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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

202012

Bogotá, D.C., 12 de octubre de 2010

Apoderado: Margarita Castellanos Abondano

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-033168- -00008-0000

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Act. 519 TRASLADOINFORME Folios: 1

ASUNTO

Radicación 07-33168

Trámite 002

Evento 001

Actuación 430

Oficio

Folios

214146

Patente de Invención



Vía PCT fase nacional



Cap. I



Cap. II



No. Sol. Internacional

PCT/US2005/031284

Fecha de Presentación Internal. 02/sep/2005

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 270 a 562 Como se presentó inicialmente.

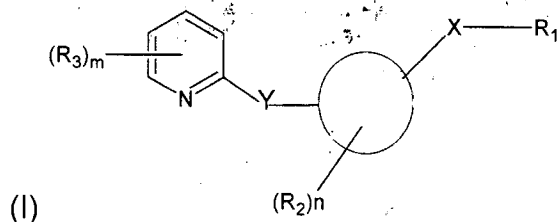
1.2. Reivindicaciones: Folios 563 a 572 Como de presentó inicialmente.

1.3. Prioridad: Filio 2: US 60/607.367; 02/sep/2004

2. Objeto de la invención

Título de la solicitud: INHIBIDORES PIRIDILO DE DE SEÑALIZACIÓN HEDGEHOG

El objeto de la invención son los derivados de piridin-2-sustituido de la fórmula:



-Reivindicaciones 1-31: Un compuesto de la fórmula (I):

-Reivindicación 32: Composiciones que los contienen

- Reivindicación 33-36: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente.
 -Reivindicación 37: Procedimiento para preparar un compuesto 1b".

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC): C07D213/40, C07D213/82, C07D213/75, C07D409/12, C07D409/12, C07D413/12, C07D417/04, C07D417/12, C07F9/142, A61K31/4418, A61K31/4427, A61P35/00

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-Las reivindicaciones 1-7 son muy amplias y especulativas, toda vez que la fórmula Markush (I) tiene un anillo piridina fijo, el resto de sus fracciones son mutantes y adicional todas sus posibles permutaciones, no encuentran sustento técnico real en la descripción, además los significados de los sustituyentes A, R₁, R₂, R₃, R₄ están en términos de denominaciones genéricas, tales como "carbociclo, heterociclo, haloalquilo, alquilo..", y términos semejantes, que encierran un incalculable número de posibles estructuras, que tampoco encuentran sustento en la descripción, además que no tiene perfectamente delimitado el alcance de la invención, todo eso es inaceptable en la reivindicaciones.

-Es especulativo porque el significado de los sustituyentes **no son extrapolaciones estrechamente relacionadas con lo que se describió**, las reivindicaciones deberían presentar una generalización razonable de los ejemplos dados en la parte descriptiva.

Por demás, el Art. 30 D486 de la C.A.N. dispone que las reivindicaciones deberán estar sustentadas **enteramente** en la memoria descriptiva. **Este es un requerimiento sustantivo y no una simple cuestión de consistencia puramente de enunciado**. Esto significa que debe existir una base técnica real en la memoria descriptiva, para el objeto de cada reivindicación y que el ámbito de las mismas no puede ser ampliado más allá de lo realmente justificado por el contenido de la memoria descriptiva; porque si se trata de extrapolar especulativamente, desde las anterioridades igualmente se puede hacer, por ejemplo el hecho de tener un sustituyente fenilo se puede extrapolar como en la solicitud a cualquier carbociclo y también a cualquier heterociclo para afectar la patentabilidad de la solicitud, o el hecho de no tener un espaciador entre el anillo piridina y el fenilo, extrapolarlo a O, S, S₂, SO₄, CHR₄, tal como se verá en las anterioridades D1-D9.

Por lo tanto el capítulo reivindicatorio no cumplen con el requisito de claridad, concisión y sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

4. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La solicitud no cumple con el requisito exigido de unidad inventiva, ya que no existe una estructura base que sea nueva e inventiva y todas las reivindicaciones conserven esas características técnicas especiales. [Características técnicas esenciales son aquellas características técnicas que a solicitud está aportando al acervo tecnológico como nuevas e inventivas.]

Como la solicitud es tan amplia y especulativa, la oficina toma por ejemplo uno grupo inventivo con los primeros significados que aparecen para cada uno de los sustituyentes y de acuerdo al sustento técnico real encontrado en la descripción formar un primer:

i)piridinil-2-; Y está ausente; A es fenilo (porque es lo único sustentado); X es NR₄C(O); R₁ es alquilo. (derivados de (piridin-2-il)fenil-carboxamida).

5. Excepción a la patentabilidad (artículo 20 D486 literal d))

-Las reivindicaciones 33-36 reclaman un método de tratamiento para el cuerpo humano o animal, por lo tanto están comprendidas por lo dispuesto en el artículo 20 D486 literal d).

6. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 02/sep/2004, se realizó la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.

Algunos de los documentos más relevantes se presentan en la siguiente tabla:

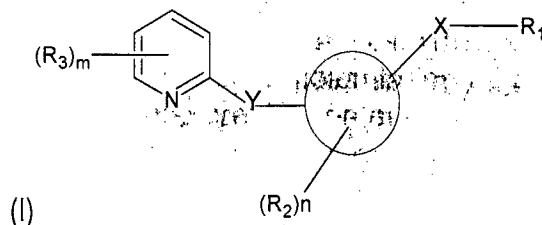
N°	Documento	Título	Fecha de Publicación*
D1	US4670441	Thiobarbituric acid derivatives and their use as anthelmintics	02/jun/1987
D2	US5990133	Indole derivatives as 5-HT receptor antagonist	23/nov/1999
D3	US4851414	Anti-dementia agent	25/jul/1989
D4	WO03032970	5'-carbamoyl-2'-methyl-1-1'-biphenyl-carboxamide derivatives and their use as P38 kinase inhibitors	24/abr/2003
D5	WO03037274	Pyrazole-amides and sulfonamides	08/may/2003
D6	WO2004058176	Acyclic pyrazole compounds for the inhibition for the mitogen activated protein kinase activated protein kinase-2	15/jul/2004
D7	WO03068747	Nicotinamide derivatives useful as P38 inhibitors	21/ago/2003
D8	WO200504152*	Heterocyclylphenyl and heterocyclylpyridil substituted azolecarboxamides as herbicides	06/may/2005
D9	WO2005033288*	HEDGEHOG pathway antagonists	14/sep/2005

*Si se trata de una solicitud colombiana esta fecha corresponde también a la fecha de presentación de la solicitud colombiana aún sin haber sido publicada o sin habersele cumplido el plazo previsto en el art.40.

5. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

5.1. Novedad (artículo 16 D486 de la C.A.N.)

-El análisis de patentabilidad se realizó sobre la materia que realmente tiene sustento técnico en la descripción, que son los derivados de (piridin-2-il)fenil-carboxamida que están comprendidos en la fórmula Markush (I):



-D1 enseña derivados 4,6-dioxo-N-fenil-2-tioxohexahidropirimidina-5-carboxamida Véase los compuestos 1.25 a 1.28, y 1,33 a 1,35 son compuestos reclamados por la solicitud en estudio y son del estado de la técnica.

-D2 describe derivados de indol-carboxamida; dentro de la fórmula Markush(I) la solicitud en estudio reclama el compuesto del ejemplo 6 de D1.

-D3 se refiere a compuestos derivados de N-[3-nitro-4-(piridin-2-ilmetil)fenil]carboxamida, véase col. 1 penúltimo párrafo – col. 2; ejemplos 1 y 2, y reivindicaciones.

-D4 se refiere a derivados de 5'-carbamoil-2'-metil-1-1'-bifenil-carboxamida; véase el ejemplo 27, compuesto que es reclamado en la solicitud como nuevo e inventivo.

-D5 se trata de compuestos derivados de Pirazol-amidas and sulfonamidas, véase el ejemplo 1113, compuesto que es reclamado en la solicitud en estudio como nuevo e inventivo.

-D6 se refiere a compuestos derivados de acíclicos-pirazoles, véase los ejemplos 85, 99 y las reivindicaciones. Es materia que la solicitud en estudio reclama como nueva e inventiva.

-D7 enseña derivados de 6-fenil-N-alkil-sustituido-piridina-3-carboxamida sustituida. Véase pags. 1-3, 7-9, 15, 22, los ejemplos 1-123 y reivindicaciones.

-D8 describe compuestos derivados de heterociclilfenil and heterociclilpiridil sustituidos, véase los ejemplos 1-4 y 10-12, materia que es reclamada en la solicitud en estudio, como nueva.

-D9 derivados de N-fenil-4-(piridin-2-il)benzamida de fórmula (I), véase los ejemplos 1-7, págs. 3, 35-37 y las reivindicaciones 1-4, es materia que la solicitud reclama como nueva.

Tal como puede verse la materia reclamada en la solicitud ya era conocida en D1-D9; por lo cual los compuestos reclamados en la solicitud no pueden considerarse nuevos, por lo tanto la solicitud no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

6. **Conclusión:**

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

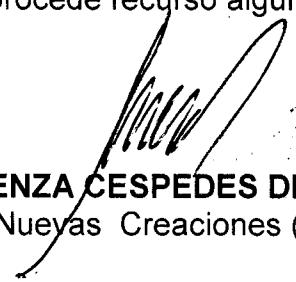
*Una solicitud que no posee novedad obviamente no posee nivel inventivo.

Doc. N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-32	Novedad
D2	1-32	Novedad
D3	1-32	Novedad

D4	1-32	Novedad
D5	1-32	Novedad
D6	1-32	Novedad
D7	1-32,37	Novedad
D8	1-32,37	Novedad
D9	1-32,37	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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (a).

El anterior requerimiento fue notificado por fijación en lista, de fecha
29 OCT. 2010

CONCEPTO TECNICO No. 3745 EXAMINADOR TECNICO Cód. No. 202012

- [54] THIOBARBITURIC ACID DERIVATIVES AND THEIR USE AS ANTHELMINTHICS
- [75] Inventors: Manfred Kühne, Pfeffingen; Jean J. Gallay, Magden, both of Switzerland
- [73] Assignee: Ciba-Geigy Corporation, Ardsley, N.Y.

- [21] Appl. No.: 751,715
- [22] Filed: Jul. 5, 1985
- [30] Foreign Application Priority Data
- Jul. 6, 1984 [CH] Switzerland 3288/84
- [51] Int. Cl.⁴ A61K 31/515; C07D 239/66; C07D 239/68
- [52] U.S. Cl. 514/270; 544/300; 544/301
- [58] Field of Search 544/300; 514/270

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- 3,961,061 6/1976 Krämer et al. 544/301
- 4,229,454 10/1980 Beriger 544/301
- 4,283,444 8/1981 de Sousa et al. 544/301
- 4,399,280 8/1983 de Sousa et al. 544/301
- 4,503,100 3/1985 de Sousa et al. 544/301

FOREIGN PATENT DOCUMENTS

- 0074335 3/1983 European Pat. Off. 544/301
- 105029 4/1984 European Pat. Off. 544/301
- 102327 7/1984 European Pat. Off. 544/301
- 2405732 8/1975 Fed. Rep. of Germany .. 544/301
- 1464326 9/1977 United Kingdom 544/301
- 2126582 3/1984 United Kingdom 544/301

OTHER PUBLICATIONS

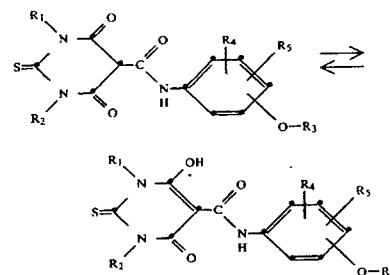
- American J. Vet. Res., vol. 37, No. 12, pp. 1515, 1516 (Dec. 76).
- American J. Vet. Res., vol. 38, No. 6, pp. 807, 808 (Jun. 77).
- American J. Vet. Res. vol. 38, No. 8, pp. 1247, 1248 (Aug. 77).
- American J. Vet. Res., vol. 38, No. 9, pp. 1464, 1426 (Sep. 77).

Primary Examiner—Donald G. Daus
Assistant Examiner—Stephan M. Kapner

Attorney, Agent, or Firm—Edward McC. Roberts;
Meredith C. Findlay

ABSTRACT

The invention relates to novel 5-phenylcarbamoylthio-barbituric acid derivatives of the general formula



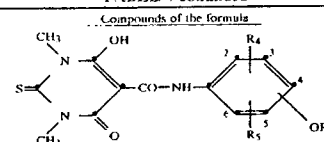
wherein

R₁ and R₂ are each independently C₁-C₃alkyl or methoxy,
R₃ is unsubstituted phenyl, unsubstituted pyridyl, or phenyl which is substituted by 1 to 3 identical or different members selected from the group consisting of C₁-C₃alkyl, C₁-C₃cycloalkyl, halogen, nitro and C₁-C₃haloalkyl containing 1 to 5 halogen atoms, or is pyridyl which is substituted by 1 to 3 identical or different members selected from the group consisting of C₁-C₃alkyl, halogen, nitro and C₁-C₃haloalkyl containing 1 to 5 halogen atoms and

R₄ and R₅ are each independently hydrogen, halogen, C₁-C₃alkyl, C₁-C₃haloalkyl containing 1 to 3 halogen atoms, or are C₁-C₃alkoxy or nitro, and to the tautomers and salts thereof, as anthelmintics. The compounds may be used by themselves or together with suitable carriers and further adjuvants for controlling helminths which are parasites of animals.

13 Claims, No Drawings

TABLE 4-continued



Compound	R ₁	R ₂	R ₄	R ₅	—OR ₃	Physical data m.p. [°C.]
1.22	CH ₃	CH ₃	2-CH ₃	6-CH ₃	4-O—C ₆ H ₄ —CF ₃ (4)-NO ₂ (2)	172-174
1.23	CH ₃	CH ₃	2-CH ₃	6-CH ₃	4-O—pyridyl(2)-CF ₃ (5)	210-211
1.24	CH ₃	CH ₃	H	H	4-O—pyridyl(2)-Cl ₂ -(3,5)	177-178
1.25	CH ₃	CH ₃	H	H	4-O—pyridyl(2)-Cl-(5-F(3))	185-187
1.26	CH ₃	CH ₃	H	H	4-O—pyridyl(2)-F ₂ -(3,5)	179-180
1.27	CH ₃	CH ₃	4-OCH ₃	H	3-O—pyridyl(2)-Cl ₂ -(3,5)	179-180
1.28	CH ₃	CH ₃	3-OCH ₃	H	4-O—pyridyl(2)-Cl ₂ -(3,5)	179-180
1.29	CH ₃	CH ₃	4-OCH ₃	H	3-O—C ₆ H ₄ —Cl(2)-CF ₃ (4)	165-168
1.30	CH ₃	CH ₃	3-OCH ₃	H	4-O—C ₆ H ₄ —Cl(2)-CF ₃ (4)	178-182
1.31	CH ₃	CH ₃	3-OCH ₃	H	4-O—pyridyl(2)-Cl(3)-CF ₃ (5)	205-207
1.32	CH ₃	CH ₃	4-OCH ₃	H	3-O—pyridyl(2)-Cl(3)-CF ₃ (5)	195-197
1.33	CH ₃	CH ₃	3-OCH ₃	H	4-O—pyridyl(2)-Cl(5)-F(3)	170-172
1.34	CH ₃	CH ₃	4-OCH ₃	H	3-O—pyridyl(2)-Cl(5)-F(3)	186-189
1.35	CH ₃	CH ₃	3-OCH ₃	H	4-O—pyridyl(2)-CF ₃ (5)	143-145

Formulation Examples (throughout, percentages are by weight)

2.1 Emulsifiable concentrates	(a)	(b)	(c)
a compound of Table 4	25%	40%	50%
calcium dodecylbenzenesulfonate	5%	8%	6%
castor oil polyethylene glycol ether (36 moles of ethylene oxide)	5%	—	—
tributylphenol polyethylene glycol ether (30 moles of ethylene oxide)	—	12%	4%
cyclohexanone	—	15%	20%
xylene mixture	65%	25%	20%

Emulsions of any required concentration can be produced from such concentrates by dilution with water.

2.2 Emulsifiable concentrates	(a)	(b)	(c)
a compound of Table 4	10%	8%	60%
octylphenol polyethylene glycol ether (4-5 moles of ethylene oxide)	3%	3%	2%
calcium dodecylbenzenesulfonate	3%	4%	4%
castor oil polyglycol ether (35 moles of ethylene oxide)	4%	5%	4%
cyclohexanone	30%	40%	15%
xylene mixture	50%	40%	15%

Emulsions of any required concentration can be obtained from this concentrate by dilution with water.

2.3. Suspension concentrate	(a)	(b)
a compound of Table 4	40%	—
ethylene glycol	10%	—
nonylphenol polyethylene glycol (15 moles of ethylene oxide)	6%	—
sodium lignosulfonate	10%	—
carboxymethyl cellulose	1%	—

-continued

2.3. Suspension concentrate	(a)	(b)
37% aqueous formaldehyde solution	0.2%	—
silicone oil in the form of a 75% aqueous emulsion	0.8%	—
water	32%	—

The finely ground active ingredient is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired concentration can be obtained by dilution with water.

2.4 Wettable powders	(a)	(b)	(c)
a compound of Table 4	25%	50%	75%
sodium lignosulfonate	5%	5%	—
oleic acid	3%	—	5%
sodium diisobutylphthalenesulfonate	—	6%	10%
octylphenol polyethylene glycol ether (7-8 moles of ethylene oxide)	—	2%	—
highly dispersed silicic acid	5%	10%	10%
kaolin	62%	27%	—

The active ingredient is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders which can be diluted with water to give suspensions of the desired concentration.

2.5 Dusts	(a)	(b)
a compound of Table 4	2%	5%
highly dispersed silicic acid	1%	5%
talcum	97%	—
kaolin	—	90%



US005990133A

United States Patent [19]

Gaster et al.

[11] Patent Number: 5,990,133

[45] Date of Patent: Nov. 23, 1999

[54] INDOLE DERIVATIVES AS 5-HT RECEPTOR ANTAGONIST

[75] Inventors: Laramie Mary Gaster, Bishop's Stortford; Paul Adrian Wyman, Epping; Keith Raymond Mulholland, Harlow; David Thomas Davies, Ware; David Malcolm Duckworth, Bishop's; Ian Thomson Forbes, Stevenage; Graham Elgin Jones, Hertford, all of United Kingdom

[73] Assignee: SmithKline Beecham p.Lc., Brentford, United Kingdom

[21] Appl. No.: 08/875,506

[22] PCT Filed: Jan. 26, 1996

[86] PCT No.: PCT/EP96/00368

§ 371 Date: Oct. 16, 1997

§ 102(e) Date: Oct. 16, 1997

[87] PCT Pub. No.: WO96/23783

PCT Pub. Date: Aug. 8, 1996

[30] Foreign Application Priority Data

Feb. 2, 1995	[GB]	United Kingdom	9502052
Apr. 25, 1995	[GB]	United Kingdom	9508327
May 3, 1995	[GB]	United Kingdom	9508967
Aug. 17, 1995	[GB]	United Kingdom	9516845
Aug. 26, 1995	[GB]	United Kingdom	9517542
Sep. 12, 1995	[GB]	United Kingdom	9518574

[51] Int. Cl.⁶ A61K 31/44; C07D 401/10; C07D 403/10

[52] U.S. Cl. 514/337; 546/277.1

[58] Field of Search 546/277.1; 514/337

[56] References Cited

FOREIGN PATENT DOCUMENTS

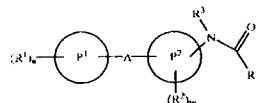
WO 92/05170 4/1992 WIPO
WO 94/04533 3/1994 WIPO
WO 94/22871 10/1994 WIPO

Primary Examiner: Alan L. Rotman

Attorney, Agent, or Firm: Linda E. Hall; Stephen A. Venetianer; Charles M. Kinzig

ABSTRACT

[57] A compound of formula (I) or a salt thereof.



wherein:

P¹ is pyridyl;

P² is phenyl;

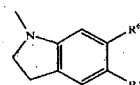
A is a bond or a chain of 1 to 5 atoms optionally substituted by C₁₋₆alkyl;

R¹ and R² groups are each independently hydrogen, C₁₋₆alkyl optionally substituted by NR¹²R¹³, C₂₋₆alkenyl, C₂₋₆alkynyl, cyano, halogen, CF₃, NR¹²R¹³, CHO, OCF₃, COR¹⁴, C₁OR¹⁴ or OR¹⁴ where R¹², R¹³ and R¹⁴ are independently hydrogen or C₁₋₆alkyl;

n and m are independently 0; 1 or 2;

R³ is hydrogen or C₁₋₆alkyl;

R⁴ is a group of formula (i):



in which:

R⁵ and R⁶ are independently hydrogen, C₁₋₆alkyl optionally substituted by one or more fluorine atoms, C₁₋₆alkylthio, C₁₋₆alkoxy or halogen.

14 Claims, No Drawings

5,990,133

23

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

EXAMPLE 4

1-[(3-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=85%, m.p.=230° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.45 (1H, m), 7.70 (4H, m), 8.05 (1H, m), 8.15 (1H, s), 8.55 (1H, m), 8.70 (1H, s), 8.90 (1H, m).

EXAMPLE 5

1-[(4-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=5%, m.p.=210° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.70 (2H, d), 7.75 (4H, m), 8.15 (1H, s), 8.60 (2H, d), 8.85 (1H, s).

EXAMPLE 6

1-[(2-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=40%, m.p.=220-225° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.40 (2H, m), 7.70 (2H, m), 7.90 (2H, m), 8.15 (1H, s), 8.35 (1H, s), 8.65 (1H, m), 8.70 (1H, s).

EXAMPLE 7

1-[4-Methyl-3-(3-Pyridyl)-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=26%, m.p.=211-212° C.

¹H NMR (D²O-DMSO) 2.2 (3H, s), 3.28 (2H, t), 3.85 (3H, s), 4.11 (2H, t), 6.44 (1H, s), 6.85 (1H, s), 7.18-7.45 (4H, m), 7.59-7.72 (1H, m), 8.22 (1H, s), 8.49-8.69 (2H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

EXAMPLE 8

1-[3-Fluoro-5-(3-pyridyl)phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=26%, m.p.=220-223° C.

¹H NMR (D²O-DMSO) 3.29 (2H, t), 3.85 (3H, s), 4.21 (2H, t), 7.23 (1H, s), 7.30 (1H, t), 7.54 (2H, m), 7.65 (1H, d), 7.76 (1H, s), 8.09 (1H, d), 8.15 (1H, s), 8.62 (1H, d), 8.78-9.00 (2H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone. m.p. 198-199° C.

EXAMPLE 9

1-[2-Fluoro-5-(3-pyridyl) phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=10%, m.p. 233° C. (decomp)

¹H NMR (D²O-DMSO) 3.20 (2H, t), 3.82 (3H, s), 3.94 (2H, t), 7.13-7.28 (2H, m), 7.38-7.58 (3H, m), 7.87 (1H, d), 7.98 (1H, s), 8.35 (1H, s), 8.55 (1H, d), 8.64 (1H, d).

EXAMPLE 10

1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl indoline.

A mixture of 1-(5-bromo-pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethylindoline (D14, 208 mg, 0.5 mmol), phenyl boronic acid (300 mg, 2.4 mmol), sodium carbonate (0.32 g, 3 mmol) and tetrakis (triphenylphosphine) palladium (0) (30 mg) in dimethoxyethane-water (5 ml-1 ml) was heated to reflux under argon for 10 h. The cooled reaction mixture was partitioned between ethyl acetate-half saturated brine. The organic extract was dried and evaporated affording a brown

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solid (0.14 g). Chromatography on silica, eluting with a gradient of 0-5% methanol in ethyl acetate afforded the title compound as a white crystalline solid (100 mg, 48%), m.p. 162-164° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.50 (3H, m), 7.80 (2H, m), 8.10 (1H, s), 8.30 (1H, m), 8.55 (1H, m), 8.75 (1H, m), 8.85 (1H, s).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

The following examples were similarly prepared:

EXAMPLE 11

1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methylthio-6-trifluoromethyl indoline.

Yield=73%, m.p.=208-214° C.

¹H NMR (D²O-DMSO) 2.50 (2H, s), 3.30 (2H, t), 4.20 (2H, t), 7.50 (4H, m), 7.70 (2H, m), 8.20 (1H, s), 8.30 (1H, m), 8.60 (1H, m), 8.75 (1H, m), 8.95 (1H, s).

EXAMPLE 12

1-[5-(3-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=29%, m.p.=113-114° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.55 (1H, m), 8.10 (1H, m), 8.15 (1H, s), 8.30 (1H, m), 8.60 (1H, d), 8.65 (1H, d), 8.80 (1H, d), 8.95 (2H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

EXAMPLE 13

1-[5-(4-Trifluoromethylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=48%, m.p.=199-202° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.89 (4H, m), 8.10 (1H, s), 8.35 (1H, m), 8.60 (1H, d), 8.80 (1H, d), 8.95 (1H, s).

EXAMPLE 14

1-[5-(4-Methylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=57%, m.p.=190-191° C.

¹H NMR (D²O-DMSO) 2.35 (3H, s), 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.30 (2H, d), 7.60 (2H, d), 8.15 (1H, s), 8.25 (1H, m), 8.55 (1H, d), 8.75 (1H, d), 8.85 (1H, s).

EXAMPLE 15

1-[5-(2-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=53%, m.p.=193-208° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (2H, m), 7.65 (2H, m), 8.10 (1H, s), 8.25 (1H, t), 8.60 (1H, d), 8.75 (1H, d), 8.90 (1H, s).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

EXAMPLE 16

1-[5-(3-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=30%, m.p.=165-167° C.

¹H NMR (D²O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.60 (1H, dd), 7.75 (1H, m), 8.0 (1H, m), 8.15 (1H, s), 8.30 (1H, t), 8.65 (1H, d), 8.70 (1H, d), 8.90 (1H, s).

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EXAMPLE 17

1-[5-(2-Pyrrolyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=20%, m.p.=218-219° C.

¹H NMR (D₂O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 6.20 (1H, m), 6.55 (1H, m), 6.90 (1H, m), 7.20 (1H, s), 8.15 (2H, m), 8.50 (1H, d), 8.60 (1H, d), 8.80 (1H, s).

EXAMPLE 18

1-[5-(4-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield=71%, m.p. 230-234° C.

¹H NMR (D₂O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.75 (2H, m), 8.15 (1H, s), 8.40 (1H, t), 8.65 (1H, d), 8.70 (2H, m), 8.85 (1H, d).

EXAMPLE 19

1-[2-(3-Pyridyl)-thiazol-4-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

A solution of acyl azide (D15) (370 mg, 1.6 mmol) in toluene (5 ml) was heated to reflux for 0.25 h. After cooling to room temperature, the solution of the isocyanate was added to a solution of 5-methoxy-6-trifluoromethyl indoline (0.35 g, 1.6 mmol) in dichloromethane (10 ml). Filtration and drying afforded the title compound as a white solid (100 mg, 15%), m.p. >200° C.

¹H NMR 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.45 (1H, m), 7.55 (1H, s), 8.15 (1H, s), 8.30 (1H, d), 8.65 (1H, dd), 9.15 (1H, m), 9.85 (1H, s).

EXAMPLE 20

1-[2-(2-Pyridyl)-thien-5-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

This was prepared from the corresponding acyl azide (D16) using the same procedure as for Example 19, affording the title compound as a pale yellow solid (0.45 g, 73%), m.p. 205-215° C.

¹H NMR (D₂O-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 6.80 (1H, d), 7.15 (1H, m), 7.25 (1H, s), 7.50 (1H, d), 7.75 (2H, m), 8.20 (1H, s), 8.45 (1H, m), 9.95 (1H, s).

EXAMPLE 21

1-(3-Fluoro-5-(4-methyl-3-pyridyl)phenylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline.

A mixture of 1-(3-fluoro-5-iodophenylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline (D17, 0.31 g, 0.65 mmol), 4-methyl-3-pyridylboronic acid (88 mg, 0.65 mmol), tetrakis(triphenylphosphine) palladium (0) (23 mg, 0.02 mmol) and sodium carbonate (0.31 g, 3.6 mmol) in 1,2-dimethoxyethane (20 mL) and water (2 mL) was heated under reflux for 24 h, then cooled and poured into water. The aqueous mixture was extracted with dichloromethane/methanol, and the organic extract was washed with brine, dried and evaporated. The residue was chromatographed on silica gel eluted with 2-3% methanol/dichloromethane to give the title compound, which was recrystallised from dichloromethane/petrol (80 mg, 28%), M.p. 191-5° C.

¹H NMR (d₆-DMSO) δ: 2.31 (3H, s), 3.28 (2H, t, J=8), 3.85 (3H, s), 4.19 (2H, t, J=8), 6.94 (1H, d, J=8), 7.22 (1H, s), 7.37 (1H, d, J=6), 7.42 (1H, s), 7.61 (1H, d, J=12), 8.12 (1H, s), 8.40 (1H, s), 8.46 (1H, d, J=6), 8.82 (1H, s).

MS (API): Found m/z=446 (MH⁺), C₂₂H₁₈N₃O₂F₄ requires M+1=446

EXAMPLE 22

1-(5-(2,6-Difluorophenyl)-3-pyridylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline.

A solution of 5-(2,6-difluorophenyl)nicotinoyl azide (D20, 0.46 g, 1.8 mmol) in toluene (10 mL) was heated

under reflux for 2 h. After cooling, a solution of 5-methoxy-6-trifluoromethyl indoline (D11, 0.40 g, 1.8 mmol) in dichloromethane (10 mL) was added and the mixture was stirred overnight at room temperature. The precipitate was filtered off and washed with petrol. The crude product was recrystallised from dichloromethane/petrol to give the title compound (0.66 g, 82%), M.p. 217-9° C.

¹H NMR (d₆-DMSO) δ: 3.29 (2H, t, J=8), 3.84 (3H, s), 4.21 (2H, t, J=8), 7.22 (1H, s), 7.29 (2H, t, J=7), 7.56 (1H, quintet, J=7), 8.11 (1H, s), 8.15 (1H, s), 8.32 (1H, s), 8.80 (1H, s), 9.93 (1H, s).

MS (API): m/z=450 (MH⁺), C₂₂H₁₆N₃O₂F₅ requires M+1=450

Found: C, 54.84; H, 3.69; N, 8.64%

C₂₂H₁₆N₃O₂F₅ requires C, 58.80; H, 3.59; N, 9.35%

EXAMPLE 23

6-Chloro-5-methyl-1-(4-methyl-3-(pyrid-3-yl)-phenylcarbamoyl) indoline

4-Methyl-3-(pyrid-3-yl) aniline (0.30 g, 0.0016 mole) in dry dichloromethane (20 mL) was added, under argon, to 1,1'-carbonyldiimidazole in dry dichloromethane (10 mL) (0.30 g, 0.0018 mole) and stirred at ambient temperature for 1 hour. The solvent was removed in vacuo and the residue dissolved in dry dimethylformamide (30 mL). 6-Chloro-5-methylindoline (see WO 95/01976) (0.27 g, 0.0016 mole) in dry dimethylformamide (10 mL) was added and the mixture heated to 100° C. for 1 hour. After cooling to ambient temperature, the solvent was removed in vacuo and the residue diluted with deionised water (15 mL), extracted into dichloromethane (2x20 mL), dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with 3% methanol/dichloromethane and the resulting solid recrystallised from ethyl acetate/methanol/60-80° petrol ether to afford the title compound (0.31 g, 57%) as a cream solid (mp 202-203° C.).

¹H NMR (270 MHz, d₆-DMSO) δ: 2.20 (3H, s), 2.24 (3H, s), 3.12 (2H, t, J=7), 4.13 (2H, t, J=7), 7.14 (1H, s), 7.25 (1H, d, J=7), 7.42-7.61 (3H, m), 7.81 (1H, t, J=3, 7), 7.89 (1H, s), 8.49-8.69 (3H, m).

MS (EI) m/z=377 (M⁺)

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

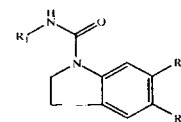
EXAMPLE 24

1-(4-Methyl-3-(pyrid-3-yl) phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl indoline

4-Methyl-3-(pyrid-3-yl) aniline (0.35 g, 0.0019 mole) in dry dichloromethane (20 mL) was added, under argon, to 1,1'-carbonyldiimidazole (0.34 g, 0.0021 mole) in dry dichloromethane (10 mL) and stirred at ambient temperature for 1 hour. The solvent was removed in vacuo and the residue dissolved in dry dimethylformamide (10 mL). 5-Thiomethyl-6-trifluoromethyl indoline (D17) (0.44 g, 0.0019 mole) in dry dimethylformamide (5 mL) was added and the mixture heated to 100° C. for 2 hours. After cooling to ambient temperature, the solvent was removed in vacuo and the residue diluted with deionised water (15 mL), extracted into dichloromethane (2x20 mL), dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 3% methanol/dichloromethane and the resulting solid was recrystallised from ethyl acetate/60-80° petrol ether to afford the title compound (0.11 g, 13%) as a cream solid (mp 221-223° C.).

¹H NMR (200 MHz; d₆-DMSO) δ: 2.20 (3H, s), 2.55 (3H, s), 3.38 (2H, t, J=8), 4.20 (2H, t, J=8), 7.26 (1H, d, J=9),

-continued-



Example No.	R ₁	R ₂	R ₃	R ₄	M.P. °C.
143	4-(Pyrid-3-yloxy)phenyl	OMe	CF ₃	CF ₃	193-194
144	6-(Pyrid-3-yloxy)pyrid-3-yl	SMc	CF ₃	CF ₃	204-206
145	6-(Pyrid-4-yloxy)pyrid-3-yl	NMc	CF ₃	CF ₃	714-716
146	6-(Pyrid-4-yloxy)pyrid-3-yl	OMe	CF ₃	CF ₃	704-206
147	4-(Pyrid-4-yloxy)phenyl	SMc	CF ₃	CF ₃	206-209
148	3-(Pyrid-3-yloxy)aminocarbonylphenyl	SMc	CF ₃	CF ₃	210-215
149	3-(Pyrid-2-yl)propenylphenyl	SMc	CF ₃	CF ₃	145-146
150	3-(Pyrid-2-yl)-1-hydroxypropylphenyl	SMc	CF ₃	CF ₃	76-80
151	4-(Pyrid-4-yloxy)aminocarbonylphenyl	SMc	CF ₃	CF ₃	136-140
152	3-(Pyrid-2-yloxy)aminocarbonylphenyl	SMc	CF ₃	CF ₃	110-112
153	3-(Pyrid-2-yloxy)aminocarbonylphenyl	NMc	CF ₃	CF ₃	92-94
154	3-(Pyrid-2-yl)methylcarbamoylphenyl	NMc	CF ₃	CF ₃	116-118
155	6-(Phenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	202-203
156	6-(2,4-Dimethylpyrid-3-yloxy)pyrid-3-yl	OMe	CF ₃	CF ₃	218-221
157	6-(2-Methylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	276-228
158	6-(4-Methoxyphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	188-189
159	6-(4-Fluoro-2-methylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	208-209
160	6-(2,4-Dimethylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	236-238
161	6-(2-Chlorophenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	238-240
162	6-(2,3-Dichlorophenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	215-220
163	6-(4-Carbamoylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	245-248
164	6-(2-Trifluoromethylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	237-238
165	6-(3-Trifluoromethylphenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	193-194
166	6-(2,6-Dichlorophenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	230-233
167	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Me	Cl	Cl	181-183
168	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Cl	Cl	Cl	225-228
169	4-Fluoro-3-(5-pyrimidinyl)phenyl	Cl	Cl	Cl	132-135
170	5-Fluoro-3-(5-pyrimidinyl)phenyl	Cl	Cl	Cl	260
171	4-Fluoro-3-(5-pyrimidinyl)phenyl	Me	Cl	Cl	211-213
172	5-Fluoro-3-(5-pyrimidinyl)phenyl	Br	CF ₃	CF ₃	214-218
173	6-(2-Methyl-1-oxo-3-oxo-3-oxo-3-yl)	OMe	CF ₃	CF ₃	252-257
174	4-Fluoro-3-(4-pyridyl)phenyl	Br	CF ₃	CF ₃	200-201
175	6-(3-Cyanophenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	136-138
176	6-(4-Cyano-phenoxy)pyrid-3-yl	OMe	CF ₃	CF ₃	188-189
177	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Br	CF ₃	CF ₃	211-213

Pharmacological data

[¹¹C]-mesorhizine binding to rat or human 5-HT_{2c} clones expressed in 293 cells in vitro

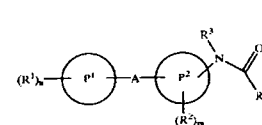
Compounds were tested following the procedure outlined in WO 94/04533. The compounds of examples 1 to 165 have pK_i values of 5.8 to 9.7.

Reversal of MCPP-induced Hypolocomotion

Compounds were tested following the procedure outlined in WO 94/04533. The compound of examples 1, 3, 7, 8, 21, 24, 25, 26, 31, 40, 42, 52, 53, 54, 55, 77, 78, 79, 80 and 81 have ID₅₀ between 0.5 and 5.5 mg/kg p.o.

We claim:

1. A compound of formula (I) or a salt thereof:



wherein:

P¹ is pyridyl;

P² is phenyl;

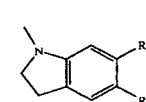
A is a bond or a chain of 1 to 5 atoms optionally substituted by C₁₋₆alkyl;

R¹ and R² groups are each independently hydrogen, C₁₋₆alkyl optionally substituted by NR¹²R¹³, C₂₋₆alkenyl, C₂₋₆alkynyl, cyano, halogen, CF₃, NR¹²R¹³, CH₃, OCF₃, COR¹⁴, CH₂OR¹⁴ or OR¹⁴ where R¹², R¹³ and R¹⁴ are independently hydrogen or C₁₋₆alkyl;

n and m are independently 0, 1 or 2;

R³ is hydrogen or C₁₋₆alkyl;

R⁴ is a group of formula (ii):



in which:

R⁵ and R⁶ are independently hydrogen, C₁₋₆alkyl optionally substituted by one or more fluorine atoms.

C_{1-6} alkylthio, C_{1-6} alkoxy or halogen, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is:

1-[3-(Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-(Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[3-(Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[3-(Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[3-(Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-(Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[2-(Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-Methyl-3-(3-Pyridyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[2-Fluoro-5-(3-pyridyl) phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-(3-Fluoro-5-(4-methyl-3-pyridyl)phenylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline,

6-Chloro-5-methyl-1-[4-methyl-3-(pyrid-3-yl)-phenylcarbamoyl] indoline,

1-(4-Methyl-3-(pyrid-3-yl) phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl indoline,

1-(3-Fluoro-5-(pyrid-3-yl)phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl indoline,

1-(4-Chloro-3-(pyrid-3-yl)phenylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline,

1-[4-Methyl-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[5-Bromo-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-4-Butyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-Methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[5-Fluoro-4-methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[3-Bromo-4-methyl-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[3-(4-Methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[5-Ethyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

6-Chloro-5-methyl-1-[4-methyl-3-(4-methyl-3-pyridyl)phenyl carbamoyl] indoline,

1-[3-(pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[3-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[3-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[4-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[4-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,

1-[3-(3-pyridylcarbonyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[3-(Pyrid-3-yl-aminosulphonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-4-yl-methylamino carbonyl)phenyl carbamoyl] indoline,

Trans-5-Methylthio-6-trifluoromethyl-1-[4-(2-ethenyl-4-pyridyl)]-phenyl carbamoyl]-indoline,

5-Methylthio-6-trifluoromethyl-1-[4-(2-ethyl(4-pyridyl)]-phenyl carbamoyl] indoline,

5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-3-ylmethyl)amido phenyl carbamoyl] indoline,

5-Methylthio-6-trifluoromethyl-1-[3-(pyrid-4-ylmethyl)amidophenylcarbamoyl] indoline,

5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-2-ylmethyl)amidophenylcarbamoyl] indoline,

1-[4-4-Fluoro-3-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

1-[4-Chloro-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 in which A is a bond.

4. A compound according to claim 1 in which R^2 is hydrogen, halogen, methyl, CF_3 or OCT_3 .

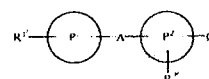
5. A compound according to claim 1 in which R^3 is hydrogen.

6. A compound according to claim 1 in which R^6 is trifluoromethyl or halogen and R^7 is C_{1-6} alkoxy, C_{1-6} alkylthio or C_{1-6} alkyl.

7. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier or excipient

8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



with a compound of formula (III);



wherein A, P^1 and P^2 are as defined in formula (I), C and D contain the appropriate functional group(s) necessary to form the moiety $-NR^5CO$ when coupled, the variables R^{1a} , R^{2a} , R^{3a} and R^{4a} are R^1 , R^2 , R^3 and R^4 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R^{1a} , R^{2a} , R^{3a} and R^{4a} , when other than R^1 , R^2 , R^3 and R^4 respectively to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and R^4 and forming a pharmaceutically acceptable salt thereof; or

(b) the coupling of a compound of formula (IV);



R^3 and R^4 respectively to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and R^4 and forming a pharmaceutically acceptable salt

9. A method of antagonizing $5HT_{2C}$ receptors by administering to a patient in need thereof, a compound of claim 1.

10. A method of treating CNS disorders by administering to a patient in need thereof, a compound of claim 1.

11. A method of treating anxiety or depression by administering to a patient in need thereof, a compound of claim 1.

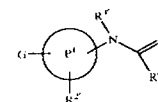
12. A compound of claim 1 which is 1-[3-Fluoro-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline

13. A method of treating anxiety or depression by administering to a patient in need thereof, a compound of claim 12.

14. A pharmaceutical composition which comprises a compound according to claim 12 and a pharmaceutically acceptable carrier or excipient.

* * * * *

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with a compound of formula (V),



wherein P^1 , P^2 , R^{1a} , R^{2a} , R^{3a} and R^{4a} are as defined above and E and G contain the appropriate functional group(s) necessary to form the A moiety when coupled and thereafter optionally and as necessary and in any appropriate order, converting any R^{1a} , R^{2a} , R^{3a} and R^{4a} , when other than R^1 , R^2 ,

[54] ANTI-DEMENTIA AGENT

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[52] U.S. Cl. 514/277
[58] Field of Search 514/277

[56] References Cited

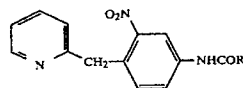
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32629 3/1985 Japan

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Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Fitzpatrick, Cella, Harper & Scinto

ABSTRACT

Disclosed are anti-dementia agents comprising an anti-amnestically effective amount of a benzylpyridine derivative of the formula



wherein R is an alkyl group. The invention also pertains to the treatment of dementia by administration of such anti-dementia agent.

4 Claims, No Drawings

ANTI-DEMENTIA AGENT

BACKGROUND OF THE INVENTION

The present invention relates to an anti-dementia agent, and more particularly to an anti-dementia agent comprising an anti-amnestically effective amount of a benzylpyridine derivative.

It is disclosed in Japanese Published Examined Patent Application No. 32629/85 that benzylpyridine derivatives related to the present invention possess an antidepressive and antiinflammatory activity. However, it is unknown that these compounds have an anti-amnestically activity and therefore, their use as an anti-dementia agent is unknown.

With the prolongation of the average span of life in recent years, the number of people with senile dementia has been rapidly increasing. Such people are afflicted with memory loss often accompanied with wandering, unclear and dangerous behavior or symptoms such as personality change and aphasia.

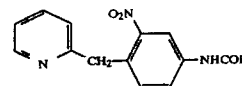
To treat senile dementia, a variety of drugs have been administered to patients in the clinical field.

Representative examples include cerebral metabolism activators such as idebenone, calcium hopatenate, and amantadine hydrochloride; cerebrovasodilators such as vinpocetine and dihydroergotoxin mesylate, (described in "Senile Dementia and Anti-dementia Agents—Aiming at Developing New Anti-dementia Agents", edited by Kenji Kosaka and Takeshi Ishii, Japan Society for Science and Technology (1987)); and oxiracetam, an experimental treatment.

Use of these drugs alleviates subjective symptoms relating to emotion. However, the main symptoms of senile dementia involving deterioration of intellectual functions such as decrease in impressibility and disorientation, are not necessarily alleviated by these treatments. Therefore, it is desirable to develop new drugs which alleviate symptoms of memory deterioration such as impressibility and orientation. To this end, it has been found that certain benzylpyridine derivatives have a strong anti-amnestically activity and are thus useful as anti-dementia agents.

SUMMARY OF THE INVENTION

The present invention provides an anti-dementia agent comprising as an anti-amnestically effective amount of a benzylpyridine derivative (hereinafter referred to as Compound (I)) represented by formula (I):



wherein R represents an alkyl group and pharmaceutically acceptable acid addition salts thereof.

In the definition of R in formula (I), the alkyl group represents a straight-chain or branched alkyl group having 1 to 17 carbon atoms, and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl and heptadecyl groups.

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Specific examples of Compound (I) useful in the present invention include the following compounds.

1. α -(p-Acetylamino-o-nitrobenzyl)pyridine (Compound A)
2. α -(p-Butyrylamino-o-nitrobenzyl)pyridine (Compound B)
3. α -(p-Valerylaminoo-nitrobenzyl)pyridine (Compound C)
4. α -(p-Hexanoylamino-o-nitrobenzyl)pyridine (Compound D)
5. α -(p-Octanoylamino-o-nitrobenzyl)pyridine (Compound E)
6. α -(p-Decanoylamino-o-nitrobenzyl)pyridine (Compound F)
7. α -(p-Myristylamino-o-nitrobenzyl)pyridine (Compound G)
8. α -(p-Stearylamino-o-nitrobenzyl)pyridine (Compound H)

The properties of these compounds are summarized in Table I.

TABLE I

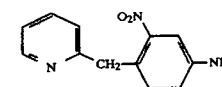
Compound	R in General Formula (I)	Melting Point (°C.)	Molecular Formula
A	CH ₃	159-160	C ₁₄ H ₁₃ N ₃ O ₃
B	(CH ₂) ₂ CH ₃	124	C ₁₆ H ₁₇ N ₃ O ₃
C	(CH ₂) ₃ CH ₃	96-97	C ₁₇ H ₁₉ N ₃ O ₃
D	(CH ₂) ₄ CH ₃	70-73	C ₁₈ H ₂₁ N ₃ O ₃
E	(CH ₂) ₆ CH ₃	92-93	C ₂₀ H ₂₅ N ₃ O ₃
F	(CH ₂) ₈ CH ₃	69-70	C ₂₂ H ₂₉ N ₃ O ₃
G	(CH ₂) ₁₂ CH ₃	83-84	C ₂₆ H ₃₇ N ₃ O ₃
H	(CH ₂) ₁₆ CH ₃	87-88	C ₃₀ H ₄₅ N ₃ O ₃

The present invention further provides a method of treating dementia comprising daily administration of an anti-amnestically effective amount of a benzylpyridine derivative.

DETAILED DESCRIPTION

Compounds A-H are known compounds described in Japanese Published Examined Patent Application No. 32629/85 or compounds which can be prepared by known methods.

For example, Compound (I) results form acylating α -(p-amino-o-nitrobenzyl)pyridine represented by formula (II):



with an acylating agent represented by formula (III):



wherein R has the same significance as described above or an acylating agent functionally equivalent thereto (for example, acid anhydrides, acid halides, and activated esters) in a suitable solvent.

Compound C is not described in said publication, and a process for preparing Compound C is described in the Reference Example.

Compound (I) which is the active ingredient in the present invention can be used as a free base or in the form of pharmaceutically acceptable acid addition salts. Suitable examples of the salts are hydrochlorides, hy-

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drobromides, sulfates, phosphates, acetates, oxalates, succinates, malates, tartrates, citrates, fumarates, etc. The salts are readily formed by treating Compound (I) with the corresponding acid in a conventional manner.

Although compound (I) or acid addition salts thereof may be used alone, they are typically formulated into various pharmaceutically acceptable preparations. Such a pharmaceutical composition can be prepared by uniformly mixing an antiamnesic effective amount of Compound (I) or an acid addition salt thereof as the active ingredient and a pharmaceutically acceptable carrier. The carrier can take various forms depending upon the form of preparation desired for administration. These pharmaceutical compositions are preferably in a unit dose form suited for oral administration or administration through injection.

For the preparation of compositions in a form suited for oral administration, any useful pharmaceutically-acceptable carriers can be used. For example, oral liquid preparations such as a suspension and a syrup can be prepared using water, sugars such as sucrose, sorbitol and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil and soybean oil, aseptic such as alkyl p-hydroxybenzoates, flavors such as strawberry flavor and peppermint, etc.

Powders, pills, capsules and tablets can be prepared using excipients such as lactose, glucose, sucrose, mannitol and Avicel, disintegrators such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin, surface active agents such as fatty acid esters, plasticizers such as glycerine, etc.

Tablets and capsules are most useful unit oral preparations due to the readiness of administration. For the preparation of tablets and capsules, solid pharmaceutical carriers are used.

A solution injection can be prepared using a carrier such as distilled water, a salt solution, a glucose solution or a mixture of a salt solution and a glucose solution.

The effective dose and the administration schedule of Compound (I) or pharmaceutically acceptable acid addition salts thereof vary depending upon mode of administration, age, body weight and conditions of a patient, etc., but generally, it is desirable to give the

effective compound in a daily dose of 5 to 500 mg, preferably 20 to 100 mg at one time or in 2 to 3 parts.

Compound (I) used in the present invention has an excellent antiamnesic activity. The following experiments tested the antiamnesic activity of Compound (I) and the toxicity thereof. The antiamnesic activity was measured by using the light-and-dark box method. Symbols of the test compounds correspond to said compounds (Table 1).

EXPERIMENT I

Activity on Electroconvulsive Shock-induced Amnesia

As the test animals, 14 to 15 dd strain male mice (body weight: 23-28 g) were used for each group. As the experimental device, a step-through type passive avoidance training box composed of a light room and a dark room (light room: 130×90×90 mm; dark room 180×90×90 mm) was used.

In the acquisition trial where learning takes place, mice put in the light room move to the dark room. Each time the mice entered the dark room, electric stimulation of 0.25 mA was given to four limbs of each mouse for 2 seconds from grids on the floor.

Amnesia-inducing treatment was performed by electroconvulsive shock (2,000 V, 25 mA, 0.2 seconds) immediately after completion of the acquisition trial. After 24 hours, the test trial was conducted to measure the length of time before the mice entered the dark room. This time period, termed the reaction latent time, was recorded. A reaction latent time longer than 600 seconds was recorded as 600 seconds.

A test compound was suspended in 0.3% sodium carboxymethyl cellulose (hereinafter referred to as "CMC"). That suspension and a control of 0.3% CMC without any test compound were respectively administered to the mice 60 minutes prior to each test trial.

The effect was evaluated by Student-t test to determine whether there was a significant difference in reaction latent time between the amnesia control group and the group administered with the test compound in the passive avoidance test trial. The results are shown in Tables 2-1 to 2-6.

TABLE 2-1

Antiamnesic Activity (mouse)				
Test Compound	Dose (mg/kg, oral)	Amnesia-inducing Treatment	Number of Animals Used	Test Trial Mean Reaction Latent Time (second)
Normal control	—	—	15	391.1 ± 42.6
Amnesic control	—	+	29	76.0 ± 14.3
Compound A	5	+	14	76.3 ± 10.6
"	10	+	14	146.7 ± 31.1
"	20	+	15	114.5 ± 28.0
"	40	+	15	135.2 ± 27.4
"	80	+	15	144.9 ± 32.3
"	160	+	15	204.9 ± 35.6
Amnesic control	—	+	30	60.2 ± 12.7
Compound B	20	+	15	90.5 ± 37.5
"	40	+	15	160.5 ± 49.6
"	80	+	15	253.7 ± 61.6
"	160	+	15	172.8 ± 60.2
Normal control	—	—	15	330.5 ± 39.9
Amnesic control	—	+	30	47.5 ± 7.5

P < 0.0001*

P < 0.05

P < 0.01

P < 0.001

P < 0.05

P < 0.01

P < 0.001

P < 0.05

P < 0.01

P < 0.001

P < 0.05

P < 0.01

P < 0.001

P < 0.05

P < 0.01

P < 0.001

P < 0.05

P < 0.01

TABLE 2-1-continued

Antiamnesic Activity (mouse)				
Test Compound	Dose (mg/kg, oral)	Amnesia-inducing Treatment	Number of Animals Used	Test Trial Mean Reaction Latent Time (second)
control	—	—	15	86.9 ± 12.5
Compound D	20	+	15	203.1 ± 40.4
"	40	+	15	274.8 ± 60.9
"	80	+	15	243.4 ± 52.5
"	160	+	15	451.3 ± 41.5
Normal control	—	—	15	100.9 ± 8.5
Amnesic control	—	+	30	138.9 ± 22.2
Compound G	20	+	15	110.5 ± 25.4
"	40	+	15	136.3 ± 17.6
"	80	+	15	247.7 ± 58.0
"	160	+	15	451.8 ± 32.8
Normal control	—	—	30	82.3 ± 11.8
Amnesic control	—	+	15	65.9 ± 10.8
Idobenzone	2.5 ^a	+	15	124.3 ± 20.3
"	5	+	15	69.5 ± 18.9
"	10	+	15	73.3 ± 12.3
"	20	+	12	187.4 ± 57.5
Calcium Hopitenate	160 ^b	+	12	138.3 ± 32.8
Vinpocetine	2.5 ^a	+	15	90.2 ± 37.9
"	5	+	15	86.2 ± 18.6
"	10	+	15	72.3 ± 15.2
"	1.25 ^a	+	15	99.5 ± 16.5
Dihydroergocristine mesylate	2.5	+	15	91.5 ± 17.3
"	5	+	15	71.3 ± 18.1
Oxiracetam	20 ^b	+	12	112.5 ± 40.0
"	40	+	12	205.9 ± 54.2
"	80	+	12	151.3 ± 44.0
Normal control	—	—	15	433.0 ± 47.4
Amnesic control	—	+	26	172.2 ± 30.4
Amitriptyline	10	+	15	147.3 ± 37.6
"	20	+	12	198.6 ± 51.5
"	40	+	14	134.9 ± 28.1
"	80	+	9	84.1 ± 17.9
"	10	+	13	163.2 ± 51.7
Desipramine	20	+	15	111.2 ± 26.1
"	40	+	14	115.4 ± 38.8
"	80	+	14	80.4 ± 16.1
Imipramine	10	+	15	236.3 ± 52.6
"	20	+	14	263.4 ± 59.1
"	40	+	15	180.0 ± 47.9
"	80	+	14	174.9 ± 44.5

Comparison with Normal Control Group (the same shall apply hereinafter.)

^aintraperitoneal administration

^boral administration

As is evident from the experimental results shown above, the reaction latent time was significantly shortened (P < 0.0001) by the amnesia-inducing treatment (electroconvulsive shock) in the amnesic control group, compared with the normal control group. With Compound B in Table 2-1, the reaction latent time was significantly prolonged at doses of 10, 40, 80 and 160 mg/kg, compared with the amnesic control group. Also with Compounds A, C, D and G in Tables 2-2, 2-3 and 2-4, the reaction latent time was prolonged.

Table 2-5 shows the results with various control drugs. None of them resulted in a significant improvement in performance over the amnesic control group.

Table 2-6 shows the results with antidepressants as reference compounds. The three drugs all caused remarkable change in behavior. In particular, ataxia in motor coordination is remarkable. The order of its intensity was:

amitriptyline > desipramine > imipramine

EXPERIMENT 3

Activity on Amnesia due to Damage of Basal Forebrain

As the test animals, 13 to 39 Wistar strain male rats (body weight: 250-300 g) were used for each group. Amnesia-inducing treatment was effected by damaging the basal forebrain through injection of 0.2 μ g/ μ l kainic acid at the basal forebrain from both sides under anesthesia with pentobarbital-Na.

After the recovery period of about 10 days following the operation, the trial for acquiring learning (training) was performed in a similar manner using the same experimental device as in Experiment 2. After 24 hours, the test trial was carried out.

Measurement of the latent time was carried out in a similar manner as in Experiment 1. Test Compound B and idebenone were suspended in 0.3% CMC, and the suspension was administered twice 60 minutes prior to the training and 60 minutes prior to the test.

Alternatively, the suspension was administered for 9 consecutive days after the recovery period. In this case, Compound B was orally administered and idebenone was intraperitoneally administered; and the training was conducted on day 8 and the test trial was conducted on day 9.

The test method using the rats with basal forebrain lesion shows an anti-amnesic activity on a model of Alzheimer disease. Namely, in a human patient with senile dementia of the Alzheimer type showing memory deficits as a main symptom, choline acetyltransferase activity in the cerebral cortex and hippocampus is markedly reduced. This is due to remarkable fall off of

In general, a worsening tendency was noted in high doses (40 to 80 mg/kg). Although some results showed a tendency of prolonging the reaction latent time (10 and 20 mg/kg), there was no significant difference and thus the results are not considered as an evidence for specific effect.

EXPERIMENT 2

Activity on Scopolamine-induced Amnesia

As the test animals, 10 to 30 Wistar strain male rats (body weight: 250-300 g) were used for each group. As the experimental device, a step-through type passive avoidance training box composed of a light room and a dark room (light room: 400 $\times$ 400 $\times$ 400 mm; dark room: 200 $\times$ 150 $\times$ 200 mm) was used.

In the acquisition trial where learning is made, rats put in the light room move to the dark room. Each time the rats entered the dark room, electric stimulation of 2 mA was given to four limbs of each rat for 3 seconds from grids on the floor.

Amnesia-inducing treatment was performed by intraperitoneal administration of scopolamine in a dose of 1.5 mg/kg 30 minutes prior to the acquisition trial (training). The test trial was carried out 24 hours after the training and the reaction latent time was measured in a similar manner as in Experiment 1.

Test Compound B and idebenone were suspended in 0.3% CMC, and imipramine was dissolved in physiological saline. Compound B and imipramine were orally administered 60 minutes before the training and idebenone was intraperitoneally administered 30 minutes before the training. The results are shown in Table 3.

TABLE 3

Antiamnesic Activity (rat)					
Test Compound	Dose (mg/kg)	Inducing Treatment	Number of Rats that Reached Standard Point ^(a)	Test Trial Mean Reaction Latent Time (second)	Comparison with Amnesic Control Group (t-test)
Normal control	—	—	14/21	466.1 $\pm$ 45.3	—
Amnesic control	—	+	0/30	54.7 $\pm$ 9.9	P < 0.0001*
Compound B	2.5	+	1/20	94.3 $\pm$ 30.3	No significant difference
"	5	+	3/17	148.9 $\pm$ 54.3	P < 0.05
"	10	+	4/20	201.2 $\pm$ 53.5	P < 0.01
"	20	+	2/17	172.4 $\pm$ 52.6	P < 0.01
"	40	+	4/20	171.2 $\pm$ 52.5	P < 0.05
Amnesic control	—	+	0/10	95.2 $\pm$ 44.8	P < 0.001
Idebenone	2.5	+	0/10	58.4 $\pm$ 19.7	no significant difference
"	5	+	0/10	110.6 $\pm$ 30.2	"
"	10	+	0/10	148.8 $\pm$ 60.2	"
Amnesic control	—	+	1/26	128.1 $\pm$ 28.2	P < 0.001
Imipramine	20	+	1/13	110.4 $\pm$ 44.3	no significant difference
"	40	+	1/13	186.6 $\pm$ 54.0	"

^(a)Standard point: 600 seconds

As is seen from the results in Table 3, Compound B showed an anti-amnesic activity by oral administration in a dose of 5 to 40 mg/kg, but idebenone and imipramine showed no anti-amnesic activity.

nerve cells in nucleus basalis Meynert, which is the initiating nucleus of cholinergic neuron, responsible for projection on the cerebral cortex. Lesion of the basal forebrain corresponding to nucleus basalis Meynert in rats causes disturbance in learning. The results in the learning-disturbed model animals are shown in Table 4.

TABLE 4

Antiamnesic Activity (rat)					
Test Compound	Dose (mg/kg)	Inducing Treatment	Number of Rats that Reached Standard Point ^(a)	Test Trial Mean Reaction Latent Time (second)	Comparison with Amnesic Control Group (t-test)
Normal control	—	—	8/13	442.2 $\pm$ 69.2	—
Sham-lesion control	—	—	6/13	364.7 $\pm$ 70.3	no significant difference ^(d)
Lesion control	—	+	0/39	45.0 $\pm$ 15.3	P < 0.001 ^(c)
Compound B ^(b)	2.5	+	1/19	121.8 $\pm$ 36.5	P < 0.05 ^(d)
"	5	+	5/19	215.5 $\pm$ 60.0	P < 0.001
"	10	+	3/18	191.2 $\pm$ 57.7	P < 0.01
"	20	+	4/18	209.2 $\pm$ 60.2	P < 0.001
"	40	+	2/18	163.0 $\pm$ 51.5	P < 0.01
Idebenone ^(b)	10	+	0/14	52.0 $\pm$ 22.1	no significant difference ^(d)
"	20	+	0/14	15.2 $\pm$ 3.4	"
"	40	+	0/14	27.7 $\pm$ 8.9	"
Lesion control	—	+	2/24	104.0 $\pm$ 35.2	P < 0.001 ^(c)
Compound B ^(b)	2.5	+	4/13	243.2 $\pm$ 73.7	no significant difference ^(d)
"	10	+	5/13	239.0 $\pm$ 78.5	P < 0.05
"	2.5	+	7/13	382.8 $\pm$ 80.2	P < 0.01 ^(d)
Idebenone ^(b)	10	+	3/13	178.2 $\pm$ 68.2	no significant difference

^(a)Standard point: 600 seconds

^(b)Administered twice

^(c)Administered for 9 days

^(d)Compared with the normal control group

^(e)Compared with the sham-lesion control group

^(f)Compared with the lesion control group

As shown in Table 4, Compound B showed an activity of alleviating learning disturbance when administered twice in a dose of 2.5 mg/kg or more. Idebenone showed no improving effect when administered twice in a similar manner in a dose of 10 to 40 mg/kg. On the other hand, in administration for 9 consecutive days, a significant (P < 0.05) improving activity was noted with Compound B in a dose of 10 mg/kg. With idebenone, an apparent improving effect was noted by intraperitoneal administration of 2.5 mg/kg. Thus, the effect was noted with Compound B both in administration of two equal doses and consecutive administration, whereas it was noted that idebenone showed the effect only in consecutive administration.

From the foregoing results, it is clear that Compound B shows an apparent improving activity in the learning-disturbed animal model.

EXPERIMENT 4

Acute Toxicity

Acute toxicity test was carried out by orally administering Compound (I) used in the present invention to mice (male) and rats (male). The results are shown in Table 5.

TABLE 5

Acute Toxicity (LD ₅₀ mg/kg, oral)		
Test Compound	Mouse	Rat
A	660	> 200
B	1534	> 850
C	> 300	> 100
D	> 1000	> 100
E	> 1000	> 100
F	> 1000	> 100

TABLE 5-continued

Acute Toxicity (LD ₅₀ mg/kg, oral)		
Test Compound	Mouse	Rat
G	> 1000	> 100

As shown in Table 5, all the compounds have only a weak toxicity and thus can be safely used over a wide range of dosages.

The results of the foregoing experiments show that the invention described herein is useful for treating individuals suffering from senile dementia, and the invention further describes the anti-amnesic effective daily dosage and methods of dosage administration.

Certain embodiments of the invention are illustrated in the following examples.

EXAMPLE 1

Tablets

2000 tablets are prepared in a conventional manner, each having the following composition and containing 20 mg of the active ingredient.

Compound B (100 g), 600 g of lactose and 250 g of potato starch were mixed, and 400 g of 10% aqueous solution of hydroxypropyl cellulose was added to the mixture. The mixture was kneaded, granulated and dried in a conventional manner. Then the granules were made uniform to form granules for tableting. After 10 g of the magnesium stearate was added, the mixture was formed into tablets using a tableting machine (Kikusui, Model RT-15) equipped with a pestle having a diameter of 8 mm to give a preparation containing 20 mg of the active ingredient in one tablet.

634

Formulation	
Compound B	20 mg
Lactose	120 mg
Potato starch	50 mg
Hydroxypropyl cellulose	3 mg
Magnesium stearate	2 mg
	200 mg

EXAMPLE 2

Granules

Compound B (20 g), 640 g of lactose and 300 g of corn starch were mixed, and 400 g of 10% aqueous solution of hydroxypropyl cellulose was added to the mixture. The mixture was kneaded, granulated and dried in a conventional manner to give granules. In 1000 mg of the granules, 20 mg of the active ingredient was contained.

Formulation	
Compound B	20 mg
Lactose	640 mg
Corn starch	300 mg
Hydroxypropyl cellulose	40 mg
	1000 mg

EXAMPLE 3

Capsules

Compound B (200 g), 995 g of Avicel and 5 g of magnesium stearate were mixed in a conventional manner. The mixture was loaded into hard capsule No. 4 with a capsule filling machine (Zanasi, Model LZ-64) (120 mg per capsule) to give capsules.

Formulation	
Compound B	20 mg
Avicel	99.5 mg
Magnesium stearate	0.5 mg
	120 mg

REFERENCE EXAMPLE

Preparation of
 α -(p-Valerylamino-o-nitrobenzyl)pyridine (Compound C)

To a solution of 2.5 g (10.9 mmol) of α -(p-amino-o-nitrobenzyl)pyridine in 25 ml of n-valeric acid was added 2.2 ml (11.2 mmol) of n-valeric anhydride. The mixture was heated at 90 to 100° C. for 4 hours. After the reaction mixture was allowed to cool to room temperature, the solvent was distilled off under reduced pressure, and 30 ml of water was added to the residue. Aqueous sodium hydroxide solution (10 N) was added dropwise with stirring and the crystals formed were taken by suction filtration. The crude crystals were recrystallized from methanol to give 1.86 g (59.8%) of Compound C as yellowish orange needles.

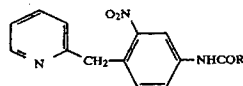
Melting point: 96°-97° C.

Elemental analysis (as $C_{17}H_{19}N_3O_3$).

Calc'd (%) C: 65.14 H: 6.11 N: 13.41. Found (%) C: 65.14 H: 6.15 N: 13.25. ^1H -NMR δ ($CDCl_3$): 0.92 (3H, t, J=2.4Hz), 1.39 (2H, m), 1.68 (2H, m), 2.34 (2H, t, J=2.4Hz), 4.44 (2H, s), 7.13-7.19 (2H, m), 7.22-7.31 (1H, m), 7.60-7.71 (2H, m), 8.05-8.09 (2H, m), 8.47-8.50 (1H, m).

What is claimed is:

1. A method of treating dementia which comprises administering to a patient suffering from dementia an antiamnestically effective amount of a benzylpyridine derivative of the formula:



wherein R represents an alkyl group or a pharmaceutically acceptable acid addition salt thereof.

2. A method of treating dementia according to claim 1 wherein said pharmaceutically acceptable acid addition salts are selected from the group consisting of hydrochloride, hydrobromide, sulfate, phosphate, acetate, oxalate, succinate, malate, tartrate, citrate and fumarate.

3. A method of treating dementia according to claim 1 wherein said antiamnestically effective amount comprises a daily dosage of from 5 to 500 mg.

4. A method of treating dementia according to claim 1 wherein said antiamnestically effective amount comprises a daily dosage of from 20 to 100 mg.

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317A00, C07D 209/14, 213/30, 213/40, 213/75, 215/12,
217A02, 239/26, 271A06, 307/81, 333/38, C07C 237/42

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(30) Priority Data:
0124928.3 17 October 2001 (17.10.2001) GB(71) Applicant (for all designated States except US): GLAXO
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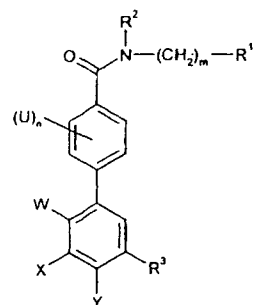
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(54) Title: 5'-CARBAMOYL-2'-METHYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS p38 KI-
NASE INHIBITORS

(I)

(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable
salts or solvates thereof, and their use as pharmaceuticals, particularly as
p38 kinase inhibitors.

Example 25: N³-[4-(Acetylamino)phenyl]-N⁴-(3-cyanophenyl)-6-methyl-1,1'-
biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride
(50mg, 0.13mmol) and 4-(acetylamino)aniline (40mg, 0.26mmol) in pyridine (1ml) were
heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum
and the residue partitioned between ethyl acetate and water. The organic fraction was
concentrated under vacuum and purified by preparative HPLC to give N³-[4-
(acetylamino)phenyl]-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.
LCMS: retention time 3.50min, MH⁺490.

Example 26: N³-(3-Carbamoyl-4-methylphenyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-
biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride
(50mg, 0.13mmol) and 5-amino-2-methylbenzamide (40mg, 0.26mmol) in pyridine (1ml)
were heated at 70°C for 15h. The pyridine was evaporated from the reaction under
vacuum and the residue partitioned between ethyl acetate and water. The organic
fraction was concentrated under vacuum and purified by preparative HPLC to give N³-
(3-carbamoyl-4-methylphenyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-
dicarboxamide. NMR: δH [2H₆] - DMSO 10.65, (1H, b), 10.25, (1H, s), 8.29, (1H, s), 8.10-
8.07, (3H, m), 7.92, (1H, dd), 7.89, (1H, d), 7.77, (1H, d), 7.74, (1H, dd), 7.69, (1H, b),
7.62, (2H, d), 7.59-7.56, (2H, m), 7.50, (1H, d), 7.36, (1H, b), 7.18, (1H, d), 2.34, (3H, s),
2.31, (3H, s). LCMS: retention time 3.38min, MH⁺489.

Example 27: N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-
3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride
(50mg, 0.13mmol) and 2-(3-aminophenyl)pyridine (45mg, 0.26mmol) in pyridine (1ml)
were heated at 70°C for 15h. The pyridine was evaporated from the reaction under
vacuum and the residue partitioned between ethyl acetate and water. The organic
fraction was concentrated under vacuum and purified by preparative HPLC to give N⁴-
(3-cyanophenyl)-6-methyl-N³-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide.
NMR: δH [2H₆] - DMSO 10.67, (1H, s), 10.39, (1H, s), 8.67, (1H, d), 8.51, (1H, t), 8.30, (1H,
m), 8.10-8.07, (3H, m), 7.98-7.87, (5H, m), 7.79, (1H, d), 7.65, (2H, d), 7.60-7.58, (2H, m),
7.51, (1H, d), 7.47, (1H, t), 7.36, (1H, m), 2.35, (3H, s). LCMS: retention time 3.81min,
MH⁺509.

Example 28: N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(5-methyl-1,2,4-oxadiazol-3-
yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride
(50mg, 0.13mmol) and 3-(3-aminophenyl)-5-methyl-1,2,4-oxadiazole (47mg, 0.26mmol)

D4

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(74) Agents: MANN, Jeffrey, S. et al.: Townsend Townsend
and Crew LLP, Two Embarcadero Center, 8th Floor, San
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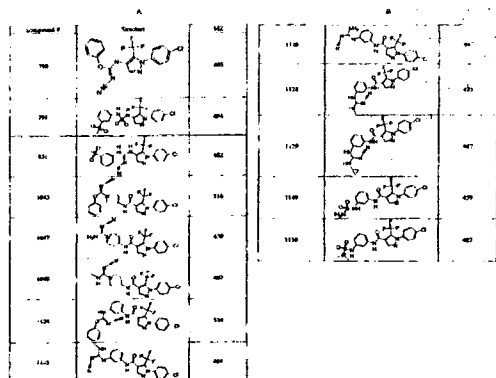
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6200 Chesden Drive, Durham, NC 27713 (US).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
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GM, GR, GU, HT, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MY, NZ, OM, PA, PE, PG, PH, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
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ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CI, CG, CM, GA, GN, GQ,
GW, ML, MR, NI, SN, TD, TG).

Declaration under Rule 4.17:

of inventorship (Rule 4.17(iv)) for US only

[Continued on next page]

(54) Title: PYRAZOLE AMIDES AND SULFONAMIDES



(57) Abstract: Compounds, compositions and methods are provided which are useful in the treatment of diseases through the inhibition of sodium ion flux through voltage-dependent sodium channels. More particularly, the invention provides pyrazole-amides and -sulfonamides, compositions and methods that are useful in the treatment of central or peripheral nervous system disorders, particularly pain and chronic pain by blocking sodium channels associated with the onset or recurrence of the indicated conditions. The compounds, compositions and methods of the present invention are of particular use for treating neuropathic or inflammatory pain by the inhibition of ion flux through a channel that includes a PNa subunit.

WO 03/037274

PCT/US02/35172

1107	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid [3-(morpholine-4-sulfonyl)-phenyl]-amide	514
1108	1-(4-Trifluoromethoxy-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (2-methyl-5-phenyl-2H-pyrazol-3-yl)-amide	495
1109	1-(4-Trifluoromethoxy-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid pyridin-4-ylamide	416
1110	3-[[1-(4-Trifluoromethoxy-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-piperidine-1-carboxylic acid tert-butyl ester	522
1111	Methanesulfonic acid 1-[1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-piperidin-4-yl ester	451
1112	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-methylsulfamoyl-phenyl)-amide	458
1113	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-pyridin-2-yl-phenyl)-amide	442
1114	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-pyridin-3-yl-phenyl)-amide	442
1115	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-pyridin-4-yl-phenyl)-amide	442
1116	1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-sulfamoyl-phenyl)-amide	428
1117	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-trifluoromethanesulfonyl-phenyl)-amide	497
1118	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-methanesulfonylamino-phenyl)-amide	458
1119	1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid [3-(2H-tetrazol-5-yl)-phenyl]-amide	433
1120	[(3-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-phenyl)-imino-methyl]-carbamic acid tert-butyl ester	

neuroindications

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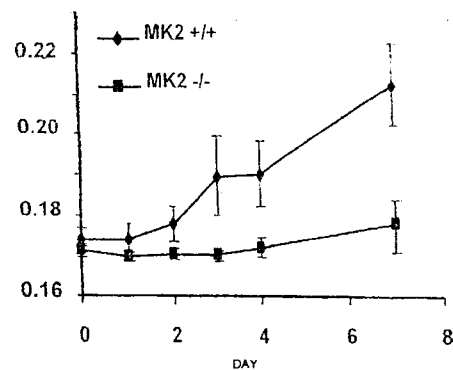
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63017 (US), MERSHON, Serena, Marie [US/US]; 303 Spring Street, Bessmer, MI 49911 (US). GRANETO, Matthew, J. [US/US]; 352 Hartwell Ct., Chesterfield, MO 63017 (US). MEYERS, Marwin, J. [US/US]; 4006 Summerfield Parkway, Saint Charles, MO 63304 (US). HEGDE, Shridhar, G. [US/US]; 130 Holly Garden Drive, Ballwin, MO 63021 (US). BUCHLER, Ingrid, P. [US/US]; 7627 Delmar Blvd., Apt. 2, South University City, MO 63130 (US). WU, Kun, K. [CA/US]; 1101 Olive Lake Drive, St. Louis, MO 63132 (US). LIU, Shuang [CNA/US]; 302 Polkinelli Dr., Schenectady, NY 12303 (US). MACRO, Kassoom [BI/US]; 106 Teneyck Place, Apt. 10, Guilderland, NY 12084 (US).
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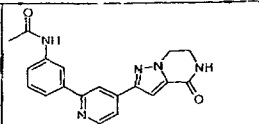
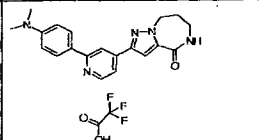
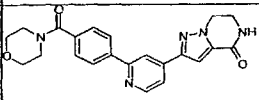
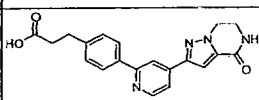
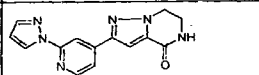
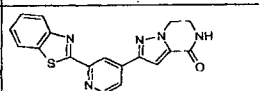
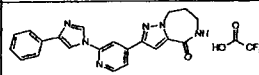
(Continued on next page)

(54) Title: ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-2
ACTIVATED PROTEIN KINASE-2

(57) Abstract: Compounds are described which inhibit mitogen activated protein kinase-activated protein kinase-2 (MK-2). Methods of making such compounds are described, as well as a method of using them for the inhibition of MK-2, and for the prevention or treatment of a disease or disorder that is mediated by TNF α , where the method involves administering to the subject an MK-2 inhibiting compound of the present invention. Pharmaceutical compositions and kits which contain the present MK-2 inhibiting compounds are also described.

85		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)pyridin-2-yl]phenyl]methanesulfonamide	2.29
86		2-[2-[4-(dimethylamino)quinazolin-6-yl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
87		2-[2-[3-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
88		2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	2.6
89		2-[2-(2,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.62
90		2-[2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	2.76
91		2-[2-(1H-pyrazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.79

Examples 85, 99, reivindicaciones

99		N-[3-[4-(4-oxo-1,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]acetamide	3.31
100		2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	3.44
101		2-[2-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.65
102		3-[4-[4-(4-oxo-1,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]propanoic acid	4.19
103		2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.2
104		2-[2-(1,3-benzothiazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.27
105		2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	4.31

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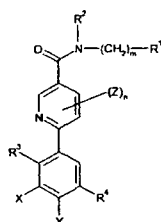
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- (71) Applicant (for all designated States except US):
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(54) Title: NICOTINAMIDE DERIVATES USEFUL AS P38 INHIBITORS



(I)

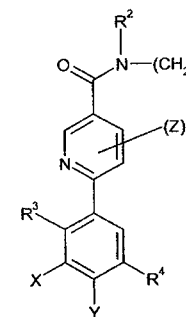
(57) Abstract: Compounds of formula (I), are inhibitors of p38 kinase and are useful in the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38.

NICOTINAMIDE DERIVATES USEFUL AS P38 INHIBITORS

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



(I)

wherein

R¹ is selected from hydrogen, C₁-alkyl optionally substituted by up to three groups selected from C₁-alkoxy, halogen and hydroxy, C₂-alkenyl, C₃-cycloalkyl optionally substituted by one or more C₁-alkyl groups, phenyl optionally substituted by up to three groups selected from R⁵ and R⁶, and heteroaryl optionally substituted by up to three groups selected from R⁵ and R⁶,

R² is selected from hydrogen, C₁-alkyl and -(CH₂)_q-C₃-cycloalkyl optionally substituted by one or more C₁-alkyl groups, or (CH₂)_mR¹ and R², together with the nitrogen atom to which they are bound, form a four- to six-membered heterocyclic ring optionally substituted by up to three C₁-alkyl groups;

R³ is chloro or methyl;

R⁴ is the group -NH-CO-R⁷ or -CO-NH-(CH₂)_q-R⁸;

R⁵ is selected from C₁-alkyl, C₁-alkoxy, -(CH₂)_q-C₃-cycloalkyl optionally substituted by one or more C₁-alkyl groups, -CONR⁹R¹⁰, -NHCOR¹⁰, -SO₂NHR⁹, -(CH₂)_sNHSO₂R¹⁰, halogen, CN, OH, -(CH₂)_sNR¹¹R¹², and trifluoromethyl;

R⁶ is selected from C₁-alkyl, C₁-alkoxy, halogen, trifluoromethyl and -(CH₂)_sNR¹¹R¹²;

See pg 1-3, 7-9, 15.22 examples 1-123
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R^7 is selected from hydrogen, C_{1-6} alkyl, $-(CH_2)_q-C_3-7$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, trifluoromethyl, $-(CH_2)_h$ heteroaryl optionally substituted by R^{13} and/or R^{14} , and $-(CH_2)_i$ phenyl optionally substituted by R^{13} and/or R^{14} ;

R^8 is selected from hydrogen, C_{1-6} alkyl, C_3-7 cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $CONHR^9$, phenyl optionally substituted by R^{13} and/or R^{14} , and heteroaryl optionally substituted by R^{13} and/or R^{14} ;

R^9 and R^{10} are each independently selected from hydrogen and C_{1-6} alkyl, or R^9 and R^{10} , together with the nitrogen atom to which they are bound, form

a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N- R^{15} , wherein the ring may be substituted by up to two C_{1-6} alkyl groups;

R^{11} is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_3-7$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups;

R^{12} is selected from hydrogen and C_{1-6} alkyl, or R^{11} and R^{12} , together with the nitrogen atom to which they are bound, form a five or six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N- R^{15} ;

R^{13} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_3-7$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $-CONR^9R^{10}$, $-NHCOR^{10}$, halogen, CN, $-(CH_2)_sNR^{11}R^{12}$, trifluoromethyl, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups;

R^{14} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-NR^{11}R^{12}$;

R^{15} is selected from hydrogen and methyl; X and Y are each independently selected from hydrogen, methyl and halogen; Z is halogen;

m is selected from 0, 1, 2, 3 and 4, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected

independently from C_{1-6} alkyl and halogen;

n is selected from 0, 1 and 2;

q is selected from 0, 1 and 2;

r is selected from 0 and 1; and

s is selected from 0, 1, 2 and 3.

According to a further embodiment of the invention there is provided a compound of formula (IA):

In a preferred embodiment, R^{10} is selected from hydrogen and C_{1-4} alkyl, in particular methyl.

In one embodiment, R^{11} is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_3-7$ cycloalkyl optionally substituted by C_{1-6} alkyl.

In a preferred embodiment, R^{11} and R^{12} , together with the nitrogen atom to which they are bound, form a five or six-membered heterocyclic ring optionally further containing one additional heteroatom N- R^{15} .

In one embodiment of the present invention, R^{13} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_3-7$ cycloalkyl, $-CONR^9R^{10}$, $-NHCOR^{10}$, halogen, CN, $-(CH_2)_sNR^{11}R^{12}$, trifluoromethyl, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups;

In a preferred embodiment, R^{13} is selected from C_{1-4} alkyl, in particular methyl, C_{1-4} alkoxy, in particular methoxy, halogen, $-(CH_2)_sNR^{11}R^{12}$, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups. In a more preferred embodiment, R^{13} is selected from $-(CH_2)_sNR^{11}R^{12}$ and heteroaryl optionally substituted by one or more R^{14} groups, in particular a five or six-membered heteroaryl containing at least one nitrogen atom, for example, pyridyl.

In a preferred embodiment R^{14} is selected from C_{1-4} alkyl, in particular methyl, C_{1-4} alkoxy, in particular methoxy, and $-NR^{11}R^{12}$.

In a preferred embodiment, R^{15} is methyl.

In a preferred embodiment, X and Y are each independently selected from hydrogen, chlorine and fluorine. In a further preferred embodiment, X is fluorine. In another preferred embodiment, Y is hydrogen.

In a preferred embodiment, Z is fluorine.

In one embodiment of the present invention, m is selected from 0, 1, 2, 3 and 4. In another embodiment of the present invention, m is selected from 0, 1, 2, 3 and 4, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl.

In a preferred embodiment, m is selected from 0, 1, 2 and 3. In a further preferred embodiment, m is selected from 0, 1 and 2, in particular 0 and 1. When the carbon chain of m is substituted, these substituents are preferably one or two methyl groups or fluorine atoms. In one embodiment, the substituents are preferably one or two methyl groups. In another embodiment, the substituents are preferably one or two fluorine atoms.

In a preferred embodiment, n is selected from 0 and 1. In particular, n is 0.

In a preferred embodiment, q is selected from 0 and 1. In particular, q is 0.

In a preferred embodiment, r is 0.

In a preferred embodiment, s is selected from 0 and 1.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the Examples. Specific examples which may be mentioned include:

6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide;

- 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-cyclopropylethyl)-nicotinamide;
 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide;
 5 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2-methylpropyl)-nicotinamide; and
 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-methylpropyl)-nicotinamide.

Further specific examples which may be mentioned include:

- 10 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutylmethyl-nicotinamide;
 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutyl-nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,4,5-trifluorobenzyl)nicotinamide;
 15 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,5-difluorobenzyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3,4-difluorobenzyl)nicotinamide;
 N-(3-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 20 N-(4-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 N-(3-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 25 N-(2-chloro-3,6-difluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3-difluoro-4-methylbenzyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3,5-trifluorobenzyl)nicotinamide;
 30 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3-fluoro-4-methylbenzyl)nicotinamide;
 N-(5-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 35 N-(2-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(4-fluorobenzyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3,4-trifluorobenzyl)nicotinamide;
 40 N-benzyl-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[3-(trifluoromethyl)benzyl]nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(1,1-dimethylbutyl)nicotinamide;
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- N-(4-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[4-(trifluoromethyl)benzyl]nicotinamide;
 5 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-{(5-methyl-2-furyl)methyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3-difluorobenzyl)nicotinamide;
 N-(3-chloro-4-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 10 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(4-methylbenzyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-{(3-methylthien-2-yl)methyl}nicotinamide;
 15 N-(3-chloro-2,6-difluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(1-ethyl-1-methylpropyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2-fluorobenzyl)nicotinamide;
 20 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(tert-pentyl)nicotinamide; and
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3-methylbenzyl)nicotinamide.

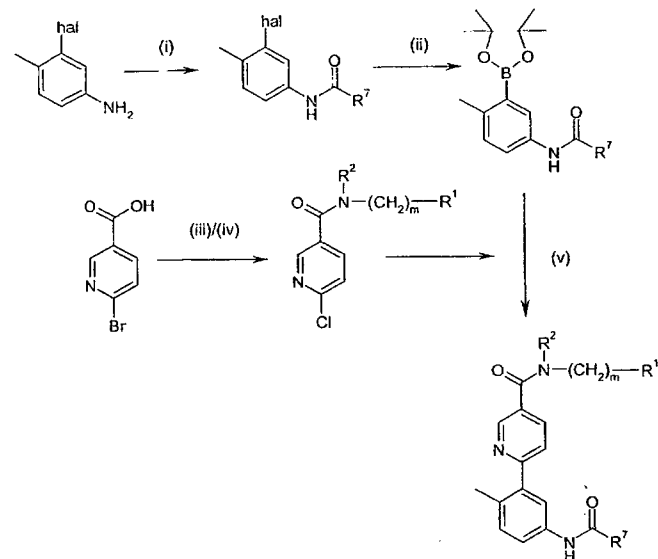
25 As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C₁₋₆alkyl group is preferred, for example methyl, ethyl, isopropyl or t-butyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms for example, trifluoromethyl.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and containing at least one double bond. For example, C₂₋₆alkenyl means a straight or branched alkenyl containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to ethenyl, propenyl, 3-methylbut-2-enyl and 1,1-dimethylbut-2-enyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C₁₋₆alkoxy group is preferred, for example methoxy or ethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms which may optionally contain up to one double bond. For example, C₃₋₇cycloalkyl means a non-aromatic ring

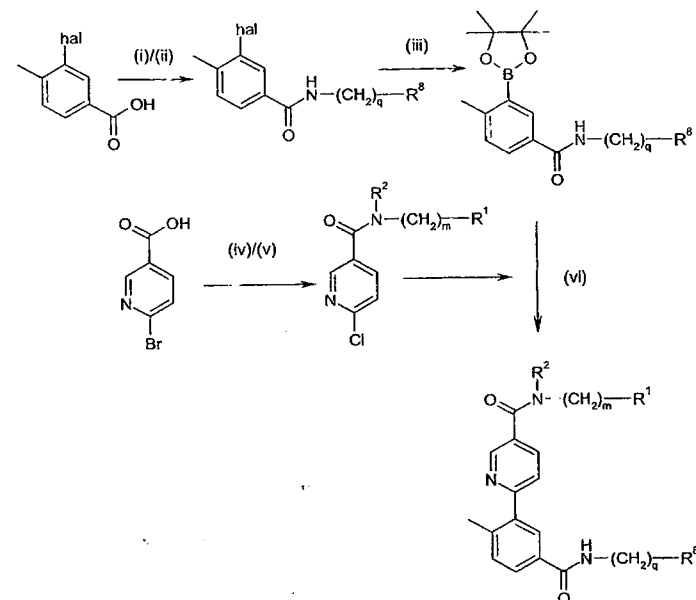
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Scheme 1

- i. R^7CO_2H , HATU, DIPEA, DMF.
- ii. Bis(pinacolato)diboron, $PdCl_2dppf$, KOAc, DMF.
- 5 iii. $SOCl_2$.
- iv. $R^1(CH_2)_mR^2NH$, Na_2CO_3 , acetone.
- v. Na_2CO_3 , tetrakis(triphenylphosphine)palladium, propan-2-ol.

For example, another general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 2 below.



Scheme 2

- i. $SOCl_2$.
- ii. $R^8(CH_2)_qNH_2$, Na_2CO_3 , acetone.
- 5 iii. Bis(pinacolato)diboron, $PdCl_2dppf$, KOAc, DMF.
- iv. $SOCl_2$.
- v. $R^1(CH_2)_mR^2NH$, Na_2CO_3 , acetone.
- vi. Na_2CO_3 , tetrakis(triphenylphosphine)palladium, propan-2-ol.

For example, another general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 3 below.

the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38 α , p38 β , p38 γ and/or p38 δ . In one embodiment, the compounds of the invention selectively inhibit the p38 α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38 β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38 α and p38 β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to said subject a therapeutically effective amount of a compound of formula (I). The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

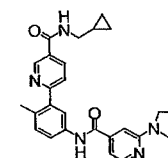
The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-

General Method B

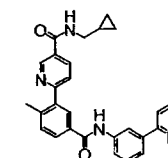
The 2-chloropyridine (0.05mmol), phenyl pinacolborane (0.05mmol), tetrakis(triphenylphosphine) palladium (1mg) and aqueous sodium carbonate (0.25ml) in propan-2-ol (1ml) were heated at 85°C under nitrogen for 18 hours. The cooled reaction was diluted with ethyl acetate (4ml) and methanol (2ml) and filtered through an SCX bond-clut (1g). The product was eluted with 10% ammonia (s.g. 0.88) in methanol. The solvents were evaporated and the residue triturated with ether.

Example 1: N-(3-[5-(Cyclopropylmethyl-carbamoyl)-pyridin-2-yl]-4-methyl-phenyl)-2-pyrrolidin-1-yl-isonicotinamide



6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (25mg, 0.098mmol) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-pyrrolidin-1-yl-isonicotinamide (Intermediate 18) (30mg, 0.074mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium (4mg) were heated at 80°C in DMF (1ml) for 18 hours. The reaction was absorbed onto silica, applied to a bond-clut (10g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%), then acetone and methanol. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to give N-(3-[5-(cyclopropylmethyl-carbamoyl)-pyridin-2-yl]-4-methyl-phenyl)-2-pyrrolidin-1-yl-isonicotinamide as a white solid (20mg). LCMS: retention time 2.42min, MH⁺ 456. NMR: δ H [²H₆]-DMSO 10.32, (1H, s), 9.09, (1H, s), 8.82, (1H, t), 8.28, (1H, m), 8.19, (1H, m), 7.85, (1H, t), 7.76, (1H, m), 7.64, (1H, m), 7.31, (1H, m), 6.98, (1H, m), 6.88, (1H, s), 3.43, (4H, m), 3.18, (2H, m), 2.31, (3H, s), 1.95, (4H, m), 1.07, (1H, m), 0.45, (2H, m), 0.25, (2H, m).

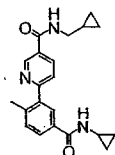
Example 2: N-Cyclopropylmethyl-6-[2-methyl-5-(3-pyridin-2-yl-phenylcarbamoyl)-phenyl]-nicotinamide



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6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (18.5mg, 0.073mmol) and 4-methyl-N-(3-pyridin-2-yl-phenyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 6) (30mg, 0.072mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium (4mg) were heated at 90°C in DMF (1ml) for 4hours. The reaction was absorbed onto silica, applied to a bond-elut (5g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%) and then acetone. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to give N-cyclopropylmethyl-6-[2-methyl-5-(3-pyridin-2-yl-phenylcarbamoyl)-phenyl]-nicotinamide as a white solid (20mg). LCMS: retention time 3.18min, MH^+ 463. NMR: δH [$^2H_6$]-DMSO 10.43, (1H, s), 9.14, (1H, s), 8.86, (1H, t), 8.69, (1H, s), 8.53, (1H, s), 8.34, (1H, d), 8.11, (1H, s), 8.01, (1H, d), 7.95-7.89, (3H, m), 7.81-7.78, (2H, m), 7.53-7.46, (2H, m), 7.38, (1H, t), 3.21, (2H, t), 2.44, (3H, s), 1.07, (1H, m), 0.47, (2H, m), 0.27, (2H, m).

Example 3: 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide



6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (25.5mg, 0.10mmol) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8) (30mg, 0.10mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium (4mg) were heated at 90°C in DMF (1ml) for 3hours. The reaction was absorbed onto silica, applied to a bond-elut (5g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%) and then acetone. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to give 6-(5-cyclopropylcarbamoyl-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide as a cream solid. LCMS: retention time 2.70min, MH^+ 350. NMR: δH [$^2H_6$]-DMSO 9.11, (1H, s), 8.84, (1H, t), 8.48, (1H, d), 8.31, (1H, dd), 7.88, (1H, s), 7.81, (1H, d), 7.70, (1H, d), 7.41, (1H, d), 3.20, (1H, t), 2.86, (1H, m), 2.37, (3H, s), 1.06, (1H, m), 0.69, (2H, m), 0.57, (2H, m), 0.46, (2H, m), 0.26, (2H, m).

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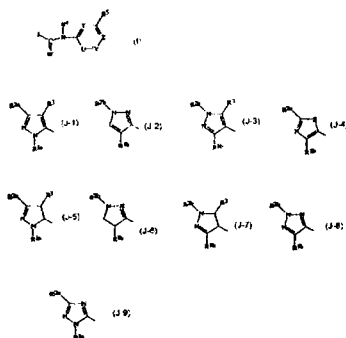
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(54) Title: HETEROCYCLYPHENYL AND HETEROCYCLYPYRIDYL-SUBSTITUTED AZOLCARBOXAMIDES AS
HERBICIDES(57) Abstract: Compounds of Formula (I), and their N-oxides and agriculturally suitable salts, are disclosed which are useful for controlling undesired vegetation wherein (I) is (J-1), (J-2), (J-3), (J-4), (J-5), (J-6), (J-7), (J-8), or (J-9); R¹ is a phenyl ring or a 5- or 6-membered heteroaromatic ring which includes at least one heteroatom selected from N, O and S, each ring optionally substituted with one or more substituents selected from R¹⁰; or R¹ is a 5- or 6-membered partially unsaturated heterocyclic ring which includes at least one heteroatom selected from N, O and S, the ring connected through a nitrogen atom or an sp² carbon atom to the remainder of Formula (I) and optionally substituted by one or more substituents selected from R¹⁰; and R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, T, U, W, Y and Z are as defined in the disclosure.

radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Steps in the following Examples illustrate a procedure for each step in an overall synthetic transformation, and the starting material for each step may not have necessarily been prepared by a particular preparative run whose procedure is described in other Examples or Steps. Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. ¹H NMR spectra are reported in ppm downfield from tetramethylsilane; ¹⁹F NMR spectra are reported in ppm relative to CF₃CCl₃; "s" means singlet, "d" means doublet, "t" means triplet, "q" means quartet, "m" means multiplet, "dd" means doublet of doublets, "ddd" means doublet of doublets of doublets, "dt" means doublet of triplets, "dq" means doublet of quartets, "br s" means broad singlet, "br d" means broad doublet.

EXAMPLE I

Preparation of 3-(1,1-dimethylethyl)-1-ethyl-N-[3-(2-pyridinyl)phenyl]-1H-pyrazole-5-carboxamide (Compound 14)

20 Step A: Preparation of ethyl 2-hydroxy-5,5-dimethyl-4-oxo-2-hexenoate

To a solution of sodium ethoxide in ethanol (250 mL, 21% by weight in ethanol, 670 mmol) was added dropwise a solution of diethyl oxalate (45.2 mL, 332.5 mmol) and pinacolone (alternatively named 3,3-dimethyl-2-butanone) (41.7 mL) in ethanol (300 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight, concentrated to its half volume and poured into ice. Concentrated hydrochloric acid was added to lower the pH to approximately 4, and then the mixture was extracted with ethyl acetate. The extracts were dried over magnesium sulfate and concentrated to give the title compound as an oil (60 g, yield 90%).

25 Step B: Preparation of ethyl 5-(1,1-dimethylethyl)-1H-pyrazole-3-carboxylate

To a solution of ethyl 2-hydroxy-5,5-dimethyl-4-oxo-2-hexenoate (i.e. the product of Step A) (45.3 g, 226 mmol) in ethanol (200 mL) and acetic acid (2 mL) was added hydrazine monohydrate (12.1 mL, 249 mmol) dropwise under nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature overnight and concentrated to give 40.8 g of the title compound.

35 ¹H NMR (CDCl₃) δ 6.7 (s, 1H), 6.60 (br s, 1H), 4.40 (q, 2H), 1.40 (t, 3H), 1.32 (s, 9H).

Step C: Preparation of ethyl 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carboxylate

To a solution of ethyl 5-(1,1-dimethylethyl)-1*H*-pyrazole-3-carboxylate (i.e. the product of Step B) (20.0 g, 102 mmol) in anhydrous *N,N*-dimethylformamide (DMF) (100 mL) at room temperature was added sequentially potassium carbonate (28.2 g, 204 mmol) and iodoethane (11.4 mL, 143 mmol). After stirring at room temperature in an inert atmosphere for 6 h, the reaction mixture was diluted with ethyl acetate (400 mL) and washed with water (2 x 50 mL). The organic phase was separated, dried and concentrated. The residue was purified by chromatography on silica gel to give the desired isomer (i.e. the title compound) as a white solid (13.8 g, 64% yield) and a minor isomer (2.1 g, 10% yield).

¹H NMR (CDCl₃) δ 6.7 (s, 1H), 4.55 (q, 2H), 4.32 (q, 2H), 1.40 (m, 6H), 1.32 (s, 9H).

¹H NMR (CDCl₃) (minor isomer) δ 6.7 (s, 1H), 4.20 (q, 2H), 4.30 (q, 2H), 1.36 (m, 6H), 1.32 (s, 9H).

Step D: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carboxylic acid

A solution of ethyl 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carboxylate (i.e. the product of Step C) (6.9 g, 30.8 mmol) in ethanol (200 mL) was stirred with an aqueous solution of sodium hydroxide (10%, 19 mL) at room temperature for 6 h. The mixture was then concentrated and acidified with 1 N hydrochloric acid. The precipitated solids were filtered and dried to give 6 g of the title acid as a white solid.

¹H NMR (CDCl₃) δ 10.00 (s, 1H), 6.80 (s, 1H), 4.60 (q, 2H), 1.40 (t, 3H), 1.32 (s, 9H).

Step E: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carbonyl chloride

A solution of 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carboxylic acid (i.e. the product of Step D) (1.2 g, 6.11 mmol) and oxalyl chloride (2 mL) in dichloromethane (30 mL) in the presence of anhydrous DMF (0.1 mL) was stirred under nitrogen atmosphere at room temperature for 4 h. The reaction mixture was then concentrated to yield the title acid chloride as a liquid.

Step F: Preparation of 3-(2-pyridinyl)benzenamine

To a solution of 2-bromopyridine (1.6 g, 10 mmol) in dimethoxyethane (50 mL) and water (17 mL) was added 3-aminophenylboronic acid hemisulfate (1.86 g, 10 mmol), sodium carbonate (5.6 g, 52.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.3 g). The mixture was heated to reflux for 5 hours and then allowed to cool to room temperature. Brine (50 mL) was added, and the mixture was extracted with ethyl acetate (3 x 25 mL). The organic extracts were dried (MgSO₄) and concentrated to leave the crude product. The crude product was purified by flash column chromatography to provide the title compound as a thick yellow oil (1.1 g).

¹H NMR (CDCl₃) δ 8.6 (m, 1H), 7.69 (m, 2H), 7.3 (m, 4H), 6.8 (m, 1H), 3.8 (br s, 2H).

Step G: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-*N*-[3-(2-pyridinyl)phenyl]-1*H*-pyrazole-5-carboxamide

To a solution of 3-(2-pyridinyl)benzenamine (i.e. the product of Step F) (0.34 g, 2 mmol) in dichloromethane (5 mL), triethylamine (0.3 mL, 2.2 mmol) was added, and the solution was cooled to 0 °C. To this a solution of 3-(1,1-dimethylethyl)-1-ethyl-1*H*-pyrazole-5-carbonyl chloride (i.e. the product of Step E) (0.43 g, 2 mmol) in dichloromethane (2 mL) was added over one minute, and then the mixture was allowed to come to room temperature while being stirred for one hour. The mixture was concentrated, and the residue was purified using a silica gel flash chromatography column eluted with hexane-ethyl acetate (8:2 and then 1:1) to provide the title compound, a compound of present invention, as a white solid (0.25 g).

¹H NMR (CDCl₃) δ 8.7 (m, 1H), 8.2 (s, 1H), 7.8 (m, 1H), 7.77 (m, 4H), 7.5 (m, 1H), 7.23 (m, 1H), 6.47 (s, 1H), 4.59 (q, 2H), 1.49 (t, 3H), 1.36 (s, 9H).

EXAMPLE 2**15 Preparation of 3-(1,1-dimethylethyl)-1-ethyl-*N*-[2-fluoro-5-(2-pyridinyl)phenyl]-1*H*-pyrazole-5-carboxamide (Compound 27)****Step A: Preparation of 2-(4-fluoro-3-nitrophenyl)pyridine**

Bromo-2-pyridinylzinc (alternatively named 2-pyridylzinc bromide, Aldrich Chemical Co., 0.5 M in tetrahydrofuran, 20 mL, 10 mmol) was added to a suspension of 4-bromo-1-fluoro-2-nitrobenzene (2.2 g, 10 mmol), and tetrakis(triphenylphosphine)palladium(0) in *N,N*-dimethylformamide (20 mL). The mixture was heated at 90 °C for 15 h and then cooled to room temperature. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed successively with water (50 mL) and brine (50 mL). The organic layer was dried (MgSO₄) and concentrated to leave the crude product. The crude product was purified by column chromatography on silica gel to provide the title compound as a yellow solid (1.6 g).

¹H NMR (CDCl₃) δ 8.72 (m, 2H), 8.3 (m, 1H), 7.77 (m, 2H), 7.43 (m, 1H), 7.39 (m, 1H).

Step B: Preparation of 2-fluoro-5-(2-pyridinyl)benzenamine

To a mixture of iron powder (0.325 g, 6 mmol) and ammonium chloride (0.325 g, 6 mmol) in water (1.5 mL) was added a solution of 2-(4-fluoro-3-nitrophenyl)pyridine (i.e. the product of Step A) (0.6 g, 2.75 mmol) in dichloromethane (2.2 mL) and isopropanol (2.2 mL). The mixture was heated at reflux over 2 h to remove the dichloromethane and then allowed to cool to room temperature. Ethyl acetate (25 mL) was added to the above mixture, which was stirred for 30 minutes and then filtered through Celite® diatomaceous filter aid. The filtrate was washed with water (10 mL) followed by brine (10 mL). The

organic layer was dried (MgSO₄) and concentrated to provide the title compound as a brown oil (0.4 g).

¹H NMR (CDCl₃) δ 8.66 (m, 1H), 7.65 (m, 1H), 7.64 (m, 1H), 7.5 (m, 1H), 7.25 (m, 2H), 7.00 (m, 1H), 3.82 (br s, 2H).

5 Step C: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-N-[2-fluoro-5-(2-pyridinyl)phenyl]-1H-pyrazole-5-carboxamide

To a solution of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxylic acid (i.e. the product of Example 1, Step D) (0.2 g, 1 mmol) in dichloromethane (2 mL) at room temperature was added sequentially 1-propanephosphonic acid cyclic anhydride (50% in ethyl acetate, 0.5 g, 1.57 mmol) and 2-fluoro-5-(2-pyridinyl)benzenamine (i.e. the product of Step B) (0.2 g, 0.106 mmol). After stirring at room temperature 2 h the mixture was concentrated, and the residue was purified using silica gel column chromatography eluted with hexane-ethyl acetate (9:1 then 8:2) to provide the title product, a compound of the present invention, as a white solid (0.25 g).

15 ¹H NMR (CDCl₃) δ 9.0 (m, 1H), 8.7 (m, 1H), 7.9 (br s, 1H), 7.8 (m, 1H), 7.75 (d, 1H), 7.24 (m, 2H), 6.5 (s, 1H), 4.6 (q, 2H), 1.44 (t, 3H), 1.34 (s, 9H).

EXAMPLE 3

Preparation of N-(2',6'-difluoro[1,1'-biphenyl]-3-yl)-3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxamide (Compound 51)

20 Step A: Preparation of 2',6'-difluoro[1,1'-biphenyl]-3-amine

To a solution of 2,6-difluorophenylboronic acid (0.8 g, 5 mmol) in a mixture of 1,2-dimethoxyethane (25 mL) and water (8 mL) was added 3-iodobenzeneamine (alternatively named 3-iodoaniline; 1.1 g, 5 mmol), sodium carbonate (2.5 g, 23.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.15 g). The mixture was heated at reflux for 4 h and then allowed to cool to room temperature. The reaction mixture was diluted with brine (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was successively washed with water (25 mL) and brine (25 mL), dried (MgSO₄) and concentrated to leave the crude product. The crude product was purified by column chromatography on silica gel eluted with hexane-ethyl acetate (9:1) to provide the title compound as a thick yellow oil (0.6 g).

¹H NMR (CDCl₃) δ 7.4 (m, 1H), 7.22 (m, 1H), 6.89 (m, 4H), 6.7 (m, 1H), 3.8 (br s, 1H).

Step B Preparation of N-(2',6'-difluoro[1,1'-biphenyl]-3-yl)-3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxamide

15 To a solution of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxylic acid (i.e. the product of Example 1, Step D) (0.2 g, 1 mmol) in dichloromethane (2 mL) at room temperature was added sequentially 1-propanephosphonic acid cyclic anhydride (50% in

ethyl acetate, 0.5 g, 1.57 mmol) and 2',6'-difluoro[1,1'-biphenyl]-3-amine (i.e. the product of Step A) (0.21 g, 0.102 mmol). After stirring at room temperature 2 h the mixture was concentrated, and the residue was purified using silica gel column chromatography eluted with hexane-ethyl acetate (9:1) to provide the title product, a compound of the present invention, as a white solid (0.20 g).

¹H NMR (CDCl₃) δ 7.73 (m, 2H), 7.6 (m, 1H), 7.43 (m, 1H), 7.4 (m, 1H), 6.95 (m, 1H), 6.48 (s, 1H), 4.58 (q, 2H), 1.42 (t, 3H), 1.33 (s, 9H).

EXAMPLE 4

Preparation of 2-(1,1-dimethylethyl)-5-ethyl-N-[3-(2-pyridinyl)phenyl]-2H-1,2,3-triazole-4-carboxamide (Compound 53)

Step A: Preparation of ethyl 5-ethyl-1,2,3-triazole-4-carboxylate

Ethyl 2-pentynoate (16.6 g, 0.132 mol) and trimethylsilylazide (38.0 g, 0.333 mol) were stirred at 100–110 °C under nitrogen for 70 h. After cooling and dilution with methanol (60 mL) a white solid precipitated. After evaporation of the mixture under reduced pressure, the residue was crystallized from ethyl ether to afford the title product as a white solid (15.7 g, 0.093 mol, 70% yield).

¹H NMR (CDCl₃) δ 4.42 (q, 2H), 3.07 (q, 2H), 1.37 (t, 3H), 1.32 (t, 3H).

Step B: Preparation of ethyl 2-(1,1-dimethylethyl)-5-ethyl-2H-1,2,3-triazole-4-carboxylate and ethyl 1-(1,1-dimethylethyl)-4-ethyl-1H-1,2,3-triazole-5-carboxylate

To a stirred solution of 5-ethyl-1,2,3-triazole-4-carboxylic acid ethyl ester (i.e. product of Step A) (1.05 g, 6.25 mmol) and *tert*-butyl alcohol (0.93 g, 12.5 mmol) in trifluoroacetic acid (6 mL) was added concentrated sulfuric acid (0.61 g, 6.25 mmol). After stirring at room temperature for 14 h, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated aqueous sodium carbonate and brine, and then dried (Na₂SO₄). After concentration, the residue was purified by column chromatography to afford ethyl 2-(1,1-dimethylethyl)-5-ethyl-2H-1,2,3-triazole-4-carboxylate (0.74 g, 3.76 mmol, 64% yield), followed by its isomer ethyl 1-(1,1-dimethylethyl)-4-ethyl-1H-1,2,3-triazole-5-carboxylate (0.24 g, 1.22 mmol, 21% yield) as colorless oils.

Ethyl 2-(1,1-dimethylethyl)-5-ethyl-2H-1,2,3-triazole-4-carboxylate:

¹H NMR (CDCl₃): 4.41 (q, 2H), 2.93 (q, 2H), 1.68 (d, 9H), 1.40 (t, 3H), 1.27 (t, 3H).

Ethyl 1-(1,1-dimethylethyl)-4-ethyl-1H-1,2,3-triazole-5-carboxylate:

¹H NMR (CDCl₃): 4.40 (q, 2H), 2.87 (q, 2H), 1.77 (d, 6H), 1.42 (t, 3H), 1.29 (t, 3H).

Step C: Preparation of 2-(1,1-dimethylethyl)-5-ethyl-N-[3-(2-pyridinyl)phenyl]-2H-1,2,3-triazole-4-carboxamide

To a stirred solution of ethyl 2-(1,1-dimethylethyl)-5-ethyl-2H-1,2,3-triazole-4-carboxylate (i.e. the first eluted product of Step B) (1.119 g, 5.64 mmol) in tetrahydrofuran (15 mL) was added a solution of lithium hydroxide (0.54 g, 22.56 mmol) in water (15 mL). The mixture was stirred at room temperature overnight, and then partitioned between ether and water. The aqueous layer was acidified with hydrochloric acid (6 N) to pH 1-2 and extracted with ethyl acetate, dried (Na₂SO₄) and concentrated to provide the carboxylic acid intermediate as a white solid (0.94 g, 5.08 mmol, 90% yield). To a solution of the carboxylic acid intermediate (0.1 g, 0.5 mmol) in dichloromethane (2 mL) at room temperature was added sequentially 1-propanephosphonic acid cyclic anhydride (50% in ethyl acetate, 0.25 g, 0.785 mmol), 3-(2-pyridinyl)benzamine (i.e. the product of Example 1, Step F) (0.1 g, 0.58 mmol) and triethylamine (0.1 mL, 0.75 mmol). After stirring at room temperature 2 h the mixture was concentrated, and the residue was purified using silica gel column chromatography eluted with hexane-ethyl acetate (9:1) to provide the title product, a compound of the present invention, as an off-white solid (0.07 g).

¹H NMR (CDCl₃) δ 7.75 (m, 2H), 8.2 (m, 1H), 8.0 (d, 1H), 7.8 (m, 1H), 7.75 (m, 2H), 7.4 (t, 1H), 7.25 (m, 1H), 3.06 (m, 2H), 1.58 (s, 9H), 1.29 (t, 3H).

EXAMPLE 5

20 Preparation of 3-(1,1-dimethylethyl)-1-ethyl-N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-pyrazole-5-carboxamide (Compound 7)

Step A: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carbonyl chloride

A solution of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxylic acid (i.e., product of Example 1, Step D) (1.96 g, 10.0 mmol) in thionyl chloride (99%, ~5 mL) was heated at reflux for about 6 h, and then allowed to cool to room temperature while being stirred overnight. The reaction mixture was then concentrated in vacuo. Dichloromethane (~10 mL) was added to the residue, and the mixture was concentrated again; this was repeated twice to provide the title compound as a yellow liquid (1.80 g, 84% yield).

¹H NMR (CDCl₃) δ 6.935 (s, 1H), 4.40-4.47 (m, 2H), 1.36-1.57 (m, 3H), 1.31-1.32 (s, 9H).

30 Step B: Preparation of N-(3-cyanophenyl)-3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxamide

A solution of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carbonyl chloride (i.e. the product of Step A) (0.49 g, 2.26 mmol) in tetrahydrofuran (~1 mL) was added dropwise to a stirred solution of 3-aminobenzonitrile (99%, 0.3 g, 2.51 mmol), triethylamine, (1.39 mL, 10.04 mmol) and 4-(dimethylamino)pyridine (catalytic amount) in tetrahydrofuran (~5 mL) at room temperature to afford a yellow solution containing white, suspended solid. The

EXAMPLE 10

Preparation of 3-(1,1-dimethylethyl)-1-ethyl-N-[6-(1H-pyrazol-1-yl)-2-pyridinyl]-1H-pyrazole-5-carboxamide (Compound 11)

Step A: Preparation of N-(6-bromo-2-pyridinyl)-3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxamide

To a solution of 3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxylic acid (i.e. the product of Example 1, Step D) (1 g) in dichloromethane (10 mL) was added sequentially a solution of 6-bromo-2-pyridinamine (0.80 g) in dichloromethane (5 mL) followed by 1-propanephosphonic acid cyclic anhydride (50% solution in ethyl acetate, 3 mL) and then 4-(dimethylamino)pyridine (0.3 g). After stirring at room temperature for 6 h, the reaction mixture was diluted with dichloromethane (20 mL) and washed with hydrochloric acid (1 N). The organic phase was separated, dried and concentrated. The residue was purified by chromatography on silica gel to give the title compound (1.24 g).

¹H NMR (CDCl₃) δ 8.42 (s, 1H, NH), 8.32 (d, 1H), 7.62 (t, 1H), 7.28 (d, 1H), 6.64 (s, 1H), 4.48 (q, 2H), 1.45 (t, 3H), 1.31 (s, 9H).

Step B: Preparation of 3-(1,1-dimethylethyl)-1-ethyl-N-[6-(1H-pyrazol-1-yl)-2-pyridinyl]-1H-pyrazole-5-carboxamide

To a solution of N-(6-bromo-2-pyridinyl)-3-(1,1-dimethylethyl)-1-ethyl-1H-pyrazole-5-carboxamide (i.e. the product of Step B) (0.35 g) in N,N-dimethylformamide (5 mL) was added sequentially pyrazole (0.30 g) and then potassium carbonate (0.5 g). The reaction mixture was then heated at 110 °C with stirring for 12 h. After cooling to room temperature the reaction mixture was diluted with dichloromethane (20 mL) and washed with hydrochloric acid (1 N). The organic phase was separated, dried and concentrated. The residue was purified by chromatography on silica gel to give the title product, a compound of the present invention, as a colorless solid (0.11 g).

¹H NMR (CDCl₃) δ 8.62 (s, 1H, NH), 8.28 (d, 1H), 8.16 (d, 1H), 7.82 (t, 1H), 7.60 (t, 1H), 7.28 (d, 1H), 6.64 (s, 1H), 6.58 (d, 1H), 4.48 (q, 2H), 1.45 (t, 3H), 1.31 (s, 9H).

EXAMPLE 11

Preparation of 1-(1,1-dimethylethyl)-3-ethyl-4,5-dihydro-N-[3-(2-pyridinyl)phenyl]-1H-pyrazole-4-carboxamide (Compound 33)

Step A: Preparation of N-(3-iodophenyl)-3-oxopentanimide

Three solutions of 3-iodobenzamine (1.03 g, 2.06 g, and 1.70 g respectively) in methyl 3-oxopentanoate (alternatively named methyl propionylacetate; 1.82 g, 3.66 g, and 2.52 g respectively) were prepared. To each solution was added 4-(dimethylamino)pyridine (30-60 mg). Each solution was heated at 180 °C for 5 minutes using a microwave reactor. The solutions were combined and most of the unreacted methyl 3-oxopentanoate was

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chromatography using ethyl acetate-hexane as eluant to provide the title product, a compound of the present invention, as a thick oil. (183 mg).

¹H NMR (CDCl₃) δ 8.71 (s, 1H), 8.69 (d, 1H), 8.05 (s, 1H), 7.73 (m, 3H), 7.60 (d, 1H), 7.41 (t, 1H), 7.22 (m, 1H), 3.58 (m, 2H), 3.28 (t, 1H), 2.41 (m, 2H), 1.23 (s, 9H), 1.16 (t, 3H).

EXAMPLE 12

Preparation of 1-(1,1-dimethylethyl)-3-ethyl-N-[3-(2-pyridinyl)phenyl]-1H-pyrazole-4-carboxamide (Compound 32)

Step A: Preparation of 1-(1,1-dimethylethyl)-3-ethyl-N-(3-iodophenyl)-1H-pyrazole-4-carboxamide

A slurry of 1-(1,1-dimethylethyl)-3-ethyl-4,5-dihydro-N-(3-iodophenyl)-1H-pyrazole-4-carboxamide (i.e. the product of Example 11, Step B) (0.30 g) and manganese(IV) oxide (0.65 g) in toluene (3 mL) was heated at 80 °C for 2 h. Then the reaction mixture was filtered through a pad of Celite® diatomaceous filter aid. The Celite® pad was washed with ethyl acetate (50 mL), and the combined filtrates were concentrated in vacuo to leave the title compound as a brown solid (0.25 g).

¹H NMR (CDCl₃) δ 7.97 (s, 1H), 7.88 (s, 1H), 7.56 (d, 1H), 7.43 (d, 1H), 7.30 (br s, 1H), 7.07 (t, 1H), 2.94 (q, 2H), 1.58 (s, 9H), 1.33 (t, 3H).

Step B: Preparation of 1-(1,1-dimethylethyl)-3-ethyl-N-[3-(2-pyridinyl)phenyl]-1H-pyrazole-4-carboxamide

A solution of 1-(1,1-dimethylethyl)-3-ethyl-N-(3-iodophenyl)-1H-pyrazole-4-carboxamide (i.e. the product of Step A) (0.25 g, 0.63 mmol), tetrakis(triphenylphosphine)palladium (72 mg) and 2-pyridylzinc bromide (0.5 M in THF, 1.32 mL) in dry tetrahydrofuran (dry, 5 mL) was stirred at room temperature for 24 h. Then additional 2-pyridylzinc bromide solution (1.32 mL) and tetrakis(triphenylphosphine)palladium (72 mg) were added. After the reaction mixture was stirred for a further 120 h additional 2-pyridylzinc bromide solution (1.80 mL) and tetrakis(triphenylphosphine)palladium (130 mg) were added. Then after stirring for 24 hr more the solvent was removed in vacuo, and the residue was taken up in ethyl acetate (30 mL) and extracted with aqueous hydrochloric acid (1 N, 3 x 20 mL). The combined aqueous acid solutions were washed with ethyl acetate (30 mL), and then the pH of the aqueous solution was increased to 8-9 by addition of 50% aqueous sodium hydroxide. The aqueous solution was extracted with ethyl acetate (3 x 100 mL), and the combined ethyl acetate extracts were dried and concentrated to leave a crude oil, which was purified by column chromatography using ethyl acetate-hexane as eluant to provide the title product, a compound of the present invention, as a white powder (50 mg).

¹H NMR (CDCl₃) δ 8.70 (d, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.85 (d, 1H), 7.85 (m, 2H), 7.70 (d, 1H), 7.52 (br s, 1H), 7.46 (t, 1H), 7.26 (m, 1H), 2.97 (q, 2H), 1.60 (s, 9H), 1.34 (t, 3H).

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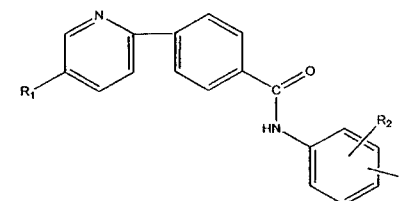
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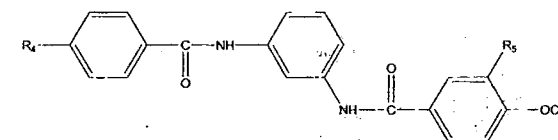
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(57) Abstract: Aromatic compounds for treating various diseases and pathologies are disclosed. The methods use of such com-
pounds are also provided. Accordingly, the present invention makes available methods and compositions for inhibiting aberrant
growth states resulting from hedgehog gain of function, *etc.* loss-of-function or *smoothed* gain-of-function.

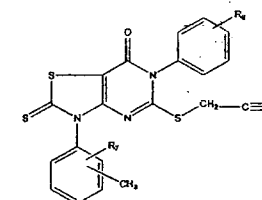
-3-



(I)

[0009] According to one embodiment of the invention, compounds having the
structure (II) are provided, or a pharmaceutically acceptable salt thereof:

(II)

[0010] According to one embodiment of the invention, compounds having the
structure (III) are provided, or a pharmaceutically acceptable salt thereof:

(III)

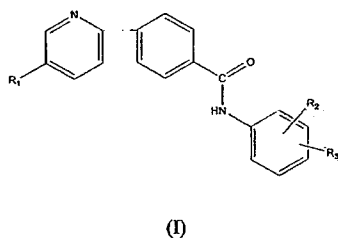
[0011] According to one embodiment of the invention, compounds having the
structure (IV) are provided, or a pharmaceutically acceptable salt thereof:

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[0118] As described in further detail below, it is contemplated that the subject methods can be carried out using a variety of different aromatic compounds, which can be readily identified, e.g., by such drug screening assays as described herein.

[0119] According to an embodiment of the invention, a first type of compound is provided for treatment of various diseases, disorders, and pathologies. The compounds of the first type can include an alkylpyridyl moiety bridged to a benzamide moiety, where the benzamide moiety can include a first substituent attached to the benzamide moiety via the nitrogen atom of the benzamide moiety. The first substituent can comprise an aryl structure which can include at least one second substituent, where the second substituent can be an unsubstituted or substituted alkyl, a halogen, an alkoxy, acetyl, or nitro.

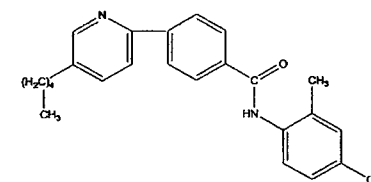
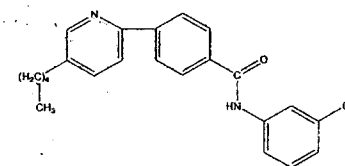
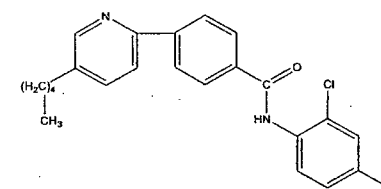
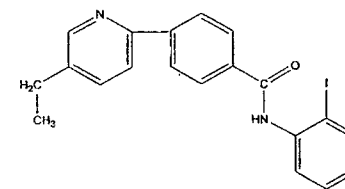
[0120] Compounds of the first type can be described as compounds having the general structure (I), or a pharmaceutically acceptable salt thereof:



[0121] In structure (I), R_1 can be an alkyl, for example, ethyl, *n*-propyl or *n*-amyl; R_2 can be hydrogen, an alkyl (e.g., methyl), halogen (e.g., chlorine), or an alkoxy group (e.g., methoxy); and R_3 can be an unsubstituted or substituted alkyl group (e.g., methyl or trifluoromethyl), halogen (e.g., chlorine or iodine), an alkoxy group (e.g., methoxy), acetyl group, or nitro group.

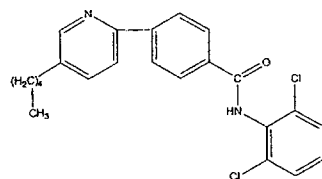
[0122] Some examples of particular compounds described by the general structure (I) include compounds having the formulae (1)-(7):

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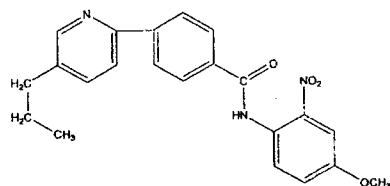


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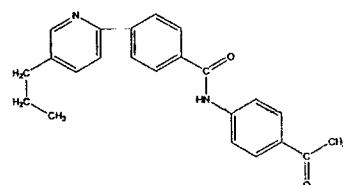
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(5)



(6)



(7)

[0123] According to an embodiment of the invention, a second type of compounds is provided for treatment of various diseases, disorders, and pathologies. The compounds of the second type can include two benzamide moieties connected with a phenylene bridge, for example, the 1,3-phenylene bridge. The benzamide moieties can include a substituent, such as *tert*-butyl, chlorine, bromine, or nitro.

[0124] Compounds of the second type can be described as compounds having the general structure (II), or a pharmaceutically acceptable salt thereof.

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