8}-X_8-(CH_2)_{n8}-R^{27}$,

- 25 wherein

$m8$ and $n8$ are the same or different and each is selected from 0 and an integer ranging from 1 to 6,

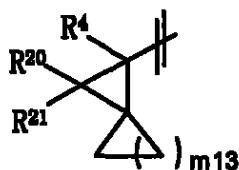
X_8 is a linker selected from the above-mentioned group A and

- 30 R^{27} is a substituent selected from the following group B, group B:

- (a) a hydrogen atom,
 (b) a halogen atom,
 (c) a hydroxyl group,
35 (d) a nitro group,
 (e) a cyano group,
 (f) a carboxyl group,
 (g) an amino group,

365
362

- (h) an amido group,
 (i) a C₂₋₆ acyl group,
 (j) a halogenated C₁₋₆ alkyl group,
 (k) a C₁₋₆ alkyl group optionally substituted by hydroxyl
 5 groups,
 (l) a C₂₋₆ alkenyl group optionally substituted by halogen
 atoms,
 (m) a C₂₋₆ alkynyl group,
 (n) a C₁₋₆ alkoxy group optionally substituted by hydroxyl
 10 groups,
 (o) a C₁₋₆ alkoxy-C₁₋₆ alkyl group,
 (p) a C₁₋₆ alkoxy-carbonyl group,
 (q) a C₁₋₆ alkyl-aminocarbonyl group optionally substituted
 by halogen atoms,
 15 (r) a mono(C₁₋₆ alkyl)amino group,
 (s) a di(C₁₋₆ alkyl)amino group,
 (t) a C₁₋₆ alkyl-carbonylamino group optionally substituted
 by halogen atoms,
 (u) a C₁₋₆ alkylsulfonyl group
 20 and
 (v) a C₁₋₆ alkylsulfonylamino group;
 or A² and R²⁷ may be taken together to form an optionally
 substituted fused ring group,
 or R² and R³ may be taken together with a carbon atom bonded
 25 thereto to form the following ring



wherein m₁₃ is selected from an integer ranging from 1 to 6,
 provided that R² and R³ are not hydrogen atoms at the same
 time;

30

R⁴ is selected from

- (1) -CO₂R⁹,
 (2) -C(O)NHO⁹,
 (3) -C(O)NH-SO₂-R⁹,

363

- (4) $-\text{C}(\text{O})\text{NHR}^9$,
(5) $-\text{SH}$,
(6) $-\text{CH}_2\text{CO}_2\text{R}^9$,
(7) $-\text{C}(\text{O})\text{R}^9$,
5 (8) $-\text{N}(\text{OH})\text{COR}^9$,
(9) $-\text{SN}_2\text{H}_2\text{R}^9$,
(10) $-\text{SONHR}^9$,
(11) $-\text{CH}_2\text{CO}_2\text{H}$,
(12) $-\text{PO}(\text{OH})_2$,
10 (13) $-\text{PO}(\text{OH})\text{NHR}^9$,
(14) $-\text{CH}_2\text{SH}$,
(15) $-\text{CH}_2\text{OH}$,
(16) $-(\text{CH}_2)_{r1}-\text{PO}(\text{OH})-(\text{CH}_2)_{r2}-\text{R}^9$,
(17) $-\text{NHR}^9$,
15 (18) $-\text{NH}-\text{NHR}^9$
and
(19) $-(\text{CH}_2)_{r1}-\text{R}^{50}$

wherein

- 20 r_1 and r_2 are the same or different and each is selected from 0 and an integer ranging from 1 to 6,
 R^9 is selected from

- (1) a hydrogen atom,
(2) an optionally substituted C_{1-10} alkyl group,
(3) an optionally substituted C_{6-14} aryl- C_{1-6} alkyl group
25 and
(4) $-(\text{CH}_2)_{m9}-\text{X}_9-(\text{CH}_2)_{n9}-\text{R}^{28}$

wherein

- m_9 and n_9 are the same or different and each is selected from 0 and an integer ranging from 1 to 6,
30 X_9 is a linker selected from the above-mentioned group A and
 R^{28} is a substituent selected from the following group C,

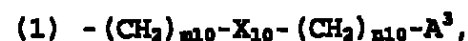
group C:

- 35 (a) a hydrogen atom,
(b) a halogen atom,
(c) a hydroxyl group,
(d) a nitro group,

367
364

- (e) a cyano group,
(f) a carboxyl group,
(g) an amino group,
(h) an amido group,
5 (i) a C₂₋₆ acyl group,
(j) a halogenated C₁₋₆ alkyl group,
(k) a C₁₋₆ alkyl group optionally substituted by hydroxyl groups,
(l) a C₂₋₆ alkenyl group optionally substituted by halogen
10 atoms,
(m) a C₂₋₆ alkynyl group,
(n) a C₁₋₆ alkoxy group optionally substituted by hydroxyl groups,
(o) a C₁₋₆ alkoxy-C₁₋₆ alkyl group,
15 (p) a C₁₋₆ alkoxy-carbonyl group,
(q) a C₁₋₆ alkyl-aminocarbonyl group optionally substituted by halogen atoms,
(r) a mono(C₁₋₆ alkyl)amino group,
(s) a di(C₁₋₆ alkyl)amino group,
20 (t) a C₁₋₆ alkyl-carbonylamino group optionally substituted by halogen atoms,
(u) a C₁₋₆ alkylsulfonyl group,
(v) a C₁₋₆ alkylsulfonylamino group,
(w) a C₃₋₁₄ hydrocarbon ring group optionally substituted by 1
25 to 5 substituent(s) selected from the above-mentioned group B and
(x) a heterocyclic group optionally substituted by 1 to 5 substituent(s) selected from the above-mentioned group B, and
30 R⁵⁰ is selected from an optionally substituted C₃₋₁₄ hydrocarbon ring group and an optionally substituted heterocyclic group;
or R⁹ of -C(O)NHR⁹, A² and the cyclopropane ring may be taken together to form an optionally further substituted fused
35 ring;

R²⁰ and R²¹ are the same or different and each is selected from

368
365

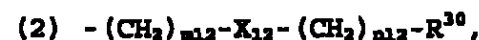
wherein

$m10$ and $n10$ are the same or different and each is selected from 0 and an integer ranging from 1 to 6,

5 X_{10} is a linker selected from the above-mentioned group A and

A^3 is selected from an optionally substituted C_{3-14} hydrocarbon ring group and an optionally substituted heterocyclic group,

10 and



wherein

$m12$ and $n12$ are the same or different and each is selected from 0 and an integer ranging from 1 to 6,

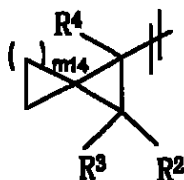
15 X_{12} is a linker selected from the above-mentioned group A and

R^{30} is a substituent selected from the above-mentioned group B;

or A^2 , R^{30} and the cyclopropane ring may be taken together to

20 form a optionally further substituted fused ring,

or R^9 of $-CO_2R^9$, R^{20} and the cyclopropane ring may be taken together to form an optionally further substituted fused ring, or R^{20} and R^{21} may be taken together with a carbon atom bonded thereto to form the following ring

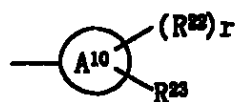


25

wherein $m14$ is selected from an integer ranging from 1 to 6; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the substituted C_{3-14} hydrocarbon ring group or the substituted heterocyclic group in A^1 is a group of the following formula:

30



Registro de la Propiedad Industrial

Oficina de Invenciones y Nuevas Tecnologías

TITULO N° 3645

La Oficina de Invenciones y Nuevas Tecnologías del Indecopi certifica que por mandato de la Resolución N° 000999-2004/OIN-INDECOPI de fecha 27 de agosto de 2004, ha quedado inscrita en el Registro de Patentes de Invención, la siguiente invención:

Denominación : DERIVADOS DE BENZODIAZEPINA COMO ANTAGONISTAS DEL RECEPTOR DE GLUTAMATO METABOTROPICO

Clasificación : C07D 243/12; C07D 243/00

Solicitud : 001098-2000

Fecha de Presentación : 12 de octubre de 2000

Fecha de Prioridad : 15 de octubre de 1999

Titular : F. HOFFMANN-LA ROCHE AG

País : Suiza

Inventores : ALEXANDER ALANINE; VINCENT MUTEL; GEO ADAM; ERWIN GOETSCHI; THOMAS JOHANNES WOLTERING

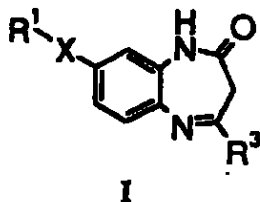
Vigencia : 12 de octubre de 2020


NÉSTOR ESCOBEDO FERBADAS
Jefe de la Oficina de Invenciones
y Nuevas Tecnologías
INDECOPI

Reivindicaciones

1. Compuestos de fórmula general I

5



en donde

X es un enlace sencillo o un grupo etinodifilo, en donde,

10

en caso de que X sea un enlace sencillo,

R¹ es halógeno; alquilo C₁-C₇; cicloalquilo C₃-C₆, benzoilo, fenilo, opcionalmente sustituido con halógeno, hidroxilo, alquilo C₁-C₇; alcoxilo C₁-C₇, halo-alcoxilo C₁-C₇, ó ciano; estirenilo; naftilo; bifenilo; benzofuranilo; ó anillo

15

heterocíclico de 5 ó 6 eslabones, que comprende tiofenilo, furanilo, piridinilo, dihidropiridinilo, tetrahidropiridinilo opcionalmente sustituido con oxo, benziloxi, metanosulfonilo, bencenosulfonilo, o acetilo;

en caso de que X sea un grupo etinodifilo,

20

R¹ es alquilo C₁-C₇, opcionalmente sustituido con hidroxilo; cicloalquilo C₃-C₆, opcionalmente sustituido con hidroxilo; cicloalquenilo C₃-C₆, opcionalmente sustituido con oxo; alquenilo C₂-C₇; fenilo, opcionalmente sustituido con halógeno, alquilo C₁-C₇, alcoxilo C₁-C₇, halo-alcoxilo C₁-C₇,

25

anillo heterocíclico de 5 ó 6 eslabones, que comprende tiofenilo, tiazolilo, piridinilo, tetrahidropiridinilo, dihidropirranilo. opcionalmente sustituido con metanosulfonil, acetilo, tert.butoxicarbonilo, ó

371

368

tert.butilcarbonilo

R³ es fenilo; piridina; tiofenilo o tiazolilo, que están
opcionalmente sustituidos con halógeno, amino, ciano, nitro,
hidroxilo, carboxilo, morfolin-4-carbonilo, carbamoilo,
5 tiocarbamoilo, N-hidroxicarbamoilo, trimetilsilil-etinilo, o
de alquinilo C₂-C₇, alcoxilo C₁-C₇, halo-alquilo C₁-C₇, N-
hidroxi-amidina, alquilosulfonamida C₁-C₇, 4-alquilo C₁-C₇-
piperazin-1-carbonilo, aminoalquilcarbonilo C₁-C₇, ó un
heterociclo aromático de 5 eslabones que comprende
10 imidazolilo, isoxazolilo, oxadiazolilo, tiazolilo,
tetrazolilo y triazolilo, que está opcionalmente sustituido
por carboxilo que está opcionalmente esterificado con
alquilo C₁-C₇ o amidado con alquilamino C₁-C₇, que está
eventualmente sustituido por hidroxilo;

15 alquilo C₁-C₇; que está opcionalmente sustituido por
hidroxilo,

Alcoxilo C₁-C₇-sulfanilalquilo C₁-C₇,

Sulfanilalquilo C₁-C₇, y amida del ácido carbotiótico,
con la condición de que, si X es un enlace sencillo y R³ es
20 piridinilo, R¹ no es metilo;
y sus sales de adición de ácido farmacéuticamente aceptables

2. Compuestos de acuerdo con la reivindicación 1, en
los que R³ es fenilo sustituido en posición meta por ciano;
halógeno; ó imidazolilo, el cual está opcionalmente
25 sustituido por alquilo inferior; ó 1,3-tiazolilo el cual
está opcionalmente sustituido por alquilo C₁-C₇, hidroxí-
alquilo C₁-C₇, carboxilo, o -CO-NH-(CH₂)₂OH; 1,2,3-
triazolilo; 1,2,4-triazolilo el cual está opcionalmente

sustituido con alquilo C₁-C₇; tetrazolilo; o isoxazolilo, que ...
está opcionalmente sustituido por alquilo C₁-C₇.

3. Los siguientes compuestos de conformidad con la reivindicación 2:

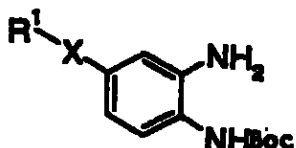
- 5 3-(4-Oxo-7-feniletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;
4-(3-Cloro-fenil)-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
4-(3-Imidazol-1-il-fenil)-8-feniletinil-1,3-dihidro-benzo
- 10 [b][1,4]diazepin-2-ona;
3-[7-(4-Fluoro-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-benzonitrilo;
8-(4-Fluoro-feniletinil)-4-(3-imidazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 15 8-(4-Fluoro-feniletinil)-4-(3-[1,2,4]triazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
8-(4-Fluoro-fenil)-4-[3-(4-metil-imidazol-1-il)-fenil]-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
8-(4-Fluoro-2-metil-fenil)-4-(3-imidazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 20 8-(4-Fluoro-2-hidroxí-fenil)-4-(3-imidazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
8-(4-Fluoro-feniletinil)-4-(3-tetrazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 25 8-(2-Fluoro-fenil)-4-(3-[1,2,3]triazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
8-(4-Fluoro-fenil)-4-[3-(3-metil-isoxazol-5-il)-fenil]-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

- 8-(2,4-Difluoro-fenil)-4-(3-[1,2,3]triazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 8-(2,3-Difluoro-fenil)-4-(3-[1,2,3]triazol-1-il-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 5 8-(2-Fluoro-fenil)-4-[3-(4-hidroximetil-tiazol-2-il)-fenil]-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- Ácido 2-(3-[7-(2-Fluoro-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-fenil)tiazol-4-carboxílico;
- Ácido 2-(3-[7-(4-Fluoro-fenil)-4-oxo-4,5-dihidro-3H-benzo
- 10 [b][1,4]diazepin-2-il]-fenil)-4-metil-tiazol-5-carboxílico (2-hidroxietil)-amida; y
- 4-[3-(4,5-Dimetil-4H-[1,2,4]triazol-3-il)-fenil]-8-(4-fluoro-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
4. Compuestos de fórmula I, de acuerdo con la
- 15 reivindicación 1, en que R³ es tiofenilo, opcionalmente sustituido con halógeno, ciano; ó piridinilo, opcionalmente sustituido con imidazolilo, ó ciano.
5. Los siguientes compuestos de conformidad con la reivindicación 4:
- 20 8-(4-Fluoro-feniletinil)-4-(2-imidazol-1-il-piridin-4-il)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;
- 2-[7-(4-Fluoro-fenil)-4-oxo-4,5-dihidro-1H-benzo[b][1,4]diazepin-2-il]-tiofeno-3-carbonitrilo;
- 4-(4-Oxo-7-feniletinil-4,5-dihidro-3H-benzo[b][1,4]
- 25 diazepin-2-il)-piridin-2-carbonitrilo; y
- 4-[7-(2,4-Difluoro-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-piridin-2-carbonitrilo.

6. Un medicamento que contiene uno o más compuestos

de cualquiera de las reivindicaciones de 1 a 5 y excipientes farmacéuticamente aceptables.

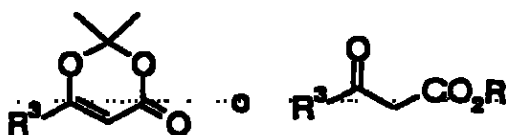
7. Un proceso para la preparación de compuestos de fórmula I tal y como se define en la reivindicación 1, comprendiendo dicho proceso hacer reaccionar un compuesto de fórmula III:



10

III

con un compuesto de fórmula IV o IVa

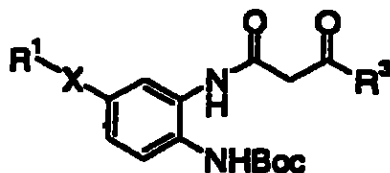


15

IV

IVa

en el que R es etilo o butilo, a un compuesto de fórmula II



20

II

que subsiguientemente es sometido a desprotección del grupo amino y a ciclación, para obtener un compuesto de fórmula I de la reivindicación 1.