CARLOS TAMAYO & ASOCIADOS
INTERNATIONAL PATENT AND TRADEMARK OFFICE

Trademark	Marcas
Patent	Patentes
Permit Health	Registros Sanitarios
Software	Soporte Lógico
Commercial Name	Nombres Comerciales
Design	Diseños

502
298

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00085238 00000006 Folios: 1
Fecha (AMD): 2003-08-28 15:33:34
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICIO
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

REF: EXPEDIENTE No.00-85238
PATENTE: "QUIMIOTERAPIA DE COMBINACION"

Estimados señores:

Con fundamento jurídico en lo dispuesto por el Artículo (44) de la Decisión (486) de la Comisión de la Comunidad Andina de Naciones (CAN) ruego a ustedes disponer lo pertinente para proceder al Examen de Patentabilidad de la Solicitud citada en la referencia, para lo cual estamos adjuntando el recibo de pago correspondiente a la tasa vigente para este caso.

En consecuencia, esperamos se surta este trámite para que el expediente siga su curso normal, hasta su concesión.

Atentamente,

CARLOS ORLANDO MAYA RODRÍGUEZ.
C.C. No. 17.117.818- Bogotá
T.P. No. 17.402- C.S.J.

Anexo.- Recibo de Pago

Carrera 7ª No. 17 - 51 Of. 710 Tels. (571) 341 9841
(571) 400 9180 (571) 286 8037 •Celular: (315) 317 1181
E-mail: trademarks1@tutopia.com • Bogotá, Colombia, S.A.
trademarks1@hotmail.com

~~303~~ 299

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00085238 00000006 Folios: 1
Fecha (AMD): 2003-08-28 15:33:34
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 60,624
FECHA : AGOSTO 27 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARLOS TAMAYO	CONSIGNACION	BANCO POPULAR	050-00110-6	3697954	27/08/2003	1,697,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
			TOTAL : $	335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00-85238**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No **525**, DE FECHA **28** DE **FEBRERO** DE **2003**,

EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **29** DE **MAYO** DE **2003**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ___ **X** _____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

US005137918A

United States Patent [19]

Weiershausen et al.

[11] Patent Number: 5,137,918

[45] Date of Patent: Aug. 11, 1992

305 301

[54] **N-(2'-AMINOPHENYL)-BENZAMIDE DERIVATIVES PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Ute Weiershausen**, Gundelfingen; **Gerhard Satzinger**, Denzlingen; **Karl-Otto Vollmer**, Freiburg; **Wolfgang Herrmann**, Merzhausen, all of Fed. Rep. of Germany

[73] Assignee: **Goedecke Aktiengesellschaft**, Salzufer, Fed. Rep. of Germany

[21] Appl. No.: **594,592**

[22] Filed: **Oct. 9, 1990**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 455,860, Dec. 15, 1989, abandoned, which is a continuation of Ser. No. 39,206, Apr. 16, 1987, abandoned.

[30] **Foreign Application Priority Data**

Apr. 22, 1986 [DE] Fed. Rep. of Germany 3613571
Jul. 26, 1986 [DE] Fed. Rep. of Germany 3625359

[51] **Int. Cl.**[5] **A61K 31/165**; C07C 237/42

[52] **U.S. Cl.** **514/616**; 514/619; 564/157; 564/168

[58] **Field of Search** 564/157, 168; 514/616, 514/619

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,004,029	1/1977	Collins et al.	424/325
4,642,379	2/1987	Beedle et al.	564/155
4,816,485	3/1989	Satzinger et al.	514/619
4,857,662	8/1989	Satzinger et al.	514/619 X
4,933,368	6/1990	Satzinger et al.	514/619 X

FOREIGN PATENT DOCUMENTS

3305755	8/1984	Fed. Rep. of Germany	564/168

OTHER PUBLICATIONS

CA 106:19956v, Moser et al., Jan. 1989.
Arsac et al., CA 88:51950j (1977).
Shchel'tsyn et al., Zh Org. Khim 1986, 22(2), 359, 365.

Primary Examiner—Carolyn S. Elmore
Attorney, Agent, or Firm—Elizabeth M. Anderson

[57] **ABSTRACT**

The present invention provides substituted N-(2'-aminophenyl)-benzamide derivatives useful for combating neoplastic diseases. The present invention also provides a process for the preparation of these benzamide derivatives, as well as pharmaceutical compositions containing them and methods for using them.

12 Claims, 7 Drawing Sheets

306
302

N-(2'-AMINOPHENYL)-BENZAMIDE DERIVATIVES PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

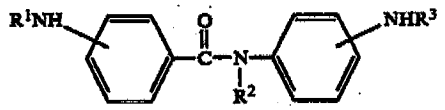
CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. application, Ser. No. 455,860, filed Dec. 15, 1989 which is a continuation of U.S. application Ser. No. 039206, filed Apr. 16, 1987, now abandoned.

BACKGROUND OF THE INVENTION

The present invention is concerned with new N-(2'-aminophenyl)-benzamide derivatives, a process for the preparation thereof, pharmaceutical compositions containing them, and the use thereof for combatting neoplastic diseases.

German Patent 33 05 755 describes compounds of the general formula I



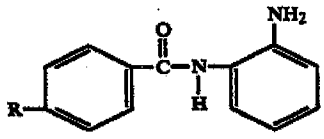
I

wherein at least one of R^1 and R^3 is a methyl radical and the other symbols R^1, R^2, and R^3, which can be the same or different, represent hydrogen atoms or methyl radicals, as being effective for combatting malignant, proliferative, and autoimmune diseases, 4-amino-N-(2'-aminophenyl)-benzamide and its N-monomethyl derivative being said to be especially effective.

Surprisingly, we have now found that the basic p-amino function, which was initially thought to be pharmacologically essential, is not responsible for the therapeutic effectiveness of these compounds but rather that the absence thereof or a chemical change or thereof into neutral-reacting groups by substitution or replacement thereof by nonbasic radicals gives rise to effective compounds with a superior compatibility.

SUMMARY AND DETAILED DESCRIPTION

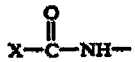
The present invention concerns new N-(2-aminophenyl)benzamide derivatives for the therapy of malignant, proliferative, and autoimmune diseases which have the general formula II



II

wherein R is a lower acylamino radical, including those with up to four carbon atoms which are optionally substituted with hydroxyl groups.

The term lower acylamino is



wherein X is hydrogen or a group of from one to three carbon atoms which may be unsubstituted or substituted by one or more hydroxyl groups.

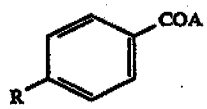
Preferred compounds of general formula (II) which contain a lower acylamino radical R include the

1) 4-acetamino-N-(2'-aminophenyl)-benzamide,
2) 4-isobutyrylamino-N-(2'-aminophenyl)-benzamide,
3) 4-formylamino-N-(2'-aminophenyl)-benzamide,
4) 4-(β-hydroxypropionylamino)-N-(2'-aminophenyl)-benzamide, and
5) 4-glycolamino-N-(2'-aminophenyl)-benzamide.

The 4-acylamino compounds 1) to 5) are new. The compound in which R is a hydrogen atom has been described (Beilstein, 13, Main Work, p. 20) without mention of its pharmacological action.

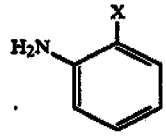
The present invention is also concerned with the use of compounds of general formula (II), wherein R can also be a hydrogen atom, for combatting neoplastic diseases.

The compounds of general formula (II) can be prepared by reacting a compound of the general formula IIIa



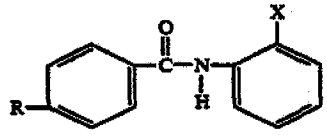
IIIa

wherein R has the same meaning as above and A is a reactive acid group, with a compound of the general formula IIIb



IIIb

wherein X is an amino group provided with a protective group or is a nitro group, to give a compound of the general formula IV



IV

wherein X and R have the above-given meanings, which is converted into a compound of general formula (II) either by reduction or by splitting off the protective group.

The reaction of compounds of general formula (IIIa) with compounds of general formula (IIIb) takes place in known manner. The reactive acid group A can, in particular, be an acid halide, acid anhydride, imidazolide, or ester group which permits a reaction with the amino group. Thus, A is preferably a halogen atom or an imidazolyl, acyl or lower alkoxy radical.

The protective group for X is one of those conventional in peptide chemistry, for example, a benzyl or carbobenzoxy radical. The reduction can be carried out with hydrogen for the use of an appropriate catalyst, for example, platinum or palladium, in such a manner that, on the one hand, the free nitro group is reduced to give a primary amino group and, on the other hand, the

protective group on the amino group is split off hydrogenolytically.

The active materials according to the present invention are advantageously administered in the form of a pharmaceutical composition which contains the active material in free form or in the form of a mixture with an appropriate pharmaceutical organic or inorganic solid or liquid carrier material, which can be administered topically, enterally, for example, orally or rectally, parenterally, for example, intramuscularly or intravenously. For the preparation of such compositions, there can be used those materials which do not react with the new compounds according to the present invention, for example, gelatine, lactose, starch, stearyl alcohol, magnesium stearate, talc, vegetable oils, benzyl alcohol, propylene glycols, petroleum jelly or other pharmaceutical carriers.

The pharmaceutical compositions can be in the form of, for example, tablets, dragees, capsules, suppositories, salves or creams or in liquid form as suspensions or emulsions. If necessary, they are sterilized and/or contain adjuvants, such as preserving agents, stabilizing agents, wetting agents or emulsifiers, solubilizing agents or salts for changing the osmotic pressure or buffers. They can also contain further active materials.

The dosage employed depends upon the nature of the disease to be treated therapeutically and upon individual factors. In general, dosages of from 10 to 300 mg and especially of from 20 to 50 mg are administered. In special cases, the individual dosage can also be higher.

DRAWINGS

FIG. 1 shows graphically that there is not statistically significant difference of the AUCs (area under the plasma concentration-time curve) found after intravenous and intragastral administration to rats at 10 mg/kg. FIG. 1 is the AUC, rat, after administration of 4-acetamino-N-(2'-aminophenyl)benzamide. The * is intragastral administration (2 mg/kg; 10 mg/kg; 50 mg/kg). The * is intravenous administration (10 mg/kg).

FIGS. 2 and 3 show graphically that the active material of the present invention is characterized, in comparison with the standard, by a longer half-life time so that it is possible to maintain a cytostatic activity level over a comparatively long period of time. In FIG. 2 the average plasma level of 4-amino-N-(2'-aminophenyl)-benzamide in rats after single administration of 10 mg/kg intragastrally (n=4). The half-life ($t_{\frac{1}{2}}$) is about 15 minutes.

FIG. 3 shows the average plasma level of 4-acetamino-N-(2'-aminophenyl)-benzamide in rats after single administration. + stands for 10 mg/kg intravenously (n=5), ∘ stands for 2 mg/kg intragastrally (n=5), for 10 mg/kg intragastrally (n=6), □ stands for 50 mg/kg intragastrally (n=5). Half-life ($t_{\frac{1}{2}}$) is about 4.2–4.5 hours.

From FIG. 4 it is evident that 5-acetamino-N-(2'-aminophenyl)-benzamide affects tumor growth in a dose-dependent manner with almost complete tumor growth inhibition in the highest dose group. FIG. 4 shows the activity of 4-acetamino-N-(2'-aminophenyl)-benzamide against methylnitrosurea-induced (MNU-induced) mammary adenocarcinoma in SD rats. is control; □ is 12.5 mg/kg; • is 10 mg/kg; and ∘ is 7.5 mg/kg.

FIGS. 5 and 6 show the antineoplastic effect of compounds A, B, C at equimolar doses (33 μmol/kg/day); is control; Δ is compound C (8.0 mg/kg), ∘ is compound B (7.5 mg/kg), and □ is compound A (8.9 mg/kg).

FIG. 7 shows the growth inhibition of AMMN-induced colon adenocarcinoma with compound A at different doses (5.3, 7.0, 9.1, and 11.9 mg/kg).

BIOLOGICAL DATA

4-Acetamino-N-(2'-aminophenyl) benzamide was used as an example of a compound according to the present invention and compared with 4-N-(2'-aminophenyl)-benzamide as standard, the outstanding inhibition action of which against various experimental tumors in vitro and in vivo is known. The testing was carried out in vivo with SD-rats against MNU-induced mammary adenocarcinoma and acetoxymethylmethylnitrosamine-induced (AMMN-induced) colon adenocarcinoma. The testing was carried out in vitro in the "colorimetric-cytotoxicity assay" using L1210 and mammary adenocarcinoma 16C tumor cells. In this test system, substances with ID_{50} values of ≦250 μg/mL are assessed as being cytostatically active.

It could be shown (see the following Table 1) that the active material 4-acetamino-N-(2'-aminophenyl)-benzamide according to the present invention:

1) acts outstandingly cytostatically; and
2) has a cytostatic activity which is about the same or better as that of the comparison standard.

TABLE 1

Test Substance	ID_{50} μg/mL
L1210 Colorimetric Cytotoxicity Assay	
(A) 4-Acetamino-N-(2'-aminophenyl)-benzamide)	3.75
(B) 4-Amino-N-(2'-aminophenyl)-benzamide	2.78
(C) 4-Methylamino-N-(2'-aminophenyl)-benzamide	4.04
Mamma Adenocarcinoma 16C Cytotoxicity Assay	
(A) 4-Acetamino-N-(2'-aminophenyl)-benzamide	0.73
(B) 4-Amino-N-(2'-aminophenyl)-benzamide	0.69
4-Isobutyrylamino-N-(2'-aminophenyl)-benzamide	0.32
4-Formylamino-N-(2'-aminophenyl)-benzamide	0.40
4-(β-Hydroxypropionyl)amino-N-(2'-aminophenyl)-benzamide	0.77
4-Glycoloylamino-N-(2'-aminophenyl)-benzamide	0.62

Surprisingly, we have found that the active material according to the present invention, 4-acetamino-N-(2'-aminophenyl)-benzamide, is considerably less toxic in the case of acute intragastral administration than the comparison standard. This was demonstrated in an orientating experiment (n=4) on male mice for the determination of the LD_{50} with a 7-day period of observation. The results are shown in the following Table 2:

TABLE 2

Test Substance	LD_{50} mg/kg
(A) 4-Acetamino-N-(2'-aminophenyl)-benzamide	1600
(B) 4-Amino-N-(2'-aminophenyl)-benzamide	625

In pharmacokinetic experiments on rats, a reduced resorption as a possible cause for the substantially improved acute compatibility of the active material according to the present invention in comparison with the standard could be excluded: the intestinal resorption of the substance took place quickly, completely, and dosage-linearly.

The bioavailability of the active material according to the present invention is 100%. No statistically signifi-

cant difference of the AUC's was found after intravenous and intragastral administration to rats of 10 mg/kg. This is shown graphically in FIG. 1 of the accompanying drawings.

Besides its better compatibility, the active material according to the present invention is also characterized, in comparison with the standard, by the longer half-life time (see FIGS. 2 and 3 of the accompanying drawings) so that it is possible to maintain a cytostatic activity level over a comparatively long period of time.

The in vivo activity of 4-acetamino-N-(2'-aminophenyl)-benzamide was tested against primary mammary adenocarcinoma induced by 3 single IV administrations of methylnitrosurea on Days 50, 71, and 92 following birth in female SD rats. As soon as tumor volumes ≧0.8 cm^3 were reached, test animals were randomized and therapy was started. The compounds A, B, and C were administered intragastrally, 5 times/-week for 5 weeks. The doses of compounds A, B, and C were respectively: A: 7.5, 8.9, 10.0 and 12.5 mg/kg/day; B: 7.5 mg/kg/day; C: 8.0 mg/kg/day. Median tumor volumes and numbers were determined weekly and compared with untreated controls. At equimolar doses (33 μmol/kg/day) the acetyldinaline (compound A) shows the highest antineoplastic effect, as can be seen from FIGS. 5 and 6. From FIG. 4 it is evident that 4-acetamino-N-(2'-aminophenyl)benzamide affects tumor growth in a dose-dependent manner with almost complete tumor growth inhibition in the highest dose group.

The activity of the compounds A, B, and C was tested in vivo against AMMN-induced colon adenocarcinoma. Male SD-rats were given 2 mg/kg/week acetoxymethylmethylnitrosamine (AMMN) intrarectally for a period of 10 weeks for tumor induction. Animals with manifest tumors were assigned randomly to the test groups. The therapy scheme is given in Table 3.

TABLE 3

Group	Number of Animals	Test Substance	Dose[a] (mg/kg/day)	Duration of Therapy (Weeks)	Total Dose (mg/kg)
K1	15	—	—	—	—
K2	20	—	—	10	0
3	15	(B)	10	10	500
4	15	(B)	7.7	10	385
5	15	(B)	5.9	10	295
6	5	(A)	11.9	10	595
7	15	(A)	9.1	10	455
8	15	(A)	7.0	10	350
9	15	(A)	5.3	10	265
10	15	(C)	13.8	10	690
11	15	(C)	10.6	10	530
12	15	(C)	8.2	10	410
13	10	(C)	6.2	10	310

[a]Application via gastric tube, 5 days per week
(A) = Compound A, (B) = Compound B, (C) = Compound C

The animals were examined twice daily. After the 10-week treatment period, the animals were sacrificed and a total necropsy performed. All tumors were individually measured and their volumes added to a total tumor volume. All three compounds show an antineoplastic effect, compounds B and A being very efficient. The optimum dose of compound B (5.9 mg/kg/day=26 μmol/kg/day) resulted in arrest of tumor growth (relative median tumor volume T/C: 10.6%). The equimolar dose of compound A (7.0 mg/kg/day) also completely inhibited further growth of colon carcinoma in the medium (T/C 11.1%). Furthermore, with a dose of compound A being 11.9 mg/kg, the growth inhibition is much less (T/C about 5%), as can be seen from FIG. 7.

Thus, the compounds according to the present invention are, in comparison with the comparison standard, 4-N-(2'-aminophenyl)-benzamide, cytostatics which are clearly improved in important biological parameters and, at the same time, are equally effective cytostatics against L1210 leukemia cells and AMMN-induced colon carcinoma and have better activity against mammary adenocarcinoma 16C.

Therefore, the new compounds according to the present invention are of therapeutic importance and are agents for the systemic and/or topical treatment of malignant neoplasias, for the treatment of benign proliferative diseases, and for the treatment of disturbances of the cellular and humoral immune system.

There is also included the possibility of a combination with therapeutics from which it is to be expected that they strengthen and favorably influence the desired effects.

The following examples are given for the purpose of illustrating the present invention:

EXAMPLE 1

4-Acetamino-N-(2'-aminophenyl)-benzamide

30 g (0.1 mole) N-(2'-aminophenyl)-4-acetylaminobenzamide are hydrogenated under standard conditions in tetrahydrofuran in the presence of 10% palladium charcoal. After removal of the catalyst, the filtrate is concentrated to about one-quarter of its volume and the precipitate obtained is filtered off with suction. If desired, the product can be recrystallized from methanol/tetrahydrofuran (1:1 v/v). Yield 18.6 g (69% of theory); m.p. 243.7° C.

The N-(2'-nitrophenyl)-4-acetylaminobenzamide used as starting material is prepared as follows: 41.3 g (0.33 mole) oxalyl chloride are added dropwise at 0°–5° C., with the exclusion of moisture, to a solution of 60.3 g (0.83 mole) dimethylformamide in 1.5 L dry ethyl acetate. After stirring for 30 minutes at this temperature, 44.8 g (0.25 mole) 4-acetamidobenzoic acid, together with 27.7 g (0.35 mole) pyridine, are added thereto and the ice bath is removed. After stirring for 3 hours at ambient temperature, the reaction mixture is mixed with a solution of 38 g (0.28 mole) o-nitroaniline and 27.7 g (0.35 mole) pyridine in 30 mL dry ethyl acetate. After stirring for 15 hours at ambient temperature, the reaction mixture is mixed with 500 mL 1N aqueous sodium hydroxide solution, the phases are separated and the aqueous phase is shaken out three times with 150 mL amounts of ethyl acetate. The combined organic phases are washed neutral with water, dried over anhydrous sodium sulfate, and concentrated to about one-third. The precipitate obtained is filtered off with suction and purified either by recrystallization or by column chromatography. Yield 15 g (20% of theory); m.p. 205.8° C.

EXAMPLE 2

4-(β-Hydroxypropanoyl)-amino-N-(2'-aminophenyl)-benzamide

2 g (4.76 mMole) N-(2, nitrophenyl) 4-(3-benzyloxypropanoylamino)-benzamide are dissolved in 300 mL ethanol and hydrogenated in the presence of 1 g 5% palladium charcoal at 80° C. for 6 hours in an autoclave. After filtration, the solvent is removed and the residue is purified by column chromatography (silica gel; meth-

ylene chloride/methanol 9:1 v/v). Yield 0.8 g (56% of theory); m.p. 197.7° C.

The compounds used as starting materials are prepared as follows:

4-(3-Benzyloxypropanoylamino)-benzoic acid

8.09 g (59 mMole) p-aminobenzoic acid, together with 4.98 g (63 mMole) pyridine, are dissolved in 100 mL dioxan and mixed at 15° C. with 11.7 g (59 mMole) 3-benzyloxypropionic acid chloride (J.C.S., Perkin I, 1976, 2229) in 2 mL dioxan. After stirring for 3 hours at ambient temperature, the reaction mixture is mixed with 300 mL water. The precipitate obtained is filtered off with suction, washed with water, and dried. Without further purification, the product is used in the next step. Yield 15.7 g (89% of theory); m.p. 162°–164° C. sinters; >200° C. decomposition.

N-(2'-Nitrophenyl)-4-(3-benzyloxypropanoylamino)-benzamide is prepared analogously to Example 1 using 12 g (40.1 mMole) 4 (3 benzyloxypropanoylamino)-benzoic acid, 6.6 g (0.13 mMole) oxalyl chloride, 9.7 g (0.13 mole) dimethylformamide, 2×4.5 g pyridine, 6.1 g (44.1 mMole) o-nitroaniline, and 280 mL dry ethyl acetate. The crude product is purified by column chromatography (silica gel; ethyl acetate/n hexane 1:5-1:1 v/v). Yield 3.5 g (21% of theory); m.p. 140° C.

EXAMPLE 3

4-Isobutyrylamino N (2'-aminophenyl) benzamide

13.1 g (40 mMole) N-(2'-nitrophenyl)-4-isobutyrylaminobenzamide are hydrogenated under standard conditions in 400 mL tetrahydrofuran in the presence of 10% palladium charcoal. After concentrating the solvent to 120 mL, the precipitated crystals are filtered off with suction. Yield 10.2 g (86% of theory); m.p. 247.6° C.

The compounds used as starting materials are prepared as follows:

4-Isobutyrylaminobenzoic acid

50 g (0.36 mole) p-aminobenzoic acid and 30 g (0.38 mole) pyridine are dissolved in 600 mL dioxan and mixed dropwise at 15° C., with the exclusion of moisture, with 40.5 g (0.38 mole) isobutyric acid chloride. After stirring for 2 hours at ambient temperature, 500 mL water are added thereto, with vigorous stirring. The precipitate obtained is filtered off with suction, washed with water, dried, and recrystallized from diisopropyl ether/ethyl acetate (3:4 v/v). Yield 22 g (30% of theory); m.p. 241° C.

N-(2'-Nitrophenyl)-4-isobutyrylaminobenzamide is prepared under the reaction conditions given in Example 5: after the addition of pyridine/o-nitroaniline, the reaction solution is stirred for 15 hours at ambient temperature and for 5 hours at boiling temperature, the following components being used: 54.6 g (74.68 mMole) dimethylformamide, 1.5 L dry ethyl acetate, 37.3 g (29.42 mMole) oxalyl chloride, 47 g (22.63 mMole) 4-isobutyrylaminobenzoic acid, 34.4 g (24.89 mMole) o-nitroaniline, and 25.6 g (32.36 mMole) pyridine. The product is recrystallized from ethyl acetate. Yield 13.3 g (18% of theory); m.p. 237.6° C.

EXAMPLE 4

4-Glycoloylamino-N-(2'-aminophenyl)-benzamide

6.08 g (15 mMole) N-(2'-nitrophenyl)-4-benzyloxyacetaminobenzamide are dissolved in 400 mL ethanol and 200 mL tetrahydrofuran and hydrogenated in an autoclave for 19 hours at 80° C. and 50 bar hydrogen pressure in the presence of 3 g 15% palladium charcoal. The contents of the autoclave are filtered while still hot and the colorless filtrate is evaporated to dryness. The crystalline residue is recrystallized from 800 mL methanol. Yield 2.6 g (63.2% of theory); m.p. 221°–223° C.

The starting materials used are prepared as follows:

4-Benzyloxyacetaminobenzoic acid

35.7 g (0.26 mole) p-aminobenzoic acid, together with 23.7 g (0.30 mole) pyridine, are dissolved in 420 mL dioxan and mixed dropwise at 15° C. with 51.7 g (0.28 mole) benzyloxyacetic acid chloride (Heterocyclic Chem., 15, 601, 1978). After stirring for 2 hours at ambient temperature, the reaction mixture is mixed with 300 mL water. The precipitate obtained is filtered off with suction, washed with water, and dried. The product is used for the next step without further purification. Yield 63 g (98.3% of theory); m.p. 178°–179° C.

N (2'-Nitrophenyl)-4-benzyloxyacetaminobenzamide

28.5 g (0.39 mole) dry dimethylformamide in 910 mL dry ethyl acetate are mixed dropwise at 2° C., under an atmosphere of nitrogen, with 21.5 g (0.17 mole) oxalyl chloride. After stirring for 30 minutes at 2°–5° C., a suspension of 37.2 g (0.13 mole) 4-benzyloxyacetaminobenzoic acid and 14.4 g (0.18 mole) pyridine in 65 mL ethyl acetate are added thereto and the ice bath is removed. After stirring for 2.5 hours at ambient temperature, the reaction mixture is mixed with a solution of 19.8 g (0.14 mole) o-nitroaniline and 14.4 g (0.18 mole) pyridine in 65 mL ethyl acetate. After stirring for 1 hour at ambient temperature, the reaction mixture is heated to the boil for 3 hours. After cooling, it is mixed with 500 mL IN aqueous sodium hydroxide solution and the phases are separated. The aqueous phase is shaken out twice with ethyl acetate. The combined organic phases are washed neutral with water and dried over anhydrous sodium sulfate. The solvent is evaporated to 150 mL and the precipitated crystals are filtered off with suction and recrystallized from 700 mL ethanol. Yield 13 g (24.7% of theory); m.p 128°–130° C.

EXAMPLE 5

N-(2'Aminophenyl)-4-formylamino-benzamide

1.92 g (67.3 mMole) N-(2'-nitrophenyl) 4-formylamidobenzamide are hydrogenated under standard conditions in 500 mL tetrahydrofuran in the presence of 10% palladium charcoal. After removal of the catalyst, the solvent is removed in a vacuum and the crystalline residue is recrystallized from tetrahydrofuran/diisopropyl ether (1:1 v/v). Yield 1.5 g (88.5% of theory); m.p. 197.7° C. (decomp.).

The starting material is prepared in the following manner:

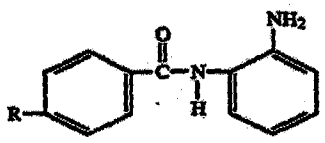
N-(2'-Nitrophenyl)-4-formylamidobenzamide

7.9 g (0.11 mole) dimethylforamimide and 80 mL dry ethyl acetate are mixed dropwise at 0°–5° C., under an atmosphere of nitrogen, with 5.9 g (46.8 mMole) oxalyl chloride. After stirring for 30 minutes at this temperature, the reaction mixture is mixed with 5.95 g (36 mMole) formyl-4-amidobenzoic acid (Chem. Ber., 23, 3625, 1890; Beilsteins Handbuch der Organidschen Chemie, pub. Springer Verlag, 1931, Vol. 14, p. 432) and 4.3 g (54 mMole) pyridine and the ice bath is removed.

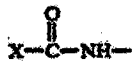
After stirring for 3 hours at ambient temperature, the solution is mixed with 5.47 g (39.6 mMole) o-nitroaniline in I5 mL dry ethyl acetate and stirred for 15 hours at ambient temperature. The solution is subsequently rendered alkaline with ammonia, washed with water, and dried over anhydrous sodium sulfate. After removal of the solvent, a crystalline residue remains behind which is recrystallized from ethyl acetate. Yield 1.5 g (14.6% of theory); m.p. 237.6° C.

We claim:

1. A compound of the formula



wherein R is a lower acylamino group



wherein X is hydrogen or a group of one to three carbon atoms unsubstituted or substituted by one or more hydroxyl groups.

2. A compound according to claim 1 and being 4-acetamino-N-(2'-aminophenyl)-benzamide.

3. A compound according to claim 1 and being 4-isobutyrylamino-N-(2'-aminophenyl)-benzamide.

4. A compound according to claim 1 and being 4-formylamino-N-(2'-aminophenyl)-benzamide.

5. A compound according to claim 1 and being 4-(β-hydroxypropionylamino)-N-(2'-aminophenyl)-benzamide.

6. A compound according to claim 1 and being glycoloylamino-N-(2'-aminophenyl)-benzamide.

7. A pharmaceutical composition effective for treating mammary adenocarcinoma 16C comprising a therapeutically effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition effective for treating L1210 leukemia comprising a therapeutically effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

9. A pharmaceutical composition effective for treating colon adenocarcinoma comprising a therapeutically effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

10. A method for treating mammary adenocarcinoma 16C in mammals which comprises administering to a mammal in need thereof a pharmaceutical composition according to claim 7 in unit dosage form.

11. A method for treating L1210 leukemia in mammals which comprises administering to a mammal in need thereof a pharmaceutical composition according to claim 8 in unit dosage form.

12. A method for treating colon adenocarcinoma in mammals which comprises administering to a mammal in need thereof a pharmaceutical composition according to claim 9 in unit dosage form.

* * * * *

D2 311 307

The Journal of Clinical Pharmacology, 1990; 30:770-788

Article

New natural products in cancer chemotherapy

WJ Slichenmyer and DD Von Hoff

Four new and clinically relevant antineoplastic natural products are reviewed. **Taxol** is derived from the bark of the western yew. It promotes the formation of microtubule bundles which deform the cytoskeleton and interfere with mitosis. Although phase II efficacy testing is incomplete, **taxol** is effective in the treatment of patients with ovarian carcinoma and has some activity in patients with non-small cell lung cancer and melanoma. It remains untested against several other neoplasms. The chief toxicities of taxol are myelosuppression, mucositis, anaphylactoid reactions, and peripheral neuropathy. Homoharringtonine is the most active and abundant of the cephalotaxine esters derived from the genus Cephalotaxus. This agent appears to act at the ribosome to inhibit protein synthesis and has clinical activity in patients with acute myelogenous leukemia. The dose limiting toxicities of homoharringtonine are hypotension and myelosuppression. SKF 104864 and CPT-11 are derivatives of camptothecin which are still in early clinical trials. They are cytotoxic in vitro, acting through an interaction with topoisomerase I to induce DNA fragmentation. The spectra of activity and toxicity of SKF 104864 and CPT-11 are still undefined. All four of these new natural products offer possibilities for clinical activity for patients with a variety of malignancies.

D3 ~~312~~ 308

The Journal of Clinical Pharmacology, 1988; 28:208-215

Article

Clinical pharmacokinetics of **carboplatin**

S Oguri, T Sakakibara, H Mase, T Shimizu, K Ishikawa, K Kimura, and RD Smyth

The pharmacokinetics of **carboplatin** were investigated in cancer patients after single, IV infusion doses of 75, 150, 247.5, 300, 375, and 450 mg/m2. Total plasma and urine platinum and plasma ultrafilterable platinum concentrations were determined by atomic absorption spectrometry. Carboplatin was analyzed in plasma by a specific high-performance liquid chromatography (HPLC) procedure. Total plasma platinum, which represented free carboplatin, protein-bound platinum and metabolites, declined triexponentially; plasma half-lives (t1/2 lambda 1, 0.2 to 0.4 hr; t1/2 lambda 2, 1.3 to 1.7 hr; t1/2 lambda 3, 22 to 40 hr) and total body clearance (CLTB 2.8 +/- 0.5 L/m2/hr) were dose independent. Maximum plasma concentrations (Cmax) and area under the plasma concentration time curve (AUC) increased proportionally with dose. Plasma ultrafilterable platinum and carboplatin concentrations at doses of 375 and 450 mg/m2 declined in a biphasic manner. Plasma carboplatin elimination (t1/2 lambda 1, 0.50 hr; t1/2 lambda 2, 2.2 hr) and CLTB (4.4 to 5.6 L/m2/hr) were also independent of dose; AUC and Cmax increased proportionally to dose. Plasma free platinum was essentially all carboplatin for 8 or 12 hours after administration. Carboplatin did not bind to plasma protein in vitro but did degrade (t1/2-26 hours) to yield a reactive intermediate that bound rapidly and irreversibly to protein. The long terminal elimination half-life of plasma platinum was associated with irreversible binding of a platinum metabonate to plasma protein. The urinary excretion of platinum (0 to 24 hours) accounted for 58 to 72% of doses in 12 to 24 hours. The remainder of the dose is slowly excreted. The pharmacokinetics, in vivo stability, protein binding, and elimination of carboplatin are distinct from the first-generation analog cisplatin.

309

313

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Marzo 14 de 2006

Doctor
CARLOS ORLANDO MAYA RODRÍGUEZ

ASUNTO	Radicación No.	00 085 238
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	3346
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 8 - 60 y el capítulo reivindicatorio de los folios 61 – 63 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 – 7 se refieren a una combinación de agentes antineoplásicos que contiene acetidinalina y paclitaxel y/o carboplatina (en cápsula ó solución estéril para inyección).

Las reivindicaciones 8 - 12 se refieren a un método para tratar cáncer que consiste en administrar una combinación.

Las reivindicaciones 13 – 15 se refieren a un juego que contiene acetidinalina en un compartimento y paclitaxel y/o carboplatina en otro u otros.

El problema planteado en esta solicitud es la necesidad de proporcionar un método para tratar cáncer.

Para resolver este problema técnico la solicitud en estudio proporciona un método para tratar cáncer que consiste en administrar una combinación de agentes antineoplásicos que contiene acetidinalina y paclitaxel y/o carboplatina (en cápsula ó solución estéril para inyección).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/555 // 31/66 // 31/28 // 31/00.

También se reivindica prioridad de las Solicitudes de Patente de los Estados Unidos US 60 164 889 de noviembre 10 de 1999 y US 60 222 561 de agosto 3 de 2000, con respecto a las cuales la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Las reivindicaciones 8 - 12 se refieren a un método para tratar cáncer que consiste en administrar una combinación.

Se observa que el método de tratamiento que comprende administrar una combinación, de las reivindicaciones 8 - 12, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método de tratamiento que comprende administrar una combinación, de las reivindicaciones 8 - 12, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

4. Unidad de Invención

El artículo 25 de la Decisión 486 establece: *"La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo".*

En una solicitud de patente se puede reivindicar:
a) una sola invención; o
b) un grupo de invenciones relacionadas entre sí por un único concepto inventivo.
Cuando se trate del caso b), se debe considerar que el concepto inventivo único que relaciona las invenciones debe ser técnico, cumplir por sí mismo con los requisitos de novedad y nivel inventivo, y ser común a todas las reivindicaciones.

Se observa que las reivindicaciones 13 – 15 se refieren a un juego que contiene acetidinalina en un compartimento y paclitaxel y/o carboplatina en otro u otros, no mantienen el principio de la unidad de invención porque los compartimentos no pertenecen al mismo campo técnico. No se observa que entre los dos inventos reivindicados: los compuestos y los compartimentos en que se pueda envasar, exista un concepto técnico inventivo único que los relacione.

Debe hacerse la corrección respectiva.

5. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al publico por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese

examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el articulo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es noviembre 10 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	US 5 137 918	Derivados N-(2'-aminophenyl)-benzamide, proceso para su preparación y composiciones farmacéuticas que los contienen	Ago 11, 1992
D2	The Journal of Clinical Pharmacology, 1990; 30:770-788 © 1990 American College of Clinical Pharmacology	New natural products in cancer chemotherapy (*)	1990
D3	The Journal of Clinical Pharmacology, 1988; 28:208-215 © 1988 American College of Clinical Pharmacology	Clinical pharmacokinetics of carboplatin	1988

6. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".*

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Las reivindicaciones 1 – 7 se refieren a una combinación de agentes antineoplásicos que contiene acetidinalina y paclitaxel y/o carboplatina (en cápsula ó solución estéril para inyección).

D1 enseña composiciones farmacéuticas que contienen 4-acetamino-N-(2'-aminophenyl)-benzamida (ver folios 308 y 310).

D2 enseña paclitaxel (Taxol) efectivo en tratamientos de cáncer de ovarios, cáncer de células no pequeñas de pulmón y melanoma (ver folio 311).

D3 enseña carboplatino para tratar cáncer (ver folio 312).

Se observa que

(a) los compuestos que caracterizan a las combinaciones de esta solicitud, es decir acetidinalina y paclitaxel y/o carboplatina eran conocidos en las anterioridades, por lo cual para una persona conocedora de la materia era evidente el elaborar las combinaciones teniendo en cuenta estos compuestos;
(b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a los compuestos que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia. Con referencia a las combinaciones reivindicadas se aclara que estas no aportan una ventaja dentro del campo técnico en estudio. Ahora bien, con respecto a las ventajas terapéuticas de la administración conjunta de acetildinalina con paclitaxel y/o carboplatina, se considera un avance en ciencias médicas porque se relaciona con ensayos clínicos durante los cuales se varían los niveles de dosificación y vías de administración y se evalúan los resultados sobre los pacientes; lo cual no se relaciona en sí con la industria farmacéutica y sus composiciones, que son las que se consideran eventualmente (caso de ser nuevas, tener nivel inventivo y aplicación industrial) como objeto de patente.
(c) el problema planteado en esta solicitud que era la necesidad de proporcionar un método para tratar cáncer se resuelve proporcionando un método para tratar cáncer que consiste en administrar una combinación de agentes antineoplásicos que contiene acetidinalina y paclitaxel y/o carboplatina, no se puede evaluar con referencia a nivel inventivo porque está exento de patentabilidad.
(d) el resultado obtenido: combinación de agentes antineoplásicos que contiene acetidinalina y paclitaxel y/o carboplatina (en cápsula ó solución estéril para inyección) no es inesperado, porque no se ha seguido un procedimiento diferente para su elaboración, ni es sorprendente para una persona normalmente conocedora de la materia el hecho de disponer acetidinalina en un compartimento y paclitaxel y/o carboplatina en otro u otros.
(e) no parece haberse superado un prejuicio técnico anterior, con la combinación farmacéutica propuesta.

Por todo lo anterior, las combinaciones reivindicadas no tienen **nivel inventivo**.

7. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5 137 918	1 – 7	Nivel inventivo
D2	The Journal of Clinical Pharmacology, 1990; 30:770-788 © 1990 American College of Clinical Pharmacology	1 – 7	Nivel inventivo
D3	The Journal of Clinical Pharmacology, 1988; 28:208-215 © 1988 American College of Clinical Pharmacology	1 – 7	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente

comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 MAR 2006

CONCEPTO TÉCNICO No. 393	EXAMINADOR TÉCNICO Código 202007

314

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-85238** EDICTO No. **10869**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **17215** de **29-JUN-2006**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "QUIMIOTERAPIA DE COMBINACION".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Orlando Maya Rodríguez, o a quien haga sus veces, en su calidad de apoderado de Warner Lambert Company., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 29 JUN. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO ESCOBAR.

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **19-JUL-2006** Este edicto se desfija hoy **02-AGO-2006** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **10869**