

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: P1.-ASTRAZENECA AB.-Solicitud de Patente de Invención en Fase Nacional PCT para "DERIVADOS E INTERMEDIARIOS DE N-ADAMANTILMETILO COMO COMPOSICIONES FARMACÉUTICAS Y PROCESOS PARA SU PREPARACIÓN".-Clase A61K 31/44.-Expediente número 04.043.373-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 15 de Febrero de 2008.

2. Con el fin de dar respuesta a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **2795**, en relación con excepciones a la patentabilidad, reivindicaciones relativas a un uso o a un segundo uso y nivel inventivo, me permito dirigir su atención a las siguientes modificaciones y argumentos técnicos, por medio de los cuales se superan completamente dichas objeciones.

3. REIVINDICACIONES

En primer lugar, me permito señalar que, acatando las objeciones presentadas por el señor Examinador en contra del capítulo reivindicatorio, es deseo del solicitante presentar un nuevo capítulo reivindicatorio que consta de **16** reivindicaciones, el cual tiene como base el capítulo reivindicatorio originalmente presentado, y en el cual se han hecho las siguientes modificaciones.

3.1 Reivindicaciones relativas a un uso.

REIVINDICACIONES 17 A 21: Con el fin de dar respuesta a la objeción presentada por el señor Examinador en contra de las reivindicaciones 17 a 21,

debido a que estas protegen un uso de la invención para diferentes fines, me permito señalar que, debidamente autorizado por mi representado, **dichas reivindicaciones han sido eliminadas del nuevo capítulo reivindicatorio.**

3.2 **Excepción a la patentabilidad.**

REIVINDICACIONES 22 Y 23: Con el propósito de acatar la objeción presentada por el señor Examinador en contra de las reivindicaciones 22 y 23 debido a que estas protegen métodos de tratamiento, me permito manifestar que, debidamente autorizado por mi representado, **dichas reivindicaciones han sido eliminadas del nuevo capítulo reivindicatorio.**

Finalmente, me permito manifestar que las modificaciones realizadas al capítulo reivindicatorio en mención **no amplían de manera alguna el alcance de la invención tal como fue originalmente presentada**, toda vez que, como se mencionó anteriormente, dichas modificaciones corresponden a la eliminación de ciertas reivindicaciones con el fin de dar respuesta a las objeciones presentadas por el señor Examinador, lo que evidentemente corresponde a una restricción de la materia objeto de la solicitud bajo estudio.

4. **ANTECEDENTES DE LA INVENCION**

El receptor P2X₇ (anteriormente conocido como receptor P2Z), que es un canal de iones de ligando bloqueado, está presente en una variedad de tipos de células, ampliamente conocidos por estar involucrados en los procesos inflamatorios/inmunes, específicamente, macrófagos, clasmato blasto, y linfocitos (T y B). La activación del receptor P2X₇ mediante nucleótidos extracelulares, en particular trifosfato de adenosina, conduce a la liberación de interleukin-1 β (IL-1 β) y a la formación de células gigantes (macrófagos/ células microgliales), degranulación (clasmato blasto) y proliferación (células T), apoptosis y pérdida de L-selectina (linfocitos). Los receptores P2X₇ también están ubicados sobre células que presentan antígenos (APC), keratinocitos, células salivares acinares (células parótidas), hepatocitos y células mesangiales.

Sería deseable elaborar compuestos efectivos como antagonistas de receptor P2X₇ para uso en el tratamiento de enfermedades inflamatorias, inmunes o cardiovasculares, en las etiologías de las cuales el receptor P2X₇ puede jugar un papel.

De conformidad con lo anterior, la presente solicitud surge como una **alternativa novedosa e inventiva en el esfuerzo por proporcionar compuestos químicos derivados de adamantano que tengan actividad farmacéutica como moduladores de la actividad del receptor P2X₇ y que puedan usarse en el tratamiento de enfermedades mediadas por dicho receptor.**

5. **NIVEL INVENTIVO**

Ahora bien, el señor Examinador en su Concepto Técnico No. **2795**, manifiesta que la presente solicitud carece de nivel inventivo con base en las enseñanzas de los siguientes documentos:

Documento DE1943404 (D1). Con respecto a este documento, el señor Examinador afirma lo siguiente:

"El documento más cercano en el estado de la técnica es D1, el cual revela compuestos similares al objeto de la presente solicitud... La principal diferencia entre la solicitud y D1 es el grupo A de la solicitud, que representa CONH ó NCO, formando una amida sustituida por un grupo aromático. En D1 se presenta una alquilamina terciaria sustituyendo el adamantano.

El Problema técnico de la presente solicitud, es decir la necesidad de compuestos útiles en el tratamiento de desórdenes inflamatorios, inmunes o cardiovasculares, se había resuelto previamente mediante compuestos ya conocidos. Por esta razón se considera que para una persona versada en la materia sería obvio considerar el grupo carbonilo como una opción para el grupo A, ya que como intermediarios de síntesis se usan compuestos derivados del ácido adamantil-acético".

Con respecto a estas afirmaciones, me permito señalar que el documento D1 citado por el Señor Examinador enseña la solución de un problema muy diferente al problema que se pretende resolver con los compuestos revelados en la presente solicitud. Mientras el documento **D1 revela adamantilaminas que son útiles como anti-depresivos, anti-Parkinson, anti-mareo, y supresores del apetito, la presente solicitud revela compuestos derivados de adamantano los cuales tienen actividad farmacológica**

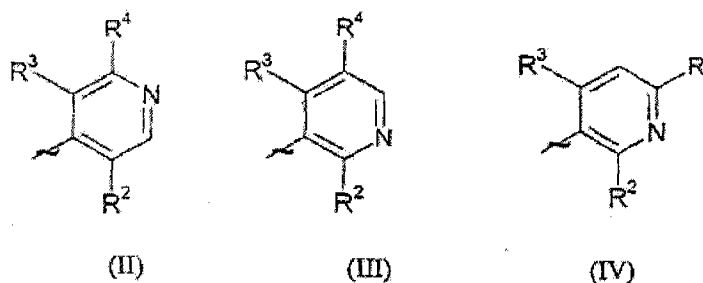
A lo anterior se une el hecho de que no existe ninguna evidencia en D1 que permita pensar que la persona versada en la materia que pretenda preparar antagonistas del receptor P2X₇, use como guía o punto de partida las enseñanzas del documento D1, ya que como se mencionó, dicho documento soluciona un problema totalmente diferente al problema resuelto en la presente solicitud, y lo hace además utilizando compuestos que no exhiben las características estructurales propias de los compuestos de la solicitud bajo estudio.



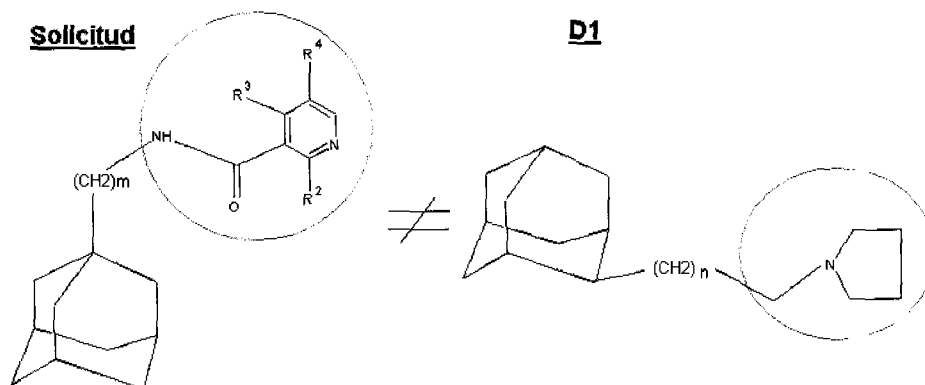
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(i) A equivale a NHC(O) , ó C(O)NH ; y

(ii) Ar equivale a uno de tres grupos piridinilo que poseen sustituyentes específicos en posiciones determinadas tal como se muestra a continuación:



Adicionalmente, en la estructura del compuesto enseñado por D1, R1 puede equivaler a hidrógeno, o alquilo C_{1-4} ; y R2 y R3 junto con el átomo de nitrógeno pueden formar un grupo pirrolidina, pero en ningún caso pueden ser un grupo piridinilo. Por lo tanto **al realizar las sustituciones correspondientes en los compuestos de la presente solicitud y en los compuestos de D1, no se obtienen compuestos que tengan características estructurales similares** tal como se muestra a continuación:



Así, es completamente claro que, a diferencia de los compuestos enseñados en la presente solicitud, **los compuestos revelados por D1 carecen de un grupo piridinilo, y de un grupo amida que sirva de puente entre el grupo adamantilo y el grupo piridinilo**. Adicionalmente, el grupo piridinilo presente en los compuestos enseñados en la presente solicitud tiene sustituyentes específicos (R2, R3, y R4) en posiciones determinadas del anillo, característica que se aleja aun más de los compuestos que enseña D1.

Sobre este punto, es importante resaltar que, en el documento D1 citado por el señor Examinador no existe ninguna sugerencia o motivación que lleve a la persona versada en la materia a realizar algún tipo de modificación estructural a los compuestos revelados en D1 con el fin de obtener los compuestos enseñados en la presente solicitud, y mucho menos que los compuestos obtenidos con dicha modificación puedan tener actividad como antagonistas del receptor P2X₇.

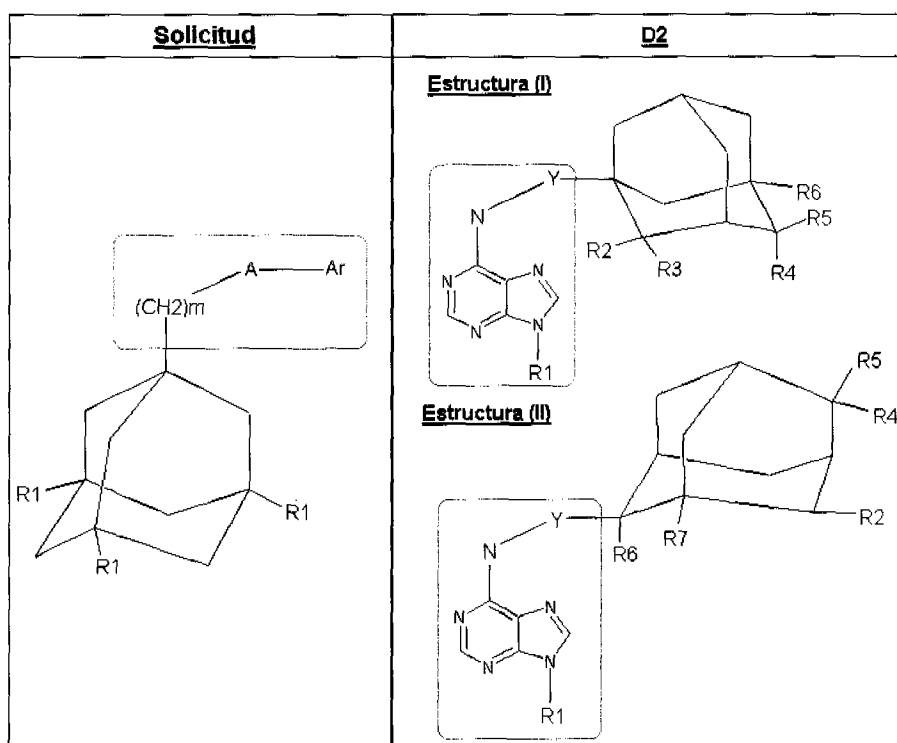
Documento US4751292 (D2). Con respecto a este documento, el señor Examinador afirma lo siguiente:

"Adicionalmente en D2 se anticipan adamantil-purinas en las cuales se forma el enlace entre el adamantano y la purina a través de la estructura Y, que puede tener grupo carbonilo o carboxamido".

A este respecto, me permito señalar que **D2 es una referencia relacionada con agroquímicos. Bajo este contexto, dicha referencia enseña compuestos químicos derivados de purinas, los cuales tienen una actividad diferente a los compuestos químicos enseñados en la presente solicitud.** Específicamente los compuestos revelados en el documento D2 son derivados de adamantil purinas que tienen actividad como estimulantes del crecimiento y división celular en plantas. Por el contrario, **la presente solicitud revela compuestos derivados de adamantano los cuales tienen actividad farmacológica como antagonistas del receptor P2X₇.**

De acuerdo con lo anterior, no existe motivación alguna para que la persona versada en la materia que pretenda preparar antagonistas del receptor P2X₇ use como guía o punto de referencia las enseñanzas del documento D2, ya que **D2 soluciona un problema totalmente diferente, y lo hace además utilizando compuestos que no exhiben las características estructurales propias de los compuestos de la solicitud bajo estudio y se refiere por lo demás a la industria agroquímica.**

Se une a lo anterior el hecho de que al realizar una comparación de las características estructurales de los compuestos revelados en el documento D2 y los enseñados en la presente solicitud se observan claramente amplias diferencias que me permito señalar a continuación:



En esta comparación se observa que los compuestos de la presente solicitud poseen un grupo adamantil y un grupo Ar unidos mediante un grupo A y un grupo $(CH_2)_m$, y tal como se mencionó anteriormente el grupo Ar equivale a un grupo piridinil con sustituyentes específicos en posiciones definidas y A corresponde a NHCO. Por el contrario, **los compuestos revelados en D2 no poseen ningún grupo piridinil sustituyendo al grupo adamantil.**

Al igual que con D1, en dicho documento no existe ninguna sugerencia o motivación que lleve a la persona versada en la materia, a realizar modificaciones estructurales en los compuestos revelados por D2 con el fin de obtener compuestos con características idénticas a los enseñados en la solicitud bajo estudio, y mucho menos que los compuestos obtenidos con tales modificaciones estructurales tengan actividad como antagonistas del receptor P2X₇.

Finalmente, y refiriéndose indistintamente a D1 y D2, el señor examinador afirma que dichos documentos "*divulgan previamente compuestos similares*" por lo que "*una persona versada en la materia motivada por tales sugerencias lograría los compuestos de esta solicitud, por lo cual no puede reconocerse nivel inventivo*".

Contrario a lo afirmado por el señor Examinador, con los argumentos expuestos ha quedado demostrado científicamente que la única similitud que guarda la invención con los documentos D1 y D2, radica que comparten un grupo adamantil, pero que cada uno independientemente desarrolla compuestos completamente diferentes, novedosos e impredecibles partiendo de las enseñanzas de cada uno, prueba de lo cual radica en su diametralmente distinta utilidad.

Invito al señor examinador para que bajo la perspectiva de los elementos técnicos suministrados realice nuevamente un análisis de patentabilidad enfocado a determinar el nivel inventivo de esta solicitud. Hago esta petición considerando los parámetros establecidos por el Artículo 18 de la Decisión Andina 486 de 2000, de acuerdo con los cuales la invención que se presenta no es "obvia" ni se deriva "de manera evidente del estado de la técnica".

Para realizar este estudio, ruego al señor Examinador tener en cuenta que, tal y como lo enseña el **Manual Andino de Patentes**, que "el estado de la técnica más cercano se encuentra en el mismo campo de la invención o trata de solucionar el mismo problema o uno semejante. Por ejemplo en el área de la química, el estado de la técnica mas cercano debe ser aquel que describa un producto estructuralmente semejante al producto de la invención o un uso o actividad semejante al de la invención."¹

Note como en este caso los documentos D1 y D2 citados se refieren a composiciones antidepresivas, para prevenir el Parkinson o enfermedades motoras, o constituyen referencias a campos de la tecnología completamente distintos como el desarrollo de derivados que son útiles en la estimulación de la división celular de plantas, desarrollo propio del sector agroquímico y no farmacéutico. Ruego al señor Examinador no perder de vista que la presente invención se refiere a compuestos efectivos como antagonistas de receptor P2X7 para uso en el tratamiento de enfermedades inflamatorias, inmunes o cardiovasculares.

Solicito igualmente al señor Examinador que para determinar si existe o no nivel inventivo en la invención que se le presente, aplique lo que se conoce como enfoque problema solución, para lo cual ya se le ha aclarado cual es el

¹ Manual para el Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina, Quito Ecuador 2004, Página 77.

campo de la técnica al que se refiere la invención, las diferencias que existen con respecto a las anterioridades citadas y cómo cada uno de los documentos citados resuelve un problema técnico distinto.

En este punto me permito señalar lo que con respecto a la evaluación de nivel inventivo bajo el enfoque problema solución considera el **Manual Andino de Patentes**:

"En resumen, el examinador debe plantearse las siguientes preguntas:

- *¿estaba un técnico con conocimientos medios en la materia en condiciones de plantearse el problema?;*
- *¿de resolverlo en la forma en que se reivindica?; y*
- *¿de prever el resultado?*

Si la respuesta es afirmativa en los tres casos, no hay nivel inventivo".²

Para la solicitud en estudio las tres respuestas serían negativas. El estado del arte citado no permite que la persona versada en la materia se plantee el problema de la necesidad de determinar compuestos útiles para tratamientos de enfermedades inflamatorias, inmunes o cardiovasculares donde el receptor P2X7 sea relevante, de igual forma no brinda elementos para que dicha persona versada en la materia resuelva dicho problema como lo hace la presente solicitud, como tampoco prever su resultado.³

Con base en los anteriores argumentos, me permito manifestar de manera respetuosa que para la persona versada en la materia no sería obvio llegar a los compuestos enseñados en la presente solicitud que tienen actividad como antagonistas del receptor P2X₇, a partir de las enseñanzas de los documentos D1 o D2, toda vez que dichos documentos enseñan la solución a problemas completamente diferente mediante el uso de compuestos que tienen características estructurales muy alejadas de las exhibidas por los compuestos de la presente solicitud. Por tal razón la presente solicitud sí posee nivel inventivo frente a las referencias citadas, de conformidad con lo establecido en el Artículo 18 de la Decisión 486 de 2000.

² Idem, Página 78.

³ En este punto quiero poner de presente que el enfoque problema solución sugerido por el Manual Andino de Patentes, a sido ratificado como una herramienta adecuada para la realización de análisis de nivel inventivo por parte del Tribunal Andino de Justicia, tal y como lo demuestra uno de sus mas recientes pronunciamientos dentro del Proceso 129 IP 2007.

Para terminar, solicito al señor Examinador que tenga en cuenta que el nivel inventivo de la presente solicitud ya mereció el otorgamiento de privilegio de patente por parte de la Oficina Europea de patentes (EP 1448195), así como de la Oficina de Marcas y Patentes de los Estados Unidos de América (US 7129246), de las cuales me permito aportar las copias correspondientes.

6. **CONCLUSIÓN**

Gracias a las modificaciones introducidas al capítulo reivindicatorio, consistentes en la eliminación de todas aquellas reivindicaciones que fueron objetadas por el examinador, se entienden superadas las objeciones referidas a inclusión de usos, así como las objeciones referidas a la inclusión de materia excluida de patentabilidad.

Así mismo, se han presentado argumentos claros que permiten determinar que mas que una semejanza, entre la invención y las referencias citadas como arte mas próximo existen ante todo trascendentales diferencias tanto en el campo técnico al que se dirigen, como a las composiciones que desarrollan y, mas importante aun, los problemas técnicos que resuelven, lo cual, aplicando los criterios generalmente aceptados para la determinación de existencia de requisitos de patentabilidad, permite concluir que la invención cuenta con nivel inventivo.

Siendo que nos encontramos ante una invención clara, referida a materia patentable de acuerdo con la legislación andina, que es claramente nueva y cuenta con nivel inventivo, atentamente solicito a so Despacho conceder el privilegio de patente solicitado.

7. Anexo me permito presentar:

- (a) Recibo número 08-36,056, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;
- (b) Copia del nuevo capítulo reivindicatorio, **que reemplaza al actualmente presentado**, en el cual se han realizado las modificaciones expuestas anteriormente; y
- (c) Copia de los capítulos reivindicatorios de las patentes concedidas para esta misma invención por la Oficina Europea de Patentes (EP 1 448 195 B1) y la Oficina de Marcas y Patentes de los Estados Unidos de América (US 7,129,246 B2).

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

Señor Superintendente,


ALICIA LLORED A RICAURTE

T.P. 53.215

Alicia Lloreda
Ricaurte

Cc # 39.690.713
Tp # 53.215


ALICIA LLORED A RICAURTE

C.C. No. 39.690.713 de Usaquén

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 36,056
FECHA : MAYO 7 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTE Y LII Lve: 379 FASENACIONAL II
Act. 444 RESPUESTA REQUE Folios: 54

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LLORED A Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	2756098	07/05/2008	1,109,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

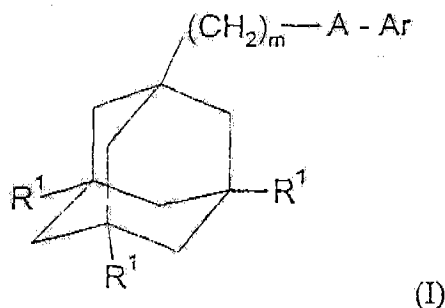
RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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REIVINDICACIONES

1. Un compuesto de fórmula:

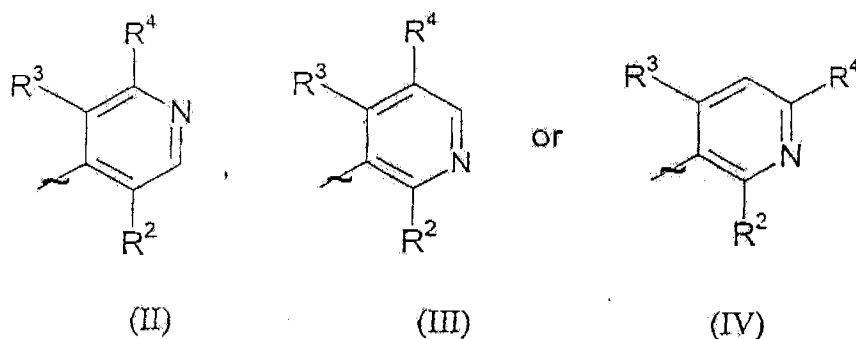


donde m representa 1, 2, o 3;

cada R¹ representa independientemente un átomo de hidrógeno o halógeno;

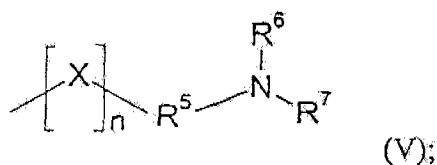
A representa C(O)NH o NHC(O);

Ar representa un grupo



alguno de R² y R³ representa halógeno, nitro, amino, hidroxilo, o un grupo seleccionado de (i) alquiloC₁-C₆ opcionalmente sustituido por al menos un átomo de halógeno, (ii) cicloalquiloC₃-C₈, (iii) alcoxiC₁-C₆ opcionalmente sustituido por al menos un átomo de halógeno, y (iv) cicloalquiloC₃-C₈, y el otro de R² y R³ representa un átomo de hidrógeno o halógeno;

R⁴ representa un grupo



X representa un átomo de oxígeno o azufre o un grupo >N-R⁸;

n es 0 o 1;

R⁵ representa un grupo alquiloC₁-C₅ que puede estar opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno y

alcoxiC₁-C₆;

R⁶ y R⁷ cada uno independientemente representa un átomo de hidrógeno, alquiloC₁-C₆ (opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno, alcoxiC₁-C₆ y (di)- alquilaminoC₁-C₄ (a su vez opcionalmente sustituido por al menos un grupo hidroxilo)), o cicloalquiloC₃-C₈ (opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno y alcoxiC₁-C₆); y

R⁸ representa un átomo de hidrógeno o un grupo alquiloC₁-C₅ que puede estar opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno y alcoxiC₁-C₆;

Con las condiciones que:

(a) cuando n es 0, A es NHC(O), y

(b) cuando n es 1, X representa oxígeno y A es C(O)NH, R⁶ y R⁷ no representan ambos simultáneamente un átomo de hidrógeno o no representan ambos simultáneamente un alquiloC₁-C₆ no sustituido, o cuando alguno de R⁶ y R⁷ representa un átomo de hidrógeno, el otro de R⁶ y R⁷ no representa un alquiloC₁-C₆ no sustituido; y

(c) cuando n es 1, X es oxígeno, azufre o >NH y A es NHC(O), R⁶ y R⁷ no representan ambos simultáneamente un átomo de hidrógeno o no representan ambos simultáneamente un alquiloC₁-C₆ no sustituido, o cuando alguno de R⁶ y R⁷ representa un átomo de hidrógeno, el otro de R⁶ y R⁷ no representa un alquiloC₁-C₆ no sustituido o -CH₂CH₂OH;

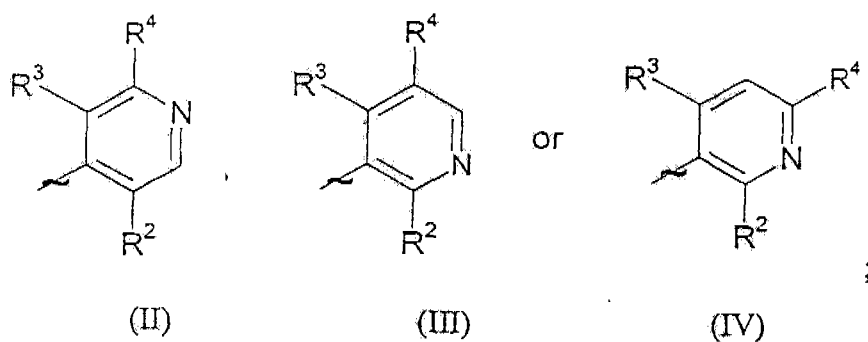
o una sal farmacéuticamente aceptable o solvato de estos.

2. Un compuesto de formula (I) según la reivindicación 1, en donde m representa 1, 2 o 3;

Cada R₁ representa independientemente un átomo de hidrógeno o halógeno;

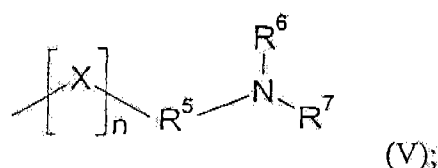
A representa C(O)NH o NHC(O);

Ar representa un grupo



alguno de R^2 y R^3 representa halógeno, nitro, amino, hidroxilo, o un grupo seleccionado de (i) alquilo C_1-C_6 opcionalmente sustituido por al menos un átomo de halógeno, (ii) cicloalquilo C_3-C_8 , (iii) alcoxi C_1-C_6 opcionalmente sustituido por al menos un átomo de halógeno, y (iv) cicloalquiloxi C_3-C_8 , y el otro de R^2 y R^3 representa un átomo de hidrógeno o halógeno;

R^4 representa un grupo



X representa un átomo de oxígeno o azufre, o un grupo $>N-R^8$;
n es 0 o 1;

R^5 representa un grupo alquilo C_1-C_5 que puede estar opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno y alcoxi C_1-C_6 ; y

R^6 , R^7 y R^8 , cada uno independientemente representa un átomo de hidrógeno o un grupo alquilo C_1-C_5 , que puede estar opcionalmente sustituido por al menos un sustituyente seleccionado de hidroxilo, halógeno y alcoxi C_1-C_6 ;

Con las condiciones que:

(d) cuando n es 0, A es $NHC(O)$, y

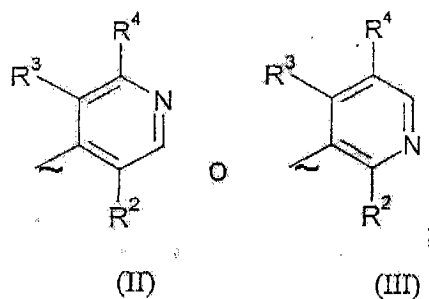
(e) cuando n es 1, X representa oxígeno y A es $C(O)NH$, R^6 y R^7 no representan ambos simultáneamente un átomo de hidrógeno o no representan ambos simultáneamente un alquilo C_1-C_5 no sustituido, o

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cuando alguno de R^6 y R^7 representa un átomo de hidrógeno, el otro de R^6 y R^7 no representa un alquilo C_1 - C_5 no sustituido; y

(f) cuando n es 1, X es oxígeno, azufre o $>NH$ y A es $NHC(O)$, R^6 y R^7 no representan ambos simultáneamente un átomo de hidrógeno o no representan ambos simultáneamente un alquilo C_1 - C_5 no sustituido, o cuando alguno de R^6 y R^7 representa un átomo de hidrógeno, el otro de R^6 y R^7 no representa un alquilo C_1 - C_5 no sustituido o $-CH_2CH_2OH$;
o una sal farmacéuticamente aceptable o solvato de estos.

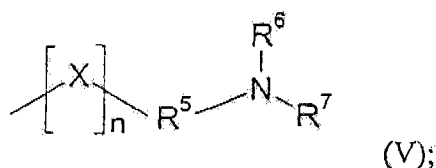
3. Un compuesto según la reivindicación 1 o 2 donde m es 1.
4. Un compuesto según las reivindicaciones 1 a 3 donde A representa $NHC(O)$.
5. Un compuesto según cualquiera de las reivindicaciones 1 a 4 donde Ar representa un grupo de formula (II) o (III).
6. Un compuesto según la reivindicación 5 donde Ar representa un grupo de formula (II).
7. Un compuesto según cualquiera de las reivindicaciones 1 a 6, donde uno de R^2 y R^3 representa un átomo de halógeno y el otro de R^2 y R^3 representa un átomo de hidrógeno.
8. Un compuesto según cualquiera de las reivindicaciones 1 a 7, donde n es 0.
9. Un compuesto según la reivindicación 1, en donde m representa 1;
cada R^1 representa un átomo de hidrógeno;
 A representa $NHC(O)$;



Ar representa un grupo

alguno de R^2 y R^3 representa un átomo de halógeno y el otro de R^2 y R^3 representa un átomo de hidrógeno;

R^4 representa un grupo



X representa un átomo de oxígeno o azufre o un grupo $>N-R^8$;
 n es 0 o 1;

R^5 representa un grupo alquilo C_1-C_3 opcionalmente sustituido por al menos un grupo hidroxilo;

R^6 y R^7 cada uno independientemente representa un átomo de hidrógeno, alquilo C_1-C_5 (opcionalmente sustituido por uno o dos sustituyentes independientemente seleccionados de hidroxilo y (di)-alquilamino C_1-C_2 (a su vez opcionalmente sustituidos por al menos un grupo hidroxilo)), o cicloalquilo C_6 (sustituido por al menos un grupo hidroxilo);

R^8 representa un átomo de hidrógeno o un grupo alquilo C_2 opcionalmente sustituido por al menos un grupo hidroxilo.

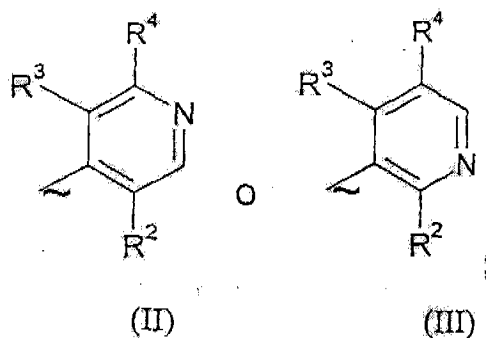
10. Un compuesto según la reivindicación 1 o 2, en donde

m representa 1;

cada R^1 representa un átomo de hidrógeno;

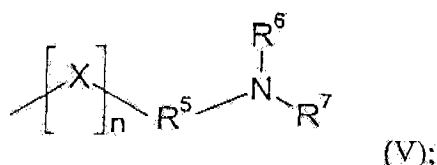
A representa $NHC(O)$;

Ar representa un grupo



alguno de R² y R³ representa un átomo de halógeno y el otro de R² y R³ representa un átomo de hidrógeno;

R⁴ representa un grupo



X representa un átomo de oxígeno o azufre o un grupo >N-R⁸;
n es 0 o 1;

R⁵ representa un grupo alquiloC₂-C₃ opcionalmente sustituido por al menos un grupo hidroxilo;

R⁶ y R⁷ cada uno independientemente representa un átomo de hidrógeno, alquiloC₁-C₅ opcionalmente sustituido por uno o dos grupos hidroxilo;

R⁸ representa un átomo de hidrógeno o un grupo alquilo C₂ opcionalmente sustituido por al menos un grupo hidroxilo.

11. Un compuesto seleccionado de cualquiera de:

N-(1-adamantilmetil)-5-cloro-2-{3-[(3-hidroxiopropil)-amino]propil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(3-hidroxiopropil)-amino]propil}isonicotinamida;

N-(1-adamantilmetil)-2-cloro-5-{3-[(3-hidroxiopropil)-amino]propil}nicotinamida;

N-(1-adamantilmetil)-2-cloro-5-(3-{[(1*S*)-2-hidroxi-1-metiletil]-amino}propil)nicotinamida;

N-(1-adamantilmetil)-2-cloro-5-(3-{[(1*R*)-2-hidroxi-1-metiletil]-amino}propil)nicotinamida;

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Clorhidrato de *N*-(1-adamantilmetil)-2-(3-aminopropil)-5-cloroisonicotinamida;

Clorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-[3-(etilamino)propil]isonicotinamida;

Clorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-({2-[(3-hidroxipropil)amino]etil}tio)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(1*R*)-2-hidroxi-1-metiletil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(1*S*)-2-hidroxi-1-metiletil]amino}propil)isonicotinamida;

Clorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(2-hidroxi-etil)amino]propil}isonicotinamida;

Clorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{2-[(3-hidroxipropil)amino]etoxi}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-({2-[(2-hidroxi-etil)amino]etil}-amino)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-[3-(isopropilamino)propil]isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(2*S*)-2-hidroxipropil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(2*R*)-2,3-dihidroxipropil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(2*S*)-2,3-dihidroxipropil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(4-metilciclohexil)amino]propil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(2-hidroxi-2-metilpropil)amino]propil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(1*R*)-1-(hidroximetil)-2-metilpropil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[2-(metilamino)etil]amino}propil)isonicotinamida;

Bis(trifluoroacetato) de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(3-(metilamino)propil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-[3-({2-[(2-hidroxi-etil)amino]etil}amino)propil]isonicotinamida;

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Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[2-(dietilamino)etil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[2-hidroxi-1-(hidroximetil)etil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(2-hidroxietil)(metil)amino]propil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(3-hidroxi-2,2-dimetilpropil)amino]propil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-(3-{[(2R)-2-hidroxipropil]amino}propil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-({[3-(metilamino)propil]amino}metil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-({[2-[(2-hidroxietil)amino]etil]amino}metil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-({[2-(metilamino)etil]amino}metil)isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(2-hidroxietil)amino]etil}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-{3-[(3-hidroxipropil)amino]etil}isonicotinamida;

Clorhidrato de *N*-(1-adamantilmetil)-5-cloro-2-[3-(metilamino)propil]isonicotinamida;

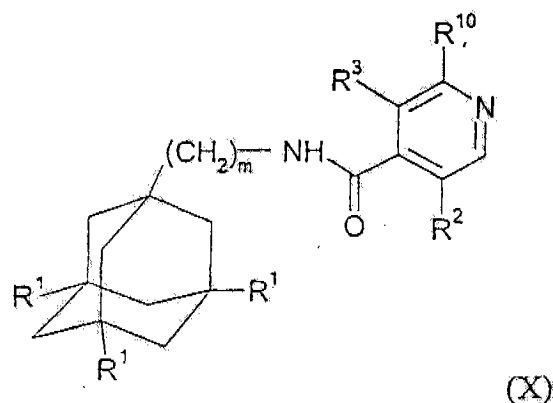
N-(1-adamantilmetil)-5-bromo-2-{[(2S)-2-hidroxi-3-(metilamino)propil]oxi}isonicotinamida;

Diclorhidrato de *N*-(1-adamantilmetil)-2-({3-[bis(3-hidroxipropil)amino]propil}amino)-3-cloroisonicotinamida;

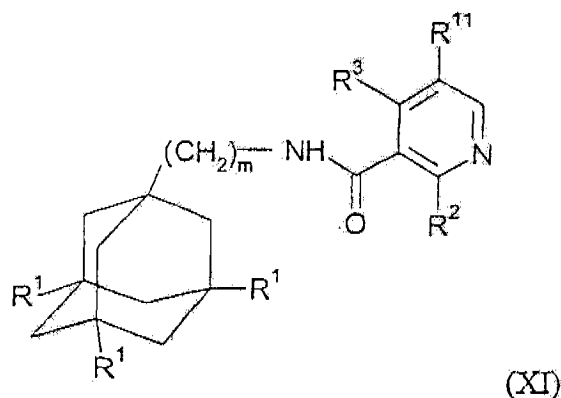
Y todas las sales y solvatos farmacéuticamente aceptables de cualquiera de estos.

12. Un proceso para la preparación de un compuesto según la reivindicación 1, que comprende:

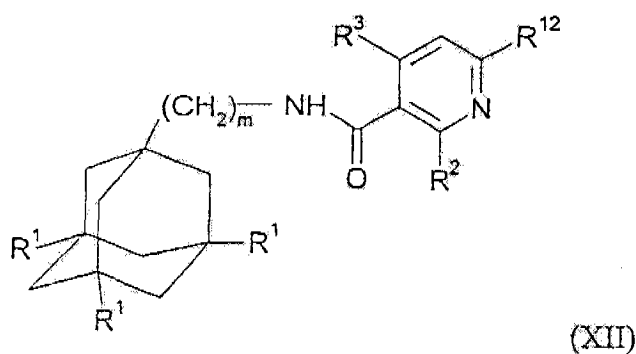
(i) cuando *n* es 0 y R^5 representa CH_2 , reaccionando con u compuesto de formula

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donde R^{10} representa $-C(O)H$ o $-CH_2L^1$, L^1 representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), o un compuesto de formula



donde R^{11} representa $-C(O)H$ o $-CH_2L^2$. L^2 representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), o un compuesto de formula



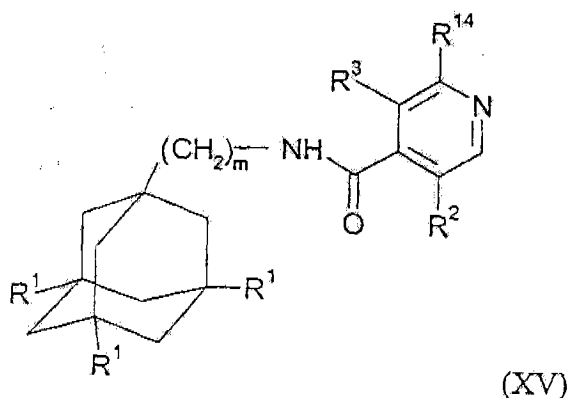
donde R^{12} representa $-C(O)H$ o $-CH_2L^3$. L^3 representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), con un compuesto de formula (XIII), HNR^6R^7 , en donde R^6 y R^7 son como se definió en la formula (I), bajo condiciones de aminación reductiva cuando R^{10} , R^{11} o R^{12} representa $-C(O)H$ o en presencia de una base adecuada cuando R^{10} , R^{11} o R^{12} representa $-CH_2L^1$, $-CH_2L^2$, o $-CH_2L^3$; o

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(ii) cuando n es 0, R^5 es $(CH_2)_2$ y R^6 y R^7 son ambos hidrógeno, reaccionando con un compuesto de formula (X) como se definió en (i) anterior, en el cual R^{10} representa $-CH_2L^1$, o un compuesto de formula (XI) como se definió en (i) anterior, en el cual R^{11} representa $-CH_2L^2$, o un compuesto de formula (XII) como se definió en (i) anterior, en el cual R^{12} representa $-CH_2L^3$, con un cianuro de metal alcalino, seguido por una reacción de hidrogenación; o

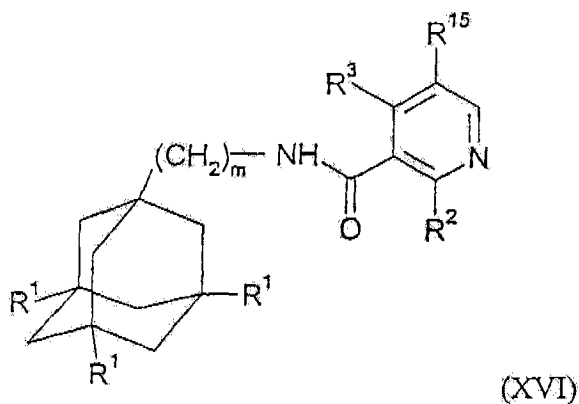
(iii) cuando n es 0, R^5 es $(CH_2)_2$ y al menos uno de R^6 y R^7 es diferente de hidrógeno, reaccionando con un compuesto como se preparó en (ii) anterior, con al menos un compuesto de formula (XIV), $R^{13}C(O)H$, donde R^{13} representa un grupo alquilo C_1-C_6 o cicloalquilo C_3-C_8 , opcionalmente sustituido como se definió para R^6 y R^7 en la formula (I), a condiciones de aminación reductiva; o

(iv) cuando n es 0 y R^5 representa un grupo alquilo C_3-C_5 opcionalmente sustituido como se definió en la formula (I), reaccionando con un compuesto de formula



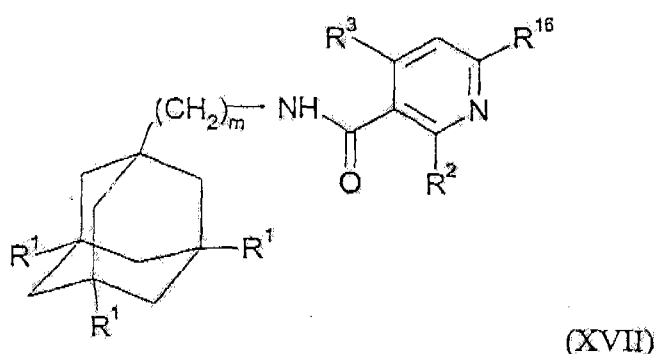
donde R^{14} representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), o

un compuesto de formula



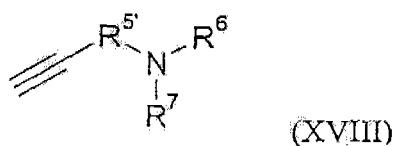
donde R^{15} representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), o

un compuesto de formula



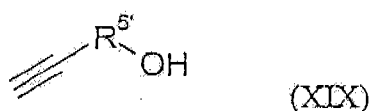
donde R^{16} representa un grupo saliente y m , R^1 , R^2 y R^3 son como se definió en la formula (I), o

un compuesto de formula



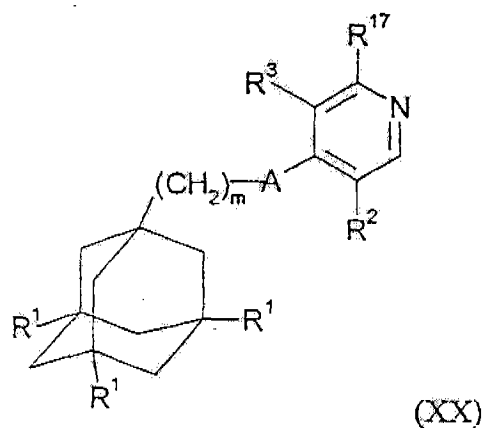
donde R^5 representa un grupo alquilo C_1-C_3 opcionalmente sustituido como se definió para R^5 en la formula (I), y R^6 y R^7 son como se definieron en la formula (I), seguido por una reacción de hidrogenación; o

(v) cuando n es 0 y R^5 representa un grupo alquilo C_3-C_5 opcionalmente sustituido como se definió en la formula (I), reaccionando con un compuesto de formula (XV), (XVI) o (XVII) como se definió en (iv) anterior, con un compuesto de formula

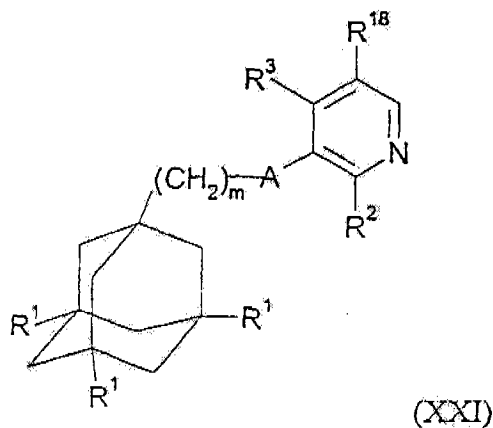


donde R^5 es como se definió en la formula (XVIII) en (iv) anterior, seguido por una reacción de hidrogenación y luego una reacción de oxidación y luego mediante reacción con un compuesto de formula (XIII) como se definió en (i) anterior a condiciones de aminación reductiva; o

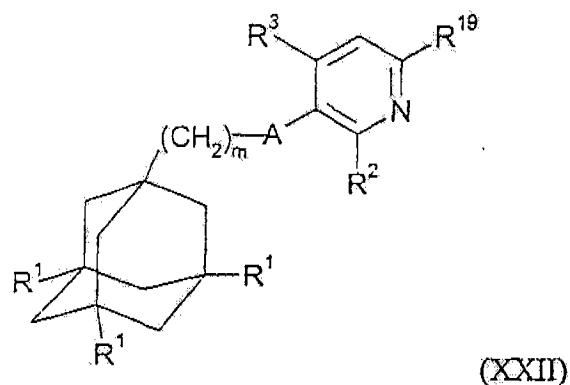
(vi) cuando n es 1 y X es oxígeno o $>N-R^8$, reaccionando con un compuesto de formula



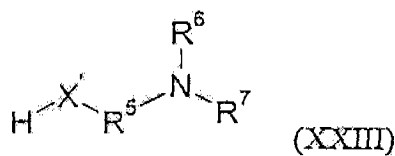
donde R^{17} representa un grupo saliente y m , A , R^1 , R^2 y R^3 son como se definió en la formula (I), o
un compuesto de formula



donde R^{18} representa un grupo saliente y m , A , R^1 , R^2 y R^3 son como se definió en la formula (I), o
un compuesto de formula

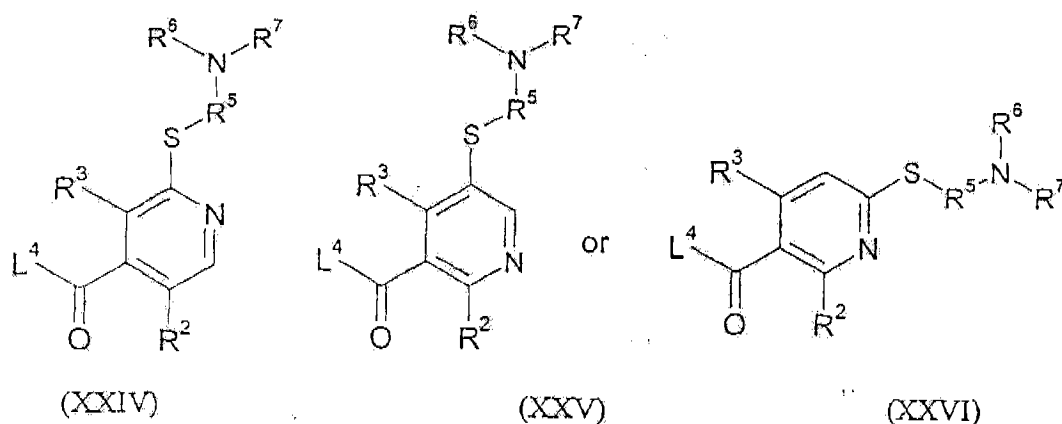


donde R^{19} representa un grupo saliente y m , A , R^1 , R^2 y R^3 son como se definió en la formula (I), con un compuesto de formula

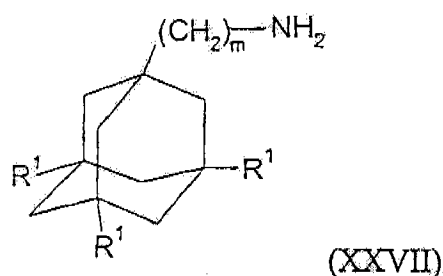


donde X' representa oxígeno o $>N-R^8$ y R^5 , R^6 , R^7 y R^8 son como se definieron en la formula (I), o

(vii) cuando A es $NHC(O)$, n es 1 y X es azufre, reaccionando con un compuesto de formula

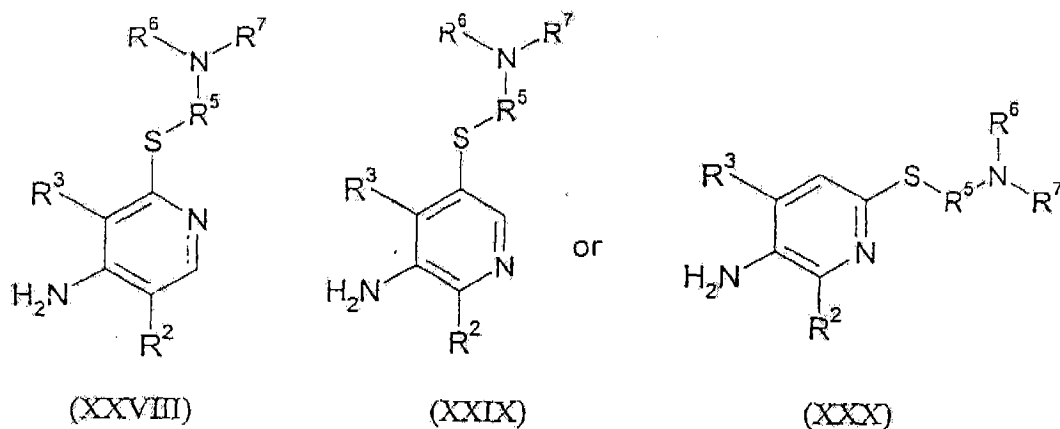


donde, en cada formula (XXIV), (XXV) y (XXVI), L^4 representa un grupo saliente y R^2 , R^3 , R^5 , R^6 y R^7 son como se definieron en la formula (I), con un compuesto de formula

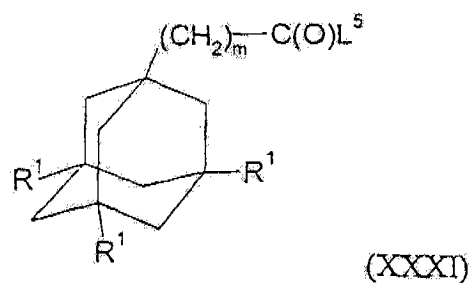


donde m y R^1 son como se definieron en la formula (I); o

(viii) cuando A es $C(O)NH$, n es 1 y X es azufre, reaccionando con un compuesto de formula

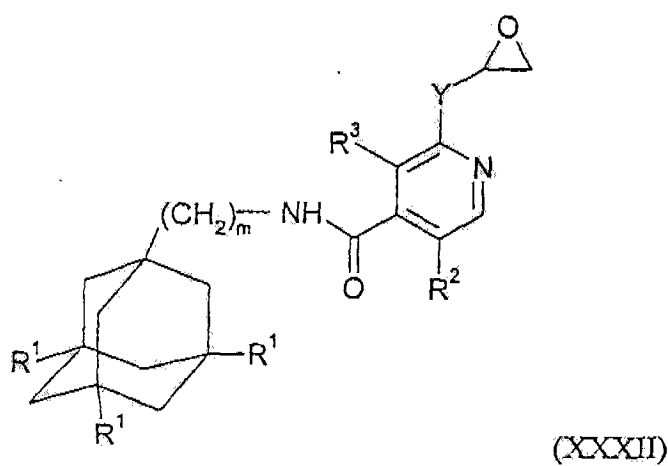


donde, en cada formula (XXVIII), (XXIX) y (XXX), R^2 , R^3 , R^5 , R^6 y R^7 son como se definieron en la formula (I), con un compuesto de formula

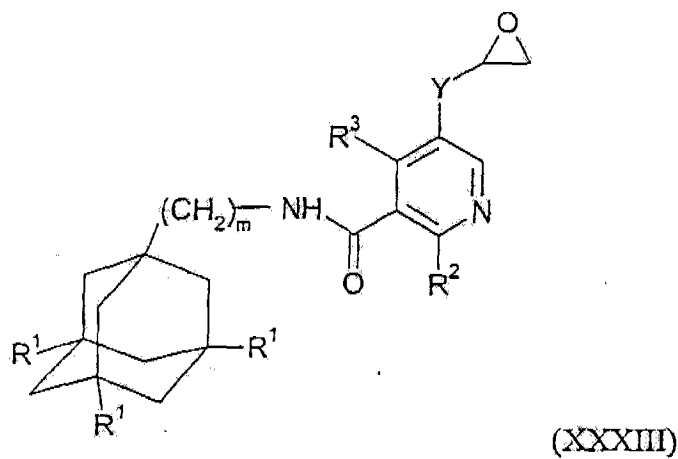


donde L^5 representa un grupo saliente y m y R^1 son como se definieron en la formula (I); o

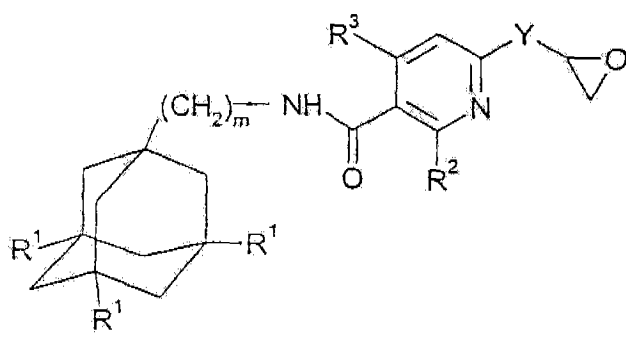
(ix) cuando n es 0 y R^5 representa un grupo alquilo C_2-C_5 sustituido como se definió en la formula (I), reaccionando con un compuesto de formula



o un compuesto de formula

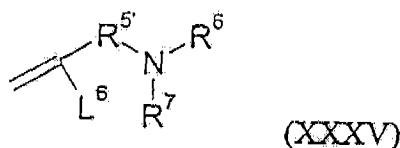


o un compuesto de formula



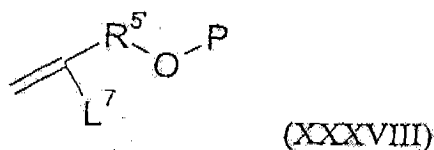
donde, en cada formula (XXXII), (XXXIII) y (XXXIV), Y representa un enlace o un alquiloC₁-C₃ y m, R¹, R² y R³ son como se definieron en la formula (I), con un compuesto de formula (XIII) como se definió en (i) anterior, y opcionalmente posteriormente reaccionando con un agente alquilante C₁-C₆ o con un agente halogenante; o

(x) cuando n es 0 y R⁵ representa un grupo alquiloC₃-C₅ opcionalmente sustituido como se definió en la formula (I), reaccionando con un compuesto de formula (XV), (XVI) o (XVII) como se definió en (iv) anterior, con un compuesto pre-tratado de formula



en el cual L⁶ representa un átomo de hidrógeno y R⁵ representa un grupo alquiloC₁-C₃ opcionalmente sustituido como se definió para R⁵ en la formula (I) y R⁶ y R⁷ son como se definieron en la formula (I), en donde el compuesto de formula (XXXV) está pre-tratado con un agente hidroborante; o

(xi) cuando n es 0 y R⁵ representa un grupo alquiloC₃-C₅ opcionalmente sustituido como se definió en la formula (I), reaccionando con un compuesto de formula (XV), (XVI) o (XVII) como se definió en (iv) anterior en presencia de un catalizador adecuado como el tetrakis(trifenilfosfina)paladio, con un compuesto pre-tratado de formula

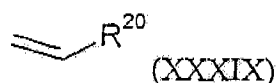


en el cual L⁷ representa un átomo de hidrógeno y R⁵ representa un grupo alquiloC₁-C₃ opcionalmente sustituido como se definió para R⁵ en la formula (I) y P es un grupo protector adecuado, en donde el compuesto de formula

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(XXXVIII) está pre-tratado con un agente hidroborante, seguido por la remoción del grupo protector P, en una reacción de desprotección, luego mediante una reacción de oxidación y luego por una reacción con un compuesto de formula (XIII) como se definió en (i) anterior a condiciones de aminación reductiva; o

(xii) cuando n es 0 y R^5 es $(CH_2)_2$, reaccionando con un compuesto de formula (XV), (XVI) o (XVII) como se definió en (iv) anterior, con un compuesto de formula



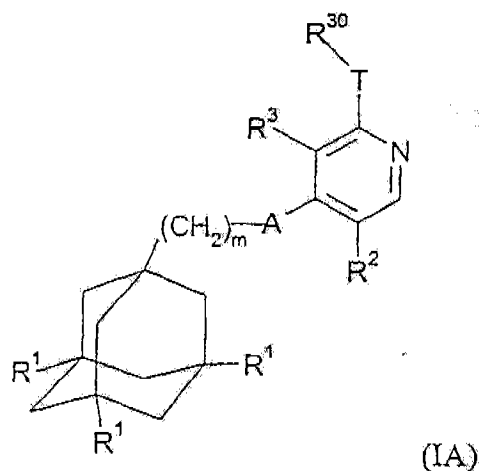
en donde R^{20} representa un grupo saliente adecuado tal como trialquilestaño, dialquilboro o zinc, en presencia de un catalizador adecuado, seguido de la reacción con un compuesto de formula (XVIII) como se definió en (i) anterior; o

(xiii) cuando n es 0 y R^5 es CH_2 , reaccionando con un compuesto de formula (XV), (XVI) o (XVII) como se definió en (iv) anterior, con un compuesto de formula (XXXIX) como se definió en (xii) anterior, seguido por una reacción de oxidación y luego la reacción con un compuesto de formula (XVIII) como se definió en (i) anterior a condiciones de aminación reductiva;

y opcionalmente después de (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii) o (xiii), realizando uno o más de los siguientes:

- Conversión del compuesto obtenido a un compuesto adicional de formula (I).
- Formación de una sal o solvato farmacéuticamente aceptable del compuesto.

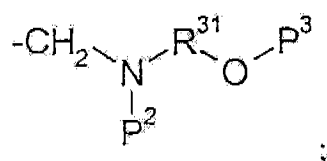
13. Un compuesto intermediario de formula



209 209

en donde T representa $-\text{C}\equiv\text{C}-$ o $-\text{CH}_2\text{CH}_2-$;

R^{30} representa $-\text{CHO}$, $-\text{CH}_2\text{OP}^1$ o un grupo de formula



P^1 representa un átomo de hidrógeno o un grupo protector adecuado;

P^2 representa un grupo protector adecuado;

P^3 representa un grupo protector adecuado;

R^{31} representa un grupo alquilo C_1-C_5 ; y

M, A, R^1 , R^2 y R^3 son como se definió en cualquiera de las reivindicaciones 1 a 10.

14. Un compuesto intermediario según la reivindicación 13, en donde:

m representa 1;

A representa $\text{NHC}(\text{O})$;

Cada R^1 representa un átomo de hidrógeno;

R^2 representa un átomo de halógeno; y

R^3 representa un átomo de hidrógeno.

15. Una composición farmacéutica que comprende un compuesto de formula (I) o una sal o solvato de este farmacéuticamente aceptable, como se reivindicó en cualquiera de las reivindicaciones 1 a 11, en asociación con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

16. Un proceso para la preparación de una composición farmacéutica como se reivindicó en la reivindicación 15 que comprende la mezcla de un compuesto de formula (I) o una sal o solvato de este farmacéuticamente aceptable, como se definió en cualquiera de las reivindicaciones 1 a 11, con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

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(54) **N-ADAMANTYLMETHYL DERIVATES AND INTERMEDIATES AS PHARMACEUTICAL COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION**

N-ADAMANTYLMETHYL-DERIVATE UND ZWISCHENPRODUKTE ALS PHARMAZEUTISCHE ZUSAMMENSETZUNGEN UND VERFAHREN ZU IHRER HERSTELLUNG

DERIVES DE N-ADAMANTYLMETHYLE ET INTERMEDIAIRES UTILISES DANS DES COMPOSITIONS PHARMACEUTIQUES ET LEURS PROCEDES DE PREPARATION

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US-A- 3 471 491 US-A- 4 751 292

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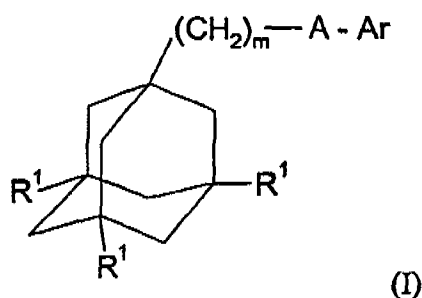
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P2X₇ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

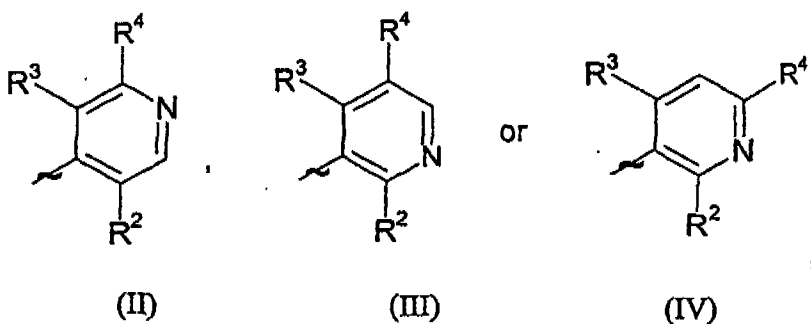
[0178] In this manner, each of the title compounds of the Examples was tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5 x 10⁶ cells/ml) containing 10⁻⁴M ethidium bromide, 25 µl of a high potassium buffer solution containing 10⁻⁵M bbATP, and 25 µl of the high potassium buffer solution containing 3 x 10⁻⁵M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of the Examples demonstrated antagonist activity, having a pIC₅₀ figure > 4.50. For example, the compounds of Example 12 and Example 26 had pIC₅₀ values of 7.1 and 7.8 respectively.

Claims

1. A compound of formula

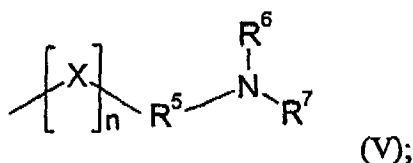


wherein m represents 1, 2 or 3;
each R¹ independently represents a hydrogen or halogen atom;
A represents C(O)NH or NHC(O);
Ar represents a group



one of R² and R³ represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C₁-C₆ alkyl optionally substituted by at least one halogen atom, (ii) C₃-C₈ cycloalkyl, (iii) C₁-C₆ alkoxy optionally substituted by at least one halogen atom, and (iv) C₃-C₈ cycloalkyloxy, and the other of R² and R³ represents a hydrogen or halogen atom; R⁴ represents a group

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X represents an oxygen or sulphur atom or a group $>\text{N}-\text{R}^8$;

n is 0 or 1;

R^5 represents a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

R^6 and R^7 each independently represent a hydrogen atom, C_1 - C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1 - C_6 alkoxy, and (di)- C_1 - C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3 - C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy); and

R^8 represents a hydrogen atom or a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

with the provisos that:

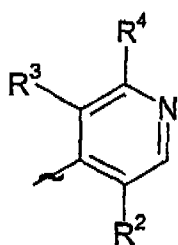
(a) when n is 0, then A is $\text{NHC}(\text{O})$, and

(b) when n is 1, X represents oxygen and A is $\text{C}(\text{O})\text{NH}$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1 - C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1 - C_6 alkyl; and

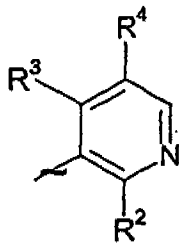
(c) when n is 1, X is oxygen, sulphur or $>\text{NH}$ and A is $\text{NHC}(\text{O})$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1 - C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1 - C_6 alkyl or $-\text{CH}_2\text{CH}_2\text{OH}$;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of formula (I) according to claim 1, wherein
 m represents 1, 2 or 3;
 each R^1 independently represents a hydrogen or halogen atom;
 A represents $\text{C}(\text{O})\text{NH}$ or $\text{NHC}(\text{O})$;
 Ar represents a group

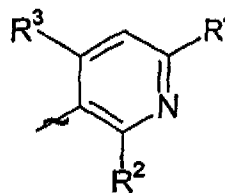


(II)



(III)

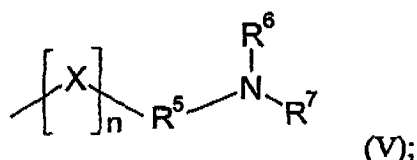
or



(IV)

one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1 - C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3 - C_8 cycloalkyl, (iii) C_1 - C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3 - C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;
 R^4 represents a group

2/3
2/3



X represents an oxygen or sulphur atom or a group >N-R⁸;

n is 0 or 1;

R⁵ represents a C₁-C₅ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy; and

R⁶, R⁷ and R⁸ each independently represent a hydrogen atom or a C₁-C₅ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

with the provisos that:

(d) when n is 0, then A is NHC(O), and

(e) when n is 1, X represents oxygen and A is C(O)NH, then R⁶ and R⁷ do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₅ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₅ alkyl, and

(f) when n is 1, X is oxygen, sulphur or >NH and A is NHC(O), then R⁶ and R⁷ do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₅ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₅ alkyl or -CH₂CH₂OH;

or a pharmaceutically acceptable salt or solvate thereof.

3. A compound according to claim 1 or claim 2, wherein m is 1.

4. A compound according to any one of claims 1 to 3, wherein A represents NHC(O).

5. A compound according to any one of claims 1 to 4, wherein Ar represents a group of formula (II) or (III).

6. A compound according to claim 5, wherein Ar represents a group of formula (II).

7. A compound according to any one of claims 1 to 6, wherein one of R² and R³ represents a halogen atom and the other of R² and R³ represents a hydrogen atom.

8. A compound according to any one of claims 1 to 7, wherein n is 0.

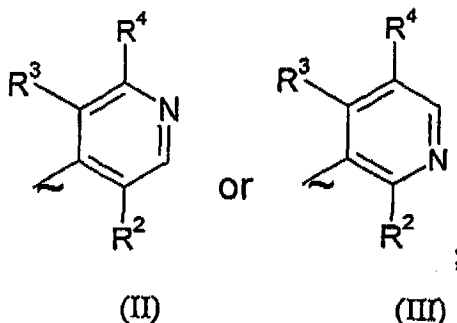
9. A compound according to claim 1, wherein

m represents 1;

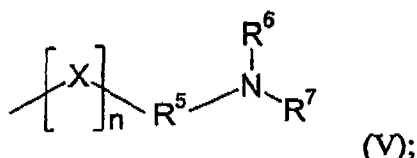
each R¹ represents a hydrogen atom;

A represents NHC(O);

Ar represents a group



one of R² and R³ represents a halogen atom, and the other of R² and R³ represents a hydrogen atom; R⁴ represents a group



X represents an oxygen or sulphur atom or a group >N-R⁸;

n is 0 or 1;

R⁵ represents a C₁-C₃ alkyl group optionally substituted by at least one hydroxyl group;

R⁶ and R⁷ each independently represent a hydrogen atom, C₁-C₅ alkyl (optionally substituted by one or two substituents independently selected from hydroxyl and (di)-C₁-C₂ alkylamino (itself optionally substituted by at least one hydroxyl group)), or C₆ cycloalkyl (substituted by at least one hydroxyl group);

R⁸ represents a hydrogen atom or a C₂ alkyl group substituted by at least one hydroxyl group.

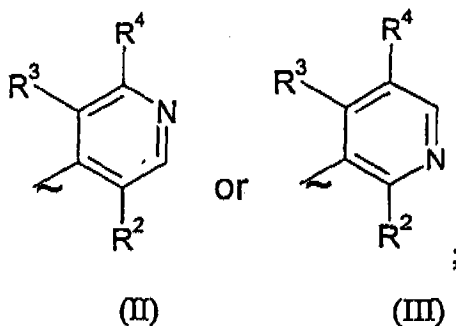
10. A compound according to claim 1 or claim 2, wherein

m represents 1;

each R¹ represents a hydrogen atom;

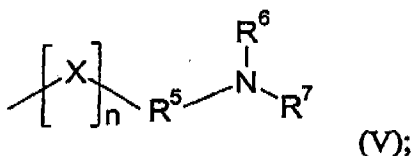
A represents NHC(O);

Ar represents a group



one of R² and R³ represents a halogen atom, and the other of R² and R³ represents a hydrogen atom;

R⁴ represents a group



X represents an oxygen or sulphur atom or a group >N-R⁸;

n is 0 or 1;

R⁵ represents a C₂-C₃ alkyl group optionally substituted by at least one hydroxyl group;

R⁶ and R⁷ each independently represent a hydrogen atom or a C₁-C₅ alkyl group optionally substituted by one or two hydroxyl groups;

R⁸ represents a hydrogen atom or a C₂ alkyl group substituted by at least one hydroxyl group.

11. A compound according to claim 1 being selected from any one of:

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)-amino]propyl}isonicotinamide,

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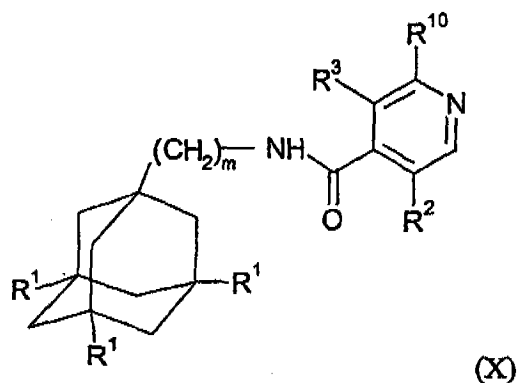
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N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-2-chloro-5-{3-[(3-hydroxypropyl)amino]propyl}nicotinamide,
N-(1-Adamantylmethyl)-2-chloro-5-{3-[(1*S*)-2-hydroxy-1-methylethyl]amino}propyl}nicotinamide,
N-(1-Adamantylmethyl)-2-chloro-5-{3-[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl}nicotinamide,
N-(1-Adamantylmethyl)-2-(3-aminopropyl)-5-chloroisonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-(ethylamino)propyl}isonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-[(3-hydroxypropyl)amino]ethylthio}isonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(1*S*)-2-hydroxy-1-methylethyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{2-[(3-hydroxypropyl)amino]ethoxy}isonicotinamide, hydrochloride
N-(1-Adamantylmethyl)-5-chloro-2-[(2-hydroxyethyl)amino]ethyl}amino}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-(isopropylamino)propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2*S*)-2-hydroxypropyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2*R*)-2,3-dihydroxypropyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2*S*)-2,3-dihydroxypropyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(4-methylcyclohexyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxy-2-methylpropyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(1*R*)-1-(hydroxymethyl)-2-methylpropyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-(methylamino)ethyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-(methylamino)propyl]amino}propyl}isonicotinamide bis(trifluoroacetate),
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]ethyl}amino}propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-(diethylamino)ethyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxy-1-(hydroxymethyl)ethyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)(methyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]propyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2*R*)-2-hydroxypropyl]amino}propyl}isonicotinamide, dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-[(3-(methylamino)propyl]amino)methyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-[(2-hydroxyethyl)amino]ethyl}amino)methyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-[(2-(methylamino)ethyl)amino]methyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]ethyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]ethyl}isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-bromo-2-[(2*S*)-2-hydroxy-3-(methylamino)propyl]oxy}isonicotinamide,
N-(1-Adamantylmethyl)-2-[(3-bis(3-hydroxypropyl)amino)propyl]amino)-3-chloroisonicotinamide dihydrochloride,

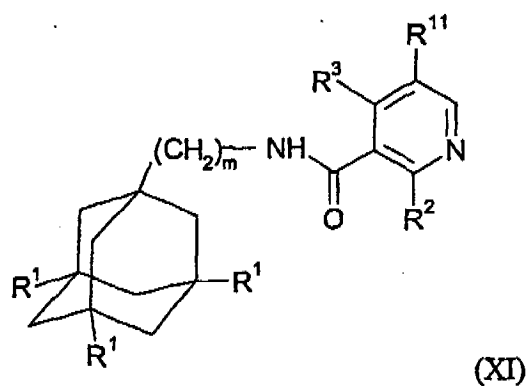
and all pharmaceutically acceptable salts and solvates thereof.

12. A process for the preparation of a compound according to claim 1, which comprises:

(i) when *n* is 0 and *R*⁵ represents CH₂, reacting a compound of formula

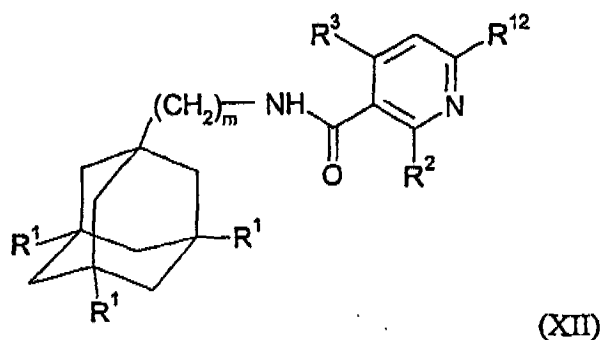


15 wherein R¹⁰ represents -C(O)H or -CH₂L¹, L¹ represents a leaving group and m, R¹, R² and R³ are as defined in formula (I), or a compound of formula



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35 wherein R¹¹ represents -C(O)H or -CH₂L², L² represents a leaving group and m, R¹, R² and R³ are as defined in formula (I), or a compound of formula

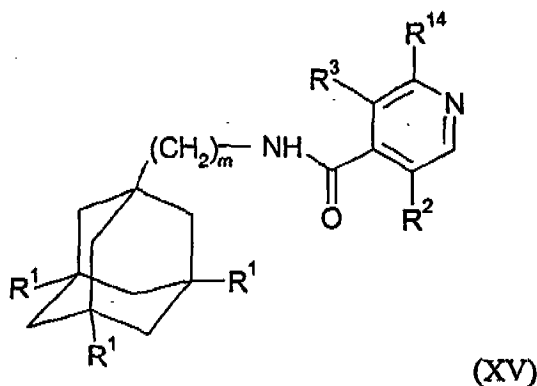


50 wherein R¹² represents -C(O)H or -CH₂L³, L³ represents a leaving group and m, R¹, R² and R³ are as defined in formula (I),

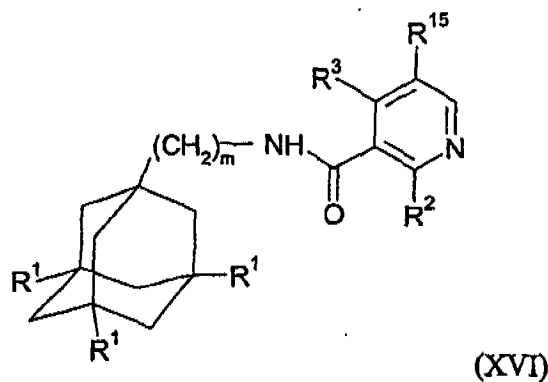
55 with a compound of formula (XIII), HNR⁶R⁷, wherein R⁶ and R⁷ are as defined in formula (I), under reductive amination conditions when R¹⁰, R¹¹ or R¹² represents -C(O)H or in the presence of a suitable base when R¹⁰, R¹¹ or R¹² represents -CH₂L¹, -CH₂L² or -CH₂L³; or

(ii) when n is 0, R⁵ is (CH₂)₂ and R⁶ and R⁷ are both hydrogen, reacting a compound of formula (X) as defined in (i) above in which R¹⁰ represents -CH₂L¹, or a compound of formula (XI) as defined in (i) above in which R¹¹

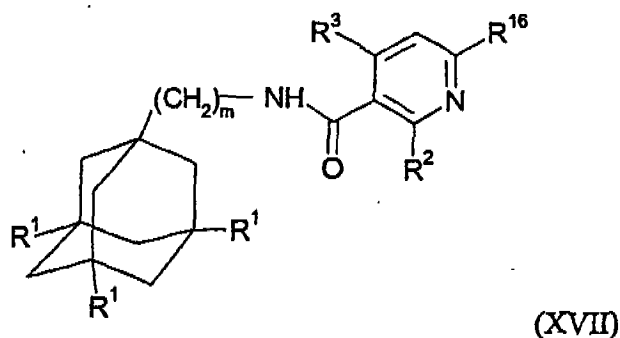
represents $-\text{CH}_2\text{L}^2$, or a compound of formula (XII) as defined in (i) above in which R^{12} represents $-\text{CH}_2\text{L}^3$, with an alkali metal cyanide, followed by a hydrogenation reaction; or
 (iii) when n is 0, R^5 is $(\text{CH}_2)_2$ and at least one of R^6 and R^7 is other than hydrogen, reacting a compound as prepared in (ii) above with at least one compound of formula (XIV), $\text{R}^{13}\text{C}(\text{O})\text{H}$, wherein R^{13} represents an optionally substituted $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_8$ cycloalkyl group as defined for R^6 and R^7 in formula (I), under reductive amination conditions; or
 (iv) when n is 0 and R^5 represents a $\text{C}_3\text{-C}_5$ alkyl group optionally substituted as defined in formula (I), reacting a compound of formula



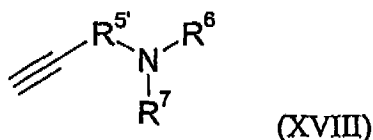
wherein R^{14} represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula



wherein R^{15} represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

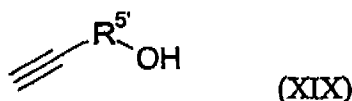


wherein R^{16} represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula



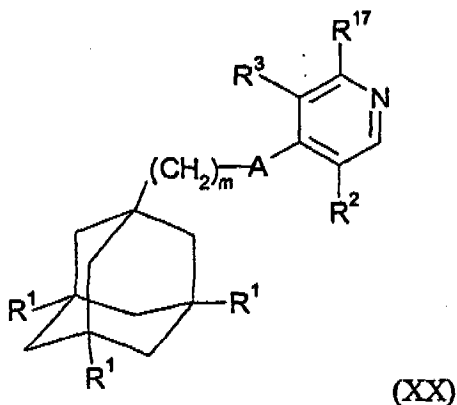
wherein $R^{5'}$ represents a C_1 - C_3 alkyl group optionally substituted as defined for R^5 in formula (I) and R^6 and R^7 are as defined in formula (I), followed by a hydrogenation reaction; or

(v) when n is 0 and R^5 represents a C_3 - C_5 alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above, with a compound of formula

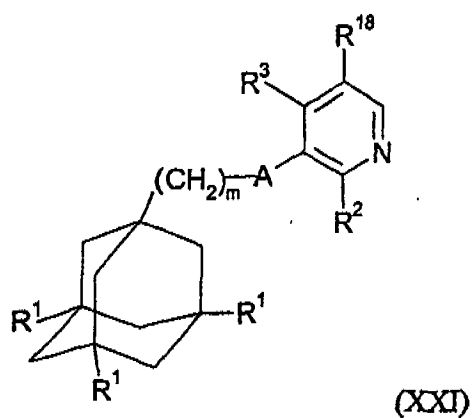


wherein $R^{5'}$ is as defined in formula (XVIII) in (iv) above, followed by a hydrogenation reaction and then an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions; or

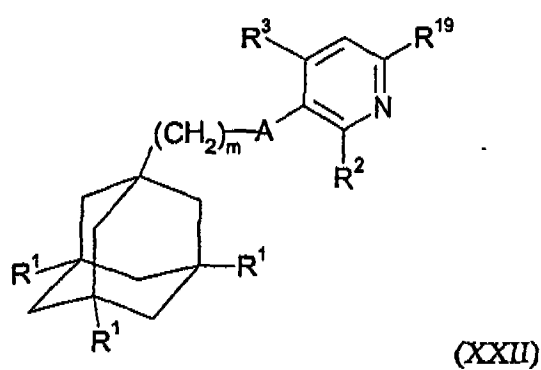
(vi) when n is 1 and X is oxygen or $>\text{N}-\text{R}^8$, reacting a compound of formula



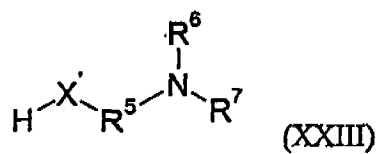
wherein R^{17} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula



wherein R^{18} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

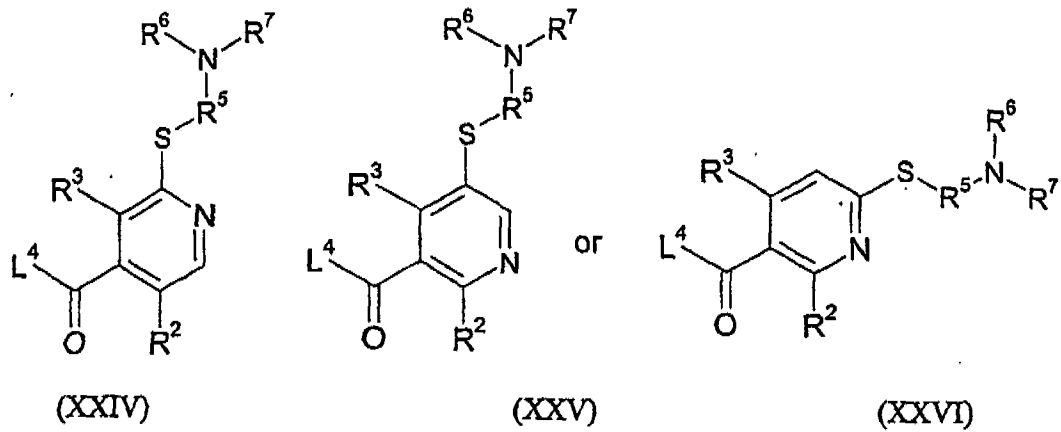


wherein R^{19} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula

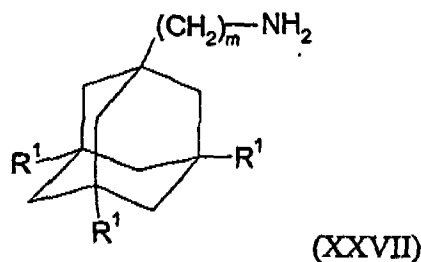


wherein X' represents oxygen or $>N-R^8$ and R^5 , R^6 , R^7 and R^8 are as defined in formula (I); or (vii) when A is $NHC(O)$, n is 1 and X is sulphur, reacting a compound of formula

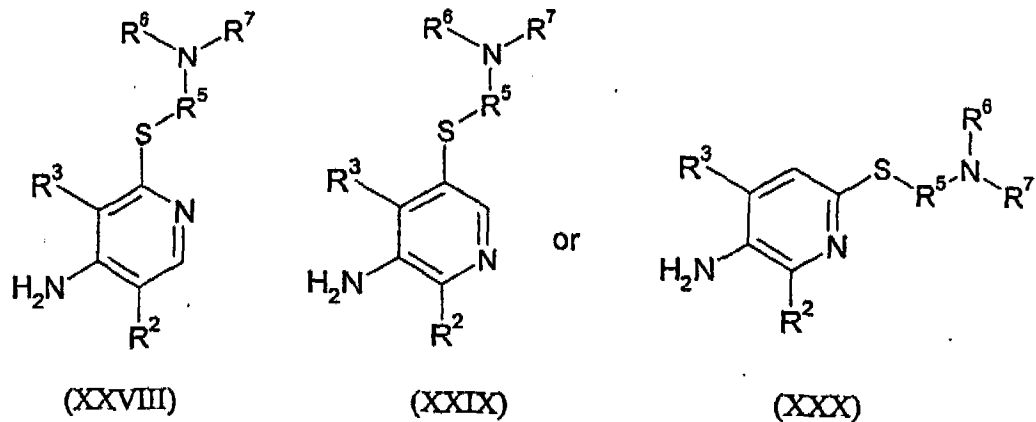
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260



wherein, in each of formulae (XXIV), (XXV) and (XXVI), L^4 represents a leaving group and R^2 , R^3 , R^5 , R^6 and R^7 are as defined in formula (I), with a compound of formula

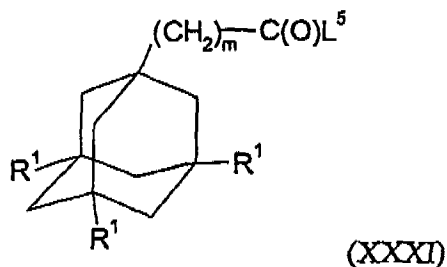


wherein m and R^1 are as defined in formula (I); or (viii) when A is $C(O)NH$, n is 1 and X is sulphur, reacting a compound of formula

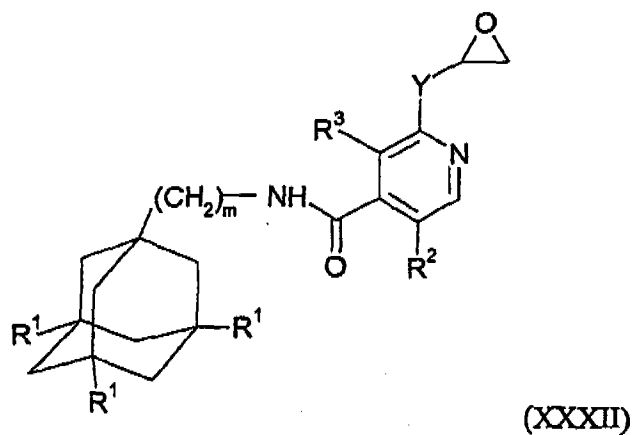


wherein, in each of formulae (XXVIII), (XXIX) and (XXX), R^2 , R^3 , R^5 , R^6 and R^7 are as defined in formula (I), with a compound of formula

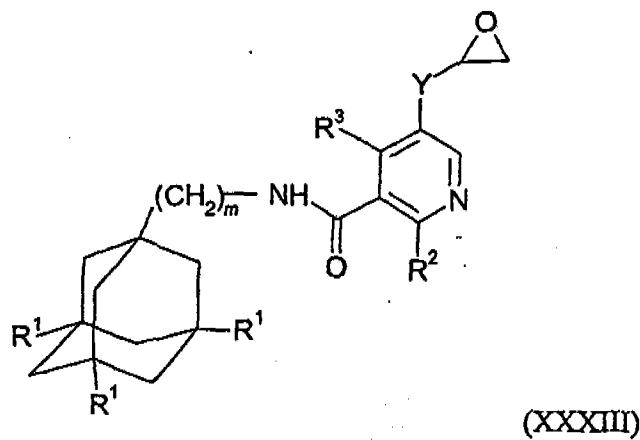
24.1



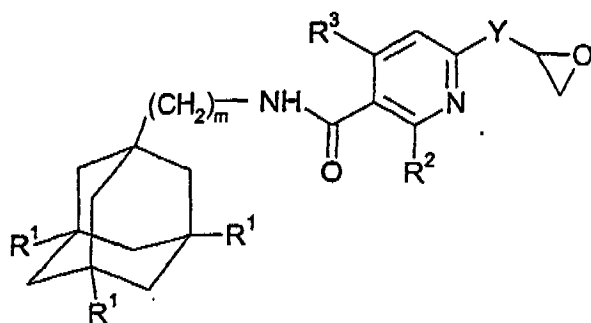
wherein L^5 represents a leaving group and m and R^1 are as defined in formula (I); or
(ix) when n is 0 and R^5 represents a C_2 - C_5 alkyl group substituted as defined in formula (I), reacting a compound of formula



or a compound of formula

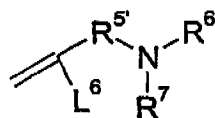


or a compound of formula



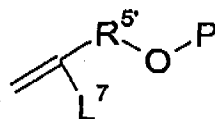
(XXXIV)

wherein, in each of formulae (XXXII), (XXXIII) and (XXXIV), Y represents a bond or a C₁-C₃ alkyl and m, R¹, R² and R³ are as defined in formula (I), with a compound of formula (XIII) as defined in (i) above, and optionally thereafter reacting with a C₁-C₆ alkylating agent or with a halogenating agent; or
(x) when n is 0 and R⁵ represents a C₃-C₅ alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above, with a pre-treated compound of formula



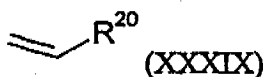
(XXXV)

in which L⁶ represents a hydrogen atom and R^{5'} represents a C₁-C₃ alkyl group optionally substituted as defined for R⁵ in formula (I) and R⁶ and R⁷ are as defined in formula (I), wherein the compound of formula (XXXV) is pre-treated with a hydroborating agent; or
(xi) when n is 0 and R⁵ represents a C₃-C₅ alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above in the presence of a suitable catalyst, with a pre-treated compound of formula



(XXXVIII)

in which L⁷ represents a hydrogen atom and R^{5'} represents a C₁-C₃ alkyl group optionally substituted as defined for R⁵ in formula (I) and P is a suitable protecting group, wherein the compound of formula (XXXVIII) is pre-treated with a hydroborating agent, followed by removal of the protecting group, P, in a deprotection reaction, then by an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions; or
(xii) when n is 0 and R⁵ is (CH₂)₂, reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above with a compound of formula



(XXXIX)

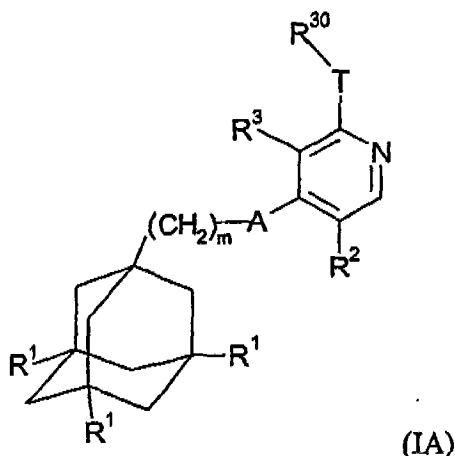
wherein R²⁰ represents a suitable leaving group, in the presence of a suitable catalyst, followed by reaction with a compound of formula (XIII) as defined in (i) above; or
(xiii) when n is 0 and R⁵ is CH₂, reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above

with a compound of formula (XXXIX) as defined in (xii) above, followed by an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions;

and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii) or (xiii) carrying out one or more of the following:

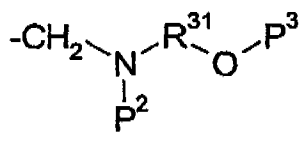
- converting the compound obtained to a further compound according to claim 1
- forming a pharmaceutically acceptable salt or solvate of the compound.

13. An intermediate compound of formula



wherein T represents $\text{—C}\equiv\text{C—}$ or $\text{—CH}_2\text{CH}_2\text{—}$;

R^{30} represents —CHO , $\text{—CH}_2\text{OP}^1$ or a group of formula



P^1 represents a hydrogen atom or a suitable protecting group;

P^2 represents a suitable protecting group;

P^3 represents a suitable protecting group;

R^{31} represents a $\text{C}_1\text{—C}_5$ alkyl group; and

m , A , R^1 , R^2 and R^3 are as defined in any one of claims 1 to 10.

14. An intermediate compound according to claim 13, wherein:

m represents 1;

A represents NHC(O) ;

each R^1 represents a hydrogen atom;

R^2 represents a halogen atom; and

R^3 represents a hydrogen atom.

15. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

16. A process for the preparation of a pharmaceutical composition as claimed in claim 15 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1

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to 11 with a pharmaceutically acceptable adjuvant, diluent or carrier.

17. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 for use in therapy.

18. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

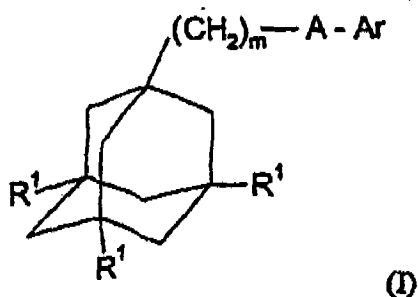
19. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

20. Use according to claim 19, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

21. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment of osteoarthritis.

Patentansprüche

1. Verbindung der Formel

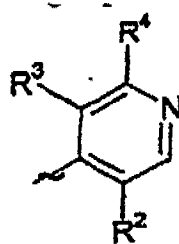


worin m für 1, 2 oder 3 steht;

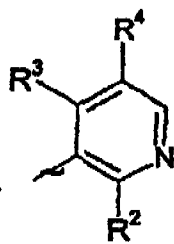
R^1 jeweils unabhängig voneinander für ein Wasserstoff- oder Halogenatom steht;

A für $C(O)NH$ oder $NHC(O)$ steht;

Ar für eine Gruppe

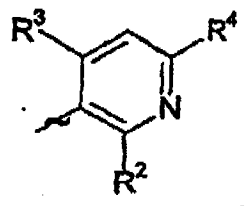


(II)



(III)

oder



(IV)

steht;

einer der Reste R^2 und R^3 für Halogen, Nitro, Amino, Hydroxyl oder eine unter (i) gegebenenfalls durch mindestens ein Halogenatom substituiertes C_1-C_6 -Alkyl, (ii) C_3-C_8 -Cycloalkyl, (iii) gegebenenfalls durch mindestens ein Halogenatom substituiertes C_1-C_6 -Alkoxy und (iv) C_3-C_8 -Cycloalkyloxy ausgewählte Gruppe steht und der andere für



US007129246B2

(12) **United States Patent**
Alcaraz et al.

(10) **Patent No.:** **US 7,129,246 B2**
(45) **Date of Patent:** **Oct. 31, 2006**

(54) **N-ADAMANTILMETHYL DERIVATIVES AND INTERMEDIATES AS PHARMACEUTICAL COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION**

(75) **Inventors:** **Lillian Alcaraz**, Loughborough (GB); **Timothy Johnson**, Loughborough (GB); **Michael Stocks**, Loughborough (GB)

(73) **Assignee:** **AstraZeneca AB**, Sodertalje (SE)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 261 days.

(21) **Appl. No.:** **10/495,711**

(22) **PCT Filed:** **Nov. 12, 2002**

(86) **PCT No.:** **PCT/SE02/02057**

§ 371 (c)(1),
(2), (4) **Date:** **May 14, 2004**

(87) **PCT Pub. No.:** **WO03/041707**

PCT Pub. Date: **May 22, 2003**

(65) **Prior Publication Data**

US 2005/0010052 A1 Jan. 13, 2005

(30) **Foreign Application Priority Data**

Nov. 16, 2001 (SE) 0103836

(51) **Int. Cl.**

A61K 31/435 (2006.01)
A61K 31/44 (2006.01)
C07D 211/72 (2006.01)
C07D 213/72 (2006.01)
C07D 211/70 (2006.01)

(52) **U.S. Cl.** **514/277; 514/352; 514/353; 514/357; 546/296; 546/297; 546/300; 546/301**

(58) **Field of Classification Search** **546/296, 546/297, 300, 301; 514/277, 352, 357**
See application file for complete search history.

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STN International, File REGISTRY, see RN 405068-97-5, 405070-41-9, 405076-22-4, Apr. 14, 2002.

STN International, File REGISTRY, see RN 445032-09-7, Aug. 30, 2002.

STN International, File CHEMCATS, Accession No. 2001:48444, May 14, 2001, NS18552, 2-Quinolincarboxamide, N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl), CAS Registry No. 313688-07-2.

STN International, File REGISTRY, see RN 401622-10-4, Mar. 24, 2002.

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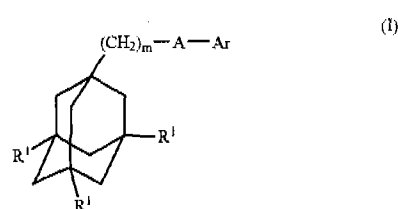
Primary Examiner—James O. Wilson

Assistant Examiner—Binta Robinson

(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

The invention provides compounds of general formula (I) in which m, A, R¹ and Ar have the meanings defined in the specification; a process for, and intermediates used in, their preparation; pharmaceutical compositions containing them; a process for preparing the pharmaceutical compositions; and their use in therapy.



19 Claims, No Drawings

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N-ADAMANTYLMETHYL DERIVATIVES AND INTERMEDIATES AS PHARMACEUTICAL COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

CROSS-REFERENCE TO RELATED APPLICATIONS

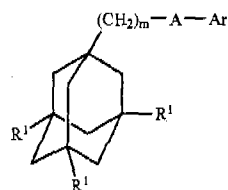
This application is the national phase application under 35 U.S.C. § 371 of PCT International Application No. PCT/SE02/02057, filed Nov. 12, 2002, which claims priority to Swedish Application Serial No. 0103836-3, filed Nov. 16, 2001.

The present invention relates to adamantane derivatives, processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

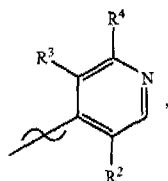
The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X₇ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of formula



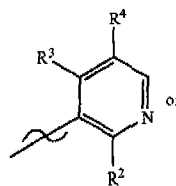
wherein m represents 1, 2 or 3, preferably 1 or 2; each R¹ independently represents a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom, preferably a hydrogen atom; A represents C(O)NH or, preferably, NHC(O); Ar represents a group



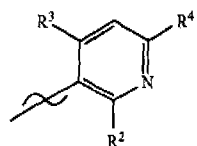
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(III)



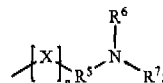
(IV)



one of R² and R³ represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C₁-C₆ alkyl optionally substituted by at least one halogen atom, (ii) C₃-C₈ cycloalkyl, (iii) C₁-C₆ alkoxy optionally substituted by at least one halogen atom, and (iv) C₃-C₈ cycloalkyloxy, and the other of R² and R³ represents a hydrogen or halogen atom;

R⁴ represents a group

(V)



X represents an oxygen or sulphur atom or a group >N-; R⁸; n is 0 or 1;

R⁵ represents a C₁-C₆ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R⁶ and R⁷ each independently represent a hydrogen atom, C₁-C₆ alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C₁-C₆ alkoxy, and (di)-C₁-C₄ alkylamino (itself optionally substituted by at least one hydroxyl group)), or C₃-C₈ cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy); and

R⁸ represents a hydrogen atom or a C₁-C₆ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

with the provisos that:

(a) when n is 0, then A is NHC(O), and

(b) when n is 1, X represents oxygen and A is C(O)NH, then R⁶ and R⁷ do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₆ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₆ alkyl; and

(c) when n is 1, X is oxygen, sulphur or >NH and A is NHIC(O), then R⁶ and R⁷ do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₆ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₆ alkyl or -CH₂CH₂OH;

or a pharmaceutically acceptable salt or solvate thereof.

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(i) tert-Butyl 3-[(4-[(1-adamantylmethyl)amino]carbonyl)-3-chloropyridin-2-yl]amino]propylcarbamate

N-(1-Adamantylmethyl)-2,3-dichloroisonicotinamide (0.4 g) and tert-butyl 3-aminopropylcarbamate (0.4 g) in DMSO (4 ml) were heated in a sealed tube at 160 C for 5 hrs. Ethyl acetate was added and the solution was washed with NaHCO₃ solution, water, KHSO₄ solution and water. The solution was dried and the solvent was evaporated. The resulting oil was subjected to flash chromatography, using ethyl acetate/hexane as eluant, to give the title compound as a colourless oil (0.41 g).

MS (ES+) 477, 479

(ii) N-(1-Adamantylmethyl)-2-[(3-aminopropyl)amino]-3-chloroisonicotinamide dihydrochloride

tert-Butyl 3-[(4-[(1-adamantylmethyl)amino]carbonyl)-3-chloropyridin-2-yl]amino]propylcarbamate (0.41 g) Example 36(i) in methanol (15 ml) was treated with a solution of HCl in 1,4-dioxane (4 ml) and the mixture was stirred at room temperature for 18 hrs. The solution was evaporated. Methanol was added and the solution was evaporated to give the title compound as a pale yellow solid.

MS (ES+) 377, 379

(iii) N-(1-Adamantylmethyl)-2-[(3-[bis(3-[(tert-butyl(dimethyl)silyl]oxy)propyl]amino]propyl]amino)-3-chloroisonicotinamide

To N-(1-adamantylmethyl)-2-[(3-aminopropyl)amino]-3-chloroisonicotinamide (0.32 g) (Example 36(ii)) and 3-[(tert-butyl(dimethyl)silyl]oxy]propanal (0.16 g) in dichloromethane (15 ml) was added sodium triacetoxyborohydride (0.18 g). The mixture was stirred for 18 hrs at room temperature. NaHCO₃ solution was added and the product was extracted into dichloromethane. The solution was dried and the solvent was evaporated. Flash chromatography, using NH₃/MeOH/CH₂Cl₂ as eluent, gave the title compound as a colourless oil.

(iv) N-(1-Adamantylmethyl)-2-[(3-[bis(3-hydroxypropyl)amino]propyl]amino)-3-chloroisonicotinamide dihydrochloride

N-(1-adamantylmethyl)-2-[(3-[bis(3-[(tert-butyl(dimethyl)silyl]oxy)propyl]amino]-propyl]amino)-3-chloroisonicotinamide (Example 36(iii)) in methanol (5 ml) was treated with HCl in 1,4-dioxane (3 ml). The mixture was stirred at room temperature for 3 hrs. The solvent was evaporated. The product was purified by reverse phase HPLC, using NH₃/H₂O/CH₃CN as eluant. The resulting oil in methanol was treated with ethereal HCl and the solvent was evaporated to yield the title compound as a white solid (0.14 g).

¹H NMR (400 MHz, DMSO-d₆) δ 8.68 (1H, t), 8.10 (1H, d), 6.86 (1H, d), 3.65–3.74 (6H, m), 3.30–3.36 (6H, m), 3.075 (2H, d), 2.12–2.22 (2H, m), 1.93–2.02 (7H, m), 1.77 (3H, d), 1.69 (3H, d), 1.62 (6H, s). MS (APCI+) 493, 495 [M+H]⁺

Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X₇ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3) p.

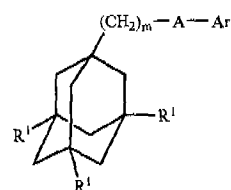
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126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

In this manner, each of the title compounds of the Examples was tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10⁶ cells/ml) containing 10⁻⁴M ethidium bromide, 25 µl of a high potassium buffer solution containing 10⁻⁵M bbATP, and 25 µl of the high potassium buffer solution containing 3×10⁻⁵M test compound. The plate was covered with a plastics sheet and incubated at 37° C. for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of the Examples demonstrated antagonist activity, having a pIC₅₀ figure >4.50. For example, the compounds of Example 12 and Example 26 had pIC₅₀ values of 7.1 and 7.8 respectively.

The invention claimed is:

1. A compound of formula



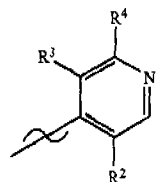
(I)

wherein m represents 1, 2 or 3;

each R¹ independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

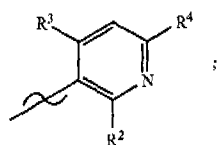
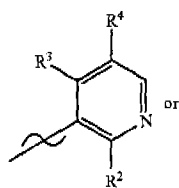
Ar represents a group



(II)

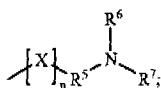
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one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3-C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

R^4 represents a group



X represents an oxygen or sulphur atom or a group $>N-R^8$;

n is 0 or 1;

R^5 represents a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

R^6 and R^7 each independently represent a hydrogen atom, C_1-C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1-C_6 alkoxy, and (di)- C_1-C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3-C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy); and

R^8 represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy; with the provisos that:

- (a) when n is 0, then A is $NHC(O)$, and
- (b) when n is 1, X represents oxygen and A is $C(O)NH$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl; and
- (c) when n is 1, X is oxygen, sulphur or NH and A is $NHC(O)$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl or $-CH_2CH_2OH$;

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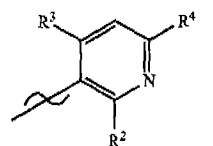
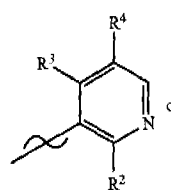
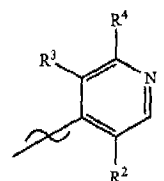
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of formula (I) according to claim 1, wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

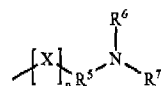
A represents $C(O)NH$ or $NHC(O)$;

Ar represents a group



one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3-C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

R^4 represents a group



X represents an oxygen or sulphur atom or a group $>N-R^8$;

n is 0 or 1;

R^5 represents a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy; and

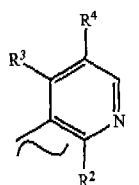
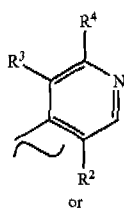
R^6 , R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

with the provisos that:

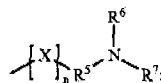
- (d) when n is 0, then A is $NHC(O)$, and
- (e) when n is 1, X represents oxygen and A is $C(O)NH$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_5 alkyl, or when one

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- of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_5 alkyl, and
- (f) when n is 1, X is oxygen, sulphur or NH and A is $NHC(O)$, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_5 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_5 alkyl or $-CH_2CH_2OH$; or a pharmaceutically acceptable salt or solvate thereof.
3. A compound according to claim 1, wherein m is 1.
4. A compound according to claim 1, wherein A represents $NHC(O)$.
5. A compound according to claim 1, wherein Ar represents a group of formula (II) or (III).
6. A compound according to claim 5, wherein Ar represents a group of formula (II).
7. A compound according to claim 1, wherein one of R^2 and R^3 represents a halogen atom and the other of R^2 and R^3 represents a hydrogen atom.
8. A compound according to claim 1, wherein n is 0.
9. A compound according to claim 1, wherein m represents 1; each R^1 represents a hydrogen atom; A represents $NHC(O)$; Ar represents a group



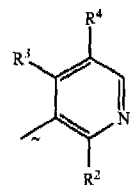
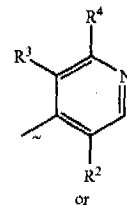
one of R^2 and R^3 represents a halogen atom, and the other of R^2 and R^3 represents a hydrogen atom; R^4 represents a group



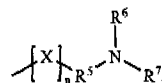
X represents an oxygen or sulphur atom or a group $>N-R^8$; n is 0 or 1; R^5 represents a C_1-C_3 alkyl group optionally substituted by at least one hydroxyl group; R^6 and R^7 each independently represent a hydrogen atom, C_1-C_5 alkyl (optionally substituted by one or two substituents independently selected from hydroxyl and

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- (di)- C_1-C_2 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_6 cycloalkyl (substituted by at least one hydroxyl group); R^8 represents a hydrogen atom or a C_2 alkyl group substituted by at least one hydroxyl group.
10. A compound according to claim 1, wherein m represents 1; each R^1 represents a hydrogen atom; A represents $NHC(O)$; Ar represents a group



one of R^2 and R^3 represents a halogen atom, and the other of R^2 and R^3 represents a hydrogen atom; R^4 represents a group



X represents an oxygen or sulphur atom or a group $>N-R^8$; n is 0 or 1; R^5 represents a C_2-C_3 alkyl group optionally substituted by at least one hydroxyl group; R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_5 alkyl group optionally substituted by one or two hydroxyl groups; R^8 represents a hydrogen atom or a C_2 alkyl group substituted by at least one hydroxyl group.

11. A compound being selected from any one of: N -(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}isonicotinamide, N -(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride, N -(1-Adamantylmethyl)-2-chloro-5-{3-[(3-hydroxypropyl)amino]propyl}nicotinamide, N -(1-Adamantylmethyl)-2-chloro-5-{3-[(1S)-2-hydroxy-1-methylethyl]amino}propyl}nicotinamide, N -(1-Adamantylmethyl)-2-chloro-5-{3-[(1R)-2-hydroxy-1-methylethyl]amino}propyl}nicotinamide, N -(1-Adamantylmethyl)-2-(3-aminopropyl)-5-chloroisonicotinamide hydrochloride, N -(1-Adamantylmethyl)-5-chloro-2-{3-(ethylamino)propyl}isonicotinamide hydrochloride,

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N-(1-Adamantylmethyl)-5-chloro-2-({2-[(3-hydroxypropyl)amino]ethyl}thio)isonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(1R)-2-hydroxy-1-methylethyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(1S)-2-hydroxy-1-methylethyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(2-hydroxyethyl)amino]propyl)isonicotinamide hydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(2-[(3-hydroxypropyl)amino]ethoxy)isonicotinamide, hydrochloride

N-(1-Adamantylmethyl)-5-chloro-2-({2-[(2-hydroxyethyl)amino]ethyl}amino)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-(isopropylamino)propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(2S)-2-hydroxypropyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(2R)-2,3-dihydroxypropyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(2S)-2,3-dihydroxypropyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(4-methylcyclohexyl)amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(2-hydroxy-2-methylpropyl)amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(1R)-1-(hydroxymethyl)-2-methylpropyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[[2-(methylamino)ethyl]amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[[3-(methylamino)propyl]amino]propyl)isonicotinamide bis(trifluoroacetate),

N-(1-Adamantylmethyl)-5-chloro-2-[(2-[(2-hydroxyethyl)amino]ethyl)amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[[2-(diethylamino)ethyl]amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(2-hydroxyethyl)(methyl)amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(3-hydroxy-2,2-dimethylpropyl)amino]propyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(2R)-2-hydroxypropyl}amino}propyl)isonicotinamide, dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-({[3-(methylamino)propyl]amino}methyl)isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-5-chloro-2-({[2-(2-hydroxyethyl)amino]ethyl}amino)methyl)isonicotinamide dihydrochloride,

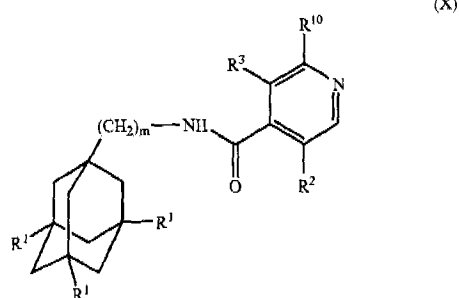
N-(1-Adamantylmethyl)-5-chloro-2-({[2-(methylamino)ethyl]amino}methyl)isonicotinamide dihydrochloride,

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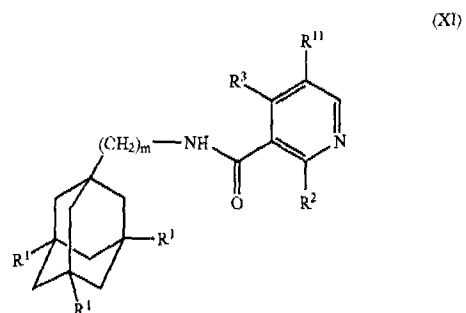
N-(1-Adamantylmethyl)-5-chloro-2-(3-[(2-hydroxyethyl)amino]ethyl)isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-(3-[(3-hydroxypropyl)amino]ethyl)isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-5-chloro-2-(3-(methylamino)propyl)isonicotinamide hydrochloride,
N-(1-Adamantylmethyl)-5-bromo-2-{{[(2S)-2-hydroxy-3-(methylamino)propyl]oxy}isonicotinamide, and
N-(1-Adamantylmethyl)-2-({[3-bis(3-hydroxypropyl)amino]propyl}amino)-3-chloroisonicotinamide dihydrochloride,

or pharmaceutically acceptable salts and solvates thereof.
12. A process for the preparation of a compound according to claim 1, which comprises:

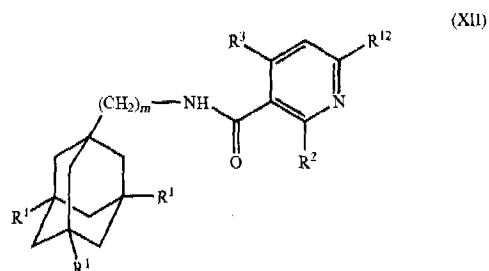
(i) when n is 0 and R⁵ represents CH₂, reacting a compound of formula



wherein R¹⁰ represents —C(O)H or —CH₂L¹, L¹ represents a leaving group and m, R¹, R² and R³ are as defined in formula (I), or a compound of formula



wherein R¹¹ represents —C(O)H or —CH₂L², L² represents a leaving group and m, R¹, R² and R³ are as defined in formula (I), or a compound of formula



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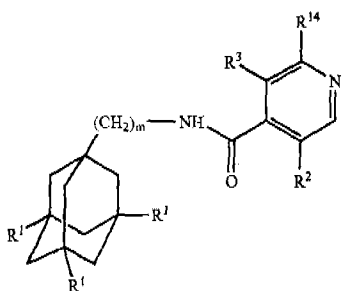
wherein R^{12} represents $-C(O)H$ or $-CH_2L^3$, L^3 represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I),

with a compound of formula (XIII), HNR^6R^7 , wherein R^6 and R^7 are as defined in formula (I), under reductive amination conditions when R^{10} , R^{11} or R^{12} represents $-C(O)H$ or in the presence of a suitable base when R^{10} , R^{11} or R^{12} represents $-CH_2L^1$, $-CH_2L^2$ or $-CH_2L^3$; or

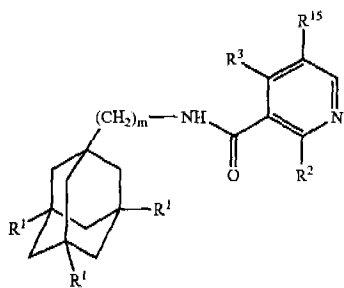
(ii) when n is 0, R^5 is $(CH_2)_2$ and R^6 and R^7 are both hydrogen, reacting a compound of formula (X) as defined in (i) above in which R^{10} represents $-CH_2L^1$, or a compound of formula (XI) as defined in (i) above in which R^{11} represents $-CH_2L^2$, or a compound of formula (XII) as defined in (i) above in which R^{12} represents $-CH_2L^3$, with an alkali metal cyanide, followed by a hydrogenation reaction; or

(iii) when n is 0, R^5 is $(CH_2)_2$ and at least one of R^6 and R^7 is other than hydrogen, reacting a compound as prepared in (ii) above with at least one compound of formula (XIV), $R^{13}C(O)H$, wherein R^{13} represents an optionally substituted C_1-C_6 alkyl or C_3-C_8 cycloalkyl group as defined for R^6 and R^7 in formula (I), under reductive amination conditions; or

(iv) when n is 0 and R^5 represents a C_3-C_5 alkyl group optionally substituted as defined in formula (I), reacting a compound of formula

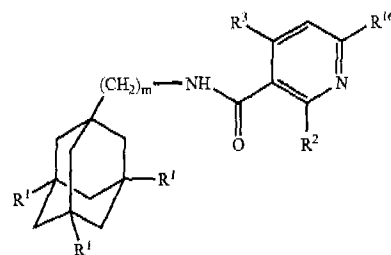


wherein R^{14} represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

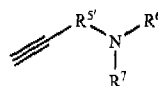


wherein R^{15} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

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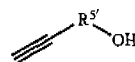


wherein R^{16} represents a leaving group and m , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula



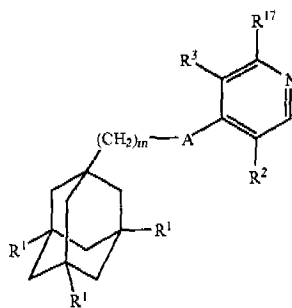
wherein $R^{5'}$ represents a C_1-C_3 alkyl group optionally substituted as defined for R^5 in formula (I) and R^6 and R^7 are as defined in formula (I), followed by a hydrogenation reaction; or

(v) when n is 0 and R^5 represents a C_3-C_5 alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above, with a compound of formula



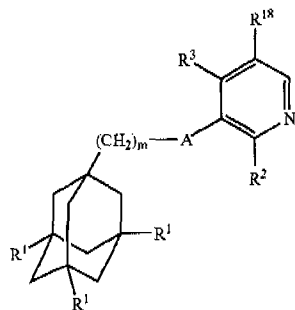
wherein $R^{5'}$ is as defined in formula (XVIII) in (iv) above, followed by a hydrogenation reaction and then an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions; or

(vi) when n is 1 and X is oxygen or $>N-R^8$, reacting a compound of formula



wherein R^{17} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

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(XXI)

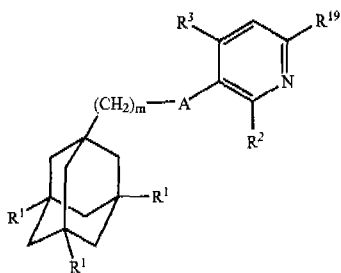
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wherein R^{18} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), or a compound of formula

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(XXII)

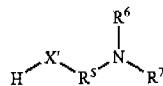
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wherein R^{19} represents a leaving group and m , A , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula

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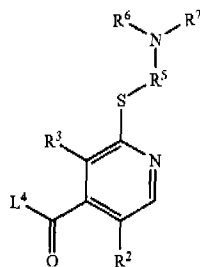


(XXIII)

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wherein X^1 represents oxygen or $>N-R^8$ and R^5 , R^6 , R^7 and R^8 are as defined in formula (I); or
(vii) when A is $NHC(O)$, n is 1 and X is sulphur, reacting a compound of formula

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(XXIV)

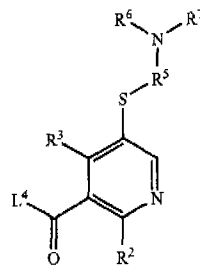
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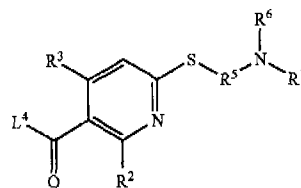
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(XXV)

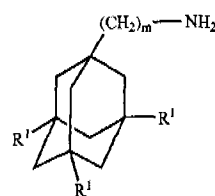
or



(XXVI)

wherein, in each of formulae (XXIV), (XXV) and (XXVI), L^4 represents a leaving group and R^2 , R^3 , R^5 , R^6 and R^7 are as defined in formula (I), with a compound of formula

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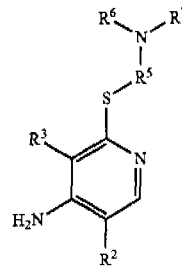
(XXVII)

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wherein m and R^1 are as defined in formula (I); or
(viii) when A is $C(O)NH$, n is 1 and X is sulphur, reacting a compound of formula

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(XXVIII)

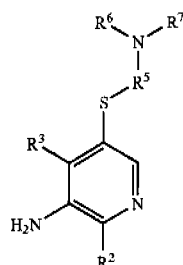
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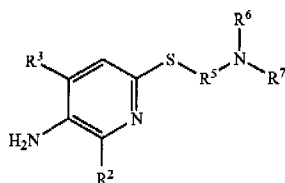
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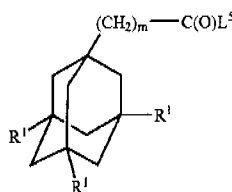
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or

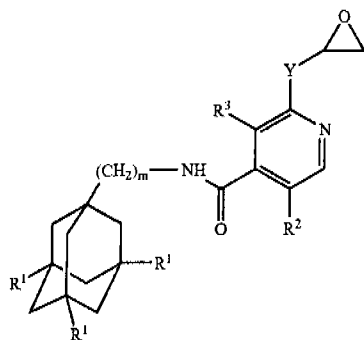


wherein, in each of formulae (XXVIII), (XXIX) and (XXX), R^2 , R^3 , R^5 , R^6 and R^7 are as defined in formula (I), with a compound of formula



wherein L^5 represents a leaving group and m and R^1 are as defined in formula (I); or

(ix) when n is 0 and R^5 represents a C_2-C_5 alkyl group substituted as defined in formula (I), reacting a compound of formula



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or a compound of formula

(XXIX)

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15

(XXX)

20

or a compound of formula

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(XXXI)

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wherein, in each of formulae (XXXII), (XXXIII) and (XXXIV), Y represents a bond or a C_1-C_3 alkyl and m , R^1 , R^2 and R^3 are as defined in formula (I),

with a compound of formula (XIII) as defined in (i) above, and optionally thereafter reacting with a C_1-C_6 alkylating agent or with a halogenating agent; or

(x) when n is 0 and R^5 represents a C_3-C_5 alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above, with a pre-treated compound of formula

(XXXII)

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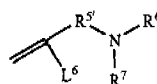
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(XXXIII)

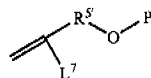
(XXXIV)

(XXXV)



in which L^6 represents a hydrogen atom and $R^{5'}$ represents a C_1-C_3 alkyl group optionally substituted as defined for R^5 in formula (I) and R^6 and R^7 are as defined in formula (I), wherein the compound of formula (XXXV) is pre-treated with a hydroborating agent; or (xi) when n is 0 and R^5 represents a C_3-C_5 alkyl group optionally substituted as defined in formula (I), reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above in the presence of a suitable catalyst, with a pre-treated compound of formula

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in which L^7 represents a hydrogen atom and R^5 represents a C_1 - C_3 alkyl group optionally substituted as defined for R^5 in formula (I) and P is a suitable protecting group, wherein the compound of formula (XXXVIII) is pre-treated with a hydroborating agent, followed by removal of the protecting group, P , in a deprotection reaction, then by an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions; or (xii) when n is 0 and R^5 is $(CH_2)_2$, reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above with a compound of formula



wherein R^{20} represents a suitable leaving group, in the presence of a suitable catalyst, followed by reaction with a compound of formula (XIII) as defined in (i) above; or

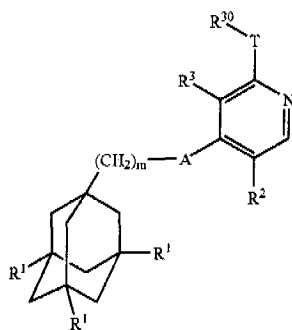
(xiii) when n is 0 and R^5 is CH_2 , reacting a compound of formula (XV), (XVI) or (XVII) as defined in (iv) above with a compound of formula (XXXIX) as defined in (xii) above, followed by an oxidation reaction and then by reaction with a compound of formula (XIII) as defined in (i) above under reductive amination conditions;

and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii) or (xiii) carrying out one or more of the following:

converting the compound obtained to a further compound according to claim 1

forming a pharmaceutically acceptable salt or solvate of the compound.

13. An intermediate compound of formula



(XXXVIII)

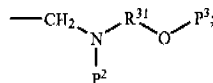
(XXXIX)

(IA)

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wherein T represents $-C\equiv C-$ or $-CH_2CH_2-$;

R^{30} represents $-CHO$, $-CH_2OP^1$ or a group of formula



P^1 represents a hydrogen atom or a suitable protecting group;

P^2 represents a suitable protecting group;

P^3 represents a suitable protecting group;

R^{31} represents a C_1 - C_5 alkyl group; and

m , A , R^1 , R^2 and R^3 are as defined in claim 1.

14. An intermediate compound according to claim 13, wherein:

m represents 1;

A represents $NHC(O)$;

each R^1 represents a hydrogen atom;

R^2 represents a halogen atom; and

R^3 represents a hydrogen atom.

15. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

16. A process for the preparation of a pharmaceutical composition as claimed in claim 15 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

17. A method of treating rheumatoid arthritis in a patient, the method comprising;

administering a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claim 1 in the treatment of rheumatoid arthritis.

18. A method of treating an obstructive airways disease in a patient, the method comprising;

administering a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claim 1 in the treatment of an obstructive airways disease.

19. The method according to claim 18, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

* * * * *



US006201024B1

235
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D4 235(12) **United States Patent**
Baxter et al.(10) **Patent No.: US 6,201,024 B1**
(45) **Date of Patent: Mar. 13, 2001**(54) **ADAMANTANE DERIVATIVES**(75) Inventors: **Andrew Baxter**, Wymeswold; **Thomas McNally**, Loughborough; **Michael Mortimore**, West Bridgford; **David Cladingboel**, Mountsorrel, all of (GB)(73) Assignee: **AstraZeneca UK Limited**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/230,478**(22) PCT Filed: **Dec. 1, 1998**(86) PCT No.: **PCT/SE98/02188**§ 371 Date: **Jan. 26, 1999**§ 102(e) Date: **Jan. 26, 1999**(87) PCT Pub. No.: **WO99/29661**PCT Pub. Date: **Jun. 17, 1999**(30) **Foreign Application Priority Data**

Dec. 5, 1997 (SE) 9704544

(51) Int. Cl.⁷ **A61K 31/166**; **A61K 31/404**;
A61K 31/44; **C07C 233/65**; **C07D 213/82**(52) U.S. Cl. **514/617**; **564/183**; **546/285**;
546/276.4; **548/469**; **548/361.1**; **544/335**;
514/345; **514/347**; **514/349**; **514/403**; **514/415**;
514/256(58) Field of Search **514/617**, **256**,
514/345, **347**, **349**, **350**, **403**, **415**; **564/183**;
546/276.4, **285**; **548/361.1**, **469**; **554/335**(56) **References Cited****U.S. PATENT DOCUMENTS**3,464,998 9/1969 Krimmel .
3,732,305 * 5/1973 Bauer et al. 260/564 R
3,789,072 1/1974 Bernstein 260/557 B**FOREIGN PATENT DOCUMENTS**0 395 093 10/1990 (EP) .
0 564 924 A2 10/1993 (EP) .
0 564 924 A3 10/1993 (EP) .
95/04720 2/1995 (WO) .
95/30647 11/1995 (WO) .**OTHER PUBLICATIONS**

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STN Int'l, accession No.: 1974:26871, "Synthesis and biological activity . . ." Danilenko et al.

STN Int'l, accession No.: 1968:402562, "Synthesis of adamantane derivatives . . ." Sasaki et al.

STN Int'l, accession No.: 1975:3853, "Aliphatic acid amide . . ." Kreutzberger et al.

Syamala et al, "Modification of Photochemical Reactivity by Cyclodextrin . . .," Tetrahedron, vol. 44, No. 23, pp. 7234 to 7242 (1988).

STN Int'l, accession No.: 1977:89560, Danilenko et al, "Synthesis and biological activity . . ." (1976), 10(8), 51-3.

STN Int'l, accession No.: 1996:34490, Kalindjian et al, "The synthesis of a radioligand with high potency . . ." Bioorg. Med. Chem. Lett., vol. 6, No. 10, pp. 1171-1174 (1996).

STN Int'l, accession No.: 1997:390174, Gibson et al, "Incorporation of conformationally constrained . . ." Bioorg. Med. Chem. Lett., vol. 7, No. 10, pp. 1289-1292 (1997).

* cited by examiner

Primary Examiner—C. S. Aulakh

(74) Attorney, Agent, or Firm—Nixon & Vanderhyc

(57) **ABSTRACT**

The invention provides adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

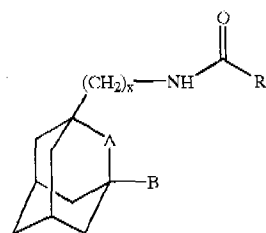
9 Claims, No Drawings

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receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 μ l of a high potassium buffer solution containing 10^{-5} M bbATP, and 25 μ l of the high potassium buffer solution containing 3×10^{-5} M test compound. The plate was covered with a plastics sheet and incubated at 37° C. for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 80 demonstrated antagonist activity, having a pIC₅₀ figure >4.50.

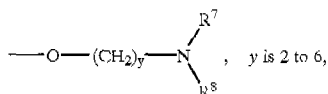
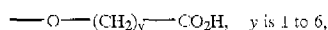
What is claimed is:

1. A compound of general formula



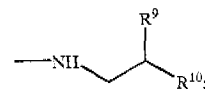
wherein x represents 1 or 2; A represents a group CH₂; B represents a hydrogen or halogen atom;

R represents a phenyl, pyridyl, indolyl, indazolyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents independently selected from the group consisting of a halogen atom, an amino, cyano, hydroxyl, nitro, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, —N(R¹)—C(=O)—R², —NR⁵R⁶, C₃-C₈-cycloalkyl, 3- to 8-membered heterocyclyl, C₃-C₈-cycloalkyloxy, C₁-C₆-alkylcarbonyl, C₁-C₆-alkylsulphinyl or C₁-C₆-alkylsulphonyl group, or a C₁-C₆-alkoxy, C₁-C₆-alkylamino, phenoxy, benzyl, C₁-C₆-alkylthio and phenylthio group optionally substituted by one or more substituents independently selected from the group consisting of a halogen atom, an amino, cyano, carboxyl, hydroxyl, nitro, 1-pyrrolidinyl, 1-piperidinyl, C₁-C₆-alkyl, C₁-C₆-alkoxy, (di)C₁-C₆-alkylamino, halo-C₁-C₆-alkyl, C₁-C₆-alkoxycarbonyl or one of the following groups:



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-continued



R¹ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

R² represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

R⁵ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

R⁶ represents a C₃-C₈-cycloalkyl group and, additionally, a C₁-C₆-alkyl group when R⁵ is not a hydrogen atom;

R⁷ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

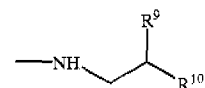
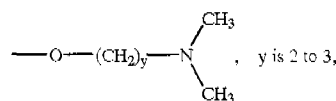
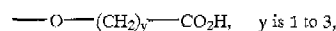
R⁸ represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

R⁹ represents a hydrogen atom or a hydroxyl group; and

R¹⁰ represents a hydrogen atom or a phenyl or imidazolyl group;

with the proviso that when B represents a hydrogen atom, and R is a phenyl- or pyridyl-containing group, the phenyl or pyridyl moiety is substituted as defined above; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein R represents a phenyl, pyridyl or indolyl group, each of which may be optionally substituted by one or two substituents independently selected from a fluorine, chlorine, bromine or iodine atom or an amino, hydroxyl, nitro, aziridinyl, pyrrolidinyl, C₁-C₄-alkyl, trifluoromethyl, —NR⁵R⁶, C₁-C₄-alkylsulphinyl or C₁-C₄-alkylsulphonyl group, or a C₁-C₄-alkoxy, C₁-C₄-alkylamino, benzyl, C₁-C₄-alkylthio or phenylthio group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, cyano, carboxyl, hydroxyl, 1-pyrrolidinyl, 1-piperidinyl, methyl, methoxy, dimethylamino, C₁-C₄-alkoxycarbonyl or one of the following groups:



3. A compound according to claim 1, wherein R⁵ represents a hydrogen atom or a C₁-C₄-alkyl group.

4. A compound according to claim 1, wherein R⁶ represents a C₁-C₄-alkyl group when R is not a hydrogen atom.

5. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:

2,4-Dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

3,5-Dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2-Chloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2,6-Dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2-Methoxy-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2-Methyl-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,



US006242470B1

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237
D5(12) **United States Patent**
Baxter et al.(10) **Patent No.: US 6,242,470 B1**(45) **Date of Patent: Jun. 5, 2001**(54) **ADAMANTANE DERIVATIVES**(75) Inventors: **Andrew Baxter**, Wymeswold; **Stephen Brough**, Selston; **Thomas McNally**, Loughborough; **Michael Mortimore**, West Bridgford, all of (GB)(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/230,511**(22) PCT Filed: **Dec. 1, 1998**(86) PCT No.: **PCT/SE98/02189**§ 371 Date: **Jan. 26, 1999**§ 102(c) Date: **Jan. 26, 1999**(87) PCT Pub. No.: **WO99/29660**PCT Pub. Date: **Jun. 17, 1999**(30) **Foreign Application Priority Data**

Dec. 5, 1997 (SE) 9704545

(51) Int. Cl.⁷ **A61K 31/425**; A61K 31/16; C07D 277/04; C07C 233/00(52) U.S. Cl. **514/368**; 514/369; 514/613; 514/623; 548/187; 548/205; 564/123; 564/191

(58) Field of Search 548/187, 205; 514/368, 369, 613, 623; 564/123, 191

(56) **References Cited****U.S. PATENT DOCUMENTS**3,464,998 9/1969 Krimmel.
3,789,072 1/1974 Bernstein.**FOREIGN PATENT DOCUMENTS**0 395 093 10/1990 (EP).
0 564 924 A2 10/1993 (EP).
95/04720 2/1995 (WO).
95/30647 11/1995 (WO).**OTHER PUBLICATIONS**STN Int'l, accession No. 1977:89560, Danilenko et al, "Synthesis and biological activity . . ." (1976), 10(8), 51-3.
STN Int'l, accession No. 1996:34490, Kalindjian et al, "The synthesis of a radioligand with high potency . . ." Bioorg. Med. Chem. Lett., vol. 6, No. 10, pp. 1171-1174 (1996).
STN Int'l, accession No. 1997:390174, Gibson et al, "Incorporation of conformationally constrained . . ." Bioorg. Med. Chem. Lett., vol. 7, No. 10, pp. 1289-1292 (1997).
Narayanan, V.L., "Adamantyl Analogs of 2'-(3-Dimethylaminopropylthio) . . .," Journal of Medicinal Chemistry, vol. 15, No. 11 (1972).
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Chemical Abstracts, AN: 1974:26871, "Synthesis and biological activity . . ." Danilenko et al.
Chemical Abstracts, AN: 1968:402562, "Synthesis of adamantane derivatives . . ." Sasaki et al.
Chemical Abstracts, AN: 1975:3853, "Aliphatic acid amide . . ." Kreutzberger et al.
Syamala et al, "Modification of Photochemical Reactivity by Cyclodextrin . . .," Tetrahedron, vol. 44, No. 23, pp. 7234 to 7242 (1988).*Primary Examiner*—Deborah C. Lambkin(74) *Attorney, Agent, or Firm*—Nixon & Vanderhye(57) **ABSTRACT**

The invention provides adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

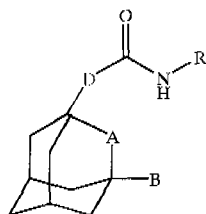
11 Claims, No Drawings

receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

In this manner, each of the title compounds of Examples 1 to 59 were tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 μ l of high potassium buffer solution containing 10^{-5} M bbATP, and 25 μ l of high potassium buffer solution containing 3×10^{-5} M test compound. The plate was covered with a plastics sheet and incubated at 37° C. for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 59 demonstrated antagonist activity, having a pIC₅₀ figure >4.50.

What is claimed is:

1. A compound of general formula



wherein A represents a CH₂ group;

B represents a hydrogen or halogen atom;

D represents a group CH₂, OCH₂, NHCH₂ or CH₂CH₂;

R represents a phenyl group, which may be optionally substituted by one or more substituents independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro, halo-C₁-C₆-alkyl, —N(R¹)—C(=O)—R², —C(O)NR³R⁴, —NR⁵R⁶, C₃-C₈-cycloalkyl, 3- to 8-membered heterocyclyl, C₃-C₈-cycloalkyloxy, C₁-C₆-alkylcarbonyl, phenoxy, benzyl, C₁-C₆-alkylthio, phenylthio, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylsulphinyl or C₁-C₆-alkylsulphonyl group, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group optionally substituted by one or more substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₆-alkoxy, (di)C₁-C₆-alkylamino, C₂-C₆-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;

R¹ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;

R² represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; and

R³, R⁴, R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; with the provisos that (i) when A is CH₂, B is H and D is CH₂, then R does not represent a phenyl, ortho-carboxyphenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-(dimethylaminoethyl)phenyl, methylphenyl or para-phenoxyphenyl group, and (ii) when A is CH₂, B is Br and D is CH₂, then R does not represent an orthocarboxyphenyl group, and (iii) when A is CH₂, B is H and D is CH₂CH₂, then R does not represent a phenyl group, and (iv) when A is CH₂, D is CH₂ or CH₂CH₂ and R represents a substituted phenyl group, the substituent or substituents present do not comprise, in an ortho position, a C₁-C₆-alkoxy group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein B represents a hydrogen atom.

3. A compound according to claim 1, wherein D represents a group CH₂, OCH₂ or NHCH₂.

4. A compound according to claim 1, wherein R represents a phenyl which may be optionally substituted by one, two or three substituents independently selected from a halogen atom or a hydroxyl, nitro or C₁-C₄-alkoxycarbonyl group, or a C₁-C₄-alkyl or C₁-C₄-alkoxy group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₄-alkoxy, (di)C₁-C₄-alkylamino, C₁-C₄-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.

5. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:

N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,

N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-[5-(3-N,N-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,

N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid, hydrochloride salt,

N-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

N-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
Alicia Lloreda

ASUNTO Radicación 04-43373
 Trámite 002
 Evento 001
 Actuación 430
 Oficio No 13763
 Folios 007

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap.I ☐ Cap. II ☒
No. Sol. Internacional PCT/SE02/02057
Fecha de Presentación Internal. 12/11/2002

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 33 a 130 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios: 193 a 209 (como se radicó en 15.05.2008)
- 1.3. Prioridad: SE 0103836-3 de 16.11.2001

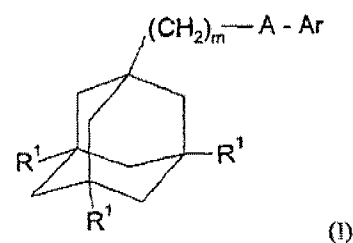
2. Objeto de la invención

- Título de la solicitud: DERIVADOS E INTERMEDIARIOS DE N-ADAMANTILMETILO COMO COMPOSICIONES FARMACEUTICAS Y PROCESOS PARA SU PREPARACIÓN, folio 1, campo 54.
- El objeto de la presente solicitud de patente de invención consiste en compuestos derivados de (I), procesos para su preparación, composiciones farmacéuticas que los contienen y procesos para su preparación:

Reivindicaciones 1-11: Compuestos de fórmula (I).
Reivindicación 12: Proceso para preparación de compuestos de la fórmula (I).
Reivindicaciones 13 y 14: Compuestos intermediarios de fórmula (IA)

Reivindicación 15: Una composición farmacéutica conteniendo compuestos de fórmula (I)

Reivindicación 16: Proceso para preparación de una composición farmacéutica conteniendo compuestos de fórmula (I)



El problema planteado en esta solicitud es la necesidad de compuestos útiles para tratamientos de enfermedades inflamatorias, inmunes o cardiovasculares en las etiologías en que el receptor P2X7 pueda jugar un papel.

Para solucionar este problema técnico la solicitud en estudio proporciona el objeto de invención descrito.

- La presente invención se catalogó en la categoría A61K31/44, según la Clasificación Internacional de Patentes (IPC).

3. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es la fecha de presentación de la solicitud prioritaria 16 de Noviembre de 2001.

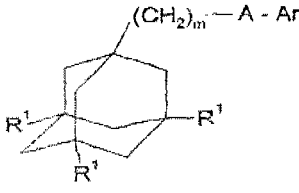
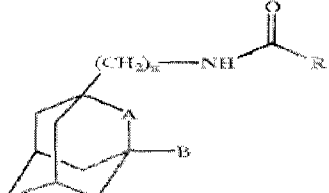
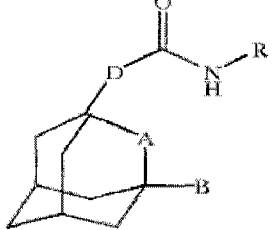
Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D4	US6201024	Adamantane derivatives	13 Mar 2001
D5	US6242470	Adamantane derivatives	5 Jun 2001

4. Análisis de patentabilidad (artículo 14 D486)

4.1. Novedad (artículo 16 D486)

- En la primera reivindicación se presentan compuestos derivados de (I) como se observa en la tabla a continuación.
- El estado de la técnica representado por D4 y D5, en sus primera reivindicación presenta compuestos de estructura idéntica según la tabla a continuación. El grupo A de la solicitud, que une el adamantilo con la piridina sustituida, está representado en D4 por la secuencia NH-CO-R, mientras en D5 por la secuencia CO-NH-R.
- El elemento característico de los compuestos reivindicados, ya era conocido en D4 y D5; por lo cual las reivindicaciones 1 y dependientes no pueden considerarse nuevas.

CARACTERÍSTICAS TÉCNICAS ESENCIALES		
SOLICITUD	D4 (US6201024)	D5 (US6242470)
Compuesto de fórmula (I) N-adamantil-metilo.	Un compuesto de formula general:	Un compuesto de formula general:
 (I)		
Donde: R1 representa H o X.	Donde: A representa un grupo CH2 u O. B representa H o halógeno	Donde: A representa un grupo CH2, CH2CH2 u O. B representa H o halógeno.
m representa 1,2 o3 A representa CONH ó NHCO Ar representa piridilo sustituido con con R2,R3, R4 que pueden ser X, NO2, NH2, OH	X representa 1 o 2 R representa fenil, piridilo, y otras opciones, cada una de los cuales puede estar opcionalmente sustituido	D representa un grupo CH2 R representa fenil, piridilo y otras opciones cada una de los cuales puede estar opcionalmente sustituido

5. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D4	US6201024	Reivindicación 1 y dependientes	Novedad
D5	US6242470	Reivindicación 1 y dependientes	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 01/06/2010

CONCEPTO TÉCNICO No. 2129	EXAMINADOR TÉCNICO Código No.202074
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