

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 12-068-973

Solicitante: NOVARTIS AG.

Apoderado: CARLOS R. OLARTE.

Título de la Nueva Creación: PROCESO PARA LA ELABORACION DE COMPUESTOS ORGANICOS.

Gaceta: 653 de 28 de septiembre de 2012, No. de publicación 1487

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica

TECNOQUIMICAS S.A.

Nombre o denominación / Razón social completa

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

Número 890 300 466-5

Dirección Calle 23 No. 7-39 Ciudad Cali

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

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

3. Datos del representante o apoderado:

<u>REYES VILLAMIZAR JOSE LUIS</u>	<u>79`152.473</u>	<u>44655</u>
Apellidos y Nombre	Documento de identificación	T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica <u>info@reyes-abogados.com</u>	No. Fax 621.25.42	Número telefónico 621.26.31
---	----------------------	--------------------------------

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

6.

Fundamentos de la oposición

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

Justificación: VER ANEXO

Prórroga:

SI

☒

NO

☐

7.

Anexos

☒

 Comprobante de pago de la tasa para la presentación de la solicitud No. 12-141249 12-141250 Fecha: Dic 20/12

☒

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

☒

 Pruebas de los fundamentos de la oposición

☒

 Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473

44655

C.C.

T.P.

SEÑOR**SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E.****S.****D.**

REF: Expediente 12-068-973**TÍTULO SOLICITADO: PROCESO PARA LA ELABORACIÓN DE
COMPUESTOS ORGÁNICOS.****PUBLICACIÓN: Gaceta 653 de 28/09/2012, número de publicación
1487.****SOLICITANTE: NOVARTIS AG.****APODERADO: CARLOS REINALDO OLARTE GARCIA.****TRÁMITE: PRESENTACIÓN DE OPOSICIÓN.**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **12-068-973**, por no cumplir con lo dispuesto por los artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

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

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite que se refiere a procesos para la elaboración de un bloqueador de los receptores de angiotensina (ARB; también denominado como antagonista de los receptores de angiotensina II o antagonista del receptor AT1), y a sales de los mismos, a intermediarios novedosos, y a los pasos del proceso; incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

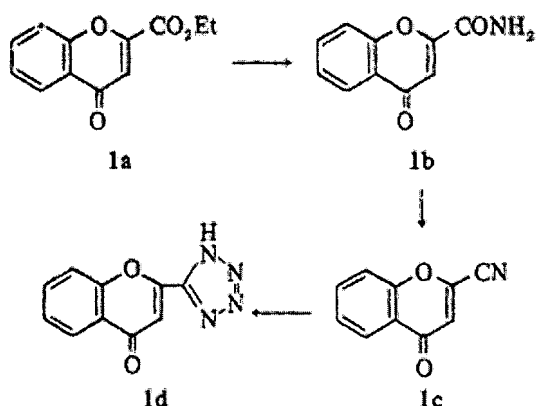
En primer lugar, y ante la revelación textual de un “uso”, específicamente en las reivindicaciones 14 y 15, es relevante señalar que dicha pretensión resulta inaceptable a la luz de la Decisión 486 en tanto los “usos” son una categoría excluida del concepto de “Productos o Procedimientos” que establece el artículo 14 de la norma citada. Lo anterior, además, en consonancia con reiteradas interpretaciones de la SIC sobre este punto.

En un segundo aspecto, y teniendo en cuenta que la solicitud colombiana en trámite menciona en sus reivindicaciones 3, 4, 8, 9 y 10 un reactivo de azida, específicamente una azida de fórmula R7R8MN en donde M es boro o aluminio para la obtención de un compuesto de fórmula I (un tetrazol 5-sustituido) a partir de un compuesto de fórmula IV (que comprende un grupo nitrilo) es importante indicar que en el estado de la técnica se reporta el documento “Benzopyrones. 7. Synthesis and Antiallergic Activity of some 2-(5-Tetazoly)chromones” publicado en el *Journal of medicinal Chemistry*, 1972, Vol. 15, N° 8. Pág 865 (D1), y en la referencia electrónica: <http://pubs.acs.org/cgi->

bin/abstract.cgi/jmcmr/1972/15/i08/f-pdf/f jm 00278a027.pdf?sessid=600613 y

que textualmente dice:

Scheme I



The carboxylic esters, prepared¹⁴ from the appropriate 2-hydroxyacetophenone and diethyl oxalate, reacted with gaseous NH_3 at 0° to give high yields of the carboxamides. Although several carboxamides of this kind are known, their dehydration to the 4-oxo-4H-1-benzopyran-2-carbonitriles has not been reported. The unsubstituted carbonitrile 1c, the only known member of this series, was synthesized¹² in five stages from 2-methylchromone *via* the 2-carboxaldehyde. A more convenient method is now described through the dehydration of the carboxamide by means of an arylsulfonyl chloride and pyridine in DMF. Other reagents,¹⁹ such as POCl_3 , $\text{PCl}_5 \cdot \text{POCl}_3$, SOCl_2 , or P_2O_5 , proved to be ineffective while benzenesulfonyl chloride in pyridine²⁰ gave a low yield. 3-Chloro-4-oxo-4H-1-benzopyran-2-carbonitrile (17c) was prepared by reacting the unsubstituted nitrile (1c) with sulfuryl chloride.

The carbonitriles were converted smoothly to the tetrazoles by reaction with sodium azide and ammonium chloride in DMF.²¹ A recent study²² showed that the pK_a of

Como se puede observar, en el artículo mencionado el grupo R corresponde a una benzopirona, y se puede obtener el **grupo tetrazol** mediante la **conversión lenta del grupo carbonitrilo** por reacción con una **azida de sodio** y cloruro de amonio en DMF.

Resulta evidente que en ambos casos la fabricación del grupo tetrazol se logra mediante el tratamiento de un compuesto R-CN con una azida, en consecuencia, la utilización de este tipo de reactivos azidicos, en especial los de fórmula R7R8MN, carece de novedad por obra de lo revelado en el artículo antes señalado.

Ahora bien, si en gracia de discusión se tratara de una solicitud novedosa por obra de la utilización de órgano-boro-azida ú órgano-alumino-azida, sería necesario entonces demostrar la falta de nivel inventivo del proceso revelado, ante el contenido de la solicitud colombiana CO 06-014-919 (equivalente a la publicación internacional WO2005/014602), así:

- En el capítulo descriptivo de dicha solicitud, se detalla:

“En la técnica se sabe que los derivados de tetrazol se pueden preparar mediante la reacción de diferentes nitrilos con azidas orgánicas en rendimientos relativamente buenos. Los representantes de las azidas correspondientes son, por ejemplo, **las azidas de órgano-estaño, que tienen algún perfil tóxico**. Éstas se tienen que manejar con un cuidado especial en los procesos de producción, provocan problemas ecológicos, y requieren de una cantidad significativa de trabajo de proceso adicional para reciclarlas desde las aguas residuales, aumentando de esta manera adicionalmente los costos de producción. Los métodos para formar tetrazol, que utilizan azidas de trialquil-amonio o azidas de tetra-alquil-amonio, **pueden formar sublimados volátiles** en los reactores de reacción a temperaturas más altas, que tienen el riesgo de explotar, y por consiguiente, no son fáciles de manejar en la producción a gran escala.

Existe una fuerte necesidad de desarrollar variantes del proceso, nuevos reactivos, e intermediarios que eliminen los inconvenientes anteriormente mencionados. En especial, se ha hecho una gran cantidad de esfuerzo para sustituir las azidas de órgano-estaño correspondientes con agentes alternativos que sean alternativas viables en la producción de tetrazoles con rendimientos suficientemente altos.

De una manera sorprendente, se ha encontrado que las azidas de órgano-boro y las azidas de órgano-aluminio se pueden utilizar como alternativas para los compuestos de órgano-estaño correspondientes” (EL REMARCADO ES NUESTRO)

También se revelan con anterioridad procesos de ciclación a partir de carbonitrilos o ciano con alquil estaño-azidas como el documento WO94/07872 (D2) publicado el 14 de abril de 1994, perteneciente a Abbott Laboratories y en el el documento WO9314086 (D3) publicado el 22 de julio de 1993 perteneciente a Syntex Inc.,

Otros documentos detallan la reacción de ciclación del anillo tetrazol a partir de ciano y azida derivados que no utilizan estaño, como los documentos:

- EP 0 796 852 "Process for preparation of 5-substituted tetrazoles" del 24 de septiembre de 1997 (D4)
- EP 0 120 483 "(1H-tetrazol-5-yl)-2(1H)-quinolinones" de octubre 3 de 1984 (D5)

Estos dos últimos documentos detallan el uso de Azida de Sodio con una amina, característica que el solicitante describe como desventajosa por la volatilidad y riesgo de explosión de los vapores y propone entonces el uso de compuestos órgano-metal azidicos de fórmula (R1) (R2) BN₃ y (R1) (R2) Al N₃, que coinciden con el reactivo R7R8MN revelado en la solicitud en cuestión.

Como vemos, en el estado del arte se encuentran múltiples ejemplos de solicitudes en las que para obtener un grupo **tetrazol** se usan compuestos de tipo nitrilo o ciano y **azidas**, lo que nos demuestra que al menos desde 1984 este procedimiento es ampliamente conocido y que dados los inconvenientes provocados por las azidas, han permitido y han conducido obviamente a los expertos en síntesis a la búsqueda de reactivos que protejan el medio ambiente y que permitan obtener procesos más limpios.

De otro lado, los compuestos azidos órgano-boranos y azido Aluminanos se reportan desde 1954 como lo detalla la siguiente referencia bibliográfica: "Gas Phase Synthesis, Structure, and Dissociation of Boron Triazide" *J. Phys. Chem.* 1995, 99, 6294- 6300 (D6) detallado en la referencia electrónica:

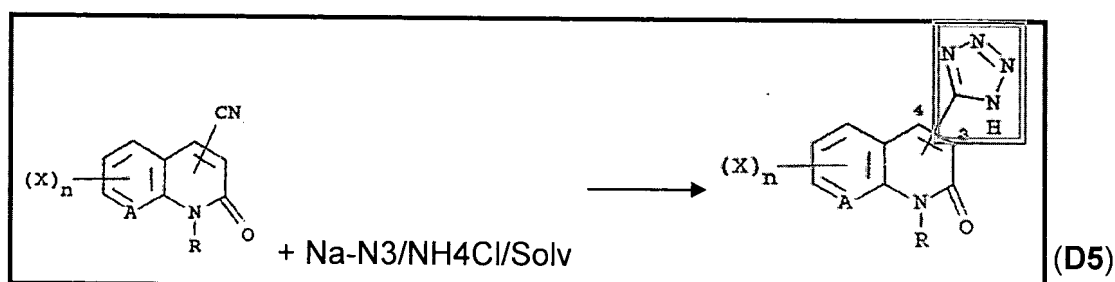
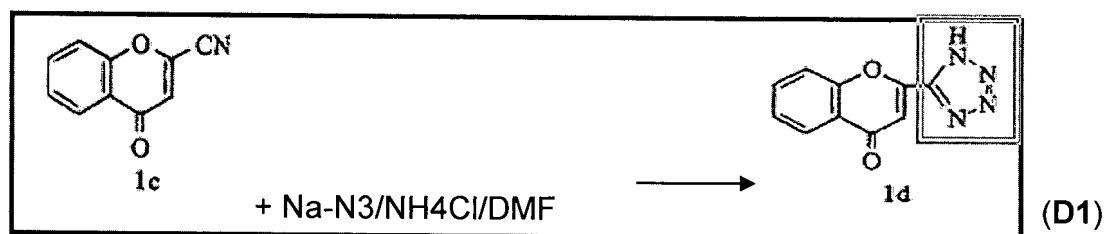
http://pubs.acs.org/cgi-bin/abstract.cgi/jpchax/1995/99/i17/f-pdf/f_j100017a007.pdf?sessid=600613, describe la síntesis de borano-azidas a partir de diboranos con HN₃, y detalla:

"Similar reactions of organic azides with halogenated boron **compounds have been used** by organic chemists for the synthesis of **heterocyclic ring compounds of nitrogen**"

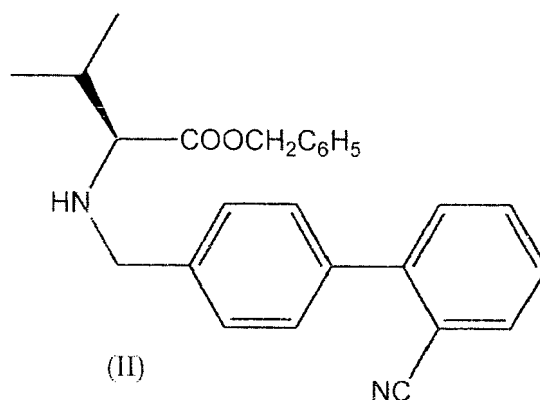
Una traducción libre dice:

"Similares reacciones de los compuestos orgánicos azidos con borano halogenados han sido usados por los químicos orgánicos para la síntesis de compuestos heterocíclicos anillados de nitrógeno."

De igual manera, el hecho de pretender proteger la obtención de antagonistas del receptor de angiotensina II mediante el proceso descrito, si bien es cierto no se ha encontrado una descripción textual del mismo, se debe tener en cuenta que éste proceso no reúne el requisito de nivel inventivo ya que al igual que los documentos citados como anterioridades la fabricación del grupo tetrazol se lleva en condiciones similares, es decir, que se hace reaccionar un compuesto de tipo nitrilo con una azida adecuada para obtener un R-tetrazol, veamos:



De otro lado, la patente europea EP 1714963 publicada el 25 de octubre de 2006, revela compuestos de la siguiente fórmula:



Con lo cual afecta la novedad del compuesto de fórmula III de la solicitud colombiana en trámite, en especial la reivindicación 12.

Finalmente, y por su patente, la patente europea EP1533305 publicada el 25 de mayo de 2005 revela:

Example 7 - 2-[(2'-Cyano-biphenyl-4-yl methyl)-pentanoyl-amino]-3-methylbutyric acid

[0037] 6.0 g (15.4 mmoles) of 4'-(4-isopropyl-5-oxo-3-pentanoyl-oxazolidin-2-yl)-biphenyl-2-carbonitrile is reacted in 30 ml of ethanol with 3.8 g of ammonium formate (61.6 mmoles) and 2 g of 5% Pd/C catalyst. The temperature is raised to 75°C, keeping these conditions for 3 hours. The mixture is cooled and the catalyst is filtered off. The organic phase is concentrated under reduced pressure to a residue to obtain 2-[(2'-cyano-biphenyl-4-yl-methyl)-pentanoyl-amino]-3-methylbutyric acid.

[0038] ¹H-NMR (CDCl₃) (0.80-1.15 (m, 9H); 1.20-1.50 (m, 2H); 1.60-1.80 (m, 2H); 2.40-2.55 (m, 2H); 2.60-2.80 (m, 1H); 3.80 (d, 0.7 H), 3.90 (d, 0.3 H); 4.45 (d, 0.7 H), 4.50 (d, 0.3 H), 4.82 (d, 0.7H), 4.85 (d, 0.3H); 7.10-7.20 (m, 4H), 7.40-7.70 (m, 4H).

Con lo que afecta la novedad del compuesto IV revelado en la solicitud colombiana en trámite, especialmente en la reivindicación 13.

En conclusión, la solicitud colombiana en cuestión carece de los requisitos fundamentales para poder otorgársele el privilegio de patente de invención, en primer lugar porque los intermediarios relacionados a los compuestos III y IV carecen de novedad y porque a su vez el procedimiento de obtención carece de nivel inventivo puesto que usa reactivos convencionales y reconocidos en el estado de la técnica para convertir un grupo nitrilo en tetrazoles 5-sustituídos.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

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

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- ❖ Artículo: "Benzopyrones. 7. Synthesis and Antiallergic Activity of some 2-(5-Tetazolyl)chromones", Journal of medicinal Chemistry, 1972, Vol. 15, N° 8. Pág 865.
- ❖ Artículo: "Gas Phase Synthesis, Structure, and Dissociation of Boron Triazide". J. Phys. Chem. 1995, 99, pág 6294.
- ❖ EP 0 796 852 A1 "Process for preparation of 5-substituted tetrazoles" del 24 de septiembre de 1997, páginas 19 a 21.
- ❖ EP 0 120 483 A1 "(1H-tetrazol-5-yl)-2(1H)-quinolinones" de octubre 3 de 1984, páginas 16 a 19.
- ❖ La patente europea EP 1714963 publicada el 25 de octubre de 2006, capítulo reivindicatorio.
- ❖ La patente europea EP1533305 publicada el 25 de mayo de 2005. Página 9.

VI. ANEXOS

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

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

VII. NOTIFICACIONES

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

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

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

⑫

EUROPEAN PATENT APPLICATION

- ⑪ Application number: 84103231.1

⑫ Date of filing: 23.03.84
- ⑪ Int. Cl.³: **C 07 D 471/04**
C 07 D 401/04, C 07 D 491/056
C 07 D 491/147, A 61 K 31/47
A 61 K 31/435
//C07D215/18, C07D215/36,
C07D215/54, (C07D471/04,
221/00, 221/00)

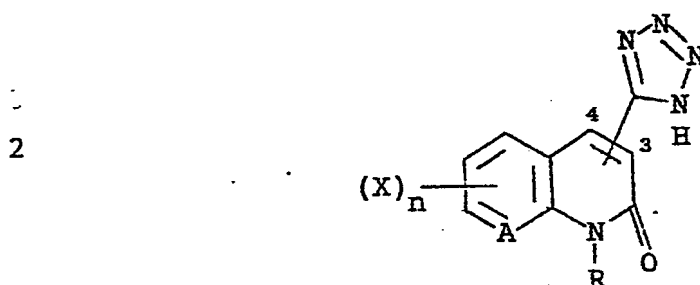
⑩ Priority: 25.03.83 US 478965 ⑬ Date of publication of application: 03.10.84 Bulletin 84/40 ⑭ Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE	⑪ Applicant: MERRELL DOW PHARMACEUTICALS INC. 2110 E. Galbraith Road Cincinnati Ohio 45215(US) ⑫ Inventor: Wright, Terry L. 545 Mount Dell Drive Clayton California 94517(US) ⑬ Representative: Vossius Vossius Tauchner Heunemann Rauh Siebertstrasse 4 P.O. Box 86 07 67 D-8000 München 86(DE)
---	---

- ⑭ (1H-tetrazol-5-yl)-2(1H)-quinolinones.
- ⑮ (1H-Tetrazol-5-yl)-2(1H)-quinolones useful as antiallergic agents are described herein. The compounds are prepared by the reaction of sodium azide and ammonium chloride with an appropriate 3-cyano-2(1H)-quinolinone.

EP 0 120 483 A1

WHAT IS CLAIMED IS:

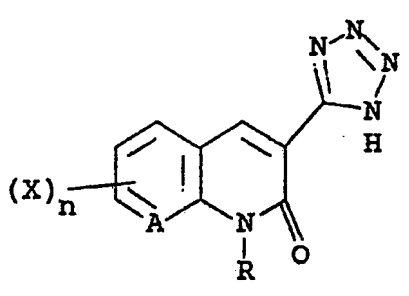
- 1 1. A compound of the formula:



- 3 wherein A is -CH= or -N=; R is H or alkyl of 1-4C; n is
 4 0, 1 or 2; X is H, alkyl of 1-4C, alkoxy of 1-4C,
 5 halogen, methylmercapto, methylsulfonyl, or two X's can
 6 be combined as methylenedioxy; with the proviso that,
 7 when X is methylmercapto or methylsulfonyl, then n must
 8 be 1; and the pharmaceutically acceptable salts thereof

- 1 2. A compound according to Claim 1 having the
 2 following formula:

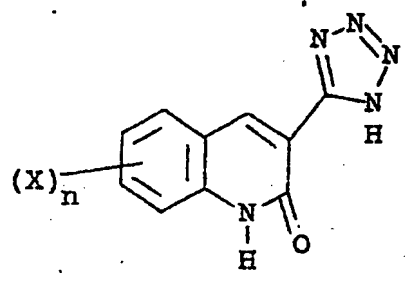
3



4 wherein A is -CH= or -N=; R is H or alkyl of 1-4C; n is
5 0, 1 or 2; X is H, alkyl of 1-4C, alkoxy of 1-4C,
6 halogen, methylmercapto, methylsulfonyl, or two X's can
7 be combined as methylenedioxy; with the proviso that,
8 when X is methylmercapto or methylsulfonyl, then n must
9 be 1; and the pharmaceutically acceptable salts thereof.

1 3. A compound according to Claim 1 having the
2 formula:

3



4 wherein n is 0, 1 or 2; X is hydrogen, alkyl of 1-4C,
5 alkoxy of 1-4C, halogen, methylmercapto, methylsulfonyl,
6 or two X's can be combined as methylenedioxy; with the
7 proviso that, when X is methylmercapto or methylsul-
8 fonyl, then n must be 1; and the pharmaceutically
9 acceptable salts thereof.

1 4. A compound according to Claim 1 which is
2 3-(1H-tetrazol-5-yl)-2(1H)-quinolinone and the pharma-
3 ceutically acceptable salts thereof.

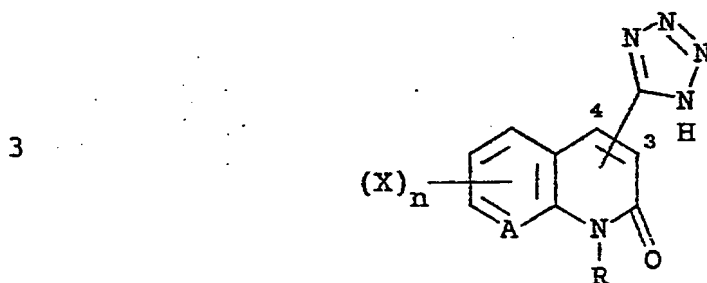
1 5. A compound according to Claim 1 which is
2 3-(1H-tetrazol-5-yl)-2(1H)-quinolinone.

1 6. A compound according to Claim 1 which is the
2 sodium salt of 3-(1H-tetrazol-5-yl)-2(1H)-quinolinone.

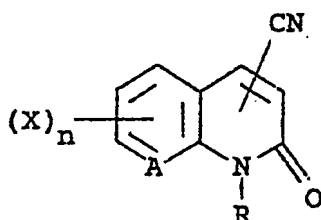
1 7. A compound according to Claim 1 which is
2 1-methyl-3-(1H-tetrazol-5-yl)-2(1H)-quinolinone.

1 8. A compound according to Claim 1 which is
2 3-(1H-tetrazol-5-yl)-2(1H)-naphthyridinone.

1 9. A process for preparing a compound of the
2 formula:



4 wherein A is -CH= or -N=; R is H or alkyl of 1-4C; n is
5 0, 1 or 2; X is H, alkyl of 1-4C, alkoxy of 1-4C,
6 halogen, methylmercapto, methylsulfonyl, or two X's can
7 be combined as methylenedioxy; with the proviso that,
8 when X is methylmercapto or methylsulfonyl, then n must
9 be 1; and the pharmaceutically acceptable salts thereof;
10 which comprises reacting a cyano-2(1H)-quinolinone of
11 the formula:

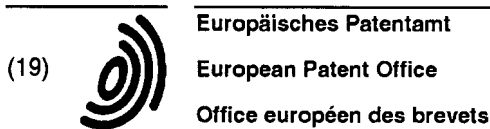


wherein n, A, R, and X are defined as above, with sodium azide and ammonium chloride in an inert solvent, to give the desired tetrazole, optionally followed by treatment with a solution of an appropriate base to give the corresponding pharmaceutically acceptable salts.

10. A process according to Claim 9 for the preparation of 3-(1H-tetrazol-5-yl)-2(1H)-quinolinone which comprises reacting 3-cyano-2(1H)-quinolinone with sodium azide with heating.

11. A compound according to claim 1 to 8 or a pharmaceutically acceptable salt thereof for use in inhibiting the results of antibody-antigen reactions in mammals.

12. Pharmaceutical compositions for preventing and treating allergic diseases comprising at least one compound according to anyone of claims 1 to 10 and a pharmaceutically acceptable carrier, excipient or diluent.



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 0 796 852 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
24.09.1997 Bulletin 1997/39

(51) Int Cl.⁶: C07D 257/04, C07D 403/10

(21) Application number: 97301876.5

(22) Date of filing: 20.03.1997

(84) Designated Contracting States:
DE GB

(30) Priority: 21.03.1996 JP 64900/96
11.09.1996 JP 240713/96

(71) Applicant: Toyo Kasei Kogyo Company Limited
Osaka-shi, Osaka-fu (JP)

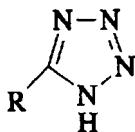
(72) Inventors:
• Koguro, Kiyoto, c/o Toyo Kasei Kogyo Co. Ltd.
Takasago-shi, Hyogo-ken (JP)
• Oga, Toshikaza, c/o Toyo Kasei Kogyo Co. Ltd.
Takasago-shi, Hyogo-ken (JP)

- Tokunaga, Norihito,
c/o Toyo Kasei Kogyo Co. Ltd.
Takasago-shi, Hyogo-ken (JP)
- Mitsui, Sunao, c/o Toyo Kasei Kogyo Co. Ltd.
Takasago-shi, Hyogo-ken (JP)
- Orita, Ryozo, c/o Toyo Kasei Kogyo Co. Ltd.
Takasago-shi, Hyogo-ken (JP)

(74) Representative: Cresswell, Thomas Anthony
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5LX (GB)

(54) Process for preparation of 5-substituted tetrazoles

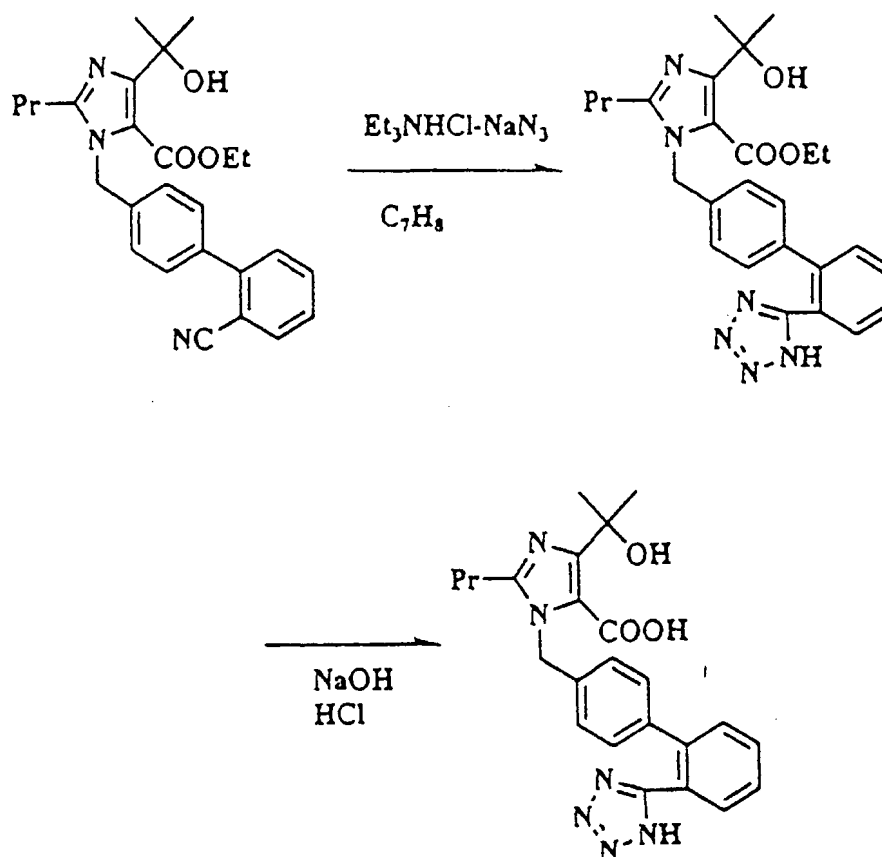
(57) A process for producing a 5-substituted tetrazole of formula (3):



(3)

wherein R is an aliphatic, alicyclic, aromatic, aromatic aliphatic, aromatic alicyclic, heterocyclic or heterocyclic aliphatic group, which process comprises reacting a nitrile with an inorganic azide salt in an aromatic hydrocarbon solvent in the presence of an amine salt.

EP 0 796 852 A1



Example 35

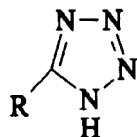
Into the same device as used in Example 34 were placed 43.5 g (0.10 mole) of ethyl ester of 1-(2'-cyanobiphenyl-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic acid, 13.1 g (0.20 mole) of sodium azide, 31.9 g (0.23 mole) of triethylamine hydrochloride and 206 ml of toluene. Thereafter, the mixture was reacted and treated in the same manner as in Example 34, giving 27.0 g (0.06 mole) of 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazole-5-yl)phenyl]phenyl]methylimidazole-5-carboxylic acid (yield 60.0% based on ethyl ester of 1-(2'-cyanobiphenyl-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic acid).

Example 36

Into the same device as used in Example 34 were placed 43.5 g (0.10 mole) of ethyl ester of 1-(2'-cyanobiphenyl-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic acid, 8.5 g (0.13 mole) of sodium azide, 20.8 g (0.15 mole) of triethylamine hydrochloride and 206 ml of toluene. The mixture was reacted and treated in the same manner as in Example 34, giving 20.3 g (0.045 mole) of 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazole-5-yl)phenyl]phenyl]methylimidazole-5-carboxylic acid (yield 45.0% based on ethyl ester of 1-(2'-cyanobiphenyl-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic acid).

Claims

1. A process for producing a 5-substituted tetrazole of formula (3):



(3)

wherein R is an aliphatic group, an alicyclic group, an aromatic group, an aromatic aliphatic group, an aromatic alicyclic group, a heterocyclic group or a heterocyclic aliphatic group, each group being unsubstituted or substituted, which process comprises reacting, in an aromatic hydrocarbon solvent in the presence of an amide salt, a nitrile of formula (1):



(1)

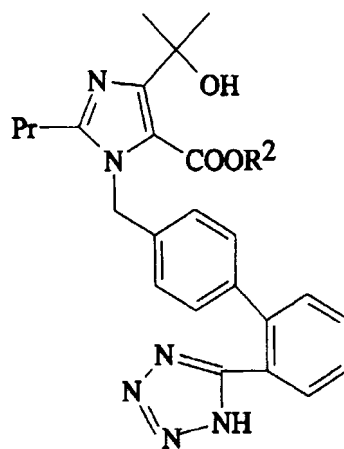
wherein R is as defined above, and an inorganic azide salt of formula (2):



(2)

wherein M is an alkali metal or an alkaline earth metal, and n is 1 or 2.

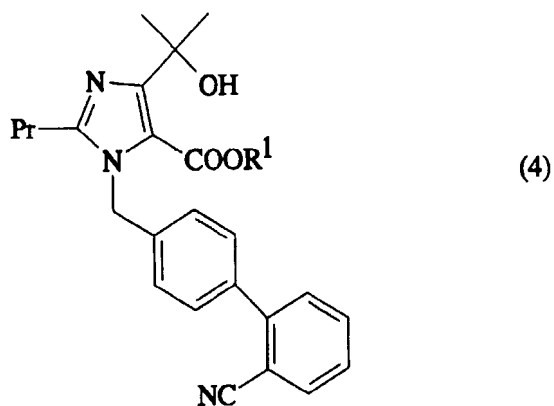
2. A process according to claim 1, wherein the inorganic azide salt is sodium azide.
3. A process according to claim 1 or 2, wherein the amine salt is triethylamine hydrochloride.
4. A process according to any one of the preceding claims, wherein the aromatic hydrocarbon solvent is toluene or xylene.
5. A process for producing a 1-(tetrazolylbiphenylmethyl)imidazole derivative of formula (5):



(5)

wherein R² is hydrogen or a C₁-C₄ alkyl group, which process comprises reacting, in an aromatic hydrocarbon solvent in the presence of an amine salt, a 1-(cyanobiphenylmethyl)imidazole derivative of formula (4):

EP 0 796 852 A1



wherein R¹ is hydrogen or a C₁-C₄ alkyl group, and an inorganic azide salt of formula (2):



wherein M is an alkali metal or an alkaline earth metal, and n is 1 or 2, and, optionally, hydrolysing the obtained compound.

- 25
- 30
6. A process according to claim 5, wherein R¹ in formula (4) is methyl or ethyl and R² in formula (5) is hydrogen.
 7. A process according to claim 5 or 6, wherein the inorganic azide salt is sodium azide.
 8. A process according to any one of claims 5 to 7 wherein the amine salt is triethylamine hydrochloride.
 9. A process according to any one of claims 5 to 8, wherein the aromatic hydrocarbon solvent is toluene or xylene.



(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
25.05.2005 Bulletin 2005/21

(51) Int Cl.7: C07D 257/04

(21) Application number: 04026903.7

(22) Date of filing: 12.11.2004

(84) Designated Contracting States: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LU MC NL PL PT RO SE SI SK TR Designated Extension States: AL HR LT LV MK YU (30) Priority: 21.11.2003 IT MI20032267 (71) Applicant: Dipharma S.p.A. 33036 Mereto di Tomba (Udine) (IT) (72) Inventors: • Verardo, Giancarlo 33170 Pordenone (IT)	• Geatti, Paola 33030 Campoformido (Udine) (IT) • Castaldi, Graziano 28072 Briona (Novara) (IT) • Toniutti, Nicoletta 33100 Udine (IT) • Allegrini, Pietro 20097 San Donato Milanese (Milano) (IT) (74) Representative: Minoja, Fabrizio Bianchetti Bracco Minoja S.r.l. Via Plinio 63 20129 Milano (IT)
--	---

- (54) A process for the preparation of valsartan and intermediates thereof
- (57) A novel process for the preparation of valsartan and novel intermediates useful in the preparation thereof.

EP 1 533 305 A1

2.1 g of triethylamine (20.8 mmoles) and 7.9 g of valeryl chloride (65.7 mmoles) are added to the mixture, that is refluxed for 2 hours, then cooled to 25°C. The organic phase is washed three times with 50 ml of water and concentrated under reduced pressure at 25-30°C, to obtain an oily residue. 50 ml of ethyl acetate are added and the organic phase is washed with a weakly basic NaOH solution, then with water to neutrality. The organic phase is washed with a sodium bisulfite solution, then with water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The oily residue is taken up with isopropanol from which the title product crystallizes (8.2 g, 21.1 mmoles; molar yield: 50%).

[0036] ¹H-NMR (CDCl₃) (0.60-1.35 (m, 11H); 1.4 (m, 2H); 1.80-2.0 (m, 0.5H); 2.20-2.40 (m, 1H), 2.80-3.00 (m, 0.5H), 4.50 (s, 0.4 H), 4.7 (s, 0.6 H), 6.5 (s, 1H), 7.3 (d, 2H); 7.54 (dd, 2H).

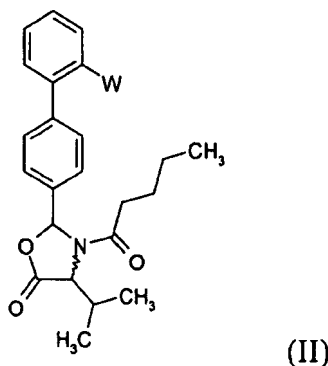
Example 7 - 2-[(2'-Cyano-biphenyl-4-yl methyl)-pentanoyl-amino]-3-methylbutyric acid

[0037] 6.0 g (15.4 mmoles) of 4'-(4-isopropyl-5-oxo-3-pentanoyl-oxazolidin-2-yl)-biphenyl-2-carbonitrile is reacted in 30 ml of ethanol with 3.8 g of ammonium formate (61.6 mmoles) and 2 g of 5% Pd/C catalyst. The temperature is raised to 75°C, keeping these conditions for 3 hours. The mixture is cooled and the catalyst is filtered off. The organic phase is concentrated under reduced pressure to a residue to obtain 2-[(2'-cyano-biphenyl-4-yl-methyl)-pentanoyl-amino]-3-methylbutyric acid.

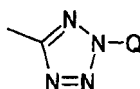
[0038] ¹H-NMR (CDCl₃) (0.80-1.15 (m, 9H); 1.20-1.50 (m, 2H); 1.60-1.80 (m, 2H); 2.40-2.55 (m, 2H), 2.60-2.80 (m, 1H); 3.80 (d, 0.7 H), 3.90 (d, 0.3 H); 4.45 (d, 0.7 H), 4.50 (d, 0.3 H), 4.82 (d, 0.7H), 4.85 (d, 0.3H); 7.10-7.20 (m, 4H), 7.40-7.70 (m, 4H).

Claims

1. A process for the preparation of valsartan, or a pharmaceutically acceptable salt thereof, which comprises opening the oxazolidinone ring in a compound having formula (II),

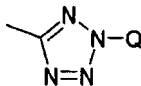


wherein W is a



group in which Q is a protecting group; or W is a -CN group, and

a) when W is a

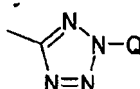


EP 1 533 305 A1

group, removing the protecting group Q; or

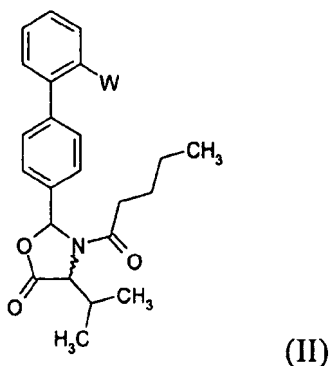
b) when W is a -CN group, converting it to a 5-tetrazolyl group; and, if desired, transforming the resulting valsartan into a pharmaceutically acceptable salt.

- 5 2. A process according to claim 1, wherein the protecting group Q is selected from triphenylmethyl, tert-butyl, C₁-C₄ alkoxymethyl, methylthiomethyl, phenyl-(C₁-C₄)alkoxymethyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, 1-methyl-1-phenylethyl, 2-(trimethylsilyl)ethyl, tetrahydropyranyl, piperonyl and benzenesulfonyl.
- 10 3. A process according to claim 1, wherein the oxazolidinone ring is opened through hydrogenolysis by hydrogenation reaction in the presence of a catalyst.
4. A process according to claim 1, wherein the oxazolidinone ring is opened through hydrogenolysis by hydrogen transfer reaction in the presence of a catalyst and a hydrogen donor.
- 15 5. A process according to claim 3 or 4, wherein the catalyst is selected from the group of heterogeneous catalysts.
6. A process according to claim 5, wherein the catalyst is Pd/C.
- 20 7. A process according to claim 4, wherein the hydrogen donor is selected from formic acid, ammonium formate, ascorbic acid, phosphinic acid, sodium phosphinate, 2-propanol, ethanol, benzyl alcohol, cyclohexene, cyclohexadiene, hydrazine, limonene, pinene and tetralin.
8. A process according to claim 7, wherein the hydrogen donor is ammonium formate.
- 25 9. A process according to any one of the above claims, wherein in a compound of formula (II) W is a

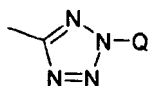


group in which Q is a protecting group.

- 35 10. Valsartan having purity equal to or higher than 99% and substantially free from tin and azide derivatives.
11. A compound having formula (II), or an isomer thereof,



wherein W is a

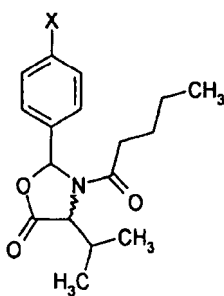


5

group in which Q is a protecting group; or W is a -CN group.

12. A compound of formula (III), or an isomer thereof,

10



15

20

(III)

wherein X is a leaving group; a -B(R₁R₂) group wherein R₁ and R₂, which can be the same or different, are halogen, hydroxy or C₁-C₄ alkoxy; a lithium or copper atom or a halogenated metal.

25

30

35

40

45

50

55



(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
25.10.2006 Bulletin 2006/43

(51) Int Cl.:
C07D 257/04 (2006.01) A61K 31/40 (2006.01)
A61P 9/12 (2006.01)

(21) Application number: **06112734.6**

(22) Date of filing: **18.04.2006**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR
 Designated Extension States:
AL BA HR MK YU

(30) Priority: **19.04.2005 IN MU04902005**

(71) Applicant: **IPCA Laboratories Limited**
Kandivli (West),
Numbai 400 067 (Maharashtra) (IN)

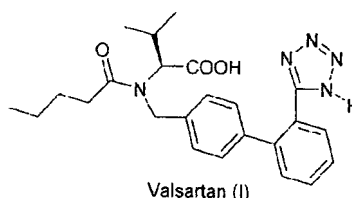
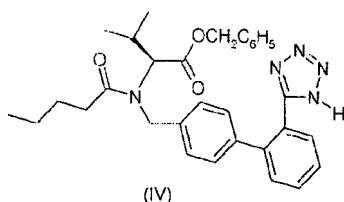
(72) Inventors:
 • **Kumar, Ashok**
(West),
400 053, Mumbai, Maharashtra (IN)
 • **Nimbalkar, Manmohan Madhavrao**
400025, Mumbai, Maharashtra (IN)

• **Barve, Sanjay Govind**
400 004, Mumbai, Maharashtra (IN)
 • **Metil, Dattatray Shamrao**
Evershine City
401 208 Thane Maharashtra (IN)
 • **Shimpukade, Bharat Dinkar**
411 033, Pune, Maharashtra (IN)
 • **Kushwaha, Lavkesh,**
307, Shri Trimurti Apt.
(East), 401 105, Thane, Maharashtra (IN)
 • **Kelkar, Rahul Suresh**
Shivaji Road,
400 068 Mumbai Maharashtra (IN)

(74) Representative: **Brand, Thomas Louis**
W.P. Thompson & Co.,
55 Drury Lane
London WC2B 5SQ (GB)

(54) **Process for the Preparation of Valsartan and its Intermediates**

(57) The present invention concerns a process for preparing valsartan of Formula I:



comprising purifying intermediate benzyl valsartan of Formula IV by crystallizing said benzyl valsartan of lower purity from a first solvent which is a ternary mixture comprising a hydrophilic solvent, a non-polar protic solvent and water; recovering benzyl valsartan from said ternary mixture followed by crystallizing benzyl valsartan from a second solvent comprising a non-polar aprotic solvent or polar aprotic solvent or their mixture; and recovering benzyl valsartan substantially free of organotin impurity; and converting said benzyl valsartan into valsartan

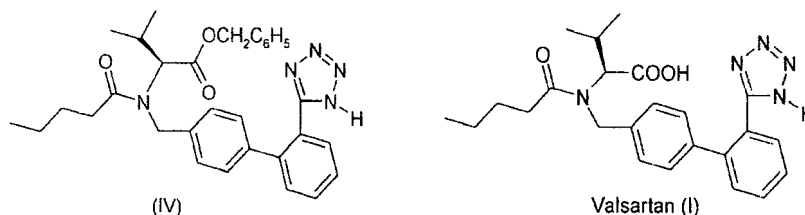
EP 1 714 963 A1

and rendered acidic with 1N hydrochloric acid solution. The product was extracted in ethyl acetate. The title compound after evaporation of solvent was obtained as oil with a purity of 86-88% as analyzed by HPLC assay.

[0071] It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

Claims

- 1. A process for preparing valsartan of Formula I comprises:**

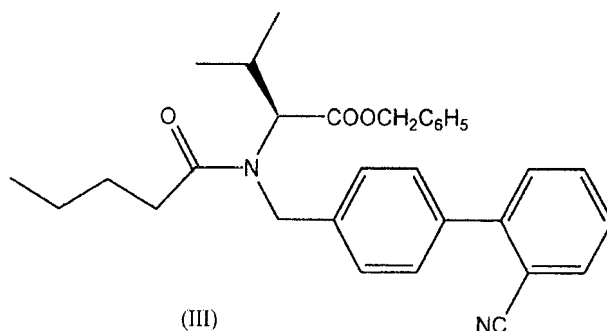


- a) purifying intermediate benzyl valsartan of Formula IV by crystallizing said benzyl valsartan from a first solvent comprising a ternary mixture of a hydrophilic solvent, a non-polar protic solvent and water; recovering benzyl valsartan from said ternary mixture followed by re-crystallizing benzyl valsartan from a second solvent comprising a non-polar aprotic solvent or polar aprotic solvent or mixture thereof; and recovering benzyl valsartan at a higher purity than the intermediate benzyl valsartan which is substantially free of organotin impurity; and
b) converting said benzyl valsartan of step (a) into valsartan.
- The process as claimed in claim 1, wherein the ternary mixture comprises hydrophilic solvents selected from C₁-C₄ alcohols and non-polar solvents selected from C₆ - C₉ aromatic hydrocarbons, C₅ - C₈ aliphatic hydrocarbons or C₅ - C₈ alicyclic hydrocarbons, or mixtures of two or more thereof.
 - The process as claimed in claim 1 or 2, wherein said ternary solvent mixture has a hydrophilic organic solvent to non-polar organic solvent ratio in the range of 1 : 0.5 to 1 : 30 parts, and wherein the hydrophilic organic solvent and non-polar organic solvent to water ratio is in the range of about 1 : 0.5 to 1 : 10 parts by weight relative to benzyl valsartan.
 - The process as claimed in any one of claims 1 to 3, wherein the hydrophilic solvent comprises isopropanol.
 - The process as claimed in any one of claims 1 to 4, wherein the non-polar solvent comprises hexane or toluene.
 - The process as claimed in any one of claims 1 to 5, wherein the second purification solvent system has a polar aprotic solvent to non-polar organic solvent ratio in the range of about 1 : 0 to 1 : 50 parts by weight relative to benzyl valsartan.
 - The process as claimed in any one of claims 1 to 6, wherein the second crystallizing solvent is selected from ethyl acetate, hexane, toluene, or mixtures of two or more thereof.
 - The process as claimed in any one of claims 1 to 7, wherein the second crystallization solvent comprises a binary mixture comprising a non-polar aprotic solvent and a polar aprotic solvent.
 - The process as claimed in claim 8, wherein the binary mixture is a combination of ethyl acetate and hydrocarbon solvent.
 - The process as claimed in any one of claims 1 to 9, wherein step (b) comprises

EP 1 714 963 A1

c) hydrogenation of benzyl valsartan obtained from step (b) in presence of palladium carbon **characterized by** catalyst quantity less than 10 % wt/wt relative to benzyl valsartan; and
d) recovering valsartan.

11. The process as claimed in claim 10, wherein the catalyst quantity is 2.5 - 5 wt % relative to benzyl valsartan.
12. The process as claimed in claim 10 or claim 11, wherein the recovered valsartan is dried below 60 °C.
13. The process as claimed in any one of claims 1 to 12, wherein the benzyl valsartan having less than about 1000 ppm (parts per million) of organotin impurity as measured by atomic emission spectroscopy and less than 0.1% of benzyl (R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine isomer as measured by HPLC area percent.
14. The process as claimed in any one of claims 1 to 13 wherein the valsartan has an enantiomeric purity greater than 99.5%.
15. The process as claimed in any one of claims 1 to 14, wherein the valsartan obtained comprises less than about 0.1% (R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine isomer.
16. The process as claimed in any one of claims 1 to 15, wherein the benzyl valsartan of Formula IV is prepared from a compound of Formula III:

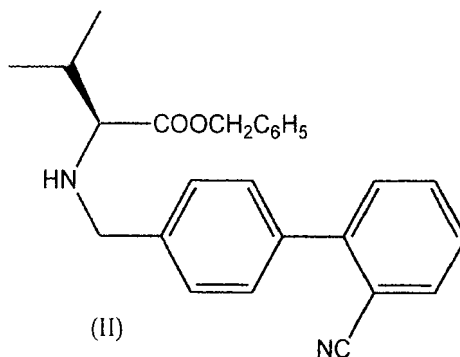


using a tributyltinazide complex in presence of a hydrocarbon solvent.

17. The process as claimed in claim 16, wherein the tributyl tin azide is prepared *in situ* from tributyltinchloride and sodium azide.
18. The process as claimed in any one of claims 1 to 17 wherein the ternary solvent mixture comprises isopropyl alcohol, hexane and water.
19. The process as claimed in any one of claims 1 to 18 wherein the second crystallization solvent is a binary mixture comprising non-polar aprotic solvent and polar aprotic solvent.
20. The process as claimed in claim 19, wherein the second crystallization solvent is a binary mixture comprising ethyl acetate and hexane.
21. A process according to any one of claims 1 to 20 for preparing valsartan of Formula I comprising:

a) reacting 4-bromomethyl-2'-cyanobiphenyl with L-valine benzyl ester or its acid salt **characterized in that** the reaction is carried out in a heterogeneous solvent mixture comprising water and non-polar hydrocarbon solvent, in presence of an inorganic base to obtain a compound of Formula II;

EP 1 714 963 A1



- b) reacting the step (a) product with valeroylchloride in presence of diisopropylethylamine **characterized in that** reaction is conducted in solvent selected from toluene or hexane.
- c) providing benzyl valsartan of Formula IV from the product of step (b) (Formula III) using an tributyltinazide;
- d) purifying said benzyl valsartan **characterized by** crystallizing from a first solvent which is a ternary mixture comprising a hydrophilic solvent, a non-polar solvent and water; recovering benzyl valsartan from said ternary mixture followed by crystallizing benzyl valsartan from a second solvent which is a binary mixture comprising ethyl acetate and hexane; and recovering benzyl valsartan substantially free of tributyltin impurity; and
- e) converting said benzyl valsartan of step (d) into valsartan using palladium carbon
- f) recovering valsartan having less than 0.1% (R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine isomer.
22. The process as claimed in claim 21, wherein the step (a) is carried out in presence of a catalyst selected from sodium iodide, potassium iodide and a phase-transfer catalyst or a combination thereof.
23. valsartan or benzyl valsartan prepared according to the process of any one of claims 1 to 22 having less than 1000 ppm (parts per million) of organotin impurity as measured by atomic emission spectroscopy and less than 0.1 % of benzyl (R)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine isomer as measured by HPLC area percent.
24. valsartan or benzyl valsartan prepared by the process of any one of claims 1 to 23, and having less than about 1000 ppm (parts per million) of organotin impurity as measured by atomic emission spectroscopy.
25. A pharmaceutical composition **characterized in that** a high purity valsartan obtained according to any one of claims 1 to 23 is put into a pharmaceutically acceptable form.
26. A pharmaceutical composition comprising valsartan prepared according to claim 25 for the use in ameliorating (combating) cardiovascular or hypertensive disorders in mammals.
27. A pharmaceutical composition according to claim 25 or 26 further comprising a diuretic agent such as hydrochlorothiazide or chlorthalidone.

Gas Phase Synthesis, Structure, and Dissociation of Boron Triazide

R. L. Mullinax, G. S. Okin, and R. D. Coombe*

Department of Chemistry, University of Denver, Denver, Colorado 80208

Received: December 1, 1994; In Final Form: January 31, 1995*

Gas phase $B(N_3)_3$ is readily prepared by a spontaneous room temperature reaction between HN_3 and BCl_3 . The infrared spectrum of the reaction products exhibits strong absorptions at 2163 and 1360 cm^{-1} and a weaker absorption near 1100 cm^{-1} . These features are assigned to $B(N_3)_3$ by comparison with results from ab initio calculations of the geometry and vibrational frequencies of the molecule. $B(N_3)_3$ has a strong UV absorption at 230 nm, with $\sigma_{230} = 1.3 \times 10^{-17} cm^2$. The density of gaseous $B(N_3)_3$ prepared in these experiments decays with a time constant near 30 min. This decay is attributed to dissociation at the vessel walls, a process which leaves a visible film. Infrared spectra of films produced by either room temperature dissociation or UV photodissociation of $B(N_3)_3$ exhibit features attributable to BN, likely in the presence of excess nitrogen.

Introduction

Nitrogen-rich molecules are well known for their ability to store energy. Recent research on such species has focused on small molecules with extremely high proportions of nitrogen, such as N_4 , N_5 , or azide-substituted compounds.¹⁻³ In this paper, we present new information about azide compounds of boron. Apart from their ability to store large amounts of energy, these species hold additional interest as possible precursors for boron nitride thin films. Both hexagonal and cubic BN films have many important applications as either wide band gap semiconductors or as tribological coatings.⁴

Boron azides have been known for more than forty years. In 1954, Wiberg and Michaud⁵ synthesized boron triazide, $B(N_3)_3$, by the reaction of diborane with HN_3 in an ether solution at low temperature. The reaction evolved H_2 to leave $B(N_3)_3$, and the conditions were adjusted to produce an H_2 yield approximately 95% of that expected from the 3:1 stoichiometry of the reaction. These authors used similar methods to produce $Al(N_3)_3$, as well as extremely energetic adducts of $B(N_3)_3$ and $Al(N_3)_3$ with NaN_3 and LiN_3 . In 1963, Paetzold⁶ reported the synthesis of Cl_2BN_3 from the reaction of BCl_3 with LiN_3 in a CH_2Cl_2 solution. The product was obtained as a crystalline solid identified as trimeric dichloroboron azide, $(BCl_2N_3)_3$. Upon heating to 200 °C, the compound converted to hexachloroborazole by loss of N_2 from the trimer and migration of the chlorine atoms. The crystal structure of $(Cl_2BN_3)_3$ was determined by Mueller⁷ in 1971, the results confirming the trimeric structure. Dichloroboron azide was also studied by Wiberg and Michaud⁸ in 1972. These authors produced it from the reaction of BCl_3 with trimethylsilyl azide in CH_2Cl_2 . In 1978, Dehnicke⁹ reported the generation of azides of aluminum, gallium, and boron from reactions of the triiodides of these metals with iodine azide in benzene. He recorded the infrared spectra of the monoazide products, I_2MN_3 , and observed the formation of oligomers of these species. Alkylboron azides have been generated using similar methods. In 1966, Paetzold¹⁰ produced $(CH_3)_2BN_3$ from the reaction of $(CH_3)_2BBr$ and tri-*n*-butylsilyl azide, obtaining the product as an explosive liquid. Recently, ab initio computational methods have been used¹¹ to determine the structure of $(CH_3)_2BN_3$. Similar reactions of organic azides with halogenated boron compounds have been used by organic chemists for the synthesis of heterocyclic ring compounds of

nitrogen. Very recently, Bochner and co-workers³ reported the synthesis of tetraazidodiborane from the gas phase reaction between HN_3 and diborane at 400 K. This species may well be an intermediate in the low-temperature, condensed phase synthesis of boron triazide described by Wiberg and Michaud⁵ in their seminal 1954 paper.

To our knowledge, boron triazide has not been explicitly studied since Wiberg and Michaud. In this paper, we describe a simple method for preparing $B(N_3)_3$ in the gas phase by the stoichiometric reaction of BCl_3 with HN_3 . The IR and UV absorption spectra of the molecule are reported, and the assignment of infrared absorption features is supported by the results of ab initio calculations of its structure and vibrational frequencies. As expected from the calculated heat of formation, gas phase $B(N_3)_3$ is found to be rather short lived, and we report measurements of its time decay at room temperature. Thermal and photolytic dissociation of $B(N_3)_3$ at room temperature produce thin films with spectroscopic features similar to those of boron nitride. The results suggest the utility of this novel species as either a high-energy material or as a precursor for BN films.

Experimental Methods

Boron triazide was generated by the spontaneous room temperature reaction between gaseous BCl_3 and gaseous HN_3 . Samples of HN_3 were produced by the well-known reaction¹² of NaN_3 with excess stearic acid near 90 °C. The HN_3 was stored in Pyrex bulbs and diluted with He to produce mixtures which were about 8% HN_3 . The purity of the HN_3 was examined by FTIR spectroscopy, and the absolute amount of HN_3 present in the mixtures was determined from UV absorption spectra. BCl_3 (CP grade) was obtained from Matheson Gas Products and was not purified further before its use in these experiments.

The gases were handled with a Monel/stainless steel vacuum system evacuated by a mechanical pump. Pressures in the system were measured with capacitance manometers. The reagents were mixed in small 10 cm cells used for recording IR and UV spectra or in a large 1 L cell used for photolysis of samples of $B(N_3)_3$. Two different small cells were used. One of these was a stainless steel cell with its internal walls coated with halocarbon wax (Halocarbon Inc.) to provide an easily passivated, nonreactive surface. This cell could be fitted with

* Abstract published in *Advance ACS Abstracts*, April 1, 1995.

Notes

References

- (1) (a) I. M. Lockhart, British Patent, 1,151,474; (b) I. M. Lockhart, D. Huckle, M. Wright, and D. A. McCarthy, submitted for publication.
- (2) J. W. Schulte, E. C. Reif, J. A. Bocher, W. A. Lawrence, and M. L. Tainter, *J. Pharm. Exp. Ther.*, **71**, 62 (1941).
- (3) D. Huckle, I. M. Lockhart, and M. Wright, *J. Med. Chem.*, **12**, 277 (1969).

Benzopyrones. 7. Synthesis and Antiallergic Activity of Some 2-(5-Tetrazolyl)chromones¹

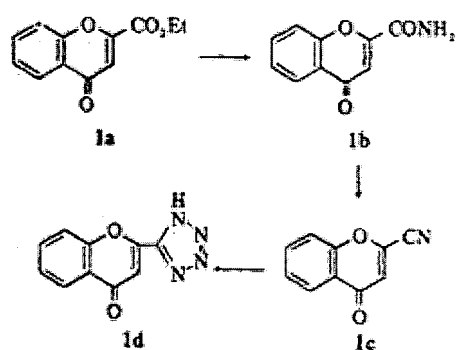
G. P. Ellis* and D. Shaw†

Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU, United Kingdom.
Received January 12, 1972

Antiallergic properties in the chromone series appear²⁻⁴ to be largely confined to those compounds which contain a carboxyl group at C-2. Replacement of a carboxyl by a 5-tetrazolyl group in a biologically active carboxylic acid⁵⁻⁸ has sometimes resulted in retention of activity but rarely in an improvement in potency. This paper reports the synthesis and antiallergic properties of a number of chromones,⁹ such as 1d and its substituted derivatives, which carry a 5-tetrazolyl group at C-2. The variations in structure are shown in Table I.

Chemistry. The title compounds which are listed in Table II were prepared by the route shown in Scheme I.

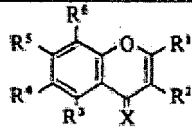
Scheme I

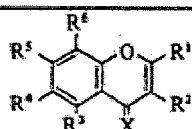


The carboxylic esters, prepared¹⁴ from the appropriate 2-hydroxyacetophenone and diethyl oxalate, reacted with gaseous NH_3 at 0° to give high yields of the carboxamides. Although several carboxamides of this kind are known, their dehydration to the 4-oxo-4H-1-benzopyran-2-carbonitriles has not been reported. The unsubstituted carbonitrile 1c, the only known member of this series, was synthesized¹² in five stages from 2-methylchromone via the 2-carboxaldehyde. A more convenient method is now described through the dehydration of the carboxamide by means of an arylsulfonyl chloride and pyridine in DMF. Other reagents,¹⁹ such as POCl_3 , PCl_5 - POCl_3 , SOCl_2 , or P_2O_5 , proved to be ineffective while benzenesulfonyl chloride in pyridine²⁰ gave a low yield. 3-Chloro-4-oxo-4H-1-benzopyran-2-carbonitrile (17c) was prepared by reacting the unsubstituted nitrile (1c) with sulfuryl chloride.

The carbonitriles were converted smoothly to the tetrazoles by reaction with sodium azide and ammonium chloride in DMF.²¹ A recent study²² showed that the pK_a of

Table I. Substituted Chromones Synthesized

Compd No.						
	R ¹	R ²	R ³	R ⁴	R ⁵	X
1	H	H	H	H	H	O
2	Me	H	H	H	H	O
3	H	H	Me	H	H	O
4	H	H	H	Me	H	O
5	H	H	H	H	Me	O
6	H	Me	H	Me	H	O
7	H	H	Cl	H	H	O
8	H	H	Br	H	H	O
9	H	H	Br	H	Br	O
10	H	H	Me	H	Br	O
11	H	OMe	H	H	H	O
12	H	H	H	OMe	H	O
13	H	H	H	OCH ₂ Ph	H	O
14	H	H	NO ₂	H	H	O
15	H	H	NO ₂	H	Me	O
16	H	H	H	H	H	S
17	Cl	H	H	H	H	O



a, R¹ = CO₂Et
b, R¹ = CONH₂
c, R¹ = CN
d, R¹ = 5-tetrazolyl

4-oxo-4H-1-benzopyran-2-carboxylic acid was 2.96. The low solubility of the corresponding tetrazole (1d) in water and ethanol caused difficulties in the accurate determination of its pK_a but, using a potentiometric method, a value (2.8) was obtained which showed that the acidity of both carboxylic acid and tetrazole are comparable.

Biological Results. The tetrazoles were screened for anti-allergic activity in rats by means of the passive cutaneous anaphylaxis test using an extract of *Nippostrongylus brasiliensis* as antigen²³ and disodium cromoglycate as standard. Those compounds which showed activity comparable with or better than disodium cromoglycate are listed in Table III. Although the nature of the test makes it difficult to quantify the results, 1d, 3d, 4d, and 14d are appreciably more potent than the standard drug. Substitution by alkyl or halogen at C-3 or C-8 lowers activity as does the replacement of the 4-oxo by 4-thioxo group. The activity level is very susceptible to comparatively small changes in the substituents at C-7 (cf. 4d, 12d, and 13d). This study shows that a carboxyl group in chromone-2-carboxylic acids may be advantageously replaced by a tetrazolyl group which confers a comparable degree of acidity on the molecule.

Four compounds, 2b, 2c, 9d, and 14b, showed activity similar to aspirin in reducing writhing induced by phenyl-quinone²⁴ but were almost inactive in the hot plate test.²⁵ The oral LD₅₀ values of all the compounds in mice were greater than 100 mg/kg.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus using a calibrated thermometer. A low value for the N content of a few tetrazoles was obtained although the combustion time was increased as recommended by the manufacturers of the instrument (Hewlett Packard).

General Method of Synthesis. (a) Ethyl 4-Oxo-4H-1-benzopyran-2-carboxylates. The esters were prepared by the method of Zagorovskii, *et al.*¹⁴ The following new substituted 4-oxo-4H-1-benzopyran-2-carboxylic acids (from EtOH) were obtained from the esters by hydrolysis with a mixture of HCl and AcOH (analyzed for Cand H): 8-methyl-, mp 272–273° dec; 5,7-dimethyl-, mp 251–252° dec;

†Science Research Council Postgraduate Student.

Notes

References

- (1) (a) I. M. Lockhart, British Patent, 1,151,474; (b) I. M. Lockhart, D. Huckle, M. Wright, and D. A. McCarthy, submitted for publication.
- (2) J. W. Schulte, E. C. Reif, J. A. Bocher, W. A. Lawrence, and M. L. Tainter, *J. Pharm. Exp. Ther.*, **71**, 62 (1941).
- (3) D. Huckle, I. M. Lockhart, and M. Wright, *J. Med. Chem.*, **12**, 277 (1969).

Benzopyrones. 7. Synthesis and Antiallergic Activity of Some 2-(5-Tetrazolyl)chromones¹

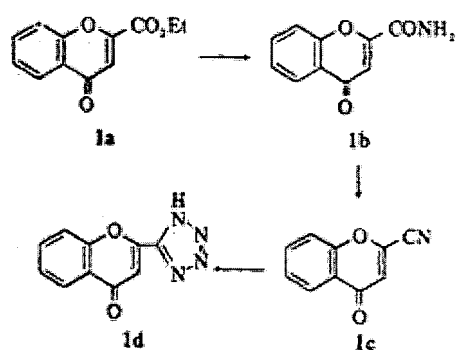
G. P. Ellis* and D. Shaw†

Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU, United Kingdom.
Received January 12, 1972

Antiallergic properties in the chromone series appear²⁻⁴ to be largely confined to those compounds which contain a carboxyl group at C-2. Replacement of a carboxyl by a 5-tetrazolyl group in a biologically active carboxylic acid⁵⁻⁸ has sometimes resulted in retention of activity but rarely in an improvement in potency. This paper reports the synthesis and antiallergic properties of a number of chromones,⁹ such as 1d and its substituted derivatives, which carry a 5-tetrazolyl group at C-2. The variations in structure are shown in Table I.

Chemistry. The title compounds which are listed in Table II were prepared by the route shown in Scheme I.

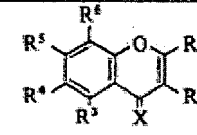
Scheme I



The carboxylic esters, prepared¹⁴ from the appropriate 2-hydroxyacetophenone and diethyl oxalate, reacted with gaseous NH_3 at 0° to give high yields of the carboxamides. Although several carboxamides of this kind are known, their dehydration to the 4-oxo-4H-1-benzopyran-2-carbonitriles has not been reported. The unsubstituted carbonitrile 1c, the only known member of this series, was synthesized¹² in five stages from 2-methylchromone via the 2-carboxaldehyde. A more convenient method is now described through the dehydration of the carboxamide by means of an arylsulfonyl chloride and pyridine in DMF. Other reagents,¹⁹ such as POCl_3 , PCl_5 - POCl_3 , SOCl_2 , or P_2O_5 , proved to be ineffective while benzenesulfonyl chloride in pyridine²⁰ gave a low yield. 3-Chloro-4-oxo-4H-1-benzopyran-2-carbonitrile (17c) was prepared by reacting the unsubstituted nitrile (1c) with sulfuryl chloride.

The carbonitriles were converted smoothly to the tetrazoles by reaction with sodium azide and ammonium chloride in DMF.²¹ A recent study²² showed that the pK_a of

Table I. Substituted Chromones Synthesized

Compd No.						
	R ⁵	R ³	R ⁴	R ²	R ⁶	X
1	H	H	H	H	H	O
2	Me	H	H	H	H	O
3	H	H	Me	H	H	O
4	H	H	H	Me	H	O
5	H	H	H	H	Me	O
6	H	Me	H	Me	H	O
7	H	H	Cl	H	H	O
8	H	H	Br	H	H	O
9	H	H	Br	H	Br	O
10	H	H	Me	H	Br	O
11	H	OMe	H	H	H	O
12	H	H	H	OMe	H	O
13	H	H	H	OCH ₂ Ph	H	O
14	H	H	NO ₂	H	H	O
15	H	H	NO ₂	H	Me	O
16	H	H	H	H	H	S
17	Cl	H	H	H	H	O

R⁵, R⁶, R³, R⁴, R², X
 a, R¹ = CO₂Et
 b, R¹ = CONH₂
 c, R¹ = CN
 d, R¹ = 5-tetrazolyl

4-oxo-4H-1-benzopyran-2-carboxylic acid was 2.96. The low solubility of the corresponding tetrazole (1d) in water and ethanol caused difficulties in the accurate determination of its pK_a but, using a potentiometric method, a value (2.8) was obtained which showed that the acidity of both carboxylic acid and tetrazole are comparable.

Biological Results. The tetrazoles were screened for anti-allergic activity in rats by means of the passive cutaneous anaphylaxis test using an extract of *Nippostrongylus brasiliensis* as antigen²³ and disodium cromoglycate as standard. Those compounds which showed activity comparable with or better than disodium cromoglycate are listed in Table III. Although the nature of the test makes it difficult to quantify the results, 1d, 3d, 4d, and 14d are appreciably more potent than the standard drug. Substitution by alkyl or halogen at C-3 or C-8 lowers activity as does the replacement of the 4-oxo by 4-thioxo group. The activity level is very susceptible to comparatively small changes in the substituents at C-7 (cf. 4d, 12d, and 13d). This study shows that a carboxyl group in chromone-2-carboxylic acids may be advantageously replaced by a tetrazolyl group which confers a comparable degree of acidity on the molecule.

Four compounds, 2b, 2c, 9d, and 14b, showed activity similar to aspirin in reducing writhing induced by phenyl-quinone²⁴ but were almost inactive in the hot plate test.²⁵ The oral LD₅₀ values of all the compounds in mice were greater than 100 mg/kg.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus using a calibrated thermometer. A low value for the N content of a few tetrazoles was obtained although the combustion time was increased as recommended by the manufacturers of the instrument (Hewlett Packard).

General Method of Synthesis. (a) Ethyl 4-Oxo-4H-1-benzopyran-2-carboxylates. The esters were prepared by the method of Zagorovskii, *et al.*¹⁴ The following new substituted 4-oxo-4H-1-benzopyran-2-carboxylic acids (from EtOH) were obtained from the esters by hydrolysis with a mixture of HCl and AcOH (analyzed for Cand H): 8-methyl-, mp 272-273° dec; 5,7-dimethyl-, mp 251-252° dec;

†Science Research Council Postgraduate Student.



31
AA 328677
NOTARIA TERCERA
ENMIENDA

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

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -
- - - - -
- - - - -
compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: -----
PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
por escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----
SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 de Bogotá, abogado en ejercicio, portador
de la T.P 44655 del C.S. de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

Como Notario Veintitres (23) días
hago constar que esta fotocopia con
a la vista
113 AGO 2007
WILLY VALE ENRIQUE
NOTARIO VEINTITRES
Bogotá D.C., Colombia

4539
0523

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3ª de Cali

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

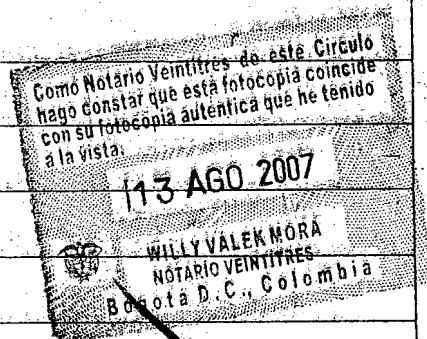
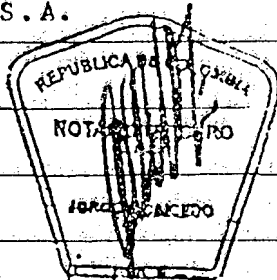
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

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

91 *Juan m Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
-/-



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 141249

Bogotá D.C., Diciembre 20 de 2012 - 16:22:17

RECIBIDO DE : REYES Y REYES ABOGADOS

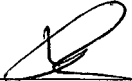
NI 900.048.328

RE

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	144444160	19/12/2012	4.100.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444171	19/12/2012	560.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444182	19/12/2012	415.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444215	19/12/2012	315.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	1144444156	19/12/2012	2.860.400.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	
			Vr.UNDITARIO
			Vr.CONCEPTO
			315.000.00
			315.000.00
			\$315.000.00

SON: **TRESCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE**

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-068973- -00005-0000

Fecha: 2012-12-27 12:02:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 33

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Diciembre 20 de 2012 - 16:22:19

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 12 - 141250

Bogotá D.C., Diciembre 20 de 2012 - 16:22:17

RECIBIDO DE : REYES Y REYES ABOGADOS NI 900.048.328 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	144444160	19/12/2012	4.100.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444171	19/12/2012	560.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444182	19/12/2012	415.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	144444215	19/12/2012	315.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	1144444156	19/12/2012	2.860.400.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-08 PRORROGA DE TERMINOS	1608 N.CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL	100.000.00	100.000.00
			\$100.000.00

SON: **CIEN MIL PESOS MONEDA CORRIENTE***

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-068973- -00005-0000

Fecha: 2012-12-27 12:02:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 33

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Diciembre 20 de 2012 - 16:22:19