



PHARMACEUTICAL COMPOSITION BASED ON POLYAROMATIC
COMPOUNDS

The present invention relates to pharmaceutical
5 composition based on polyaromatic compounds which are
useful in particular as antitumor medicinal products.

In 1999, the cytotoxic treatments (chemotherapy) used
to reduce the size of cancer tumors, to contain the
10 development of the tumoral process or even, in all too
few cases, to eliminate lumps of cancer cells and the
risk of metastases, combine chemical substances
recently introduced with others which have been used
for a few decades. For example, 5-fluorouracil (5-FU),
15 which has been known for nearly 40 years as one of the
most active treatments for colorectal cancer, may be
replaced with one or other of the inhibitors specific
for topoisomerase I (irinotecan or topotecan) when the
tumor is no longer sensitive to 5-FU. More generally,
20 the therapeutic arsenal available for treating
colorectal cancers is also enriched by the availability
of oxaliplatin, novel in situ "donors" of 5-FU or
selective inhibitors of thymidylate synthase. This co-
existence is not limited to the treatment of colorectal
25 cancers since, in addition, the chemotherapy of breast,
ovarian and lung cancers now makes wide use of the
family of taxane derivatives (paclitaxel and
docetaxel). The need for more effective and better-
tolerated treatments, thus improving the survival and
30 quality of life of the patients, is imperative since,
again taking the example of colorectal tumors, it has
been estimated (S.L. Parker, T. Tong, S. Bolden et al.,
CA Cancer J. Clin., 1997) that, in the United States
alone, more than 131 000 new cases were diagnosed in
35 1997, of which 54 000 were responsible for the death of
the patients. It is the awareness of this situation
which has incited the inventors to focus their
attention on a family of polyaromatic compounds that



have as yet been little studied, identified in
Ascidians of warm seas, to develop a novel medicinal
chemistry intended to select synthetic compounds
derived from chemical design/modulation research and
5 endowed with significant therapeutic cytotoxic
activity.

The seas and oceans which cover more than 70% of the
world's surface are home to marine plants and sponges
10 whose progressive systematic pharmacognosic study shows
that these living species may contain complex alkaloids
with advantageous pharmacological properties. For
example, the sponges *Cryptotheca crypta* and
Halichondria okadai have been the subject of in-depth
15 research since the discovery of the presence, in their
cells, of cytarabin or of halichondrin B. This is
likewise the case for the family of tunicates, since
the isolation of aplidin from the tunicate *Aplidium*
albicans which lives in the Balearic islands (Spain).
20 Alkaloids of tetrahydroisoquinolone structure have been
isolated from the ascidian *Ecteinascidia turbinata*.
Among these, ecteinascidin-743 has been the subject of
in-depth preclinical studies (E. Igbicka et al., NCI-
EORTC symposium, 1998; Abst. 130 p. 34), and also of
25 clinical tests intended to define its therapeutic
potential as an anticancer medicinal product (A. Bowman
et al., NCI-EORTC symposium, 1998; Abst. 452 p. 118;
M. Villanova-Calero et al., NCI-EORTC symposium, 1998;
Abst. 453 p. 118; M.J.X. Hillebrand et al., NCI-EORTC
30 symposium, 1998; Abst. 455 p. 119; E. Citkovic et al.,
NCI-EORTC symposium, 1998; Abst. 456 p. 119). Novel
pentacyclic acridine derivatives have also formed the
subject of pharmacochemical studies (D.J. Hagan et al.,
J. Chem. Soc., Perkin Transf., 1997; 1: 2739-2746).

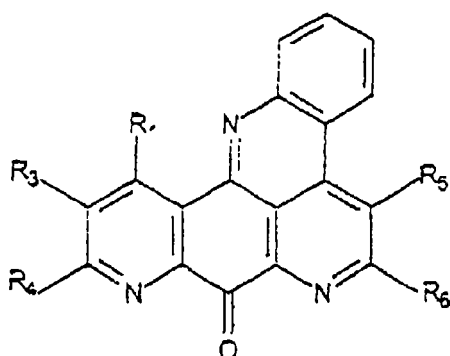
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Among these compounds, mention may be made of meridine,
an natural alkaloid extracted from the ascidian
Amphicarpa meridiana or from the marine sponge *Corticum*
sp. Meridine was isolated by Schmitz et al. (J. Org.

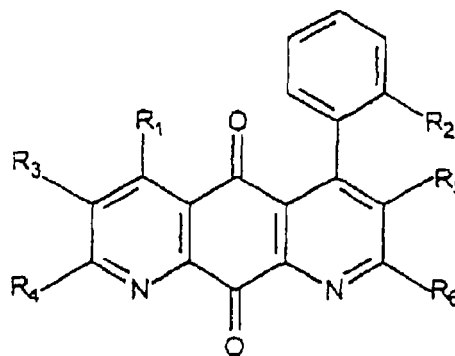
Chem. 1991; 56: 804-808) and then described for its antiproliferative properties on a model of murine leukemia (P388) and its antifungal properties in patent US-A-5 182 287 (Gunawardana et al. of January 23, 1993). Its antifungal properties were described by McCarthy et al. (J. of Nat. Products 1992; 55: 1664-1668) along with its cytotoxic properties on two human cell lines: colon cancer cells (HT-29) and lung carcinoma cells (A549), which were reported by Longley et al. (J. of Nat. Products 1993; 56: 915-920). The synthesis of meridine has been carried out according to various processes by Kitahara et al. (Chem. Pharm. Bull 1994; 42: 1363-1364), Bontemps et al. (Tetrahedron 1997; 37: 1743-1750) and Kitahara et al. (Tetrahedron 1998; 54: 8421-8432).

Among these compounds, mention may also be made of cystodamine, a pentacyclic alkaloid isolated from the Ascidian *Cystodytes dellechiaiei* by Bontemps et al. (Tetrahedron lett., 1994; 35: 7023-7026) which has activity on human leukemia lymphoblasts.

The subject of the present invention is a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formulae:



Formula I



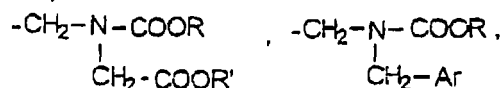
Formula II

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in which:

R₁, R₃, R₄, R₅ and R₆ are chosen from hydrogen, halogens

and hydroxyl, $-\text{CHO}$, $-\text{OR}$, $-\text{COOH}$, $-\text{CN}$, $-\text{CO}_2\text{R}$, $-\text{CONHR}$,
 $-\text{CONRR}'$,



$-\text{NH}_2$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$, $-\text{NHCOR}$,
 5 morpholino, nitro and $-\text{SO}_3\text{H}$ groups,

R and R' being chosen from C_1 - C_6 alkyl groups and Ar
 being a C_6 - C_{14} aryl group,

10 R_2 is chosen from nitro and $-\text{NHCOCF}_3$ groups,

and the addition salts of these compounds with
 pharmaceutically acceptable acids.

15 A subject of the present invention is, more
 particularly, compounds chosen from the compounds of
 formula I and of formula II in which:

R_1 , R_3 and R_4 are chosen from hydrogen, halogens,
 20 hydroxyl, $-\text{CHO}$, $-\text{OR}$, $-\text{COOH}$, $-\text{CN}$, $-\text{CO}_2\text{R}$, $-\text{CONHR}$,
 $-\text{CONRR}'$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$, $-\text{NHCOR}$,
 morpholino, nitro and $-\text{SO}_3\text{H}$ groups,

R_2 is chosen from nitro and $-\text{NHCOCF}_3$ groups,

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and the addition salts of these compounds with
 pharmaceutically acceptable acids.

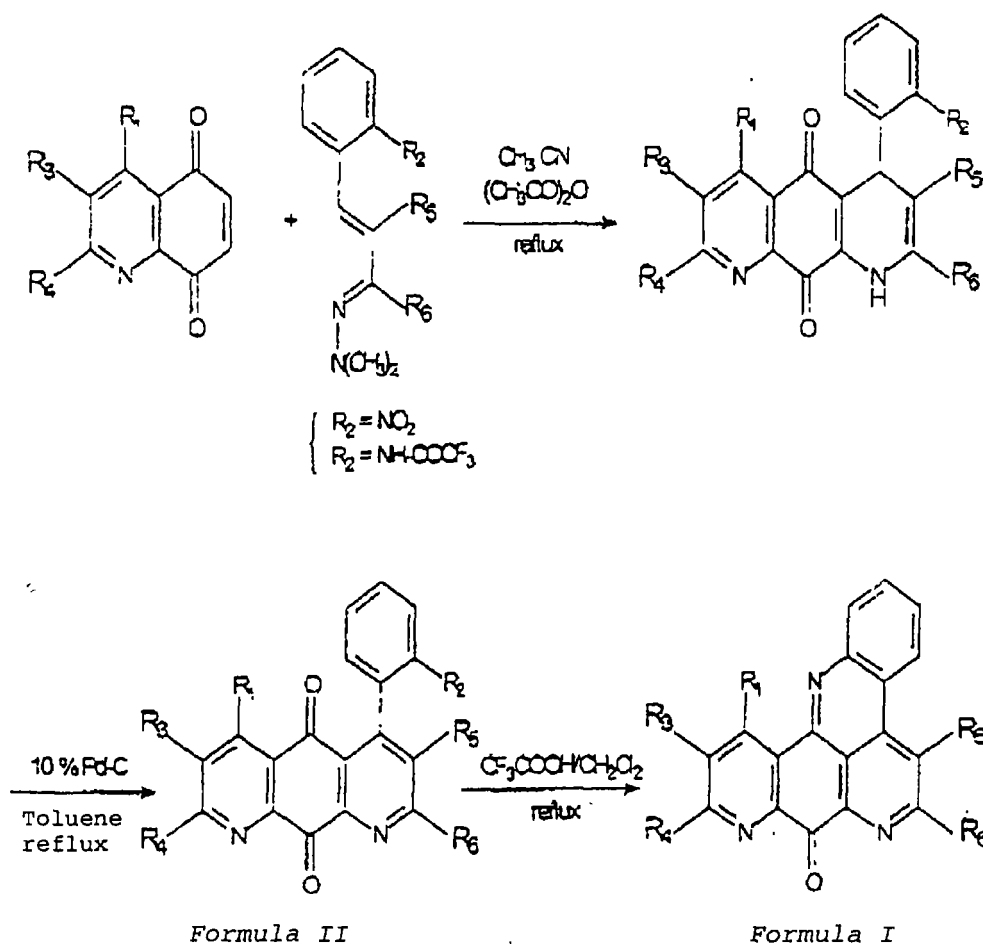
In one preferred embodiment, a subject of the invention
 30 is a pharmaceutical composition comprising an effective
 amount of a compound chosen from the compounds of
 formula I in which R_1 is chosen from hydrogen and
 methoxy and $-\text{N}(\text{CH}_3)_2$ groups and the compounds of
 formula II in which R_1 is chosen from hydrogen and
 35 methoxy, $\text{N}(\text{CH}_3)_2$ and $-\text{NHCOCF}_3$ groups and R_2 is an
 $-\text{NHCOCF}_3$ group, and the addition salts of these
 compounds with pharmaceutically acceptable acids.

In another form, a subject of the invention is a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formula I in which R_3 is a $-\text{COOEt}$ group and the
5 compounds of formula II in which R_3 is a $-\text{COOEt}$ group and R_2 is chosen from $-\text{NHCOCF}_3$ and $-\text{NO}_2$ groups, and the addition salts of these compounds with pharmaceutically acceptable acids.

10 In another form, a subject of the invention is a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formula I in which R_4 is a methoxy group and the compounds of formula II in which R_4 is a methoxy group
15 and R_2 is chosen from $-\text{NHCOCF}_3$ and $-\text{NO}_2$ groups, and the addition salts of these compounds with pharmaceutically acceptable acids.

The expression "addition salts with pharmaceutically
20 acceptable acids" denotes salts which give the biological properties of the free bases, without having an adverse effect. These salts may be, in particular, those formed with mineral acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or
25 phosphoric acid; acidic metal salts, such as disodium orthophosphate and monopotassium sulfate, and organic acids.

In general, the compounds of formulae I and II are
30 obtained according the general reaction scheme described by Kitahara *et al.* (Chem Pharm. Bull 1994; 42: 1363-1364) and Kitahara *et al.* (Tetrahedron 1998; 54: 8421-8432). According to this scheme, the compounds of formula II may be prepared by a hetero Diels-Alder
35 reaction between a quinoline-5,8-dione substituted in position 4 and a substituted aza-diene, followed by dehydrogenation of the intermediate dihydrogenated compound. The compounds of formula I are prepared from the compounds of formula II by cyclization:



5 The examples which follow illustrate the preparation of the compounds of formulae I and II.

EXAMPLE 1:

10 **6-Chloro-4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]-quinoline-5,10-dione**
(CR 8250)

15 1.2 g (4 mmol) of 4-(2-trifluoroacetamidophenyl)-1-dimethylamino-1-aza-1,3-butadiene and 1 mL of acetic anhydride are added to a solution of 0.7 g (3.63 mmol) of 4-chloroquinoline-5,8-dione in 50 mL of CH_3CN . The reaction medium is refluxed for 6 hours and the solvent is evaporated off on a rotary evaporator. After purification by filtration through silica (99.5/0.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), 0.46 g of adduct is obtained. This
20 compound is dissolved in 100 mL of toluene, 4 g of Pd/C

(10%) are added and the reaction medium is refluxed for 2 hours. After filtering and washing the residue with MeOH and then with CH₂Cl₂, the filtrate is concentrated on a rotary evaporator and then purified by flash chromatography on a column of silica (98/2 CH₂Cl₂/MeOH) to give 87 mg of compound CRL 8250 in the form of a golden-yellow powder.

• Yield: 6%.

• Melting point: 152°C.

• ¹H NMR (CDCl₃): 7.21 (d, 1H, J = 9 Hz); 7.46 (dd, 1H, J = 7.5 and 7.5 Hz); 7.58 (m, 2H); 7.72 (m, 2H); 7.81 (s, 1H); 8.94 (d, 1H, J = 5.1 Hz); 9.13 (d, 1H, J = 4.7 Hz).

• ¹³C NMR (CDCl₃): 115.49 (q, J = 287.2 Hz); 125.55; 128.11; 128.27; 129.20; 129.35; 130.16; 131.02; 131.32; 131.52; 133.58; 145.13; 147.57; 148.24; 149.85; 154.35; 154.86; 155.34 (q, J = 37 Hz); 179.28; 182.40.

EXAMPLE 2:

6-Bromo-4-(2-trifluoroacetamidophenyl)pyrido-[3,2-g]quinoline-5,10-dione

1) Synthesis of 4-bromo-5,8-dimethoxyquinoline:

3 g (9.35 mmol) of 5,8-dimethoxy-4-quinolyl triflate and 8.2 g (94.2 mmol) of LiBr are added to 60 mL of dioxane and the mixture is refluxed for 30 min. 200 mL of water are then added and the mixture is extracted with ethyl acetate (3 times 200 mL). The organic phases are dried over MgSO₄ and the solvent is then evaporated off on a rotary evaporator to give 2.3 g of yellow crystals.

- Yield: 91%.
 - Melting point: 86°C.
- 5 • ^1H NMR (CDCl_3): 3.90 (s, 3H); 4.02 (s, 3H); 6.89 (d, 1H, $J = 8.8$ Hz); 6.97 (d, 1H, $J = 8.8$ Hz); 7.71 (d, 1H, $J = 4.4$ Hz); 8.57 (d, 1H, $J = 4.4$ Hz).
- 10 • ^{13}C NMR (CDCl_3): 56.10; 56.26; 107.54; 107.89; 120.49; 128.08; 128.79; 141.81; 148.18; 148.85; 149.44.

2) Synthesis of 4-bromoquinoline-5,8-dione

100 mg (0.373 mmol) of 4-bromo-5,8-dimethoxyquinoline
15 are dissolved in 8 mL of CH_3CN and 4 mL of water at room temperature. 0.6 g (1.11 mmol) of cerium ammonium nitrate (CAN) is added and the mixture is stirred for 30 min. After evaporating off the CH_3CN on a rotary evaporator, 100 mL of water are added and the medium is
20 extracted with CHCl_3 (3 times 100 mL). After drying the organic phases over MgSO_4 and evaporating off the solvent on a rotary evaporator, 83 mg of quinone are obtained in the form of a pinkish powder.

- 25 • Yield: 93%.
- Melting point: 190°C.
- 30 • ^1H NMR (CDCl_3): 7.06 (d, 1H, $J = 10$ Hz); 7.12 (d, 1H, $J = 10$ Hz); 7.93 (d, 1H, $J = 5.2$ Hz), 8.73 (d, 1H, $J = 5.2$). ^{13}C NMR (CDCl_3): 126.71; 132.83; 134.13; 136.89; 139.16; 148.95; 152.88; 181.53; 182.6.
- 35 • ^{13}C NMR (CDCl_3): 126.71; 132.83; 134.13; 136.89; 139.16; 148.95; 152.88; 181.53; 182.6.

3) Synthesis of 6-bromo-4-(2-trifluoroacetamidophenyl)-pyrido[3,2-g]quinoline-5,10-dione

3.6 g (12.6 mmol) of 4-(2-trifluoroacetamidophenyl)-
5 1-dimethylamino-1-aza-1,3-butadiene and 5 g of SiO₂ are
added to a solution of 2 g (8.4 mmol) of
4-bromoquinoline-5,8-dione in 220 mL of CH₃CN. The
reaction medium is refluxed for 10 hours and the
solvent is evaporated off on a rotary evaporator. After
10 purification by flash chromatography on a column of
silica (99.5/0.5 CH₂Cl₂/MeOH), 0.58 g of adduct is
obtained. This compound is dissolved in 21 mL of
toluene, 2.1 g of Pd/C (10%) are added and the reaction
medium is refluxed for 4 hours. After filtering and
15 washing the residue, the filtrate is concentrated on a
rotary evaporator and then purified by flash
chromatography on a column of silica (98/2 CH₂Cl₂/MeOH)
to give 0.19 g of the compound in the form of an orange
powder.

20

- Yield: 5%.

- Melting point: 145°C.

25 • ¹H NMR (CDCl₃): 7.21 (dd, 1H, J = 7.2 and 1.2 Hz);
7.44 (ddd, 1H, J = 7.2 and 7.2 and 1.2 Hz); 7.55
(ddd, 1H, J = 7.2 and 7.2 and 1.2 Hz); 7.57 (d, 1H,
J = 4.8 Hz); 7.69 (dd, 1H, J = 7.2 and 1.2 Hz); 7.91
(d, 1H, J = 4.8 Hz); 8.20 (broad s, 1H); 8.73 (d, 1H,
30 J = 4.8 Hz); 9.05 (d, 1H, J = 4.8 Hz).

• ¹³C NMR (CDCl₃): 115.12 (q, J = 287.1 Hz); 125.41;
127.71; 128.94; 129.30; 129.30; 129.72; 130.91;
131.10; 132.89; 133.31; 134.26; 147.35; 147.79;
35 149.24; 153.44; 154.30; 154.78 (q, J = 36.8 Hz);
178.86; 182.05.

EXAMPLE 3:**6-Nitro-4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]-quinoline-5,10-dione**

5

1) Synthesis of 4-nitro-5,8-dimethoxyquinoline:

1.89 g (8.47 mmol) of 4-chloro-5,8-dimethoxyquinoline, 0.69 g (10.06 mmol) of NaNO₂ and 2.9 g (10.59 mmol) of tetrabutylammonium chloride are dissolved in 50 mL of CH₂Cl₂ and 50 mL of water. The mixture is left stirring at room temperature for 3 days. The organic phase is recovered and the aqueous phase is extracted 3 times with CH₂Cl₂. The organic phases are combined and then dried over MgSO₄. After evaporating off the solvent, the residue is fractionated by flash chromatography on a column of silica (98/2 CH₂Cl₂/MeOH) and 1.2 g of 4-nitro-5,8-dimethoxyquinoline are obtained in the form of a bright yellow powder.

20

- Yield: 60%.

- Melting point: 169°C.

25 • ¹H NMR (CDCl₃): 3.85 (s, 3H); 4.05 (s, 3H); 6.92 (d, 1H, J = 8.8 Hz); 7.07 (d, 1H, J = 8.8 Hz); 7.36 (d, 1H, J = 4.4 Hz); 9.01 (d, 1H, J = 4.4 Hz).

30 • ¹³C NMR (CDCl₃): 56.41; 56.52; 107.61; 108.99; 111.02; 113.69; 141.99; 146.48; 149.31; 149.53; 152.68.

2) Synthesis of 4-nitroquinoline-5,8-dione

35 400 mg (1.71 mmol) of 4-nitro-5,8-dimethoxyquinoline are dissolved in 10 mL of CH₃CN and 5 mL of water at room temperature. 2.8 g (5.2 mmol) of cerium ammonium nitrate are added and the reaction medium is stirred for 15 min. After evaporating off the CH₃CN on a rotary evaporator, 10 mL of water are added and the medium is

extracted with CH_2Cl_2 (3 times 20 mL). After drying the organic phases and evaporating off the solvent on a rotary evaporator, 290 mg of 4-nitroquinoline-5,8-dione are obtained in the form of an orange powder.

5

- Yield: 83%.
- Melting point: 180°C.

- 10 • ^1H NMR (CDCl_3): 7.10 (d, 1H, $J = 10.4$ Hz); 7.23 (d, 1H, $J = 10.4$ Hz), 7.64 (d, 1H, $J = 5.6$ Hz), 9.24 (d, 1H, $J = 5.6$ Hz).
- ^{13}C NMR ($\text{DMSO}-d_6$): 118.49; 120.00; 137.89; 139.26;
- 15 148.83; 152.83; 156.38; 181.07; 182.04.

3) Synthesis of 6-nitro-4-(2-trifluoroacetamidophenyl)-pyrido[3,2-g]quinoline-5,10-dione (CRL 8267)

- 20 1.5 g (7.35 mmol) of 4-nitroquinoline-5,8-dione, 4.2 g (14.7 mmol) of 4-(2-trifluoroacetamidophenyl)-1-dimethylamino-1-aza-1,3-butadiene and 7.5 mL of acetic anhydride in 100 mL of CH_3CN are refluxed for 18 hours. After evaporating off the solvent on a rotary
- 25 evaporator and purifying by flash chromatography on a column of silica (95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), 0.8 g of adduct is obtained. This compound is dissolved in 30 mL of toluene, 2.5 g of Pd/C (10%) are added and the mixture is refluxed for 5 hours. After filtering off and
- 30 washing the residue, the filtrate is concentrated on a rotary evaporator and then purified by flash chromatography on a column of silica (95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 0.4 g of the compound in the form of an beige-colored powder.

35

- Yield: 13%.
- Melting point: 158°C.

- ^1H NMR (CDCl_3): 7.34 (d, 1H, $J = 7.2$ Hz); 7.45 (d, 1H, $J = 7.2$ Hz); 7.54 (m, 2H); 7.69 (d, 1H, $J = 4.4$ Hz); 7.77 (d, 1H, $J = 4.4$ Hz); 8.04 (s, 1H); 9.18 (d, 1H, $J = 4.4$ Hz); 9.32 (d, 1H, $J = 4.4$ Hz).

5

- ^{13}C NMR (CDCl_3): 115.41 (q, $J = 287$ Hz); 120.85; 122.58; 126.51; 128.16; 129.25; 129.33; 130.39; 130.64; 131.42; 134.24; 148.11; 148.18; 149.11; 154.51; 155.21 (q, 37 Hz); 155.77; 157.13; 177.79; 180.54.

10

EXAMPLE 4:**4-(2-Trifluoroacetamidophenyl)pyrido[3,2-g]quinoline-
5,10-dione (CRL 8277)**

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1 g (6.3 mmol) of quinoline-5,8-dione, 3.59 g (12.6 mmol) of 4-(2-trifluoroacetamidophenyl)-1-dimethylamino-1-aza-1,3-butadiene and 7.5 mL of acetic anhydride in 175 mL of CH_3CN are refluxed for 24 hours. After evaporating off the solvent on a rotary evaporator and purifying by filtration on silica (95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), the adduct is obtained. This compound is dissolved in 150 mL of toluene, 6.2 g of Pd/C (10%) are added and the reaction medium is refluxed for 12 hours. After filtering off and washing the residue with MeOH and then with CHCl_3 , the filtrate is concentrated on a rotary evaporator and then purified by flash chromatography on a column of silica (95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 0.125 g of compound CRL 8277 in the form of a yellow powder.

20

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30

- Yield: 5%.

- Melting point: 205°C.

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- ^1H NMR (CDCl_3): 7.20 (dd, 1H, $J = 8$ and 1.2 Hz); 7.46 (ddd, 1H, $J = 8$ and 8 and 1.2 Hz); 7.58 (d, 1H, $J = 4.4$ Hz); 7.59 (ddd, 1H, $J = 8$ and 8 and 1.2 Hz); 7.74

(m, 3H); 8.42 (dd, 1H, $J = 8$ and 1.6 Hz); 9.14 (dd, 1H, 4.4 and 1.6 Hz); 9.16 (d, 1H, $J = 4.4$ Hz).

- ^{13}C NMR (CDCl_3): 115.46 (q, $J = 291$ Hz); 125.26;
5 127.45; 127.94; 128.54; 129.01; 129.99; 130.49;
131.15; 131.50; 133.90; 135.57; 147.84; 147.99;
149.68; 154.93; 155.39 (q, $J = 40$ Hz); 155.86;
179.66; 183.19.

10 **EXAMPLE 5:**

**6-Methoxy-4-(2-trifluoroacetamidophenyl)pyrido-
[3,2-g]quinoline-5,10-dione (CRL 8275)**

15 3.5 g (16 mmol) of 4-methoxyquinoline-5,8-dione, 7 g
(24 mmol) of 4-(2-trifluoroacetamidophenyl)-1-dimethyl-
amino-1-aza-1,3-butadiene and 15 mL of acetic anhydride
in 200 mL of CH_3CN are refluxed for 18 hours. After
evaporating off the solvent on a rotary evaporator and
20 purifying by filtration through silica (99.5/0.5
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), 3 g of adduct are obtained. This compound
is dissolved in 150 mL of toluene, 6 g of Pd/C (10%)
are added and the reaction medium is refluxed
overnight. After filtering off and washing the residue
25 with MeOH and then with CHCl_3 , the filtrate is
concentrated on a rotary evaporator and then purified
by flash chromatography on a column of silica (95/5
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 0.6 g of the compound in the form
of a pale green powder.

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- Yield: 9%.
- Melting point: 158°C.
- 35 • ^1H NMR (CDCl_3): 4.04 (s, 3H); 7.22 (d, 1H, $J = 6$ Hz);
7.24 (dd, 1H, $J = 1.6$ and 7.6 Hz); 7.46 (dd, 1H, $J =$
7.6 and 7.2 Hz); 7.56 (d, 1H, $J = 4.8$ Hz); 7.60 (dd,
1H, $J = 7.6$ and 7.2 Hz); 7.79 (d, 1H, $J = 8.4$ Hz);
7.97 (s, 1H); 8.95 (d, 1H, $J = 6$ Hz); 9.13 (d, 1H,

J = 5.2 Hz)

- ^{13}C NMR (CDCl_3): 65.84; 111.53; 115.34 (q, J = 305 Hz); 120.60; 125.44; 127.82; 129.09; 129.46; 129.80; 131.28; 131.70; 133.83; 147.15; 148.22; 150.08; 154.29; 155.09 (q, 42 Hz); 156.07; 165.95; 180.26; 183.00.

EXAMPLE 6:

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6-(Dimethylamino)-4-(2-trifluoroacetamidophenyl)pyrido-[3,2-g]quinoline-5,10-dione (CRL 8426)

Dimethylamine hydrochloride (0.37 g; 4.6 mmol) and NaOH (0.18 g; 4.6 mmol) are successively added to a solution of the chloro compound CRL 8250 (0.5 g; 1.15 mmol) in water (12 mL) and THF (25 mL). The reaction medium is heated at 60°C for 3 hours. After concentrating on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (98/2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give, successively, 40 mg of compound CRL 8427 and 70 mg of compound CRL 8426. The compound CRL 8426 is obtained in the form of an orange powder and is characterized by:

25

- Yield: 14%.

- Melting point: 150°C.

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- IR(KBr): 3175; 1724; 1701; 1654 cm^{-1} .

- MS: m/z 440 (100); 353 (15); 69 (84).

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- ^1H NMR (CDCl_3): 2.75 (s, 6H); 6.94 (d, 1H, J = 6 Hz); 7.07 (dd, 1H, J = 7.7 and 1.5 Hz); 7.32 (ddd, 1H, J = 7.7, 7.7 and 0.7 Hz); 7.49 (d, 1H, J = 5 Hz); 7.55 (ddd, 1H, J = 7.7, 7.7 and 1.7 Hz); 7.85 (d, 1H, J = 7.7 Hz); 8.29 (broad s, 1H); 8.55 (d, 1H, J = 6 Hz); 9.05 (d, 1H, J = 5 Hz).

- ^{13}C NMR (CDCl_3): 43.21; 112.58; 115.58 (q, $J = 287$ Hz); 119.13; 125.29; 126.72; 129.03; 129.60; 130.30; 131.13; 132.77; 133.28; 146.18; 147.82; 149.71; 151.05; 153.28; 154.76; 155.76 (q, $J = 37$ Hz); 180.48; 183.96.

EXAMPLE 7:**10 6-(Acetamido)-4-(2-trifluoroacetamidophenyl)pyrido-[3,2-g]quinoline-5,10-dione (CRL 8428)****1) Synthesis of 4-azido-5,8-dimethoxyquinoline**

15 16.7 g of NaN_3 are added to a solution of 10 g (44.7 mmol) of 4-chloro-5,8-dimethoxyquinoline in a DMF/ H_2O mixture (160 mL/60 mL). The reaction medium is heated at 90°C for 2 h 30 min. After cooling, the mixture is hydrolyzed with 500 mL of saturated NH_4Cl solution and is extracted with CHCl_3 (3 times 150 mL). After drying over MgSO_4 , the organic phases are concentrated on a rotary evaporator and the DMF is then removed under vacuum (2 mmHg). 8.7 g of azide are obtained in the form of a brown powder.

25

- Yield: 85%.
- Melting point: 106°C .
- 30 • ^1H NMR (CDCl_3): 3.86 (s, 3H); 3.95 (s, 3H); 6.75 (d, 1H, $J = 8.6$ Hz); 6.89 (d, 1H, $J = 8.6$ Hz); 7.10 (d, 1H, $J = 4.8$ Hz); 8.72 (d, 1H, $J = 4.8$ Hz).
- ^{13}C NMR (CDCl_3): 55.77; 56.50; 106.44; 107.49; 110.76; 35 114.20; 142.25; 145.45; 148.82; 148.96; 149.13.

2) Synthesis of 4-amino-5,8-dimethoxyquinoline

12 g (45.8 mmol) of triphenylphosphine are added in a

single portion to a solution of 8.7 g (37.8 mmol) of 4-azido-5,8-dimethoxyquinoline in a THF/H₂O mixture (110 mL/110 mL). The reaction medium is stirred at ambient temperature for 2 hours and then concentrated on a rotary evaporator. The residue is acidified with 200 mL of 1N HCl and extracted with ether (3 times 500 mL). The aqueous phase is then basified with 250 mL of 1N NaOH and re-extracted with CHCl₃ (3 times 250 mL). After drying over MgSO₄ and evaporating off the solvent on a rotary evaporator, the expected amine is obtained quantitatively in the form of brown powder, which decomposes before melting.

- ¹H NMR (CDCl₃): 3.86 (s, 3H); 3.94 (s, 3H); 5.93 (broad s, 2H); 6.39 (d, 1H, J = 5.2 Hz); 6.55 (d, 1H, J = 8.8 Hz); 7.77 (d, 1H, J = 8.8 Hz); 8.36 (d, 1H, J = 5.2 Hz).
- ¹³C NMR (CDCl₃): 55.77; 55.80; 102.22; 104.73; 106.32; 111.14; 142.45; 149.48; 149.55; 150.81; 152.09.

3) Synthesis of 4-acetamido-5,8-dimethoxyquinoline

A suspension of 3 g (14.7 mmol) of 4-amino-5,8-dimethoxyquinoline and of 0.72 g (5.88 mmol) of DMAP in 30 mL of acetic anhydride is stirred at ambient temperature for 24 hours. After concentrating on a rotary evaporator, the reaction medium is washed with 40 mL of saturated NaHCO₃ solution and then extracted with CHCl₃ (3 times 50 mL). The extracts are dried over MgSO₄ and the solvent is evaporated off, followed by evaporation of the remaining acetic anhydride by azeotropic entrainment with benzene. 2.7 g of the expected derivative are obtained in the form of a yellow powder.

- Yield: 74%.
- Melting point: 152°C.

- ^1H NMR (CDCl_3): 2.26 (s, 3H); 4.03 (s, 6H); 6.81 (d, 1H, $J = 8.4$ Hz); 6.90 (d, 1H, $J = 8.4$ Hz); 8.62 (d, 1H, $J = 4.8$ Hz); 8.78 (d, 1H, $J = 4.8$ Hz); 10.86 (broad s, 1H).

- ^{13}C NMR (CDCl_3): 14.15; 44.29; 44.91; 93.65; 94.89; 98.22; 99.96; 129.73; 131.69; 137.16; 138.35; 138.57; 157.42.

10

4) Synthesis of 4-acetamidoquinoline-5,8-dione

22 g (40.1 mmol) of cerium ammonium nitrate are added, at 0°C , to a solution of 5 g (20.3 mmol) of 4-acetamido-5,8-dimethoxyquinoline in a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ mixture (50 mL/50 mL). The reaction medium is stirred for 1 h 45 min and is then basified with 500 mL of saturated NaHCO_3 solution. 200 mL of H_2O are added and the mixture is extracted with CHCl_3 (3 times 500 mL). After drying over MgSO_4 and evaporating off the solvent, 3.4 g of expected product are obtained in the form of a brown-yellow powder, which is used rapidly for the following step since the product is unstable.

- Yield: 77%.

- ^1H NMR (CDCl_3): 2.28 (s, 3H); 6.97 (d, 1H, $J = 10.4$ Hz); 7.08 (d, 1H, $J = 10.4$ Hz); 8.83 (d, 1H, $J = 5.6$ Hz); 8.88 (d, 1H, $J = 5.6$ Hz); 11.75 (broad s, 1H).

30

- ^{13}C NMR (CDCl_3): 26.00; 114.40; 117.75; 138.41; 139.31; 147.34; 148.60; 155.73; 170.53; 182.96; 189.75.

35

5) Synthesis of 6-(acetamido)-4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8248)

5 g (17.5 mmol) of 4-(2-trifluoroacetamidophenyl)-

1-dimethylamino-1-aza-1,3-butadiene, 6 mL of acetic anhydride and 4.4 g of Pd/C (10%) are successively added to a solution of 4-acetamidoquinoline-5,8-dione (3.4 g, 15.7 mmol) in 270 mL of acetonitrile. The
5 reaction medium is refluxed for 15 hours under nitrogen. After evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (CHCl₃ and then 98/2 CHCl₃/MeOH) to give a powder which is then washed with
10 hot ether. 80 mg of CRL 8248 are obtained in the form of a brown powder.

- Yield: 1%.
- 15 • Melting point: > 260°C.
- IR(CHCl₃): 3410; 3277; 1719; 1707; 1702.
- MS: m/z 454 (9); 412 (7); 343 (100); 300 (17).
- 20 • ¹H NMR (CDCl₃): 2.23 (s, 3H); 7.25 (dd, 1H, J = 7.7 and 1.5 Hz); 7.48 (ddd, 1H, J = 7.3, 7.7 and 1.1 Hz); 7.53 (dd, 1H, J = 4.8 Hz); 7.60 (ddd, 1H, J = 7.7, 7.3 and 1.5 Hz); 7.78 (d, 1H, J = 7.3 Hz); 7.93
25 (broad s, 1H); 8.86 (d, 1H, J = 5.7 Hz); 8.93 (d, 1H, J = 5.7 Hz); 9.08 (d, 1H, J = 4.8 Hz).
- ¹³C NMR (CDCl₃): 25.20; 115.63 (q, J = 288 Hz); 115.93; 116.66; 126.61; 127.86; 128.75; 129.11;
30 129.28; 131.31; 131.62; 134.87; 146.17; 146.82; 148.33; 149.60; 154.30; 154.82; 154.94 (q, J = 36 Hz); 170.13; 179.34; 186.80.

EXAMPLE 8:

35

8-Hydroxy-4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]-quinoline-5,10-dione (CRL 8429)

1.9 g (6.5 mmol) of 4-(2-trifluoroacetamidophenyl)-1-

dimethylamino-1-aza-1,3-butadiene, 2.2 mL of acetic anhydride and 1.6 g of Pd/C (10%) are successively added to a solution of 5,8-dioxocarbostyryl (1.04 g, 5.9 mmol) in 500 mL of acetonitrile. The reaction medium is refluxed for 15 hours under nitrogen. After evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (CH₂Cl₂ and then 95/5 CH₂Cl₂/MeOH) to give 400 mg of a yellow powder of compound CRL 8249 (or of its oxo tautomer in position 8).

- Yield: 16%.

- Melting point: > 260°C.

- IR(CHCl₃): 1664, 1685, 1735, 3334, 3401 cm⁻¹.

- MS: m/z 413 (33); 344 (17); 301 (100); 177 (44).

- ¹H NMR (CDCl₃): 6.90 (dd, 1H, J = 9.9 Hz); 7.19 (dd, 1H, J = 7.8 and 1.5 Hz); 7.47 (ddd, 1H, J = 7.8, 7.8 and 1.1 Hz); 7.60 (m, 2H); 7.68 (m, 2H); 7.93 (d, 1H, J = 9.9 Hz); 9.09 (d, 1H, J = 4.8 Hz).

- ¹³C NMR (CDCl₃): 115.56 (q, J = 288 Hz); 126.34; 126.90; 127.08; 128.69; 129.12; 130.89; 134.61; 135.63; 146.85; 148.02; 150.56; 151.70; 152.83; 154.92; 155.57 (q, J = 38 Hz); 161.92; 169.63; 179.50; 181.13.

EXAMPLE 9:

8-Methoxy-4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]-quinoline-5,10-dione (CRL 8455)

2 mL (31.8 mmol) of methyl iodide and 500 mg (1.8 mmol) of Ag₂CO₃ are added to 400 mg (0.97 mmol) of compound CRL 8429 dissolved in 100 mL of CHCl₃. The mixture is

stirred in the absence of light and at ambient temperature for 60 hours. After evaporating off the solvent, the crude product obtained is purified by flash chromatography (CH₂Cl₂) to give 52 mg of compound 5 CRL 8455 in the form of a yellow powder.

- Yield: 11%.

- Melting point: > 260°C.

- IR(CHCl₃): 1602, 1669, 1701, 1737, 3404 cm⁻¹.

- MS: m/z 427 (17); 426 (30); 357 (14); 315 (74); 314 (100); 286 (7); 177 (23).

- ¹H NMR (CDCl₃): 4.19 (s, 3H); 7.06 (d, 1H, J = 8.8 Hz); 7.20 (dd, 1H, J = 7.3 and 1.1 Hz); 7.44 (dd, 1H, J = 8.1 and 7.0 Hz); 7.53 (d, 1H, J = 5.0 Hz); 7.57 (ddd, 1H, J = 7.3, 7.0 and 1.1 Hz); 7.74 (d, 1H, J = 8.1 Hz); 7.93 (broad s, 1H); 8.19 (d, 1H, J = 8.8 Hz); 9.09 (d, 1H, J = 5.0 Hz).

- ¹³C NMR (CDCl₃): 55.06; 115.02; 115.56 (q, J = 276 Hz); 117.80; 125.22; 125.68; 127.80; 128.95; 129.76; 130.94; 131.58; 134.23; 137.53; 147.47; 147.55; 149.65; 154.30; 155.41 (q, J = 38 Hz); 167.73; 179.60; 182.71.

EXAMPLE 10:

Ethyl 4-(2-trifluoroacetamidophenyl)-5,10-dioxopyrido-[3,2-g]quinoline-7-carboxylate (CRL 8454)

1) Synthesis of ethyl 5,8-dioxoquinoline-3-carboxylate

7.4 g of cerium ammonium nitrate are added at ambient temperature to a solution of 1 g (3.83 mmol) of ethyl 5,8-dimethoxyquinoline-3-carboxylate in a CH₃CN/H₂O mixture (45 mL/23 mL). The reaction medium is stirred

for 1 hour and the acetonitrile is then evaporated off. The medium is basified by adding 17 mL of saturated NaHCO₃ solution. 60 mL of H₂O are added and this mixture is then extracted with CH₂Cl₂ (3 times 100 mL). After
5 drying over MgSO₄ and evaporating off the solvent, 0.8 g of ethyl 5,8-dioxoquinoline-3-carboxylate is obtained.

• Yield: 91%.

10

• Melting point: 124°C.

• ¹H NMR (CDCl₃): 1.45 (t, 3H; J = 7.3 Hz); 4.49 (q, 2H, J = 7.3 Hz); 7.13 (d, 1H, J = 10.4 Hz); 7.22 (d, 1H, J = 10.4 Hz); 8.99 (d, 1H, J = 2.2 Hz); 9.58 (d, 1H, J = 2.2 Hz).

15

• ¹³C NMR (CDCl₃): 14.22; 62.48; 128.62; 129.86; 135.98; 138.29; 139.33; 149.14; 155.17; 163.44; 182.40; 183.63.

20

2) Synthesis of ethyl 4-(2-trifluoroacetamidophenyl)-5,10-dioxopyrido[3,2-g]quinoline-7-carboxylate (CRL 8454)

25

0.61 g (2.14 mmol) of 4-(2-trifluoroacetamidophenyl)-1-dimethylamino-1-aza-1,3-butadiene and then 1.4 mL of acetic anhydride are successively added to a solution of ethyl 5,8-dioxoquinoline-3-carboxylate (0.45 g, 1.94 mmol) in 50 mL of acetonitrile. The reaction
30 medium is refluxed for 24 hours under nitrogen. After evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (CH₂Cl₂, and then 98/2 CH₂Cl₂/MeOH) to remove the unreacted starting materials.
35 After concentrating the other fractions obtained, 20 mL of chloroform and 630 mg of MnO₂ are added thereto. The mixture is stirred for 3 hours and a second filtration through silica (CH₂Cl₂) is performed to give the

compound CRL 8454 in the form of a brown powder (27 mg).

• Yield: 3%.

5

• Melting point: 124°C.

• IR(CHCl₃): 1681, 1709, 1730, 3401 cm⁻¹.

10 • MS: m/z 469 (17); 468 (6); 357 (100); 356 (81); 329 (17); 328 (6).

15 • ¹H NMR (CDCl₃): 1.42 (t, 3H, J = 7 Hz); 4.45 (q, 2H, J = 7 Hz); 7.22 (dd, 1H, J = 7.7 and 1.5 Hz); 7.47 (ddd, 1H, J = 7.7, 7.7 and 0.8 Hz); 7.61 (ddd, 1H, J = 7.7, 7.7 and 1.5 Hz); 7.63 (d, 1H, J = 4.8 Hz); 7.68 (broad s, 1H); 7.74 (d, 1H, J = 8.1 Hz); 9.00 (d, 1H, J = 1.9 Hz); 9.20 (d, 1H, J = 4.8 Hz); 9.65 (d, 1H, J = 1.9 Hz).

20

• ¹³C NMR (CDCl₃): 14.11; 62.56; 115.46 (q, J = 287 Hz); 125.73; 127.50; 127.99; 129.01; 129.97 (2); 130.23; 131.27; 131.43; 134.16; 136.91 (2); 148.32; 149.53; 154.88; 155.57 (q, J = 38 Hz); 155.76; 163.11; 25 179.05; 182.10.

EXAMPLE 11:

30 **6-Chloro-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8296)**

This compound was synthesized according to the process described by Kitahara et al., Tetrahedron, 1998, 54, 8421-8432.

35

EXAMPLE 12:

6-Methoxy-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8243)

5

This compound was synthesized according to the process described by Kitahara et al., Tetrahedron, 1998, 54, 8421-8432.

10 **EXAMPLE 13:**

6-Amino-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8300)

15 This compound was synthesized according to the process described by Kitahara et al., Tetrahedron, 1998, 54, 8421-8432.

EXAMPLE 14:

20

8-Hydroxy-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8456)

2.06 g (9.42 mmol) of 4-(2-nitrophenyl)-1-dimethyl-
25 amino-1-aza-1,3-butadiene and 8.2 mL of acetic anhydride are successively added to a solution of 5,8-dioxocarbostyryl (1.5 g, 8.56 mmol) in 300 mL of acetonitrile. The reaction medium is refluxed for 85 hours under nitrogen. After evaporating off the
30 solvent on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (CH₂Cl₂ and then 99/1 CH₂Cl₂/MeOH) to give 205 mg of a yellow powder of the compound CRL 8456 (or of its oxo tautomer in position 8).

35

- Yield: 7%.
- Melting point: > 260°C.

- IR(CHCl₃): 1666, 1687 cm⁻¹.
 - MS: m/z 301 (100; M-NO₂); 273 (21); 261 (25).
- 5 • ¹H NMR (DMSO-d₆): 6.71 (d, 1H, J = 9.0 Hz); 7.35 (d, 1H, J = 7.7 Hz); 7.70 (d, 1H, J = 5.0 Hz); 7.74 (ddd, 1H, J = 7.7; 6.6 and 0.9 Hz); 7.81 (d, 1H, J = 9.0 Hz); 7.85 (ddd, 1H, J = 7.7; 6.6 and 0.9 Hz); 8.29 (d, 1H, J = 7.7 Hz); 9.06 (d, 1H, J = 5.0 Hz).
- 10 • ¹³C NMR (DMSO-d₆): 114.02; 114.46; 122.55; 124.12; 125.79; 129.12; 129.82; 130.23; 134.13; 135.53; 146.44; 147.80; 148.05; 153.20; 165.33; 175.50; 180.30 (1 C not observed).

15

EXAMPLE 15:**8-Methoxy-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-5,10-dione (CRL 8457)**

20

1.2 mL (19.27 mmol) of methyl iodide and 158 mg (1.8 mmol) of Ag₂CO₃ are added to 100 mg (0.288 mmol) of the compound CRL 8456 dissolved in 75 mL of CHCl₃. The mixture is stirred in the absence of light at 50°C for 25 48 hours. After evaporating off the solvent, the crude product obtained is purified by flash chromatography (CH₂Cl₂) to give 56 mg of the compound CRL 8457 in the form of a yellow powder.

30

- Yield: 54%.
- Melting point: > 260°C.
- IR(CHCl₃): 1670, 1701 cm⁻¹.

35

- MS: m/z 361 (2); 315 (42); 314 (100); 286 (32); 257 (7); 188 (15).
- ¹H NMR (CDCl₃): 4.21 (s, 3H); 7.06 (d, 1H, J =

8.8 Hz); 7.27 (dd, 1H, J = 7.5 and 1.5 Hz); 7.45 (d, 1H, J = 4.8 Hz); 7.69 (ddd, 1H, J = 1.5; 8.2 and 7.5 Hz); 7.77 (ddd, 1H, J = 7.5; 8.2 and 1.1 Hz); 8.20 (d, 1H, J = 8.4 Hz); 8.34 (dd, 1H, J = 8.2 and 1.1 Hz); 9.14 (d, 1H, J = 4.8 Hz).

• ^{13}C NMR (CDCl_3): 55.00; 117.62; 124.77; 125.53; 126.64; 128.51; 129.40; 129.85; 133.93; 135.03; 137.64; 146.82; 147.68; 149.25; 149.43; 154.24; 167.63; 179.85; 182.07.

EXAMPLE 16:

Ethyl 4-(2-nitrophenyl)-5,10-dioxopyrido[3,2-g]-quinoline-7-carboxylate (CRL 8453)

0.33 g (1.47 mmol) of 4-(2-nitrophenyl)-1-dimethylamino-1-aza-1,3-butadiene and 1.4 mL of acetic anhydride are successively added to a solution of ethyl 5,8-dioxoquinoline-3-carboxylate (0.3 g, 1.29 mmol) in 50 mL of acetonitrile. The reaction medium is refluxed for 64 hours under nitrogen. After evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (CH_2Cl_2 and then 98/2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give the compound CRL 8453 in the form of a brown powder (53 mg).

- Yield: 10%.
- Melting point: the product decomposes.
- IR(CHCl_3): 1680, 1706, 1728 cm^{-1} .
- MS: m/z 357 (100); 356 (85); 329 (17); 328 (8).
- ^1H NMR (CDCl_3): 1.41 (t, 3H, J = 7 Hz); 4.44 (q, 2H, J = 7 Hz); 7.28 (dd, 1H, J = 7.7 and 1.5 Hz); 7.54 (d, 1H, J = 4.8 Hz); 7.72 (dd, 1H, J = 8.0 and

1.5 Hz); 7.80 (ddd, 1H, $J = 7.7, 8.0$ and 1.5 Hz);
8.37 (dd, 1H, $J = 8.0$ and 1.5 Hz); 8.97 (d, 1H, $J =$
2 Hz); 9.21 (d, 1H, $J = 4.8$ Hz); 9.65 (d, 1H, $J =$
2 Hz).

5

- ^{13}C NMR (CDCl_3): 14.19; 62.49; 124.91; 127.08; 128.93;
129.74; 129.78; 129.82; 130.23; 134.13; 134.45;
137.05; 146.80; 149.40; 149.85; 149.88; 155.11;
155.99; 163.26; 179.28; 181.96.

10

EXAMPLE 17:

12-Chlorobenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one (CRL 8242)

15

A suspension of 100 mg (0.274 mmol) of the compound of
Example 11 and 200 mg (10 equivalents) of zinc powder
in 3 mL of glacial acetic acid is stirred at ambient
temperature for 2 h 30 min. The reaction medium is
20 poured into 50 mL of saturated NaHCO_3 solution
containing 4 g of CAN; the mixture is stirred for 5 min
and then extracted with CHCl_3 (3 times 50 mL). After
drying the organic phases over MgSO_4 and evaporating
off the solvent on a rotary evaporator, the residue
25 obtained is chromatographed on a column of silica (97/3
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 83 mg of compound in the form of
yellow crystals.

30

- Yield: 95%.
- Melting point: $> 260^\circ\text{C}$.
- ^1H NMR (CDCl_3): 7.77 (d, 1H, $J = 4.8$ Hz); 7.80 (dd,
1H, $J = 8$ and 8 Hz); 7.89 (dd, 1H, $J = 8$ and 8 Hz);
35 8.25 (d, 1H, $J = 8$ Hz); 8.51 (d, 1H, $J = 8$ Hz); 8.61
(d, 1H, $J = 5.6$ Hz); 8.84 (d, 1H, $J = 4.8$ Hz); 9.28
(d, 1H, $J = 5.6$ Hz).
- ^{13}C NMR (CDCl_3): 118.06; 120.19; 129.79; 122.65;

129.42; 129.95; 131.66; 131.77; 132.01; 137.88;
144.71; 145.78; 147.01; 149.77; 150.27; 151.22;
176.83; 179.88.

5 **EXAMPLE 18:**

12-Nitrobenzo[*b*]pyrido[4,3,2-*de*][1,7]phenanthroline-8-one (CRL 8273)

10 365 mg (0.826 mmol) of the compound of Example 3 and
2 mL of trifluoroacetic acid in 20 mL of CH₂Cl₂ are
refluxed for 3 hours. After evaporating off the solvent
on a rotary evaporator, the residue is taken up in
20 mL of 1N NaOH and 20 mL of CHCl₃ and the reaction
15 medium is stirred overnight. The organic phase is
recovered and the aqueous phase is extracted with CHCl₃
(5 times 20 mL). After drying the organic phases over
MgSO₄ and evaporating off the solvent on a rotary
evaporator, the residue is purified by flash
20 chromatography on a column of RP8 grafted silica (60/40
MeOH/H₂O) to give 135 mg of compound in the form of
pale orange-yellow crystals.

• Yield: 50%.

25

• Melting point: > 260°C.

• ¹H NMR (CDCl₃): 7.26 (d, 1H, J = 5.6 Hz); 7.87 (ddd,
1H, J = 8.4 and 8.4 and 1.2 Hz); 7.97 (ddd, 1H, J =
30 8.4 and 8.4 and 1.2 Hz); 8.23 (dd, 1H, J = 8.4 and
1.2 Hz); 8.64 (dd, 1H, J = 8.4 and 1.2 Hz); 8.67 (d,
1H, J = 5.6 Hz); 8.79 (d, 1H, J = 5.6 Hz); 9.39 (d,
1H, J = 5.6 Hz).

35 • ¹³C NMR (CDCl₃): 116.47; 116.96; 117.65; 119.76;
121.70; 123.32; 129.31; 129.63; 132.56; 137.88;
142.46; 147.52; 148.85; 151.53; 152.11; 153.68;
167.23; 180.33.

EXAMPLE 19:**Benzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one
(CRL 8299)**

5

30 mg (0.0756 mmol) of the compound of Example 4 and 1 mL of trifluoroacetic acid in 2 mL of CH₂Cl₂ are refluxed for 3 hours. After evaporating off the solvent on a rotary evaporator, the residue is taken up in 2 mL of 1N NaOH and 2 mL of CHCl₃ and the mixture is stirred overnight. After recovering the organic phase, the aqueous phase is extracted with CHCl₃ (5 times 10 mL). After drying the organic phases over MgSO₄ and evaporating off the solvent on a rotary evaporator, 17 mg of compound are obtained in the form of yellow-colored crystals.

- Yield: 80%.
- Melting point: > 260°C.
- ¹H NMR (CDCl₃): 7.94 (dd, 1H, J = 4.4 and 8 Hz); 7.97 (dd, 1H, J = 8.2 and 8.2 Hz); 8.10 (dd, 1H, J = 8.2 and 8.2 Hz); 8.48 (d, 1H, J = 8.2 Hz); 8.76 (d, 1H, J = 8.2 Hz); 8.80 (d, 1H, J = 5.2 Hz); 9.23 (dd, 1H, J = 1.6 and 4.4 Hz); 9.49 (d, 1H, J = 5.2 Hz); 9.50 (dd, 1H, J = 1.6 and 8 Hz).
- ¹³C NMR (CDCl₃): 118.06; 119.82; 121.88; 123.02; 128.07; 129.33; 131.44; 131.98; 132.98; 134.17; 138.08; 145.62; 147.27; 147.50; 147.76; 150.46; 153.18; 180.94.

35

EXAMPLE 20:**12-Methoxybenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one (CRL 8276)**

This compound was synthesized according to the process

described by Kitahara et al., Tetrahedron, 1998, 54, 8421-8432.

EXAMPLE 21:

5

12-Bromobenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one trifluoroacetate (CRL 8259)

200 mg (0.42 mmol) of the compound of Example 2 and 3
10 drops of trifluoroacetic acid in 50 mL of CH₂Cl₂ are refluxed for 30 min. After evaporating off the solvent on a rotary evaporator, the residue is purified by flash chromatography on RP8 grafted silica (50/50 MeOH/H₂O) to give 130 mg of compound CRL 8259 in the
15 form of orange-colored crystals.

• Yield: 65%.

• ¹H NMR (DMSO-d₆): 6.66 (m, 1H); 7.35 (d, 1H, J =
20 7.2 Hz); 7.43 (m, 2H); 7.51 (d, 1H, J = 8 Hz); 7.54 (d, 1H, J = 5.2 Hz); 7.97 (m, 1H); 8.99 (d, 1H, J = 5.2 Hz); 10.9 (s, 1H).

• ¹³C NMR (DMSO-d₆): 115.66 (q, J = 287.1 Hz); 118.30;
25 124.28; 126.48; 127.36; 128.53; 128.71; 129.31; 131.38; 131.49; 135.91; 147.11; 147.40; 152.83; 154.88 (q, J = 36.6 Hz); 178.87 (4 C are not observed).

30 **EXAMPLE 22:**

12-Nitrobenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one trifluoroacetate (CRL 8258)

35 150 mg (0.34 mmol) of the compound of Example 3 and 8 drops of trifluoroacetic acid are dissolved in 10 mL of CH₂Cl₂ and the mixture is refluxed for 3 hours. After evaporating off the solvent on a rotary evaporator, the residue obtained is purified by flash chromatography on

RP8 grafted silica (60/40 MeOH/H₂O) to give 123 mg of compound CRL 8258 in the form of dark orange-yellow crystals.

5 • Yield: 82%.

• Melting point: > 260°C.

10 • ¹H NMR (DMSO-d₆): 6.65 (m, 1H); 7.47 (d, 1H, J = 8 Hz); 7.20 (m, 2H); 7.54 (d, 1H, J = 8 Hz); 7.57 (d, 1H, J = 4.8 Hz); 8.00 (m, 1H); 9.02 (d, 1H, J = 4.8 Hz); 10.90 (s, 1H).

15 • ¹³C NMR (DMSO-d₆): 115.66 (q, J = 287 Hz); 118.27; 122.18; 122.24; 126.48; 127.36; 128.53; 128.71; 129.31; 131.40; 131.47; 135.91; 147.13; 147.38; 152.85; 154.88 (q, J = 36.6 Hz); 178.85; (3 C are not observed).

20 **EXAMPLE 23:**

12-Dimethylaminobenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one (CRL 8427)

25 40 mg of CRL 8427 were obtained in the form of a red powder according to the process described in Example 6.

• Yield: 11%.

30 • Melting point: 238°C.

• IR(KBr): 1690 cm⁻¹.

• MS: m/z 326 (44); 311 (100); 254 (14).

35

• ¹H NMR (CDCl₃): 3.10 (s, 6H); 7.10 (d, 1H, J = 5.5 Hz); 7.73 (dd, 1H, J = 6.8 and 6.8 Hz); 7.87 (dd, 1H, J = 6.8 and 6.8 Hz); 8.22 (d, 1H, J = 6.8 Hz); 8.54 (m, 2H); 8.59 (d, 1H, 5.5 Hz); 9.26 (d, 1H, J =

5.2 Hz).

- ^{13}C NMR (CDCl_3): 44.07; 113.72; 117.93; 119.68; 120.41; 122.89; 128.44; 130.47; 131.74; 137.82; 145.29; 146.53; 149.38; 150.06; 150.32; 151.18; 156.85; 181.72 (1 C not observed).

EXAMPLE 24:

10 10-Hydroxybenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one (CRL 8432)

22 mL of 1N NaOH are added to 180 mg (0.44 mmol) of compound CRL 8429 (Example 8) dissolved in 70 mL of CHCl_3 . The reaction medium is stirred overnight. After neutralization with acetic acid, the organic phase is recovered and the aqueous phase is extracted with a 95/5 $\text{CHCl}_3/\text{MeOH}$ mixture (3 times 50 mL). After drying over MgSO_4 and concentrating on a rotary evaporator, 110 mg of a purple powder of compound CRL 8432 (or of its exo tautomer in position 10) are obtained.

- Yield: 85%.
- Melting point: $> 260^\circ\text{C}$.
- IR(KBr): 1664, 1608 cm^{-1} .
- MS: m/z 229 (100); 298 (66); 271 (17); 270 (13); 243 (39); 242 (29).
- ^1H NMR ($\text{DMSO}-d_6$): 6.91 (d, 1H, $J = 9.2$ Hz); 7.84 (d, 1H, $J = 7.8$ and 8.8 Hz); 7.97 (dd, 1H, $J = 7.8$ and 7.8 Hz); 8.21 (d, 1H, $J = 7.8$ Hz); 8.71 (d, 1H, $J = 9.2$ Hz); 8.87 (d, 1H, $J = 8.8$ Hz); 9.04 (d, 1H, $J = 5.5$ Hz); 9.27 (d, 1H, $J = 5.5$ Hz).

EXAMPLE 25:**10-Methoxybenzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one (CRL 8452)**

5

A mixture of the compound CRL 8457 (Example 15 - 52 mg, 0.14 mmol) and Pd/C (10%, 50 mg) in 30 mL of methanol are hydrogenated at atmospheric pressure. The reaction medium is maintained under a hydrogen atmosphere for 30 minutes. After evaporating off the solvent, the crude product obtained is purified by flash chromatography on silica (CH₂Cl₂) to give the compound CRL 8452 in the form of a yellow powder (10 mg).

15

- Yield: 22%.

- Melting point: >260°C.

- IR(CDCl₃): 1684 cm⁻¹.

20

- MS: m/z 313 (35); 312 (100); 283 (52); 282 (98); 254 (22).

25

- ¹H NMR (CDCl₃): 4.22 (s, 3H); 7.20 (d, 1H, J = 8.8 Hz); 7.75 (ddd, 1H, J = 8.1; 8.1 and 1.1 Hz); 7.88 (ddd, 1H, J = 8.1; 8.1 and 1.1 Hz); 8.24 (d, 1H, J = 8.1 Hz); 8.54 (d, 1H, J = 8.1 Hz); 8.58 (d, 1H, J = 5.5 Hz); 9.13 (d, 1H, J = 8.8 Hz); 9.29 (d, 1H, J = 5.5 Hz).

30

- ¹³C NMR (CDCl₃): 52.77; 116.70; 117.05; 118.95; 120.91; 122.27; 127.21; 128.08; 130.52; 131.12; 135.99; 137.19; 145.09; 145.48; 146.81; 147.38; 149.62; 165.29; 180.04.

35

EXAMPLE 26:**Ethyl 8-oxobenzo[b]pyrido[4,3,-de][1,7]phenanthroline-11-carboxylate (CRL 8447)**

5

A mixture of compound CRL 8453 (60 mg, 0.15 mmol) and of Pd/C (10%, 48 mg) in 10 mL of methanol are hydrogenated at atmospheric pressure. The reaction medium is maintained under a hydrogen atmosphere for 10 2 hours. After evaporating off the solvent, the crude product obtained is purified by flash chromatography on silica (98/2 CH₂Cl₂/MeOH) to give the expected compound CRL 8447 in the form of a yellow powder (33 mg).

15

- Yield: 63%.

- Melting point: >260°C.

- IR(CHCl₃): 1693, 1726 cm⁻¹.

20

- MS: m/z 355 (100).

25

- ¹H NMR (CDCl₃): 1.53 (t, 3H, J = 7.3 Hz); 4.57 (q, 2H, J = 7.3 Hz); 7.86 (ddd, 1H, J = 8.0, 8.0 and 1.1 Hz); 7.99 (ddd, 1H, J = 8.0, 8.4 and 1.1 Hz); 8.42 (d, 1H, J = 8.4 Hz); 8.64 (d, 1H, J = 8.0 Hz); 8.70 (d, 1H, J = 5.5 Hz); 9.37 (d, 1H, J = 5.5 Hz); 9.59 (d, 1H, J = 2.2 Hz); 9.90 (d, 1H, 2.2 Hz).

30

- ¹³C NMR (CDCl₃): 13.01; 60.97; 116.85; 118.69; 120.56; 121.68; 128.30; 128.49; 130.31; 130.79; 131.29; 134.52; 136.82; 144.27; 145.31; 145.83; 148.13; 149.29; 151.91; 162.90; 178.99.

35

The results of the pharmacological tests, presented below, demonstrate the cytotoxic properties of the compounds of formulae I and II, and also the maximum tolerated doses.

1- Determination of the maximum tolerated dose (MTD)

The evaluation of the maximum tolerated dose was carried out on 4- to 6-week-old B6D2F1/Jico mice. The compounds were administered intraperitoneally at increasing doses ranging from 2.5 to 160 mg/kg. The value of the MTD (expressed in mg/kg) is determined from observing the survival rate of the animals over a period of 14 days after a single administration of the product under consideration. The change in the weight of the animals is also monitored over this period.

The results of the estimation of the maximum tolerated dose (MTD) are collated in table I below:

TABLE I

CRL compounds	MTD (mg/kg)
CRL 8348 (Meridine)	>160
Cystodamine	>160
CRL 8276 (Example 20)	80
CRL 8299 (Example 19)	80
CRL 8243 (Example 12)	>160
CRL 8296 (Example 11)	80
CRL 8300 (Example 13)	80
CRL 8275 (Example 5)	80
CRL 8277 (Example 4)	>40
CRL 8242 (Example 17)	>160
CRL 8250 (Example 1)	20
CRL 8258 (Example 22)	40
CRL 8273 (Example 18)	>80
CRL 8259 (Example 21)	40
CRL 8267 (Example 3)	20
CRL 8426 (Example 6)	>160
CRL 8428 (Example 7)	>160
CRL 8427 (Example 23)	>160
CRL 8429 (Example 8)	40
CRL 8432 (Example 24)	>160

2- Cytotoxic activity on tumor cell lines in culture

The influence of the compounds of formulae I and II on
5 neoplastic cells was evaluated using the MTT
colorimetric test. The principle of the MTT test is
based on the mitochondrial reduction by metabolically
active live cells of the yellow-colored product MTT
10 (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
bromide) to a blue-colored product, formazan. The
amount of formazan thus obtained is directly
proportional to the amount of live cells present in the
culture well(s). This amount of formazan is measured by
spectrophotometry.

15

The cell lines are maintained in monolayer culture at
37°C in stoppered culture dishes containing 25 MM HEPES
MEM (Minimum Essential Medium) base medium. This
medium, which is suitable for growing a range of varied
20 diploid or primary mammalian cells, is then
supplemented:

- with a an amount of 5% FCS (Fetal Calf Serum)
decomplemented at 56°C for 1 hour,
- with 0.6 mg/mL of L-glutamine,
- 25 - with 200 IU/mL of penicillin,
- with 200 mg/mL of streptomycin,
- with 0.1 mg/mL of gentamicin.

The 12 human cancer cell lines used were obtained from
30 the American Type Culture Collection (ATCC, Rockville,
MD, USA). These 12 cell lines are:

- U-373MG (code ATCC: HTB-17) and U-87MG (code
ATCC: HTB-14) which are two glioblastomas,
- SW1088 (code ATCC: HTB-12) which is an
35 astrocytoma,
- A549 (code ATCC: CCL-185) and A-427 (code ATCC:
HTB-53) which are two non-small-cell lung
cancers,
- HCT-15 (code ATCC: CCL-225) and LoVo (code

ATCC: CCL-229) which are two colorectal cancers,

- T-47D (code ATCC: HTB-133) and MCF7 (code ATCC: HTB-22) which are two breast cancers,
 - 5 - J82 (code ATCC: HTB-1) and T24 (code ATCC: HTB-4) which are two bladder cancers,
 - PC-3 (code ATCC: CRL-1435) which is a prostate cancer.
- 10 Experimentally: 100 μ l of a cell suspension containing 200 000 to 50 000 (depending on the cell type used) cells/mL of culture medium are inoculated in flat-bottomed 96-well multi-well plates and are incubated at 37°C under an atmosphere comprising 5% CO₂ and 70%
15 humidity. After incubating for 24 hours, the culture medium is replaced with 100 μ l of fresh medium containing either the various test compounds at concentrations ranging from 10⁻⁵ to 10⁻¹⁰ M or the solvent used to dissolve the test products (control
20 condition). After incubating for 72 hours under the above conditions, the culture medium is replaced with 100 μ l of a yellowish solution of MTT dissolved at a rate of 1 mg/mL in RPMI 1640. The microplates are reincubated for 3 hours at 37°C and then centrifuged
25 for 10 minutes at 400 $\times$ g. The yellowish solution of MTT is removed and the blue formazan crystals formed at the cellular level are dissolved in 100 μ l of DMSO. The microplates are then agitated for 5 minutes. The intensity of the resulting blue coloration, and thus of
30 the conversion of the yellow MTT product into blue formazan by the cells that are still alive at the end of the experiment is quantified by spectrophotometry using a DYNATECH IMMUNOASSAY SYSTEM machine at wavelengths of 570 nm and 630 nm corresponding,
35 respectively, to the maximum absorption wavelengths of formazan and to the background noise. Software built into the spectrophotometer calculates the average optical density values and also the standard deviation (Std. Dev.) and standard error of mean (SEM) values.

The inhibitory activity on the cell growth of the compounds of formula I and of formula II on the different tumor cell lines was compared with that of the natural product meridine (CRL 8348). All of the compounds of formula I and of formula II show significant inhibitory activity on the cell proliferation of the 12 human tumor lines: U-87MG, U-373MG, SW 1088, T24, J82, HCT-15, LoVo, MCF7, T-47D, A549, A-427 and PC-3 with an inhibitory concentration 50 (IC_{50}) which is between $10^{-6}M$ and $10^{-10}M$, depending on the compounds and the tumor lines tested. By way of example, the values of the concentrations flanking the IC_{50} which are obtained on the various cell lines are given in table II:

TABLE II

CELL LINES	COMPOUNDS (Concentration M)				
	CRL8348 (meridine)	CRL8276	CRL8299	CRL8275	CRL8277
U-87MG	$[10^{-6}, 10^{-7}]$	$<10^{-10}$	$<10^{-10}$	$<10^{-10}$	$[10^{-9}, 10^{-10}]$
U-373MG	10^{-7}	$<10^{-10}$	$[10^{-9}, 10^{-10}]$	$<10^{-10}$	$[10^{-8}, 10^{-9}]$
SW1088	$[10^{-5}, 10^{-6}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$
T24	$[10^{-7}, 10^{-8}]$	$[10^{-8}, 10^{-9}]$	$<10^{-10}$	$[10^{-8}, 10^{-9}]$	$[10^{-7}, 10^{-8}]$
J82	$[10^{-5}, 10^{-6}]$	$[10^{-9}, 10^{-10}]$	$[10^{-8}, 10^{-9}]$	$[10^{-9}, 10^{-10}]$	$[10^{-7}, 10^{-8}]$
HCT-15	$[10^{-6}, 10^{-7}]$	$[10^{-8}, 10^{-9}]$	$[10^{-8}, 10^{-9}]$	$[10^{-8}, 10^{-9}]$	$[10^{-8}, 10^{-9}]$
LoVo	$[10^{-7}, 10^{-8}]$	$[10^{-9}, 10^{-10}]$	$[10^{-7}, 10^{-8}]$	$[10^{-9}, 10^{-10}]$	$[10^{-8}, 10^{-9}]$
MCF7	$[10^{-7}, 10^{-8}]$	$<10^{-10}$	$[10^{-9}, 10^{-10}]$	$[10^{-9}, 10^{-10}]$	$[10^{-8}, 10^{-9}]$
T-47D	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$	10^{-8}	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$
A549	$[10^{-7}, 10^{-8}]$	$[10^{-9}, 10^{-10}]$	$[10^{-7}, 10^{-8}]$	$<10^{-10}$	$[10^{-8}, 10^{-9}]$
A-427	$[10^{-6}, 10^{-7}]$	$[10^{-8}, 10^{-9}]$	$[10^{-9}, 10^{-10}]$	$[10^{-8}, 10^{-9}]$	$[10^{-7}, 10^{-8}]$
PC-3	$[10^{-6}, 10^{-7}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$	$[10^{-7}, 10^{-8}]$

Table III gives the results of the average IC_{50} values (in nM) (calculated from the cytotoxic activity on the 12 tumor lines studied) and the MTD/ IC_{50} ratios (these ratios are calculated by forming the ratio of the MTD values and the IC_{50} values expressed as numbers without

units).

TABLE III

CRL compounds	IC ₅₀ (nM)	MTD/IC ₅₀	MTD/IC ₅₀ *
CRL 8348 (Meridine)	170	0.94	1
Cystodamine	100	1.6	1.7
CRL 8276 (Example 20)	2.1	38.1	40.5
CRL 8299 (Example 19)	2.2	36.4	38.7
CRL 8275 (Example 5)	2.3	34.8	37
CRL 8277 (Example 4)	12.5	6.4	6.8

- 5 *: the ratio MTD/IC₅₀ for the various compounds was estimated taking as reference a ratio equal to 1 for meridine.

10 The compounds described show, on the tumor cell line models, IC₅₀ values (nM) which are less than or equivalent to those of the natural compounds (meridine and cystodamine). Their maximum tolerated doses are close to those of meridine and cystodamine. When their IC₅₀ value is markedly less than that of the natural
15 products, the tolerance/cytotoxic activity ratios for the compounds illustrated in the present invention then become markedly greater than that of meridine and cystodamine, as indicated in Table III. These compounds may thus be used as antitumor medicinal products, for
20 their cytotoxic properties, at tissue concentrations that are higher than those induced with the natural products meridine and cystodamine. They are thus characterized by better therapeutic manageability.

25 By virtue of their cytotoxic properties, the compounds of formulae I and II as described, or in the form of acceptable pharmaceutical salts or solvates, may be used as active principles of medicinal products.

30 The compounds of formulae I and II are generally administered in dosage units established either per m² of body surface or per kg of weight. The said dosage

units are preferably formulated in pharmaceutical compositions in which the active principle is mixed with one (or more) pharmaceutical excipient(s).

- 5 The compounds of formulae I and II above may be used, according to the cancer pathology of the individual to be treated, at doses of between 0.05 and 350 mg/m² of body surface, preferably at doses from 0.5 to 50 mg/m²/day for a curative treatment in the acute
10 phase as a function of the number of treatment cycles of each cure. For maintenance treatment, the compounds of formulae I and II will advantageously be used at doses from 0.05 to 25 mg/m²/day and preferably at doses from 0.1 to 1.5 mg/m²/day depending on the number of
15 treatment cycles of the cure.

In the pharmaceutical compositions of the present invention for oral or intravenous administration, the active principles may be administered in unit forms of
20 administration, mixed with conventional pharmaceutical supports that are suitable for human therapy. The suitable unit forms of administration comprise oral-route forms such as tablets, which may be splittable, or gel capsules, implants and intravenous
25 administration forms.

For a parenteral administration (intravenous infusion at a constant flow rate), sterile aqueous suspensions, sterile isotonic saline solutions or sterile and
30 injectable solutions which contain pharmacologically compatible dispersants and/or solubilizing agents, for example propylene glycol or polyethylene glycol, are used.

35 Thus, to prepare an aqueous solution for intravenous injection intended for an infusion performed over 1 to 24 h, it is possible to use a co-solvent: an alcohol such as ethanol, a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such

as Tween® 80.

When a solid composition in the form of tablets is prepared, a wetting agent such as sodium lauryl sulfate may be added to the micronized or unmicronized active principle, and the whole is mixed with a pharmaceutical vehicle such as silica, gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets may be coated with sucrose, with various polymers or with other suitable materials, or alternatively they may be treated such that they have sustained or delayed activity and such that they continuously release a predetermined amount of active principle.

A preparation as gel capsules is obtained by mixing the active principle with a diluent such as a glycol or a glycerol ester and by incorporating the mixture obtained into soft or hard gel capsules.

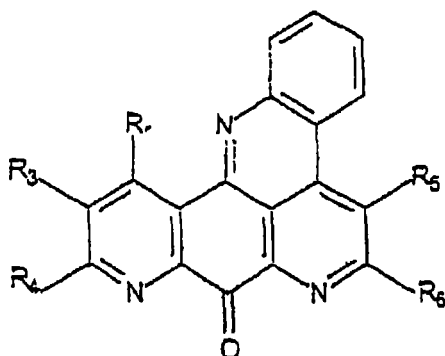
The active principle may also be formulated in the form of microcapsules or microspheres, optionally with one or more supports or additives.

The active principle may also be presented in the form of a complex with a cyclodextrin, for example α -, β - or γ -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin or methyl- β -cyclodextrin.

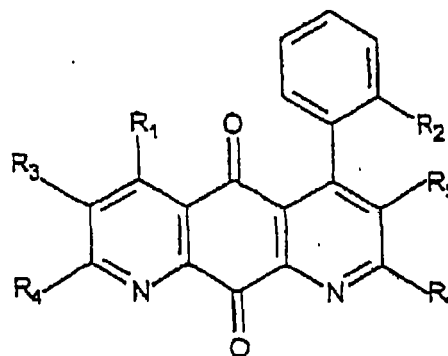
The compounds of formulae I and II will be used in the treatment of most solid tumors on account of their powerful cytotoxic activities, in particular for treating cerebral tumors, lung cancers, ovarian and breast tumors, colorectal cancers, prostate cancers and testicular tumors.

CLAIMS

1. A pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formulae:



Formula I



Formula II

in which:

R_1 , R_3 , R_4 , R_5 and R_6 are chosen from hydrogen, halogens and hydroxyl, -CHO, -OR, -COOH, -CN, -CO₂R, -CONHR, -CONRR', -CH₂-N-COOR, -CH₂-N-COOR, -CH₂-COOR', -CH₂-Ar

-NH₂, -NHR, -N(R)₂, -NH-CH₂-CH₂-N(CH₃)₂, -NHCOR, morpholino, nitro and -SO₃H groups,

R and R' being chosen from C₁-C₆ alkyl groups and Ar being a C₆-C₁₄ aryl group,

R_2 is chosen from nitro and -NHCOCF₃ groups,

with the exclusion of the compounds of formula I in which R_1 = -OH or -NH₂ and R_3 , R_4 , R_5 and R_6 = H,

and the addition salts of these compounds with pharmaceutically acceptable acids.

2. The pharmaceutical composition as claimed in claim 1, comprising an effective amount of a

compound chosen from the compounds of formula I and of formula II in which R_1 , R_3 and R_4 are chosen from hydrogen, halogens, hydroxyl, -CHO, -OR, -COOH, -CN, -CO₂R, -CONHR, -CONRR', -NH₂, -N(R)₂, -NHR, -NH-CH₂-CH₂-N(CH₃)₂, -NHCOR, morpholino, nitro and -SO₃H groups,

R_2 is chosen from nitro and -NHCOCF₃ groups,

and the addition salts of these compounds with pharmaceutically acceptable acids.

3. The pharmaceutical composition as claimed in claim 2, comprising an effective amount of a compound chosen from the compounds of formula I in which R_1 is chosen from hydrogen and methoxy and -N(CH₃)₂ groups and the compounds of formula II in which R_1 is chosen from hydrogen and methoxy, -N(CH₃)₂ and -NHCOCF₃ groups and R_2 is an -NHCOCF₃ group, and the addition salts of these compounds with pharmaceutically acceptable acids.

4. The pharmaceutical composition as claimed in claim 2, comprising an effective amount of a compound chosen from the compounds of formula I in which R_3 is a -COOEt group and the compounds of formula II in which R_3 is a -COOEt group and R_2 is chosen from -NHCOCF₃ and -NO₂ groups, and the addition salts of these compounds with pharmaceutically acceptable acids.

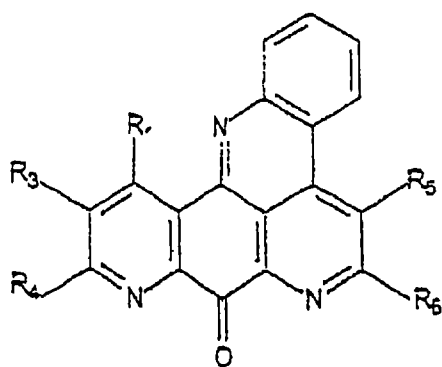
5. The pharmaceutical composition as claimed in claim 2, comprising an effective amount of a compound chosen from the compounds of formula I in which R_4 is a methoxy group and the compounds of formula II in which R_4 is a methoxy group and R_2 is chosen from -NHCOCF₃ and -NO₂ groups, and the addition salts of these compounds with

pharmaceutically acceptable acids.

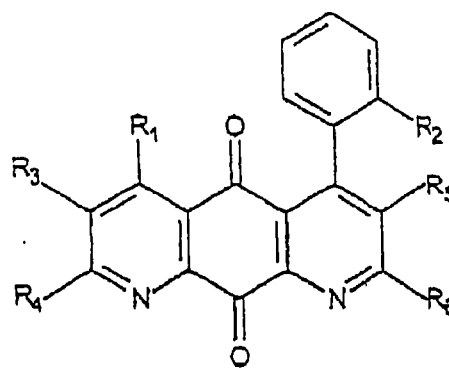
6. A compound which is:

- 5 4-(2-trifluoroacetamidophenyl)pyrido[3,2-g]-
 quinoline-5,10-dione,
 6-methoxy-4-(2-trifluoroacetamidophenyl)pyrido-
 [3,2-g]quinoline-5,10-dione,
 6-(dimethylamino)-4-(2-trifluoroacetamidophenyl)-
10 pyrido[3,2-g]quinoline-5,10-dione,
 6-(acetamido)-4-(2-trifluoroacetamidophenyl)-
 pyrido[3,2-g]quinoline-5,10-dione,
 8-methoxy-4-(2-trifluoroacetamidophenyl)pyrido-
 [3,2-g]quinoline-5,10-dione,
15 ethyl 4-(2-trifluoroacetamidophenyl)-5,10-dioxo-
 pyrido[3,2-g]quinoline-7-carboxylate,
 8-methoxy-4-(2-nitrophenyl)pyrido[3,2-g]quinoline-
 5,10-dione,
 ethyl 4-(2-nitrophenyl)-5,10-dioxopyrido[3,2-g]-
20 quinoline-7-carboxylate,
 benzo[b]pyrido[4,3,2-de][1,7]phenanthroline-8-one,
 12-dimethylaminobenzo[b]pyrido[4,3,2-de][1,7]-
 phenanthroline-8-one,
 10-hydroxybenzo[b]pyrido[4,3,2-de][1,7]phen-
25 anthroline-8-one,
 10-methoxybenzo[b]pyrido[4,3,2-de][1,7]phen-
 anthroline-8-one,
 11-ethylbenzo[b]pyrido[4,3-de][1,7]phen-
 anthrolinecarboxylate-8-one,
30 and the salts thereof with pharmaceutically
 acceptable acids.

7. The use of a compound chosen from the compounds of formulae:



Formula I



Formula II

in which:

- 5 R_1, R_3, R_4, R_5 and R_6 are chosen from hydrogen, halogens and hydroxyl, $-\text{CHO}$, $-\text{OR}$, $-\text{COOH}$, $-\text{CN}$, $-\text{CO}_2\text{R}$, $-\text{CONHR}$, $-\text{CONRR}'$, $-\text{CH}_2-\text{N}-\text{COOR}$, $-\text{CH}_2-\text{N}-\text{COOR}$, $-\text{CH}_2-\text{COOR}'$, $-\text{CH}_2-\text{Ar}$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{NH}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$, $-\text{NHCOR}$,
 10 morpholino, nitro and $-\text{SO}_3\text{H}$ groups,

R and R' being chosen from C_1-C_6 alkyl groups and Ar being a C_6-C_{14} aryl group,

- 15 R_2 is chosen from nitro and $-\text{NHCOCF}_3$ groups,

with the exclusion of the compounds of formula I, in which $R_1 = -\text{OH}$ or $-\text{NH}_2$ and R_3, R_4, R_5 and $R_6 = \text{H}$,

- 20 and the addition salts of these compounds with pharmaceutically acceptable acids,

for the manufacture of an antitumor medicinal product.

25

30

8. The pharmaceutical composition as claimed in claim 1, comprising an effective amount of a compound of formula (I), wherein $R_1 = OR$.
- 5 9. The pharmaceutical composition as claimed in claim 1, comprising an effective amount of a compound of formula (I), wherein R_1 is other than a $-OR$.