JOSE LLOREDA CAMACHO & CO.

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

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERC
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**GLAXO WELLCOME SpA**.-Solicitud de Patente de Invención para "**DERIVADOS HETEROCICLICOS**".-Clase **A.61**.-Expediente número **00-093.651.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 30 de Marzo de 2006.

2. El señor Examinador en el Concepto Técnico No. **483**, objeta la claridad de las reivindicaciones 2 y 3 de la solicitud en estudio con base en los siguientes argumentos:

- **Reivindicación 2**: "Se observa que no menciona en forma clara si se refiere a una sola forma cristalina en especial ó a todas las formas cristalinas que pudieran obtenerse posteriormente a partir de la cristalización en diversos solventes".

  Sobre este particular, me permito manifestar a ese Despacho, que debidamente autorizado por mí representado se ha modificado dicha reivindicación, presentándola como sigue: "Un compuesto de acuerdo con la reivindicación 1, donde dicho compuesto es una forma cristalina", siendo importante anotar que a partir de la descripción, específicamente de la página 3 línea 11 a la página 5 línea 6 y de la página 15 línea 1 a la página 16 línea 15 se encuentra pleno sustento para la reivindicación en mención. Con el fin de demostrar que la reivindicación hace referencia a cualquier forma cristalina que pueda ser obtenida y que dicha reivindicación encuentra pleno sustento en la descripción, me permito resaltar que la página 5 línea 3 de la solicitud presentada contiene el siguiente texto: "El compuesto de la invención se puede obtener en más de una forma cristalina. Se puede entender que la invención incluye todas estas formas o una mezcla de las mismas". De acuerdo con esto, queda establecido que la reivindicación reclama cualquier forma cristalina que pueda obtenerse del compuesto, y que la descripción provee el sustento para ello.

- **Reivindicación 3**: "Menciona "la forma cristalina del ejemplo 1", se observa que las reivindicaciones no deben hacer referencia a la descripción. Debe hacerse claridad a ese respecto".

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Sobre este particular, me permito manifestar que es deseo del solicitante introducir las características técnicas del ejemplo 1 en la reivindicación 3, para presentarla como sigue:

"Una forma cristalina de un compuesto de acuerdo con las reivindicaciones 1 ó 2 teniendo el patrón de difracción de polvo por rayos X expresado en términos de ángulos 2θ y espaciamientos "d" como se observa a continuación:

Ángulo (°2 θ)	Valor d (A)
5.480	16.114
8.233	10.731
10.942	8.079
15.299	5.787
16.424	5.393
16.658	5.317
19.116	4.639
19.553	4.536
20.505	4.328
21.939	4.048
22.787	3.899
23.154	3.838
23.381	3.801
24.194	3.676
25.225	3.528
25.802	3.450
26.484	3.363
27.524	3.238
27.865	3.199
28.547	3.124
38.345	2.346

Aclarando, que dicha modificación no amplía el alcance de la presente solicitud toda vez que para superar la objeción del señor Examinador se está describiendo claramente cuál es la forma cristalina reclamada, y como se mencionó anteriormente, la información es extraída del ejemplo 1 del capítulo reivindicatorio de la solicitud en estudio.

3. Adicionalmente, el señor Examinador objeta la reivindicación 7 por hacer referencia al uso del compuesto.

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Sobre este particular, me permito manifestar que debidamente autorizado por mí representado se **desiste** de la reivindicación 7 del capítulo reivindicatorio de la presente solicitud.

4. Por otro lado, me permito manifestar que es deseo del solicitante realizar una modificación a la descripción de la solicitud en estudio debido a un error involuntario, hasta ahora desapercibido que se originó en el momento de la transcripción:

El texto de la página 22 líneas 5 a 22 que hace referencia al intermediario 3 se ha cambiado por el texto que presento a continuación:

COMPUESTO INTERMEDIO 3:
(±) E-Etilo 2-(5-cloro-2-yodoanilino)-4-(2-oxo-1-fenil-3-pirrolidiniliden) butanoato (3a);(±)-Z-Etilo 2-(5-cloro-2-yodoanilino)-4-(2-oxo-1-fenil-3-pirrolidiniliden) butanoato (3b)

A una solución del compuesto intermedio 2 (2.4g) en acetonitrilo (100 mL) a temperatura ambiente, se adicionaron bromuro de tributil (2-oxo-1-fenilpirrolidin-1-il) fosfonio (3.7 g) y DBU (13 mL) y la agitación se continuó durante toda la noche a -20°C. La solución cruda se vació en 200 mL de acetato de etilo y se lavó con una solución saturada de NH_4Cl (2 x 150 mL), luego con agua y salmuera. La fase orgánica se secó y se concentró para dar el producto crudo como una mezcla 4/1 de los compuestos 3a/3b. La purificación mediante la cromatografía en columna (ciclohexano/ acetato de etilo 80/20) dio los compuestos del título 3a (2.16g) y 3b (0.5g) como aceites incoloros.

Me permito aclarar que la modificación anterior no amplía el alcance de la presente solicitud toda vez que es evidente que se cometió un error involuntario al momento de la transcripción ya que no es coherente que se pretenda obtener el intermediario 3 a partir del mismo intermediario 3 así como que los dos compuestos contemplados en el intermediario 3 sean denominados 4a y 4b en lugar de 3a y 3b aún cuando en la página siguiente (18) se encuentra la lista de señales del espectro RMN ^1H para los compuestos **3a** y **3b**. El sustento para dicha modificación puede encontrarse en la página 16 líneas 16-19 de la descripción, en la cual se menciona que la preparación del enantiómero A del compuesto (I) puede hacerse de acuerdo con los procedimientos descritos en **WO 99/64411** de la cual anexo copia de la portada y las páginas 26 y 27 para que se verifiquen los hechos que se expondrán a continuación:

El intermediario 3 de la solicitud en estudio, es un duplicado del intermediario experimental 4 de la publicación PCT No. **WO 99/64411** a la cual se hace referencia. De ésta manera, el texto de la presente solicitud "intermediario 3" que

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está contenido en el procedimiento experimental para la síntesis del intermediario 3 es un obvio e inadvertido error involuntario que tuvo lugar durante la transcripción del procedimiento citado en el documento **WO 99/64411** en el cual el intermediario 3 (empleado en la síntesis del intermediario 4 que es, como se mencionó anteriormente el equivalente al intermediario 3 de la solicitud que nos ocupa) es bromuro de tributil (2-oxo-1-fenilpirrolidin-1-il) fosfonio. De esta manera, desaparece la inconsistencia presentada en la descripción sin incluir en ningún momento materia alguna que no haya sido contemplada desde el inicio.

Para finalizar, teniendo en cuenta las modificaciones realizadas al capítulo reivindicatorio de la solicitud presentada, se superan las objeciones de claridad realizadas por el señor Examinador toda vez que se ha establecido sin lugar a dudas a qué se refieren las reivindicaciones 2 y 3, estando dichas modificaciones plenamente sustentadas en la descripción de la presente solicitud y adicionalmente se ha **eliminado** la reivindicación dirigida al uso del compuesto reclamado. Finalmente, la modificación realizada a la descripción elimina las incongruencias existentes sin introducir materia nueva a la solicitud, estando dichas modificaciones sustentadas en el contenido de la descripción de la solicitud en estudio.

5. Anexo me permito presentar:

(i) Recibo número 06 – 39,937 expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;

(ii) Copia de las nuevas páginas 22 de la descripción y 34, 35 y 36 del capítulo reivindicatorio, **que reemplazan las originalmente presentadas**, y en las cuales se han realizado las modificaciones expuestas anteriormente; y

(iii) Copia de la portada y las páginas 26-27 de la publicación **WO 99/64411** a la que se hace referencia en este memorial.

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

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. 22 JUN2006
Ante mi JUAN MANUEL ROTERO MEDINA
NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(ron): Alicia Lloreda Ricaurte

quien (es) exhibió(eron) la(s) C.C.
39.690.713

y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya (s) y que el contenido del mismo es cierto. En constancia se firma esta diligencia.

ALICIA LLOREDA RICAURTE
C.C. No. 39.690.713 de Usaquén

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 39,937
FECHA : MAYO 26 DE 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 00-093651- -00010-0000
Fec: 2006-06-23 17:19:58 Dep. 2020 NUECREACIONES
Tra. 2 PATENTES
Eve: 1 REGDEPOSITO
Act 444 RESPUESTAREQUE Folios: 12

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47518784	26/05/2006	2,972,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	95,000.00
		TOTAL : $	95,000.00

SON: NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

RMN^1 (DMSO) δ (ppm) 9.80 (t, 1H), 7.57 (d, 1H), 6.55 (d, 1H), 6.51 (dd, 1H), 4.99 (d, 1H), 4.46 (m, 1H), 4.24 (q, 2H), 3.08 (m, 2H), 1.28 (t, 3H).

Compuesto intermedio 3:

(±) E-Etilo 2-(5-cloro-2-yodoanilino)-4-(2-oxo-1-fenil-3-pirrolidiniliden) butanoato (3a); (±)-Z-Etilo 2-(5-cloro-2-yodoanilino)-4-(2-oxo-1-fenil-3-pirrolidiniliden) butanoato (3b).

A una solución del compuesto intermedio 2 (2.4g) en acetonitrilo (100 mL) a temperatura ambiente, se adicionaron bromuro de tributil (2-oxo-1-fenilpirrolidin-1-il) fosfonio (3.7 g) y DBU (13 mL) y la agitación se continuó durante toda la noche a -20°C. La solución cruda se vació en 200 mL de acetato de etilo y se lavó con una solución saturada de NH_4Cl (2 x 150 mL), luego con agua y salmuera. La fase orgánica se secó y se concentró para dar el producto crudo como una mezcla 4/1 de los compuestos 3a/3b. La purificación mediante la cromatografía en columna (ciclohexano/ acetato de etilo 80/20) dio los compuestos del título 3a (2.16g) y 3b (0.5g) como aceites incoloros.

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REIVINDICACIONES

~~Meglumina~~ → (1-metilamino-1-deoxi-D-glucitol)

1. La sal de meglumina del enantiómero A caracterizada porque es de ácido 7-cloro-4-(2-oxo-1-fenil-3-pirrolidiniliden)-1,2,3,4-tetrahidro-2-quinolincarboxílico.

2. Un compuesto de acuerdo con la reivindicación 1, donde dicho compuesto es una forma cristalina.

3. Una forma cristalina de un compuesto de acuerdo con las reivindicaciones 1 ó 2 teniendo el patrón de difracción de polvo por rayos X expresado en términos de ángulos 2θ y espaciamientos "d" como se observa a continuación:

Ángulo (°2θ)	Valor d (A)
5.480	16.114
8.233	10.731
10.942	8.079
15.299	5.787
16.424	5.393
16.658	5.317
19.116	4.639
19.553	4.536
20.505	4.328
21.939	4.048
22.787	3.899

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Ángulo (°2θ)	Valor d (A)
23.154	3.838
23.381	3.801
24.194	3.676
25.225	3.528
25.802	3.450
26.484	3.363
27.524	3.238
27.865	3.199
28.547	3.124
38.345	2.346

4. Un procedimiento para la preparación del compuesto reclamado en cualquiera de las reivindicaciones 1 a 3, caracterizado porque comprende mezclar el enantiómero A de ácido 7-cloro-4-(2-oxo-1-fenil-3-pirrolidiniliden)-1,2,3,4-tetrahidro-2-quinolincarboxílico con meglumina en un solvente adecuado.

5. Un procedimiento para la preparación de una forma cristalina de conformidad con la reivindicación 2 o 3, caracterizado porque comprende cristalizar la sal de meglumina de una mezcla de agua y un solvente orgánico miscible en agua o de una mezcla de solventes adecuados.

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6. Una composición farmacéutica caracterizada porque comprende un compuesto reclamado en cualquiera de las reivindicaciones 1 a 3 para mezclar con uno o más portadores o excipientes fisiológicamente aceptables.

00-093.651

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/04, A61K 31/47, C07D 401/14 | A1

(11) International Publication Number: WO 99/64411

(43) International Publication Date: 16 December 1999 (16.12.99)

(21) International Application Number: PCT/EP99/03936

(22) International Filing Date: 8 June 1999 (08.06.99)

(30) Priority Data:

9812410.0	10 June 1998 (10.06.98)	GB
9812408.4	10 June 1998 (10.06.98)	GB

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

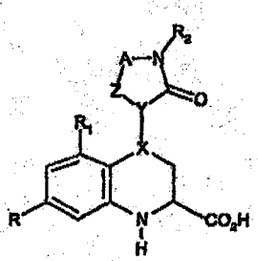
Published
With international search report.

(71) Applicant *(for all designated States except US)*: GLAXO WELLCOME SPA [IT/IT]; Via Alessandro Fleming, 2, I–37100 Verona (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DI FABIO, Romano [IT/IT]; Glaxo Wellcome S.p.A., Via Alessandro Fleming, 2, I–37100 Verona (IT).

(74) Agent: FILLER, Wendy, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(54) Title: TETRAHYDROQUINOLINE DERIVATIVES AS GLYCINE ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I), or a salt or a non toxic metabolically labile esters thereof, wherein Y represents a carbon atom; Z is the group CH which is linked to the group Y via a double bond and X is CH or Z is methylene or NR_{11} and X is a carbon atom linked to the group Y via a double bond; A represents a C_{1-2}alkylene chain and which chain may be substituted by one or two groups selected from C_{1-6}alkyl optionally substituted by hydroxy, amino, C_{1-4}alkyl amino or C_{1-4}dialkyl amino or which chain may be substituted by the group =O; R represents a halogen atom or C_{1-4}alkyl group; R_1 represents a hydrogen, a halogen atom or C_{1-4}alkyl group; R_2 represents optionally substituted phenyl, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, processes for their preparation and their use as glycine antagonists.

Then, 3,5,-chloro-2iodoaniline was added, and the mixture refluxed for 1 hr. Then mixture was cooled, filtered througt celite to eliminate the MgSO4, and concentrated. The resulting brown oil was dissolved in dichloromethane (15ml) cooled to -78°C and $Yb(OTf)_3xH_2O$ (0.186g) was added. The suspension was stirred for 5 mins at -78°C, then the vinyloxytrimethylsilane (0.29g) was added and the temperature was risen to 20°C. After 1 hr at that temperature a saturated solution of NH4Cl (20 cc) was added followed by ethyl acetate (30ml). The organic phase was washed with brine (20 ml) and dried over sodium sulphate and concentrated to give the crude product, which was purified by column chromatography (cyclohexane, then cyclohexane/ethyl acetate 85/15) to give the title compound (0.562 g) as a colourless oil.
NMR ($CDCl_3$) δ (ppm) 9.65 (s, 1H), 7.00 (d, 1H), 6.70 (d, 1H), 5.60 (d, 1H), 4.80 (m, 1H) 4.10 (q, 2H), 3.10 (m, 2H), 1.15 (t, 3H).

Intermediate 3

Tributyl (2-oxo-1-phenylpyrrolidin-1-yl) phosphonium bromide

N,N,N'N'-Tetramethylethylene diamine (23.3ml) was added to a solution of N-phenylpyrrolidinone (5g) in dichloromethane (50ml). The solution was cooled to 0-5° and trimethylsilyl triflate (8.4ml) was added over *ca* 20 mins maintaining the temperature in the range 0-5°. The resultant solution was stirred for 10 mins and a solution of pyridinium bromide perbromide (13g) in acetonitrile (20ml) was added over *ca* 20 mins maintaining the temperature in the range 0-10°. The resultant suspension was stirred at 0-5° for *ca* 60 mins. Aqueous sodium bicarbonate solution (50ml) was added, cautiously. The mixture was stirred for *ca* 5 mins and the layers are separated.The aqueous phase was diluted with water (20ml) and back extracted with dichloromethane (20ml). The combined organic phases were washed with further sodium bicarbonate solution (50ml), 2M hydrochloric acid (2x50ml) and water (50ml), back extracting each wash with dichloromethane (10ml). The organic solution was dried ($MgSO_4$) and concentrated on a rotavapor. The red/brown solid was stirred with ethyl acetate (50ml) and warmed to give a solution which was then cooled and tributylphosphine (8.5ml) was

added.The solution was heated to reflux and maintained at reflux for 2.5 hours. The solution was allowed to cool to room temperature and was then cooled to 0-5°. The resulting suspension was aged at 0-5° for *ca* 60 min.The product was isolated by vacuum filtration and then washed with ethyl acetate:t-butylmethylether (1:1, 40ml) and dried in a vacuum oven at 45° to give the title compound as a white crystalline solid (10.12g), mp 127-128°.

Intermediate 4

(±) E-Ethyl 2-(5-chloro-2-iodoanilino)-4-(2-oxo-1-phenyl-3-pyrrolidinylidene) butanoate (4a);(±)-Z-Ethyl 2-(5-chloro-2-iodoanilino)-4-(2-oxo-1-phenyl-3-pyrrolidinylidene) butanoate(4b)

To a solution of intermediate 2 (2.4g) in acetonitrile (100 ml) at r.t. intermediate 3(3.7 g) and DBU (13 ml) were added and stirring was continued overnight at -20°C. The crude solution was poured into 200 ml of ethyl acetate and washed with a saturated solution of NH_4Cl (2 x 150 ml), then with water and brine. The organic phase was dried and concentrated to give the crude product as a 4/1 mixture of 4a/4b compounds. Purification by column chromatography (cyclohexane/ethyl acetate 80/20) gave the title 4a (2.16 g) and the 4b (0.5g) compounds as colourless oils.

Intermediate 4a

NMR ($CDCl_3$) δ (ppm) 7.72 (d, 2H), 7.56 (d, 1H), 7.38 (t, 2H), 7.16 (t, 1H), 6.6 (m, 1H), 6.50 (dd, 1H), 6.49 (d, 1H), 4.88 (d, 1H), 4.26 (m, 3H), 3.87 (t, 2H), 2.79 (m, 4H), 1.30 (t, 3H)

Intermediate 4b

NMR ($CDCl_3$) δ (ppm) 7.69 (d, 2H), 7.52 (d, 1H), 7.38 (t, 2H), 7.17 (t, 1H), 6.47 (d, 1H), 6.44 (dd, 1H), 5.98 (m, 1H), 5.00 (d, 1H), 4.22 (m, 2H), 4.13 (m, 1H), 3.84 (t, 2H), 3.2-3.6 (m, 2H), 2.85 (m, 2H), 1.26 (t, 3H)

Intermediate 5

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 491/052, C07B 57/00, A61K 31/41, C07C 215/10 // (C07D 491/052, 311:00, 209:00)

A1

(11) International Publication Number: WO 95/27713

(43) International Publication Date: 19 October 1995 (19.10.95)

(21) International Application Number: PCT/GB95/00857

(22) International Filing Date: 11 April 1995 (11.04.95)

(30) Priority Data:

9407225.3	12 April 1994 (12.04.94)	GB
9501455.1	25 January 1995 (25.01.95)	GB

(71) Applicant *(for all designated States except US)*: CHIROSCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ADGER, Brian, Michael [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). DYER, Ulrich, Conrad [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). WOODS, Martin [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). ANDREWS, John, Francis, Paul [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). BAKER, Helen, Frances [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

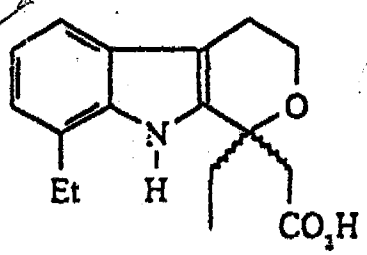
(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: PROCESS FOR THE RESOLUTION OF ETODOLAC USING GLUCAMINE DERIVATIVES

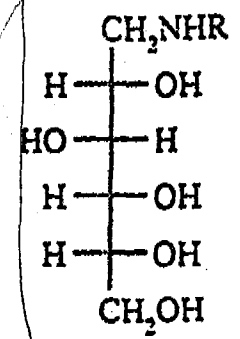
(57) Abstract

Salts of Glucamine or N-(C_{1-4}alkyl)glucamine (formula 1) with S-etodolac, (formula 2) preferably the meglumine salt, are particularly suitable for rapid-onset analgesic effect. These salts can be prepared by resolving racemic etodolac using as the resolving agent glucamine or an N-(C_{1-4}alkyl) glucamine. In addition, water-soluble S-etodolac salts in general can be used in the manufacture of medicaments for the use in rapid-onset analgesia and in managing chronic pain, and are particularly suitable for sustained-release formulations.



(+/- etodolac)

(2)



(1)

sal meglumina

PROCESS FOR THE RESOLUTION OF ETODOLAC USING GLUCAMINE DERIVATIVES

Field of the Invention

This invention relates to etodolac, and in particular to novel enantiomeric salts thereof, a process for making those salts, and their use in the manufacture of medicaments.

Background of the Invention

Etodolac is a chiral compound. It is a non-steroidal analgesic and anti-inflammatory agent which is marketed in racemic form. Its analgesic properties and preparation are described in US-A-3843681 and sustained-release formulations containing it are described in EP-A-0309157. The existence of its meglumine and glucamine acid addition salts is disclosed in US-A-4748174, although the preparation and properties of these salts is not.

It has been found that the required biological activity of etodolac generally resides in only one of its enantiomers, for instance as described by Demerson et al, J. Med. Chem., (1983) 26:1778. Consequently, there is a need for a process to produce that single enantiomer. An existing resolution procedure is disclosed in US-A-4520203, and involves crystallisation of a single diastereoisomeric salt formed with etodolac and the alkaloidal base cinchonine. However, a disadvantage with this process is that the resolving agent used is both expensive and toxic.

Another resolution procedure is disclosed in US-A-4515961 and resolves etodolac as a conglomerate from a solution of the racemate.

Summary of the Invention

According to a first aspect of the present invention, a compound that is a glucamine or an N-(C_{1-4} alkyl)-glucamine salt of (S)-etodolac, preferably the meglumine salt of (S)-etodolac. The meglumine salt has a surprisingly short t_{max}, thus making it particularly suitable for rapid-onset analgesic effect. In addition, surprisingly, the use of the meglumine salt of (S)-etodolac leads to a reduction in variation in plasma concentrations

coatings such as sugar-based materials, or films such as hydroxymethyl cellulose; flavours and/or sweeteners such as phenylalanine and saccharin; and colourings such as titanium dioxide or iron oxides. Such excipients are typically used in their standard amounts.

(S)-etodolac or a salt thereof, can be the sole pharmaceutically-active agent in a drug formulation. Alternatively, it can be combined with other pharmaceutically-active agents, such as a gastroprotectant eg misoprostol or cyclodextrins; analgesics, e.g. opiates or paracetamol; other NSAIDs; adjuvants, e.g. caffeine; or cough-cold remedies, e.g. anti-histamines or sedatives.

It is envisaged that in addition to being useful in rapid onset analgesia and in managing chronic pain, (S)-etodolac, or a salt thereof, may have a number of other medical indications, for instance in inhibiting joint alkylosis; in inhibiting bone resorption; and in treating gout.

The novel enantiomeric salts of the invention can be prepared by resolving etodolac as outlined in Scheme 1 below where the resolving agent is, for example, meglumine (N-methyl-(D)-glucamine). In principle either the (S) or (R) enantiomer of etodolac in the salt form can be obtained depending upon the conditions used, and the free acid isolated if so desired.

The procedure is especially expedient since:

(i) racemic etodolac is readily available through methods established on an industrial scale; and

(ii) unlike cinchonine, (-)-meglumine is a pharmaceutically-acceptable counterion for a drug salt-form, so that cleavage of the salt after resolution is not obligatory, thereby potentially reducing the number of process steps to a suitable drug formulation.

Suitable solvents for the resolution include any available ethers, esters, ketones, amides, alcohols, nitriles, water and mixtures thereof. It is necessary that the starting material dissolves in the solvent at ambient

or elevated temperature, and that precipitation of the respective etodolac salt is possible therefrom. Preferred solvents are polar solvents such as ketones, alcohols, nitriles, amides and water. Most preferred solvents are alcohols, particularly alkanols, especially ethanol and isopropanol.

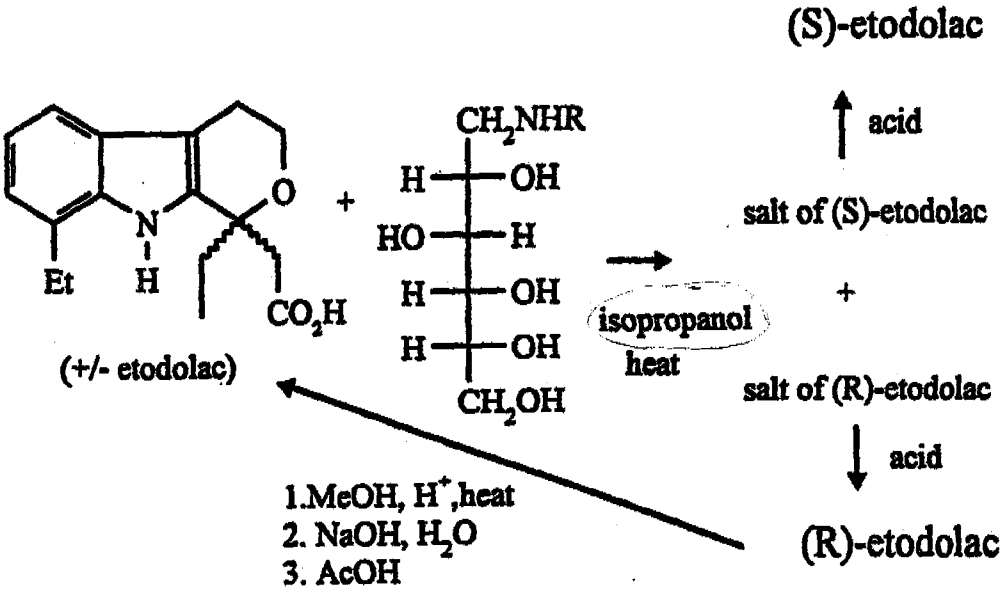
The concentration of racemic etodolac in the solvent depends upon the nature of the solvent and the temperature of crystallisation to be used. Preferably, it will be in the range 0.01 to 2.5 g/ml, and most preferably between 0.1 to 0.2 g/ml.

The temperature of crystallisation depends upon the concentration of the drug and the nature of the solvent. Preferably it is in the range 0 to 70°C, and most preferably 35 to 55°C using ethanol or isopropanol at a concentration of 0.15 g/ml based on racemic etodolac. Crystallisation can be facilitated by seeding, preferably using crystals that are significantly enriched in one enantiomer, and more preferably using 100% ee of the desired enantiomer.

It has also been found that enantiomeric esters of etodolac can be racemised effectively upon treatment with a catalytic amount of an acid or acid resin in an organic solvent. This is wholly surprising because heating etodolac free acid under acidic conditions leads to its decomposition, as described by Lee et al, J. Pharm. Sci., (1988) 77(1):81-86. Suitable acids are preferably inexpensive acids such as hydrochloric acid, sulphonic acid resin or sulphuric acid. Most preferably the acid is concentrated sulphuric acid. Suitable organic solvents are ethers, esters, ketones, amides, alcohols, nitriles and mixtures thereof, preferably alcohols, most preferably an alcohol corresponding to the alkoxy group of the respective ester.

Alternatively, the above racemisation can be carried out by treating an enantiomeric ester with a catalytic

Scheme 1


(S)-etodolac
acid
salt of (S)-etodolac
+
salt of (R)-etodolac
acid
(R)-etodolac
isopropanol
heat
(+/- etodolac)
CH2NHR
H OH
HO H
H OH
H OH
CH2OH
Et
H
N
O
CO2H
1.MeOH, H+,heat
2. NaOH, H2O
3. AcOH

CLAIMS

1. A glucamine or an N-(C_{1-4} alkyl)glucamine salt of (S)-etodolac.

2. A salt according to claim 1 in an enantiomeric excess of at least 80% with respect to the (R)-enantiomer.

3. A salt according to claim 1 or claim 2 which is the meglumine salt.

4. Use of a water-soluble (S)-etodolac salt for the manufacture of a medicament for use in rapid-onset analgesia.

5. Use of a water-soluble (S)-etodolac salt for the manufacture of a medicament for use in managing chronic pain.

6. Use according to claim 4 or claim 5, wherein the salt is that defined in any of claims 1 to 3.

7. Use according to claim 6, wherein the salt is the meglumine salt.

8. A sustained-release formulation comprising (S)-etodolac, or a salt thereof.

9. A formulation according to claim 8, comprising a salt as defined in any of claims 1 to 3.

10. A formulation according to claim 9, comprising the meglumine salt of (S)-etodolac.

11. A process for the resolution of etodolac, comprising using as the resolving agent glucamine or an N-(C_{1-4} alkyl)-glucamine.

12. A process according to claim 11, wherein the resolving agent is meglumine.

13. A process according to claim 11 or claim 12, which is conducted in an alcoholic solvent.

14. A process according to any of claims 11 to 13, wherein the product comprises the (S)-enantiomer of etodolac, or a salt thereof.

15. A process for the resolution of etodolac according to any of claims 11 to 14, which additionally comprises racemising the unwanted enantiomer by formation of an ester of the carboxylate function and then acid treatment.

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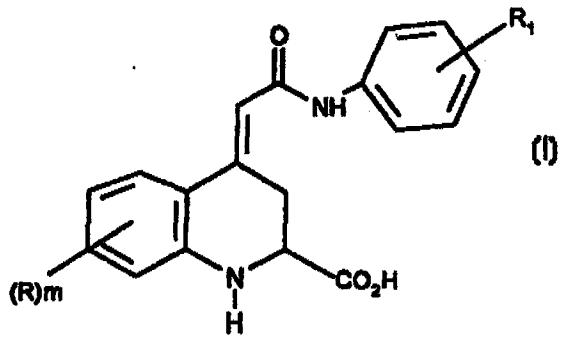
(57) Abstract

Compounds of formula (I) or a salt, or metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2 or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2; R_1 represents a group $(CH_2)nCN$, $-CH=CHR_3$, $(CH_2)nNHCOCH_2R_4$ or $O(CH_2)pNR_5R_6$; R_3 represents cyano or the group COR_7; R_4 represents alkoxy or a group $NHCOR_8$; R_5 and R_6 each represent independently hydrogen or alkyl, or R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9; R_7 represents an alkoxy, amino or hydroxyl group; R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, aryl or heterocyclic group; R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein R_{10} represents hydrogen or alkyl group; R_{11} represents optionally substituted alkyl, aryl, heterocyclic or cycloalkyl group; n is zero or an integer from 1 to 4; p is an integer from 2 to 4, processes for their preparation and to their use in medicine.



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147 145

trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2;

R_1 represents a group $(CH_2)nCN$, $-CH=CHR_3$, $(CH_2)nNHCOCH_2R_4$ or $O(CH_2)pNR_5R_6$; R_3 represents cyano or the group COR_7;

R_4 represents alkoxy or a group $NHCOR_8$;

R_5 and R_6 each represent independently hydrogen or alkyl, or

R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9;

R_7 represents an alkoxy, amino or hydroxyl group;

R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, phenyl, heteroaryl or heterocyclic group;

R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein

R_{10} represents hydrogen or alkyl group;

R_{11} represents optionally substituted alkyl, phenyl, heteroaryl , heterocyclic or cycloalkyl group;

n is zero or an integer from 1 to 4; p is an integer from 2 to 4.

In compounds of formula (I) the exocyclic double bond is in the trans (E) configuration.

For use in medicine the salts of the compounds of formula (I) will be physiologically acceptable thereof. Other salts however may be useful in the preparation of the compounds of formula (I) or physiologically acceptable salts thereof. Therefore, unless otherwise stated, references to salts include both physiologically acceptable salts and non-physiologically acceptable salts of compounds of formula (I).

Suitable physiologically acceptable salts of compounds of the invention include base addition salts and where appropriate acid addition salts.

Suitable physiologically acceptable base addition salts of compounds of formula (I) include alkali metal or alkaline earth metal salts such as sodium, potassium, calcium, and magnesium, and ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, phenylbenzylamine, ethanolamine diethanolamine and N-methyl glucosamine).

The compounds of formula (I) and/or salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

Compounds of formula (I) and in particular the base addition salts thereof e.g. sodium salt have been found to have an advantageous profile of solubility in water.

The term alkyl as used herein as a group or part of a group refers to a straight or branched chain alkyl group containing from 1 to 4 carbon atom examples of such groups including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, secondary butyl or tertiary butyl.

The term optionally substituted alkyl as used herein refers to an alkyl group as defined above and which is substituted by one or more hydroxy, carboxyl, and amino groups.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term heteroaryl refers to a 5 or 6 membered heteroaryl group in which the 5-membered heteroaryl group contains 1 or 2 heteroatoms selected from oxygen sulphur or nitrogen and the 6-membered heteroaryl group containing 1 or 2 nitrogen atoms.

Examples of suitable heteroaryl groups include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridinyl, and pyrimidinyl.

The term optionally substituted phenyl refers to a phenyl group substituted with up to 3 substituents selected from halogen, C1-4 alkyl, C1-4 alkoxy, amino,alkylamino,hydroxy, trifluoromethyl, carboxyl or methoxycarbonyl.

The term cycloalkyl refers to a C_{3-7}cycloalkyl group which may optionally be substituted by 1 or 2 C_{1-4} alkyl groups e.g cyclopropyl, cyclobutyl,cyclopentyl, cyclohexyl cycloheptyl or 2-methylcyclohexyl.

The term optionally substituted heterocyclic group refers to 5-7 membered saturated heterocyclic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen. Examples of suitable groups containing a single heteroatom include tetrahydropyranyl e.g. 4-tetrahydropyranyl, pyrrolidinyl e.g 2 or 3 pyrrolidinyl, piperidinyl e.g 4- or 3-piperidinyl and N-substituted derivatives therefore (e.g. N-alkyl such as e.g. methyl or N-acyl such as N-alkanoyl e.g.

A particularly preferred class of compounds are those wherein R_1 is the group CH_2CN, $-CH=CHR_3$ (wherein R_3 is C_{1-4}alkoxycarbonyl eg butoxycarbonyl, carbamoyl or cyano), $(CH_2)_nNHCOCH_2R_4$ (wherein n is zero and R_4 is C_{1-4}alkoxy, eg methoxy or $NHCOR_8$ wherein R_8 is C_{1-4}alkyl eg isopropyl), eg R_1 is 2-methoxyacetylamino or isobutyrylamino-methylcarbonylamino, or R_1 is $O(CH_2)pNR_5R_6$ (wherein p is 2, R_5 is hydrogen and R_8 is COR_9 wherein R_9 is C_{1-4}alkyl eg isopropyl, or NR_5R_6 represents a morpholino group) eg R_1 is 2-isobutyryl aminoethoxy or 2-morpholino-4-ylethoxy.

Specific preferred compounds of the invention include:

(±) (E) 5,7- Dichloro- 4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (+,-) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-methylcarbonylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
and physiologically acceptable salts e.g. sodium salt , metabolically labile esters or enantiomers thereof.

Further specific preferred compounds of the invention include:

(±) (E) 5,7- Dichloro- 4-(4-cyanomethyl-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 5,7- Dichloro- 4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-tert-butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7- dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
and physiologically acceptable salts e.g. sodium salt , metabolically labile esters or enantiomers thereof.

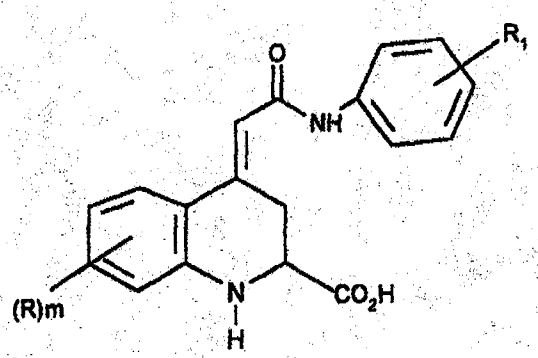
The compounds of formula (I) and/or physiologically acceptable salts thereof are excitatory amino acid antagonists. More particularly they are potent antagonists at the strychnine insensitive glycine binding site associated with the NMDA receptor complex. As such they are potent antagonists of the NMDA receptor complex. These compounds are therefore useful in the treatment or prevention of neurotoxic damage or neurodegenerative diseases. Thus the compounds are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, anaesia, hypoxia, anoxia, perinatal asphyxia cardiac arrest. The compounds are also useful in the treatment of chronic neurodegenerative diseases such as; Huntingdon's disease, Alzheimer's senile dementia, amyotrophic lateral sclerosis, Glutaric Acidaemia type, multi-infarct dementia, status epilecticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced neurodegeration (e.g. AIDS, encephalopaties), Down syndrome, epilepsy, schizophrenia, depression, anxiety, pain, migraine, headaches including cluster headaches and or tension headaches, neurogenic bladder, irritative bladder disturbances, drug dependency, including withdrawal symptoms from alcohol, cocaine, opiates, nicotine, benzodiazepine, and emesis.

The potent and selective action of the compound of the invention at the strychnine- insensitive glycine binding site present on the NMDA receptor complex may be readily determined using conventional test procedures. Thus the ability to bind at the strychnine insensitive glycine binding site was determined using the procedure of Kishimoto H et al. J Neurochem 1981, 37 1015-1024. The selectivity of the action of compounds of the invention for the strychnine insensitive glycine site was confirmed in studies at other ionotropic known excitatory amino acid receptors. Thus compounds of the invention were found to show little or no affinity for the kainic acid (kainate) receptor, a-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor or at the NMDA binding site.

Compounds of the invention have also been found to inhibit NMDA induced convulsions in mice using the procedure Chiamulera C et al. Psychopharmacology (1990) 102, 551-552.

Claims

1. A compound of formula (I)



(I)

a salt, or a metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2;

R_1 represents a group $(CH_2)nCN$, $-CH=CHR_3$, $(CH_2)nNHCOCH_2R_4$ or $O(CH_2)pNR_5R_6$; R_3 represents cyano or the group COR_7;

R_4 represents alkoxy or a group $NHCOR_8$;

R_5 and R_6 each represent independently hydrogen or alkyl, or

R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9;

R_7 represents an alkoxy, amino or hydroxyl group;

R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, phenyl, heteroaryl or heterocyclic group;

R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein

R_{10} represents hydrogen or alkyl group;

R_{11} represents optionally substituted alkyl, phenyl, heteroaryl , heterocyclic or cycloalkyl group;

n is zero or an integer from 1 to 4; p is an integer from 2 to 4.

2. A compound of formula(I) as claimed in claim 1, a physiologically acceptable salt or a metabolically labile ester thereof.

3. A compound of formula(I) as claimed in claim 1 or 2 wherein m is 1 or 2, and R is halogen atom in the 5 and /or 7 position.

4. A compound of formula(I) as claimed in any of claims 1 to 3 wherein m is 2 and R is chlorine in the 5 and 7 position.

5. A compound of formula(I) as claimed in any of claims 1 to 4 wherein R_1 is the group $(CH_2)nCN$, - $CH=CHR_3$, wherein R_3 is cyano or COR_7, in which R_7 is C_{1-4} alkoxy, amino, $(CH_2)nNHCOCH_2R_4$ wherein R_4 is C_{1-4} alkoxy, $NHCOR_8$ wherein R_8 is hydrogen or C_{1-4}alkyl ,$O(CH_2)pNR_5R_6$ wherein R_5 and R_6 are hydrogen or NR_5R_6 represents morpholino or R_5 represents hydrogen and R_6 is COR_9 wherein R_9 is hydrogen or C_{1-4}alkyl, n is zero, 1 or 2; p is 2, 3 or 4

6 A compound of formula (I) as claimed in claim 5 wherein R_1 is the group cyanomethyl , $CH=CHR_3$, wherein R_3 is a t-butoxycarbonyl, carbamoyl,cyano group, 2-isobutyrylamino-ethoxy, 2-methoxy-acetylamino, isobutirrylamino methylcarbonylamino, 2-morpoholin-4yl-ethoxy.

7 A compound selected from

(±) (E) 5,7- Dichloro- 4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-methylcarbonylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E) 5,7- Dichloro- 4-(4-cyanomethyl-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E,E) 5,7- Dichloro- 4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E,E) 4-[4-(2-tert-butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E,E) 4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7- dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

(±) (E) 5,7- Dichloro- 4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;