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Pharmaceutical compositions comprising 2-quinolones

The present invention relates to pharmaceutical compositions comprising 2-quinolones or derivative compounds.

A cancer is a disorder of the somatic genes in the course of which genetic dysfunctions are amplified as the tumoral process progresses from the state of precancerous lesion to that of malignant transformation, the cancer tumor becoming metastatic and often resistant to cytotoxic medicines.

Despite the very considerable efforts made in all the developed countries, in particular through experimental and clinical research programs, mortality due to various cancers (solid tumors and hematological neoplasties) remains unacceptably high. In many countries, cancer is the second most common cause of death, just after cardiovascular diseases.

In terms of newly diagnosed cancers, the distribution between solid tumors and hematological neoplasties (bone marrow, blood, lymphatic system) shows that 9 out of 10 cancers are solid tumors. In contrast with what is observed in hematological oncology (therapeutic successes in 40% to 90% of cancers of blood cells), only a small number of advanced or disseminated solid tumors respond to chemotherapy treatments alone. It is partly for this reason that the overall death by cancer grew in the USA between 1973 and 1992.

Unfortunately, it is not certain that this tendency may be reversed merely by the appearance, alongside the established chemotherapy arsenal, of new antitumor medicines such as taxanes (paclitaxel and docetaxel) which interfere with the formation of microtubules (W.P. McGuire et al., Am. Intern. Med., 1989), topoisomerase I inhibitors derived from camptothecin (topotecan and irinotecan), vinorelbine (novel alkaloid derived from periwinkle), gemcitabine

(novel cytotoxic antimetabolite), raltitrexed (thymidylate synthetase inhibitor) and miltefosine (first representative of the alkyl-lysophospholipid family). These treatments are added, either as a first line treatment or as a second line treatment, to medicines whose specific activity is now well recognized, such as doxorubicin, cysplatin, vincristine, methotrexate and 5-fluorouracil.

One of the most difficult current problems in anticancer chemotherapy is due to the fact that many populations of malignant cells show considerable resistance to the established cytotoxic substances. Usually, this situation results from the existence of multi-drug-resistance genes or from the frequency of genetic mutations in certain types of tumors. Thus, the treatment of cancers requires novel approaches, complementary to those currently used, and designed to better combat the extension and heterogeneity of the tumor load and the acquisition of "cytotoxic multi-drug" resistance.

Among these novel approaches, some are already promising. This is the case for the induction of apoptosis, the inhibition of tumor angiogenesis and of metastatic processes, not to mention gene therapy or immunotherapy.

The inventors have become interested in a different approach. The desired objective was to make the population of tumor cells more sensitive to the standard anticancer treatments in order to achieve a twofold benefit:

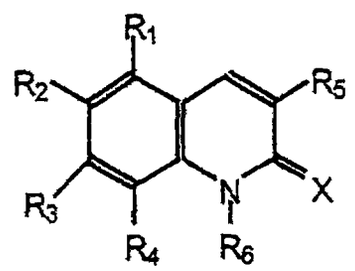
1) to increase the cytotoxic activity and thus the efficacy, and

2) to reduce the frequency and severity of certain side effects by means of reducing the dosage which might follow the induction of the increase in the antitumor efficacy.

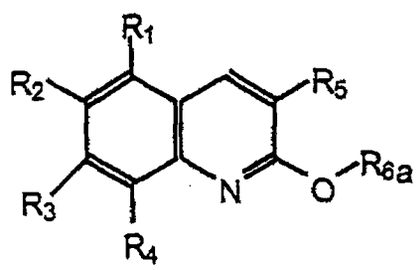
It is this strategy which underlies the discovery of compositions capable of inducing a highly significant increase in the cytotoxic activity of

tested anticancer medicines. These compositions have the capacity either of stimulating the recruitment of clonogenic cells in the tumor, thus making it more sensitive to the conventional treatment with cytotoxic agents, or of inhibiting the proliferation of clonogenic cells, thus contributing toward the regression of the tumor.

A subject of the present invention is thus the use, in the treatment of cancers with at least one antitumor agent chosen from cytotoxic agents, of a compound having activity on the proliferation of clonogenic cells in tumors, chosen from the compounds of formulae:



(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group -OCOR_8, a phenyl (C_1-C_4 alkoxy) group, a group -O-SO_2-R'_8, R'_8 being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_{6a} is chosen from a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_9 being a C_1-C_4 alkyl group,

A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group $-COOR_{11}$, $-CONR_{12}R_{13}$, a group $-NR_{14}R_{15}$ and a group $-COR_{16}$,

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a $-CO-CH_2-CH_2-$ group.

The cytotoxic agents may be used at their usual dose and, in this case, their efficacy is improved, or at lower doses given the increase in their antitumor efficacy.

In one preferred embodiment, the compound used is a compound of formula (I) in which:

- R_1 is a C_1-C_4 alkoxy group
- R_2 is a hydrogen atom
- R_3 is a C_1-C_4 alkoxy group
- R_4 is a hydrogen atom,

and in particular a compound of formula (I) in which:

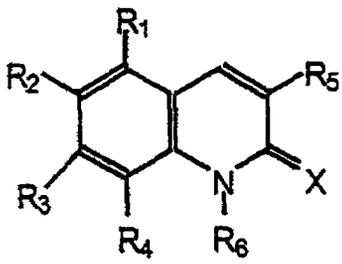
- R_5 is a 4-(C_1-C_4 alkoxy)phenyl group,

and most particularly a compound of formula (I) in which:

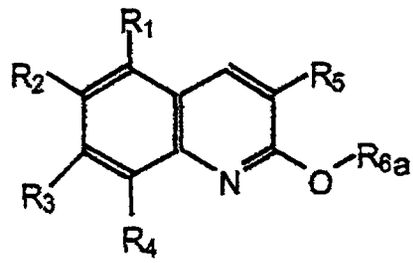
- R_1 is a methoxy group,
- R_3 is a methoxy group, and
- R_5 is a 4-methoxyphenyl group.

It has also been discovered that at least some of the compounds of formula (I) had antitumor activity themselves.

A subject of the present invention is also a composition having activity on the proliferation of clonogenic cells in tumors by interfering with the generation of clonogenic cells, either by stimulating proliferation and recruitment, or by inhibiting proliferation, and which comprises an effective amount of a compound of formulae:



(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group -OCOR_8, a phenyl (C_1-C_4 alkoxy) group, a group -O-SO_2-R'_8, R'_8 being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_{6a} is chosen from a group -CO-R_9 and a group -A-R_{10},

R_9 being a C_1-C_4 alkyl group,

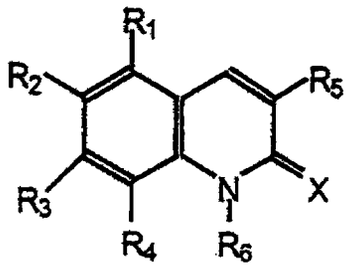
A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group -COOR_{11}, -CON$R_{12}R_{13}$, a group -N$R_{14}R_{15}$ and a group -COR_{16},

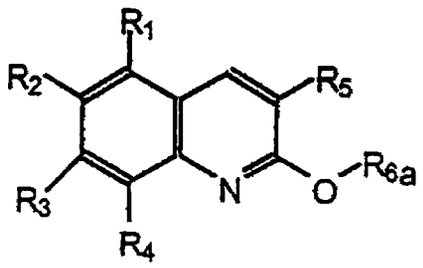
R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a -CO-CH_2-CH_2- group.

A subject of the present invention is also novel compounds, namely compounds of formulae:



(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group -OCOR_8, a phenyl (C_1-C_4 alkoxy) group, a group -O-SO_2-R'$_8$, R'$_8$ being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_{6a} is chosen from a group -CO-R_9 and a group -A-R_{10},

R_9 being a C_1-C_4 alkyl group,

A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group -COOR_{11}, -CONR$_{12}$R$_{13}$, a group -NR$_{14}$R$_{15}$ and a group -COR$_{16}$,

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a -CO-CH_2-CH_2- group,

with the exclusion of the compounds in which X = O, R_6 = H and two of the substituents R_1, R_2, R_3 and R_4 are OH or OCH_3.

In the chemotherapy treatment of cancers with cytotoxic agents, the compounds of formulae (I) and (Ia) can be administered at the start of the chemotherapy treatments either once or over several days at the start of these treatments (for example for 5 to 7 days) and, depending on the chemotherapy protocol, at the start of each treatment cycle (for example for 2 to 5 days) in the course of each cure.

The compounds of formulae (I) and (Ia) are advantageously administered by infusion (generally in 1 to 3 hours) at doses of from 5 to 50 mg/kg/day or 200 to 2000 $mg/m^2/day$.

In order to obtain a maximal effect on the production (inhibition or stimulation) of clonogenic cells, the compounds of formulae (I) and (Ia) should be administered such that the tissue concentrations obtained are as high as can possibly be envisaged.

For the treatment protocols in the acute phases of the cures, the intravenous route is preferred, using:

- ready-to-use infusion solutions (bags, bottles, etc.) intended to be administered without any modification, by intravenous infusion using an infusion line and at the recommended rate:

- lyophilizates to be redissolved for intravenous infusion using pharmaceutical solutions known to those skilled in the art;

- for maintenance treatments, it is also possible to envisage the oral route when the chemotherapy treatment favors the oral administration of cytostatic agents. To this end, lozenges (for oral or perlingual absorption), immediate-release or delayed-release tablets, oral solutions, suspensions, granules, gel capsules, etc. may be used.

The cytotoxic agents may be chosen from:

i) intercalating agents, in particular doxorubicin (Adriamycin), daunorubicin, epirubicin, idarubicin, zorubicin, aclarubicin, pirarubicin, acridine, mitoxanthrone, actinomycin D, eptilinium acetate;

ii) alkylating agents chosen from platinum derivatives (cisplatin, carboplatin, oxaliplatin);

iii) a compound chosen from the other groups of alkylating agents:

- cyclophosphamide, ifosfamide, chlormetrine, melphalan, chlorambucil, estramustine,
- busulfan, mitomycin C,
- nitrosoureas: BCNU (carmustine), CCNU (lomustine), fotemustine, streptozotocin,
- triazines or derivatives: procarbazine, dacarbazine,
- pipobroman,
- ethyleneimines: altretamine, triethylene-thiophosphoramide,

iv) a compound chosen from the other groups of antimetabolic agents:

- antifolic agents: methotrexate, raltitrexed,
- antipyrimidine agents: 5-fluorouracil (5-FU), cytarabine (Ara-C),
- hydroxyurea
- antipurine agents: purinethol, thioguanine, pentostatin, cladribine,
- cytotoxic nucleoside synthesis inducers: gemcitabine,

v) a compound chosen from the other groups of tubulin-affinity agents,

- vinca alkaloids which disrupt the mitotic spindle: vincristine, vinblastine, vindesine, navelbine,
- agents which block the depolymerization of the mitotic spindle: paclitaxel, docetaxel,
- agents which induce DNA cleavage by inhibition of topoisomerase II: etoposide, teniposide,
- topoisomerase I inhibitors which induce DNA cleavage: topotecan, irinotecan,

vi) a DNA splitting or fragmenting agent, such as bleomycin,

vii) one of the following compounds: plicamycin, L-asparaginase, mitoguazone, dacarbazine,

viii) an anticancer progestative steroid; medroxyprogesterone, megestrol,

ix) an anticancer estrogen steroid: diethylstilbestrol; tetrasodium fosfestrol,

x) an antiestrogen agent: tamoxifen, droloxifen, raloxifen, aminoglutethimide,

xi) a steroidal antiandrogenic agent (eg cyproterone) or a non-steroidal antiandrogenic agent (flutamide, nilutamide).

In particular, the compounds of formulae (I) and (Ia) may be combined with all the major treatments with cytotoxic agents used in solid tumor polychemotherapies, such as:

- doxorubicin
- alkylating agents: oxazophorines (cyclophosphamide, ifosfamide, chlorambucil, melphalan)
- nitrosoureas
- mitomycin C
- antimetabolites such as methotrexate, 5-FU, Ara-C, capecitabine
- agents which interfere with tubulin: vinca alkaloids (vincristine, vinblastine, vindesine, navelbine), taxoids (paclitaxel, docetaxel), epipodophyllotoxin derivatives (etoposide, teniposide)
- bleomycin
- topoisomerase I inhibitors: topotecan, irinotecan.

Similarly, the compounds of formulae (I) and (Ia) may be combined with the treatments with the major cytotoxic agents used in oncohematology for the treatment of blood cancers:

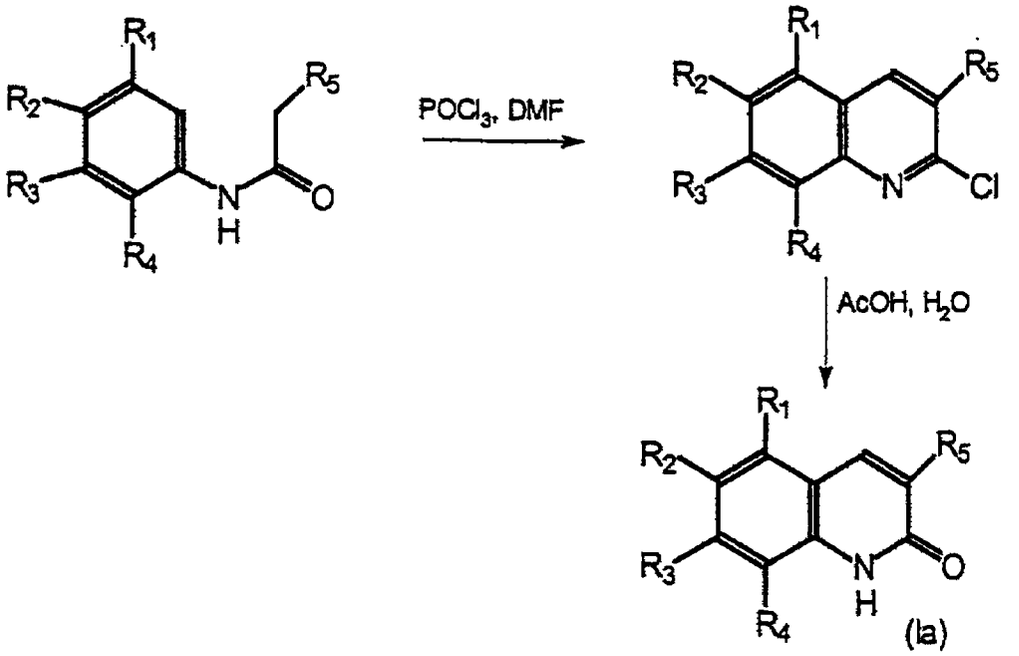
- Hodgkin's disease: cyclophosphamide, mechlorethamine, chlorambucil, melphalan, ifosfamide, etoposide, doxorubicin, daunorubicin;
- acute leukemias: methotrexate, 6-mercaptopurine, cytarabine, vinblastine, vincristine, doxorubicin, daunorubicin, L-asparaginase;
- non-Hodgkin's malignant lymphomas: mechlorethamine, chlorambucil, cyclophosphamide, melphalan,

ifosfamide, methotrexate, cytarabine, vinblastine, vincristine, etoposide, doxorubicin, daunorubicin, carmustine, lomustine, cisplatin;

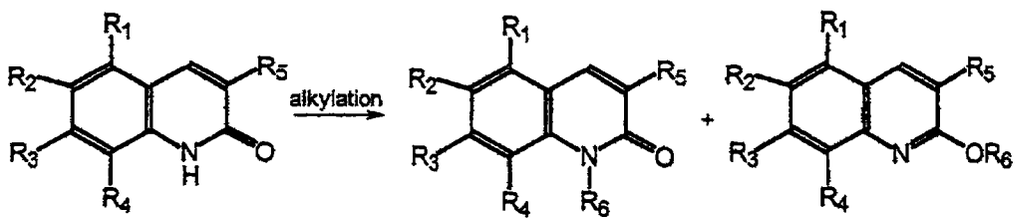
- chronic lymphoid leukemias: mechlorethamine, chlorambucil, cyclophosphamide, melphalan, ifosfamide.

In general, the compounds of formula (I) may be prepared according to the following reaction schemes:

SCHEME I



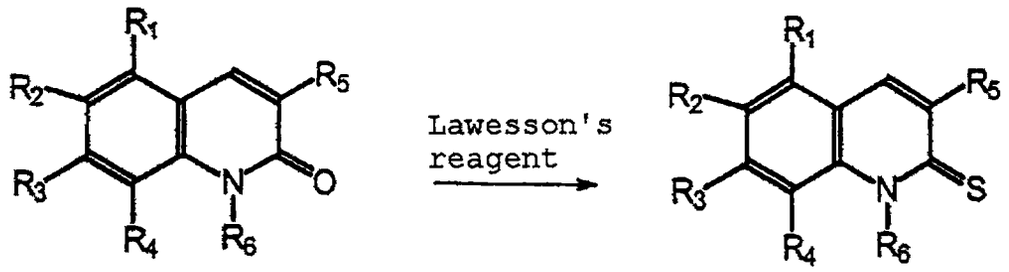
SCHEME II



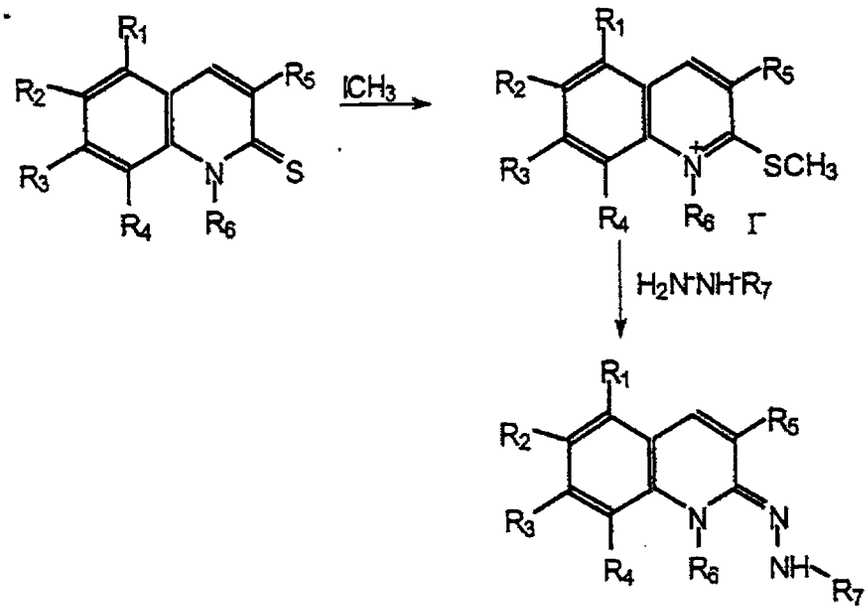
A reagent of the type XR_6 in which X = I, Br or Cl may be used as alkylating agent.

As a variant, a compound $CH_2 = CH-R$ can be used to attach a group $R_6 = -CH_2-CH_2-R$ (corresponding to the group $-A-R_{10}$ defined above).

SCHEME III



SCHEME IV



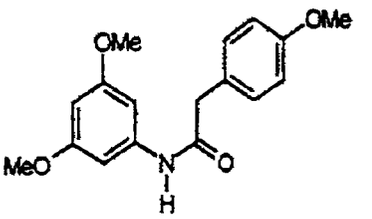
In addition, it is possible to convert some or all of the alkoxy groups into hydroxyl groups according to known methods. Similarly, the hydroxyl groups may be converted into ester or sulfonate according to the known methods.

Similarly, it is possible to convert a group $-A-COOR_{11}$, in which R_{11} is an alkyl or phenylalkyl group, into a group -A-COOH and to convert a group -A-COOH into a group $-A-CONR_{12}R_{13}$, according to known methods.

The compounds in which R_4 and R_6 form a $-CO-CH_2-CH_2-$ group can be obtained by cyclization of a compound in which R_4 = H and R_6 = $-CH_2-CH_2-COOH$.

EXAMPLE 1: 5,7-Dimethoxy-3-(4-methoxhphenyl)-1,2-dihydro-2-quinolinone (compound 1)

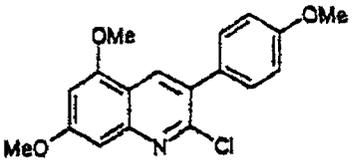
a) *N*-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)acetamide (compound 2)



500 mg (3.3 mmol) of 3,5-dimethoxyaniline are dissolved in toluene (7 ml) at 0°C, under a nitrogen atmosphere. A solution of 4-methoxyphenylacetyl chloride (0.5 ml, 3.3 mmol) in 5 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 1 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is crystallized from petroleum ether to give 810 mg (82%) of compound **2**.

- m.p. 135-137°C (toluene)
- IR (KBr) n 3292, 1658, 1615 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.66 (s, 2H, CH_2), 3.74 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 6.20 (t, 1H, J = 2.2 Hz, H_{Ar}), 6.62-6.66 (m, 2H, H_{Ar}), 6.95 (d, 2H, J = 7.5 Hz, H_{Ar}), (broad s, 1H, NH), 7.23 (d, 2H, J = 7.5 Hz, H_{AR}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.0, 55.3, 55.4 (2), 96.7, 97.9 (2), 114.4 (2), 126.2, 130.7 (2), 139.4, 159.0, 161.0 (2), 169.5.
- MS (ionspray): 302 $(M+1)^+$

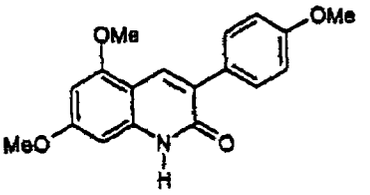
b) 2-Chloro-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydroquinoline (compound 3)



0.31 ml (4.0 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 1.75 ml (20.0 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C, followed by addition of 810 mg of amide **2** (2.7 mmol). The reaction mixture is warmed to room temperature with stirring and is then heated at 75°C for 2.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with 30% aqueous ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (eluent: 3/7 EtOAc/PE) to give 270 mg (30%) of compound **3**.

- m.p. 156-157°C (toluene)
- ^1H NMR (250 MHz, $CDCl_3$): d 3.87 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.52 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.97-7.01 (m, 3H, H_{Ar}), 6.95 (d, 2H, J = 8.7 Hz, H_{Ar}), 8.35 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.9 MHz, $CDCl_3$): d 55.3, 55.7, 55.8, 98.6, 98.9, 113.6 (2), 115.8, 125.9, 130.5, 131.0 (2), 133.8, 149.0, 150.5, 156.0, 159.4, 162.1.
- MS (ionspray): m/z 330 $(M+1)^+$, 332 $(M+3)^+$

c) 5,7-Dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 1)



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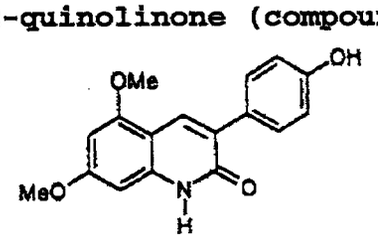
Compound **3** (250 mg, 0.76 mmol) dissolved in acetic acid (1.2 ml, 26.25 mmol per mmol of **3**) and

water (0.04 ml, 2.77 mmol per mmol of **3**) is refluxed for 3 h. The acetic acid is evaporated off. The residue obtained is taken up in water, neutralized with 25% sodium hydroxide solution and finally extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, this operation bringing about crystallization of the final product. The crystals thus obtained are filtered off to give 200 mg (85%) of compound **1**.

The overall yield for the synthesis carried out to obtain compound **1** is 21%.

- m.p. 254-255°C (EtOAc)
- IR (KBr) n 1664, 1628, 1573, 1518 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.35 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.45 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.95 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.66 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.96 (s, 1H, H_{Ar}), 11.76 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, DMSO=d_6): d 55.1, 55.4, 55.9, 90.0, 93.0, 104.6, 113.3 (2), 126.5, 129.0, 129.6 (2), 130.2, 140.5, 156.6, 158.7, 161.5, 161.9.
- MS (ionspray): m/z 312 $(M+1)^+$
- *Anal.* calculated for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.29; H, 5.40; N, 4.55.

EXAMPLE 2: 5,7-Dimethoxy-3-(4-hydroxyphenyl)-1,2-dihydro-2-quinolinone (compound 4)



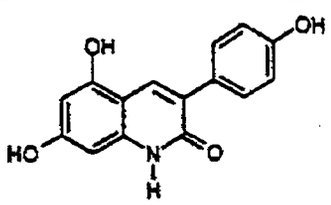
(CRL8284)

530 mg (1.70 mmol) of compound **1** are dissolved in 15 ml of acetic acid, under an inert atmosphere. A commercial solution of 48% HBr in water (2.65 ml) is added dropwise (exothermic reaction) to the reaction mixture. The final solution is refluxed with stirring for 5 h. After cooling, the reaction is diluted by

addition of water and is then neutralized with 10% sodium hydroxide solution (pH = 6-7). The product is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is purified by chromatography on a column of silica (eluent: 9/1 CH_2Cl_2/MeOH) to give 175 mg (35%) of compound **4**.

- m.p. 275-276°C (EtOAc)
- IR (KBr) n 1628, 1604, 1558, 1518 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.35 (d, 1H, J = 2.5 Hz, H_{Ar}), 6.43 (d, 1H, J = 2.5 Hz, H_{Ar}), 6.78 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.55 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.92 (s, 1H, H_{Ar}), 9.48 (s, 1H, OH), 11.72 (broad s, 1H, NH)
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 55.4, 55.9, 90.0, 93.0, 104.7, 114.8 (2), 126.9, 127.4, 129.6, 129.8 (2), 140.4, 156.6, 156.9, 161.6, 161.8
- MS (ionspray): m/z 298 $(M+1)^+$
- *Anal.* calculated for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.90; H, 5.09; N, 4.90.

EXAMPLE 3: 5,7-Dihydroxy-3-(4-hydroxyphenyl)-1,2-dihydro-2-quinolinone (compound 5)



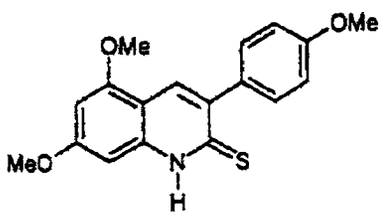
(CRL8311)

1.0 g (3.2 mmol) of compound **1** is dissolved in 15 ml of acetic acid, under an inert atmosphere. A commercial solution of 48% HBr in water (5 ml) is added dropwise (exothermic reaction) to the reaction mixture. The final solution is refluxed with stirring for 3 days. After cooling, the reaction is diluted by addition of water and is then neutralized with 10% sodium hydroxide solution (pH = 6-7). The product is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under

reduced pressure. The residue obtained is purified by chromatography on a column of silica (eluent: 9/1 CH_2Cl_2/MeOH) to give 320 mg (37%) of compound **5**.

- m.p. > 280°C
- ^1H NMR (250 MHz, DMSO-d_6): d 6.11 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.18 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.76 (d, 2H, J = 8.6 Hz, H_{Ar}), 7.52 (d, 2H, J = 8.6 Hz, H_{Ar}), 7.89 (s, 1H, H_{Ar}), 9.42 (s, 1H, OH), 9.84 (s, 1H, OH), 10.21 (s, 1H, OH), 11.46 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 91.3, 96.4, 103.5, 114.7 (2), 125.1, 127.8, 129.4 (2), 130.4, 140.7, 155.3, 156.6, 160.1, 161.8.
- MS (ionspray): m/z 270 $(M+1)^+$
- *Anal.* calculated for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.80; H, 4.00; N, 5.40.

EXAMPLE 4: 5,7-Dimethoxy-3-(4-methoxhphenyl)-1,2-dihydro-2-quinolinethione (compound 6)



(CRL8271)

100 mg (0.32 mmol) of compound **1** are dissolved in 15 ml of toluene (hot dissolution), under an inert atmosphere. 260 mg (0.64 mmol, 2 eq) of Lawesson's reagent are added to the reaction mixture. The final solution is refluxed for 18 h. After cooling, the toluene is evaporated off. The residue obtained is purified by chromatography on a column of silica (eluent: 9/1 CH_2Cl_2/EtOAc) to give 81 mg (77%) of compound **6**.

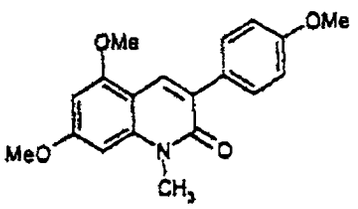
- m.p. 229-230°C (Et_2O)
- IR (KBr) 1636, 1610, 1524 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.49 (d, 1H, J = 1.9 Hz, H_{Ar}), 6.79 (d, 1H, J = 1.9 Hz, H_{Ar}), 6.92 (d, 2H, J = 8.7 Hz, H_{Ar}), 7.49 (d, 2H, J = 8.7 Hz, H_{Ar}), 7.78 (s, 1H, H_{Ar}), 13.50 (broad s, 1H, NH).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 55.1, 55.6, 56.1, 90.2, 95.2, 108.9, 112.9 (2), 128.2, 130.7 (2), 132.0, 136.3, 140.9, 156.4, 158.5, 162.5, 180.5.

· MS (ionspray): m/z 328 $(M+1)^+$

· *Anal.* calculated for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 66.30; H, 5.30; N, 4.35.

EXAMPLE 5: 5,7-Dimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2-dihydro-2-quinolinone (compound 7)



(CRL8244)

600 mg (1.93 mmol) of compound **1** are dissolved in 30 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 93 mg (3.86 mmol, 2 eq) of NaH, washed beforehand with petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of methyl iodide (0.48 ml, 7.72 mmol, 4 eq) diluted in 5 ml of DMF is added to the medium. The reaction is heated at 90°C for 18 hours. After cooling, water is added to the reaction mixture and the solution is then stirred for 15 min. The solid obtained is collected by filtration through a sinter funnel and then rinsed with water. The solid is dissolved in CH_2Cl_2 and washed twice with water. The organic phase obtained is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (8/2 CH_2Cl_2/EtOAc) to give 408 mg (68%) of compound **7** and 157 mg (25%) of derivative **7a**.

Compound **7**

· m.p. 125°C (EtOAc/PE)

· IR (KBr) n 1635, 1596, 1590, 1514 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 3.73 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 3.91 (s, 6H, OCH_3), 6.30 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.37 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94

(d, 2H, J = 7.5 Hz, H_{Ar}), 7.67 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.12 (s, 1H, H_{Ar}).

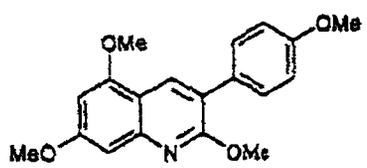
· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 30.3, 55.3, 55.5, 55.8, 90.2, 92.6, 106.1, 113.5 (2), 127.0, 130.0, 130.1 (2), 130.2, 141.7, 157.6, 159.1, 162.2 (2).

· MS (ionspray): m/z 326 $(M+1)^+$

· *Anal.* calculated for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.00; H, 5.73; N, 4.24.

Compound **7a**:

2,5,7-Trimethoxy-3-(4-methoxyphenyl)quinoline



· m.p. 106-107°C (EtOAc/PE)

· IR (KBr) n 1621, 1515, 1265 cm^{-1}

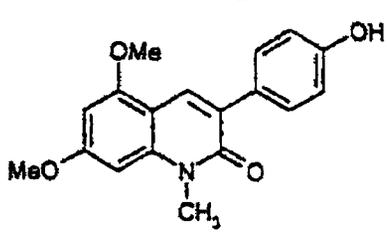
· ^1H NMR (250 MHz, $CDCl_3$): d 3.86 (s, 3H, OCH_3), 3.94 (s, 6H, OCH_3), 4.08 (s, 3H, OCH_3), 6.40 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.85 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.97 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.57 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.26 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 53.5, 55.3, 55.5, 55.6, 95.9, 98.5, 112.8, 113.6 (2), 122.1, 129.6, 130.5 (2), 132.3, 147.9, 156.3, 158.9, 160.6, 161.3.

· MS (ionspray): 326 m/z $(M+1)^+$

· *Anal.* calculated for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.89; H, 5.81; N, 4.10.

EXAMPLE 6: 5,7-Dimethozy-3-(4-hydroxyphenyl)-1-methyl-1,2-dihydro-2-quinolinone (compound 8)

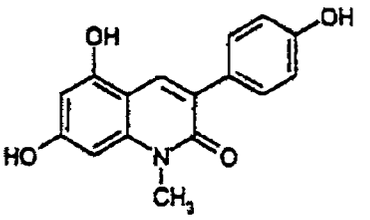


408 mg (1.3 mmol) of compound **7** are dissolved in 15 ml of acetic acid, under an inert atmosphere. A

commercial solution of 48% HBr in water (2 ml) is added dropwise (exothermic reaction) to the reaction mixture. The final solution is refluxed with stirring for 5 h. After cooling, the reaction is diluted by addition of water and is then neutralized with 10% sodium hydroxide solution (pH = 6-7). The product is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (eluent: 7/3 CH_2Cl_2/EtOAc) to give 220 mg (56%) of compound **8**.

- m.p. 204-205°C (EtOAc)
- ^1H NMR (250 MHz, DMSO-d_6): d 3.63 (s, 3H, NCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.46 (d, 1H, J = 1.9 Hz, H_{Ar}), 6.54 (d, 1H, J = 1.9 Hz, H_{Ar}), 6.76 (d, 2H, J = 8.5 Hz, H_{Ar}), 7.48 (d, 2H, J = 8.5 Hz, H_{Ar}), 7.93 (s, 1H, H_{Ar}), 9.47 (s, 1H, OH).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 30.5, 56.1, 56.5, 91.3, 93.4, 105.3, 115.2 (2), 126.5, 128.4, 129.2, 130.2 (2), 141.7, 157.4 (2), 161.4, 162.5.
- MS: m/z 312 $(M+1)^+$
- *Anal.* calculated for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.65; H, 5.59; N, 4.60.

EXAMPLE 7: 5,7-Dihydroxy-3-(4-hydroxyphenyl)-1-methyl-1,2-dihydro-2-quinolinone (compound 9)



(CRL8321)

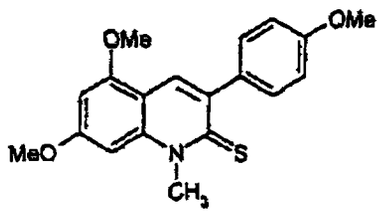
1. Method A: 200 mg (0.61 mmol) of compound **7** are dissolved in 15 ml of acetic acid, under an inert atmosphere. A commercial solution of 48% HBr in water (1 ml) is added dropwise (exothermic reaction) to the reaction mixture. The final solution is refluxed with stirring for 3 days. After cooling, the reaction is diluted by addition of water and is then neutralized

with 10% sodium hydroxide solution (pH = 6-7). The product is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (eluent: 9/1 CH_2Cl_2/MeOH) to give 61 mg (35%) of compound **9**.

2. Method B: 1.0 g (3.1 mmol) of compound **7** is dissolved in 15 ml of dichloromethane, under an inert atmosphere. At 0°C, 1.81 ml (19.0 mmol, 6 eq) of boron tribromide are added dropwise (exothermic reaction) to the reaction mixture. The final solution is stirred at room temperature for 18 h. The reaction is hydrolyzed by addition (dropwise) of water and is then neutralized with 10% sodium hydroxide solution (pH = 6-7). The product is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified on a column of silica (eluent: 9/1 CH_2Cl_2/MeOH) to give 688 mg (76%) of compound **9**.

- m.p. > 280°C (EtOAc)
- ^1H NMR (250 MHz, DMSOd-$_6$): d 3.53 (s, 3H, CH_3), 6.25 (s, 2H, H_{Ar}), 6.76 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.47 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.92 (s, 1H, H_{Ar}), 9.42 (s, 1H, OH), 10.00 (s, 1H, OH), 10.35 (s, 1H, OH).
- ^{13}C NMR (62.90 MHz, DMSOd-$_6$): d 29.7, 91.8, 96.5, 103.5, 114.7 (2), 124.3, 128.4, 129.7 (3), 141.7, 155.9, 156.7, 160.6, 161.1.
- MS (ionspray): m/z 284 $(M+1)^+$
- *Anal.* calculated for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.68; H, 4.46; N, 4.78.

EXAMPLE 8: 5,7-Dimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2-dihydro-2-quinolinethione (compound 10)

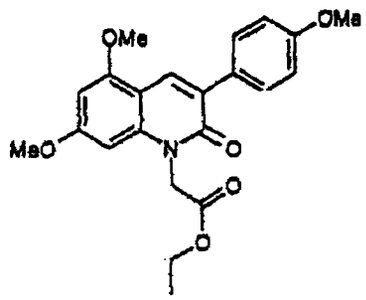


(CRL8245)

500 mg (1.5 mmol) of compound **7** are dissolved in 30 ml of toluene, under a nitrogen atmosphere. 870 mg (2.1 mmol, 1.4 eq) of Lawesson's reagent are added to this reaction mixture. The reaction is refluxed for 12 h. After cooling, the solvent is evaporated off. The residue obtained is purified by chromatography on a column of silica (3/7 EtOAc/PE) to give 376 mg (72%) of compound **10**.

- m.p. 176-177°C (EtOAc/PE)
- IR (KBr) 1613, 1570, 1512 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.39 (s, 3H, NCH_3), 6.39 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.56 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.93 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.43 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.97 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 39.5, 55.2, 55.6, 55.9, 91.1, 94.6, 109.9, 113.1 (2), 126.6, 130.8 (2), 134.3, 138.6, 142.7, 157.6, 158.8, 162.7, 184.5.
- MS: m/z 342 $(M+1)^+$
- *Anal.* calculated for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.70; H, 5.53; N, 4.03.

EXAMPLES 9: Ethyl 2-[5,7-dimethoxy-3-(4-hydroxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]acetate (compound 11)



(CRL8314)

1.0 g (3.2 mmol) of compound **1** is dissolved in 30 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 115 mg (4.8 mmol, 1.5 eq) of NaH, washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of ethyl bromoacetate (0.72 ml, 6.4 mmol, 2 eq) in 5 ml of DMF is added to the medium. The reaction is heated at 90°C for 2-3 h. After cooling, water is added to the reaction mixture, which is then stirred for 15 min. The solution is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (7/3 CH_2Cl_2/EtOAc) to give 890 mg (70%) of compound **11** and 318 mg (25%) of derivative **11a**.

*Compound **11**:*

- m.p. 160-161°C (EtOAc/PE)
- IR (KBr) 1735, 1647, 1609 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 1.6 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.22 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 5.10 (s, 2H, CH_2CO), 6.14 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.30 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.69 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.18 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 14.2, 44.8, 55.3, 55.5, 55.9, 61.6, 90.0, 92.8, 106.2, 113.5 (2),

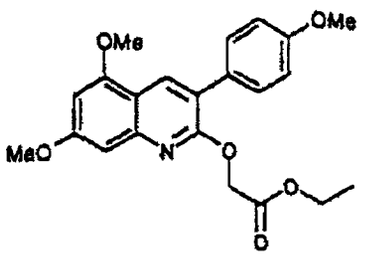
126.6, 129.6, 130.1 (2), 131.0, 141.1, 157.8, 159.2, 161.9, 162.5, 168.4.

· MS (ionspray): m/z 398 $(M+1)^+$

· *Anal.* calculated for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.60; H, 6.03; N, 3.75.

Compound ***11a***

Ethyl 2-([5,7-dimethoxy-3-(4-methoxyphenyl)-2-quinolinyl]oxy)acetate



· m.p. 95-96°C (EtOAc/PE)

· IR (KBr) n 1754, 1622, 1516, 1265 cm^{-1}

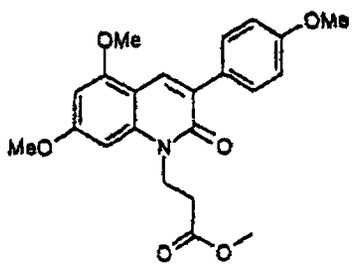
· ^1H NMR (250 MHz, $CDCl_3$): d 1.27 (t, 3H, J = 7.1 Hz, CH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.24 (q, 2H, J = 7.1 Hz, OCH_2), 5.05 (s, 2H, NCH_2), -6.40 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.76 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.98 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.68 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.30 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 14.2, 55.3, 55.5, 55.7, 60.9, 62.7, 96.2, 98.6, 113.4, 113.7 (2), 121.7, 129.2, 130.6 (2), 132.8, 147.3, 156.3, 158.8, 159.1, 161.4, 169.5.

· MS (ionspray): m/z 398$(M+1)^+$

· *Anal.* calculated for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.63; H, 5.90; N, 3.60.

EXAMPLE 10: Methyl 3-[5,7-dimethoxy-3-(4-hydroxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanoate (compound 12)

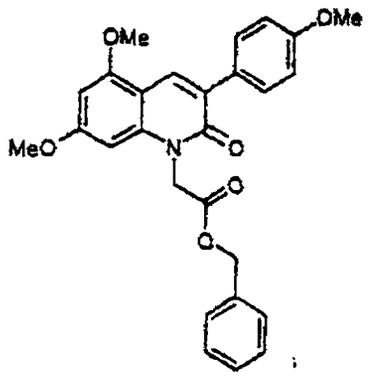


(CRL8318)

1.0 g (3.2 mmol) of compound **1** is dissolved in 20 ml of anhydrous *N,N*-dimethylformamide (DMF) in the presence of 2.9 ml of methyl acrylate (32.0 mmol, 10 eq), under a nitrogen atmosphere. At 0°C, 2-3 drops of Triton B are added to the reaction solution. The mixture is stirred for 4 h at room temperature. The DMF and methyl acrylate are evaporated off under reduced pressure. The residue obtained is taken up in ethyl acetate and washed twice with water. The organic phase obtained is dried over $MgSO_4$ and then evaporated under reduced pressure. The crude product is purified by chromatography on a column of silica (8/2 CH_2Cl_2/EtOAc) to give 1.06 g (83%) of compound **12**.

- m.p. 100-101°C (EtOAc)
- IR (KBr) 1725, 1638 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.78 (t, 2H, J = 8.0 Hz, CH_2), 3.68 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 3.88 (s, 6H, OCH_3), 4.57 (t, 2H, J = 8.0 Hz, CH_2), 6.26 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.46 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.92 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.66 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.11 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 31.9, 39.1, 51.8, 55.2, 55.5, 55.7, 89.8, 92.6, 106.2, 113.4 (2), 126.5, 129.5, 129.9 (2), 130.3, 140.5, 157.6, 159.0, 161.7, 162.4, 172.0.
- MS (ionspray): m/z 398 $(M+1)^+$
- *Anal.* calculated for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.55; H, 5.70; N, 3.50.

EXAMPLE 11: Benzyl 2-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]acetate (compound 13)



300 mg (0.96 mmol) of compound **1** are dissolved in 10 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 35 mg (1.40 mmol, 1.5 eq) of NaH, washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of benzyl bromoacetate (0.31 ml, 1.90 mmol, 2 eq) diluted in 5 ml of DMF is added to the medium. The reaction is heated at 90°C for 2 h. After cooling, water is added to the reaction mixture, which is then stirred for 15 min. The solution is extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (eluent: CH_2Cl_2) to give 317 mg (72%) of compound **13** and 88 mg (20%) of derivative **13a**.

*Compound **13**:*

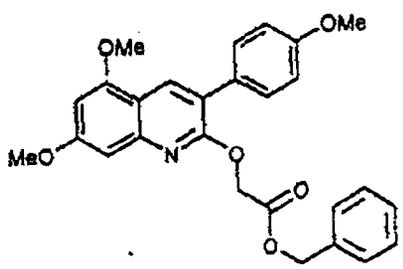
- m.p. 199-200°C (Et_2O wash)
- IR (KBr) 1748, 1642, 1617 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.68 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.16 (s, 2H, CH_2), 5.21 (s, 2H, CH_2), 6.03 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.27 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.25-7.32 (m, 5H, H_{Ar}), 7.68 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.17 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.7, 55.3, 55.4, 55.8, 67.1, 89.8, 93.0, 106.2, 113.5 (2), 126.5,

128.3 (2), 128.4, 128.5 (2), 129.5, 130.1 (2), 131.1, 135.3, 141.0, 157.8, 159.2, 161.8, 162.4, 168.3.

· MS (ionspray): m/z 460 $(M+1)^+$

*Compound **13a**:*

Benzyl 2-([5,7-dimethoxy-3-(4-methoxyphenyl)-2-quinolinyl]oxy)acetate



· m.p. 114-115°C (ether)

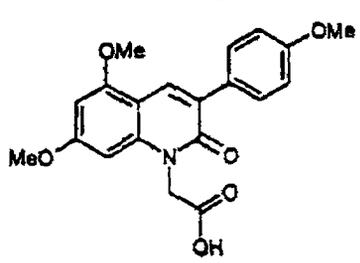
· IR (KBr) n 1761, 1621, 1517 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 6.44 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.76 (d, 2H, J = 2.0 Hz, H_{Ar}), 7.00 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.26-7.38 (m, 5H, H_{Ar}), 7.71 (d, 2H, J = 8.0 Hz, H_{Ar}), 8.36 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 55.2, 55.4, 55.5, 62.6, 66.4, 96.2, 98.5, 113.4, 113.6 (2), 121.6, 128.0 (2), 128.4 (3), 129.0, 130.5 (2), 132.7, 135.6, 147.2, 156.1, 158.6, 159.0, 161.3, 169.3.

· MS (ionspray): m/z 460 $(M+1)^+$

EXAMPLE 12: 2-[5,7-Dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]acetic acid (compound 14)



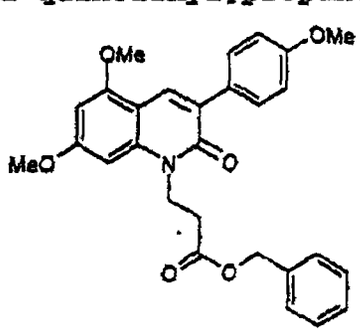
(CRL8317)

1.0 g (2.2 mmol) of benzyl ester **13** is dissolved in dioxane (30 ml) in a round-bottomed flask.

10% palladium-on-charcoal (100 mg) is added to the reaction solution. The debenzylation reaction is carried out using Parr apparatus under 40 psi of hydrogen at room temperature for 4 h. The reaction medium is filtered through Celite and the filtrate is evaporated under reduced pressure. The crystalline product obtained is washed with ether to give 764 mg (95%) of compound **14**.

- m.p. 179-180°C (Et_2O wash)
- IR (KBr) 1732, 1614, 1583 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.02 (s, 2H, CH_2), 6.46 (s, 1H, H_{Ar}), 6.47 (s, 1H, H_{Ar}), 6.93 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.62 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.03 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d: 44.9, 55.5, 56.1, 56.6, 91.3, 93.3, 105.3, 113.8 (2), 125.7, 129.4, 130.1 (2), 130.4, 141.3, 157.6, 159.1, 161.3, 162.8, 170.1.
- MS (ionspray): m/z 370 $(M+1)^+$
- *Anal.* calculated for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.00; H, 5.25; N, 3.85.

EXAMPLE 13: Benzyl 3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanoate (compound 15)

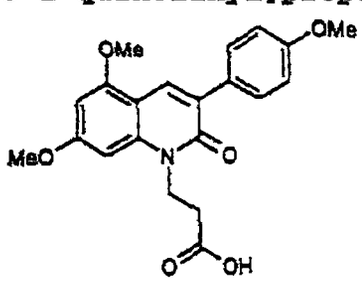


150 mg (0.48 mmol) of compound **1** are dissolved in 10 ml of anhydrous *N,N*-dimethylformamide (DMF) in the presence of 782 mg (4.8 mmol, 10 eq) of benzyl acrylate, under a nitrogen atmosphere. At 0°C, 2-3 drops of Triton B are added to the reaction solution. The solution is stirred for 18 h at room

temperature. The solvents are evaporated off under reduced pressure. The residue obtained is taken up in ethyl acetate and washed twice with water. The organic phase obtained is dried over $MgSO_4$ and then evaporated under reduced pressure. The crude product is purified by chromatography on a column of silica (4/6 EtOAc/PE) to give 200 mg (88%) of compound **15**.

- m.p. 124-125°C (Et_2O/PE)
- IR (KBr) 1731, 1635, 1600 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.86 (t, 2H, J = 8.0 Hz, $COCH_2$), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.63 (t, 2H, J = 8.0 Hz, NCH_2), 5.14 (s, 2H, CH_2Ph), 6.29 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.49 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.30-7.35 (m, 5H, H_{Ar}), 7.68 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.13 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 32.2, 39.1, 55.2, 55.4, 55.7, 66.5, 89.7, 92.6, 106.2, 113.4 (2), 126.5, 128.1 (2), 128.2, 128.4 (2), 129.5, 129.9 (2), 130.4, 135.5, 140.5, 157.6, 159.0, 161.7, 162.4, 171.3.
- MS (ionspray): m/z 474 $(M+1)^+$

EXAMPLE 14: 3-[5,7-Dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanoic acid (compound 16)



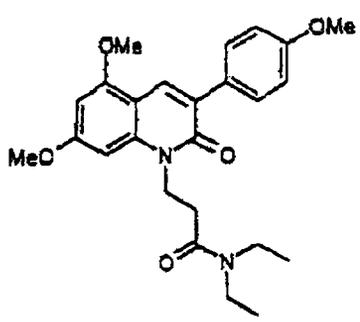
(CRL8319)

1.0 g (2.1 mmol) of benzyl ester **15** is dissolved in dioxane (30 ml) in a round-bottomed flask. 10% palladium-on-charcoal (100 mg) is added to the reaction solution. The debenzylation reaction is carried out using Parr apparatus under 40 psi of hydrogen for 48 h. The reaction medium is filtered through Celite and the filtrate is evaporated under

reduced pressure to give, after washing with ether, 780 mg (97%) of compound **16**.

- m.p. 194-195°C (Et_2O wash)
- IR (KBr) 1724, 1637, 1612, 1604 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 2.60 (t, 2H, J = 7.5 Hz, $COCH_2$), 3.78 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.48 (t, 2H, J = 7.5 Hz, NCH_2), 6.48 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.62 (broad s, 1H, H_{Ar}), 6.95 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.62 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.00 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d: 32.0, 38.9, 55.1, 55.7, 56.1, 90.6, 93.0, 105.0, 113.3 (2), 125.6, 129.3, 129.5, 129.8 (2), 140.5, 157.2, 158.7, 160.6, 162.4, 172.5.
- MS: m/z 384 $(M+1)^+$
- *Anal.* calculated for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.60; H, 5.51; N, 3.70.

EXAMPLE 15: *N,N*-Diethyl-3-[5,7-dimethoxy-3-(4-methoxy-phenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanamide (compound 17)



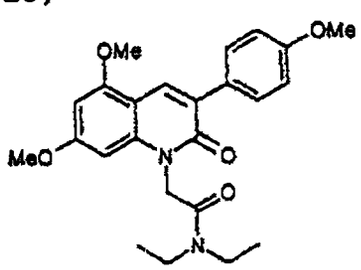
(CRL8283)

1.0 g (2.6 mmol) of compound **16** is dissolved in 25 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 353 mg (2.6 mmol) of hydroxybenzotriazole and 540 mg (2.6 mmol) of cyclohexylcarbodiimide are added to the reaction solution. The reaction is stirred for 10 minutes at 0°C, followed by addition of 0.26 ml (2.6 mmol) of diethylamine. The final solution is stirred for 2 h at 0°C and then for 24 h at room temperature. The dicyclohexylurea is removed by filtration. The filtrate is extracted with

ethyl acetate (twice). The organic phase collected is washed several times with water. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (7/3 CH_2Cl_2/EtOAc) to give 680 mg (60%) of compound **17**.

- m.p. 137-138°C (EtOAc wash)
- IR (KBr) 1636, 1617 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 1.07-1.21 (m, 6H, CH_3), 2.78 (t, 2H, J = 8.0 Hz, $COCH_2$), 3.30 (q, 2H, J = 7.0 Hz, NCH_2), 3.39 (q, 2H, J = 7.0 Hz, NCH_2), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.65 (t, 2H, J = 8.0 Hz, NCH_2), 6.29 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.73 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.67 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.15 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d; 13.1, 14.4, 31.0, 40.1, 40.5, 42.2, 55.3, 55.8 (2), 89.9, 93.1, 106.3, 113.5 (2), 126.6, 129.7, 130.0 (2), 130.5, 140.9, 157.6, 159.1, 162.1, 162.6, 169.9.
- MS (ionspray): m/z 439 $(M+1)^+$
- *Anal.* calculated for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.27; H, 6.80; N, 6.40.

EXAMPLE 16: *N,N*-Diethyl-2-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]acetamide (compound 18)



(CRL8315)

1.0 g (3.2 mmol) of compound **1** is dissolved in 30 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 115 mg (4.8 mmol, 1.5 eq) of NaH, washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of 2-chloro-*N,N*-diethylacetamide

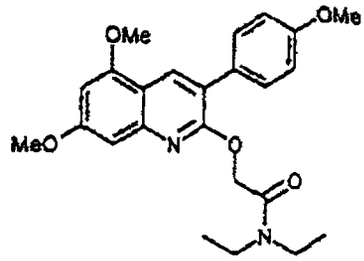
(0.88 ml, 6.4 mmol, 2 eq) diluted in 5 ml of DMF is added to the medium. The reaction is heated at 90°C for 3 h. After cooling, water is added to the reaction mixture. The reaction solution is extracted with ethyl acetate (twice). The organic phase obtained is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (7/3 CH_2Cl_2/EtOAc) to give 820 mg (61%) of compound **18** and 408 mg (30%) of derivative **18a**.

*Compound **18***:

- m.p. 178-179°C (EtOAc)
- IR (KBr) 1642, 1617, 1601 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 1.10-1.23 (m, 6H, CH_3), 3.38-3.49 (m, 4H, CH_2), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.17 (s, 2H, NCH_2CO), 6.28 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.34 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.93 (d, 2H, J = 7.0 Hz, H_{Ar}), 7.66 (d, 2H, J = 7.0 Hz, H_{Ar}), 8.17 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 13.0, 14.2, 40.9, 41.6, 45.3, 55.3, 55.5, 55.8, 90.8, 92.8, 106.3, 113.4 (2), 126.6, 129.9, 130.1 (2), 131.0, 141.7, 157.6, 159.0, 161.9, 162.3, 166.3.
- MS (ionspray): m/z 425 $(M+1)^+$
- *Anal.* calculated for $C_{24}H_{28}N_2O_5$: C, 67.91, H, 6.65; N, 6.60. Found: C, 67.62; H, 6.44; N, 6.50.

*Compound **18a**:*

***N,N*-Diethyl-2-([5,7-dimethoxy-3-(4-methoxyphenyl)-2-quinolinyl]oxy)acetamide (18a)**



- m.p. 146-147°C (EtOAc/PE)
- IR (KBr) n 1654, 1624, 1517 cm^{-1}

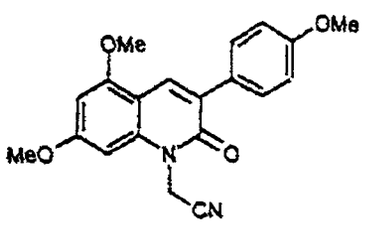
· ^{1}H NMR (250 MHz, $CDCl_3$): d 1.14 (t, 3H, J = 7.5 Hz, CH_3), 1.28 (t, 3H, J = 7.5 Hz, CH_3), 3.36-3.47 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.17 (s, 2H, NCH_2), 6.38 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.73 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.97 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.75 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.28 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 12.9, 14.2, 40.2, 55.2, 55.4, 55.6, 63.0, 95.8, 98.4, 113.3, 113.5 (2), 121.9, 129.2, 130.6 (2), 132.5, 147.3, 156.2, 158.9, 161.1, 167.3.

· MS (ionspray): m/z 425 $(M+1)^+$

· *Anal.* calculated for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.85; H, 6.70; N, 6.51.

EXAMPLE 17: [5,7-Dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]acetonitrile (compound 19)



(CRL8255)

1.0 g (3.2 mmol) of compound **1** is dissolved in 30 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 115 mg (4.8 mmol, 1.5 eq) of NaH, washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of bromoacetonitrile (0.45 ml, 6.4 mmol, 2 eq) diluted in 5 ml of DMF is added to the medium. The reaction is heated for 3 h at 90°C. After cooling, water is added to the reaction mixture. The reaction solution is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (7/3 CH_2Cl_2/EtOAc) to give 683 mg (61%) of compound **19** and 336 mg (30%) of derivative **19a**.

Compound **19**:

· m.p. 208-209°C (EtOAc)

· IR (KBr) 2216, 1660, 1607 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 3.84 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 6.36 (s, 2H, H_{Ar}), 6.95 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.65 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.17 (s, 1H, H_{Ar}).

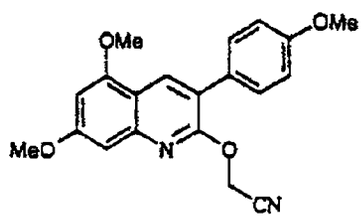
· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 30.4, 55.3, 55.8, 56.0, 90.0, 93.5, 106.2, 113.6 (2), 114.8, 126.3, 129.0, 130.0 (2), 131.7, 139.8, 158.1, 159.4, 161.1, 163.0.

· MS (ionspray): m/z 351 $(M+1)^+$

· *Anal.* calculated for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.30; H, 5.00; N, 7.90.

Compound **19a**:

2-([5,7-Dimethoxy-3-(4-methoxyphenyl)-2-quinolinyl]oxy)-acetonitrile (compound 19a)



· m.p. 149-150°C (ether)

· IR (KBr) n 1623, 1586, 1516, 1265 cm^{-1}

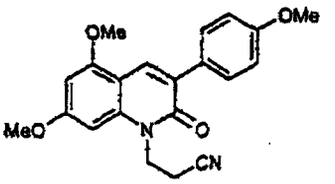
· ^1H NMR (250 MHz, $CDCl_3$): d 3.87 (s, 3H, OCH_3), 3.95 (s, 6H, OCH_3), 5.17 (s, 2H, OCH_2), 6.45 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.87 (d, 1H, J = 2.0 Hz, H_{Ar}), 7.99 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.54 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.34 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 50.1, 55.3, 55.6, 55.7, 96.9, 98.6, 113.8 (2), 113.9, 116.1, 121.3, 128.4, 130.5 (2), 133.5, 147.1, 156.3, 157.2, 129.3, 161.8.

· MS (ionspray): m/z 351 $(M+1)^+$

· *Anal.* calculated for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.03; N, 7.88.

EXAMPLE 18: 3-[5,7-Dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanenitrile (compound 20)

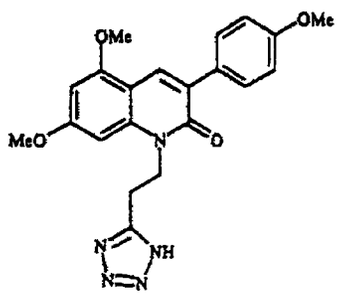


(CRL8247)

500 mg (1.6 mmol) of compound **1** and 0.8 ml (12 mmol) of acrylonitrile are dissolved in 10 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 2 drops of Triton B are added to the reaction solution. The reaction is monitored by TLC. At the end of the reaction, the solvents are evaporated off. The residue is taken up in ethyl acetate and washed several times with water. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (7/3 CH_2Cl_2/EtOAc) to give 365 mg (63%) of compound **20**.

- m.p. 156-157°C (EtOAc/PE)
- IR (KBr) 2241, 1639 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.88 (t, 2H, J = 7.1 Hz, CH_2CN), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.59 (t, 2H, J = 7.1 Hz, NCH_2), 6.33 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.45 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.95 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.66 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.17 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 15.9, 39.4, 55.3, 55.7, 55.9, 89.9, 93.0, 106.4, 113.6 (2), 117.7, 126.6, 129.2, 130.0 (2), 131.1, 140.5, 158.0, 159.3, 161.8, 162.7.
- MS (ionspray): m/z 365 $(M+1)^+$
- *Anal.* calculated for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.40; H, 5.40; N, 7.80.

EXAMPLE 19: 1-[2-(1*H*-1,2,3,4-Tetrazol-5-yl)ethyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 21)

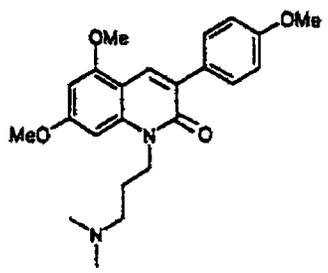


(CRL8256)

350 mg (0.90 mmol) of compound **20** and 0.42 ml (1.53 mmol) of tributyltin azide are dissolved in 20 ml of anhydrous toluene, under an argon atmosphere. The reaction solution is stirred at 105°C for 65 h. After cooling, the solvent is evaporated off under reduced pressure. The residue obtained is purified by chromatography on a column of silica (9/1 CH_2Cl_2/MeOH) to give 333 mg (85%) of compound **21**.

- m.p. 234-235°C (Et_2O wash)
- IR (KBr) 1618, 1594 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.33 (t, 2H, J = 6.0 Hz, CH_2), 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.67 (t, 2H, J = 6.0 Hz, CH_2), 6.48 (s, 1H, H_{Ar}), 6.52 (s, 1H, H_{Ar}), 6.96 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.59 (d, 2H, J = 9.0 Hz, H_{Ar}), 8.01 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 21.4, 40.8, 55.1, 55.6, 56.1, 90.4, 93.0, 105.0, 113.3 (2), 125.5, 129.3, 129.6, 129.7 (2), 140.4, 153.7, 157.2, 158.7, 160.7, 162.4.
- MS (ionspray): m/z 408 $(M+1)^+$
- *Anal.* calculated for $C_{21}H_{20}N_5O_4$: C, 61.91; H, 5.20; N, 17.19. Found: C, 62.00; H, 5.19; N, 17.30.

EXAMPLE 20: 1-[3-(Dimethylamino)propyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 22)



(CRL8254)

1.0 g (3.2 mmol) of compound **1** is dissolved in 20 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 115 mg of NaH (4.8 mmol, 1.5 eq), washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of 3-dimethylaminopropyl chloride (777 mg, 7.3 mmol, 2.25 eq) in 5 ml of DMF is added to the medium. The reaction is heated for 2-3 h at 90°C. After cooling, water is added to the reaction mixture, followed by stirring for 15 min. The solution is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (8/2 Et_2O/MeOH and then 9/1 CH_2Cl_2/MeOH) to give 887 mg (70%) of compound **22** and 317 mg (25%) of derivative **22a**.

Compound **22**:

- m.p. 94-95°C (Et_2O wash)
- IR (KBr) 1635, 1598 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 1.91-2.04 (m, 2H, CH_2), 2.28 (s, 6H, CH_3), 2.46 (t, 2H, J = 7.2 Hz, CH_2), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.36 (t, 2H, J = 7.2 Hz, CH_2), 6.29 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.54 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.68 (d, 2H, J = 8.8 Hz, H_{AR}), 8.13 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 25.5, 41.8, 45.6 (2), 55.4, 55.5, 55.8, 57.1, 90.3, 92.6, 106.4, 113.5

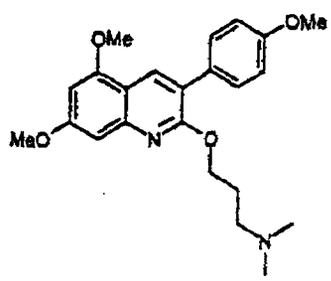
(2), 126.9, 130.0, 130.1 (2), 130.3, 141.1, 157.6, 159.1, 162.0, 162.3.

· MS: m/z 397 $(M+1)^+$

· *Anal.* calculated for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.40; H, 6.97; N, 7.15.

Compound **22a**:

N,N-Dimethyl-2-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-quinolyl]oxy-1-propanamide (compound 22a)



· m.p. 54-55°C (ether)

· IR (KBr) n 1621, 1584, 1515 cm^{-1}

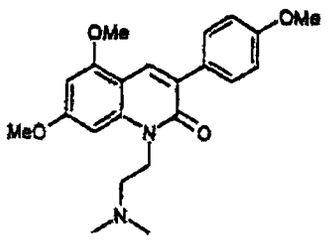
· ^1H NMR (250 MHz, $CDCl_3$): d 1.96-2.07 (m, 2H, CH_2), 2.26 (s, 6H, NCH_3), 2.47 (t, 2H, J = 6.5 Hz, NCH_2), 3.84 (s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 4.53 (t, 2H, J = 6.5 Hz, OCH_2), 6.39 (d, 1H, J = 2.2 Hz, H_{Ar}), 6.82 (d, 1H, J = 2.2 Hz, H_{Ar}), 6.96 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.57 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.26 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 27.0, 45.4 (2), 55.2, 55.5 (2), 56.6, 64.2, 95.8, 98.5, 112.7, 113.4 (2), 121.9, 129.6, 130.5 (2), 132.1, 147.9, 156.2, 158.8, 160.2, 161.2.

· MS (ionspray): m/z 397 $(M+1)^+$

· *Anal.* calculated for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.53; H, 6.92; N, 7.16.

EXAMPLE 21: 1-[2-(Dimethylamino)ethyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 23)



(CRL8316)

250 mg (0.8 mmol) of compound **1** are dissolved in 15 ml of anhydrous *N,N*-dimethylformamide (DMF), under a nitrogen atmosphere. At 0°C, 29 mg (1.2 mmol, 1.5 eq) of NaH, washed beforehand in petroleum ether, are added portionwise to the reaction solution (exothermic reaction). A solution of 2-dimethylamino-ethyl chloride (230 mg, 2.5 mmol, 3 eq) in 5 ml of DMF is added to the medium. The reaction is heated for 2-3 h at 90°C. After cooling, water is added to the reaction mixture, followed by stirring for 15 min. The solution is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (3/7 Et_2O/EtOAc and then 9/1 CH_2Cl_2/MeOH) to give 205 mg (67%) of compound **23** and 92 mg (30%) of derivative **23a**.

Compound **23**:

- m.p. 113-114°C (Et_2O wash)
- IR (KBr) 1645, 1617, 1604 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.39 (s, 6H, CH_3), 2.65 (t, 2H, J = 7.8 Hz, CH_2), 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.44 (t, 2H, J = 7.8 Hz, CH_2), 6.28 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.49 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.67 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.12 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 41.6, 45.8 (2), 55.3, 55.6, 55.8 (2), 90.1, 92.7, 106.4, 113.5 (2), 126.9,

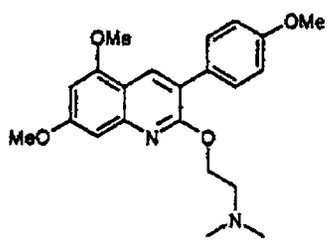
129.8, 130.1 (2), 130.4, 141.1, 157.7, 159.1, 161.9, 162.4.

· MS (ionspray): m/z 383 $(M+1)^+$

· *Anal.* calculated for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.37; H, 6.98; N, 7.51.

Compound **23a:**

N,N-Dimethyl-2-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-quinolyl]oxy-1-ethanamine



· m.p. 49-50°C (ether wash)

· IR (KBr) n 1621, 1584, 1515 cm^{-1}

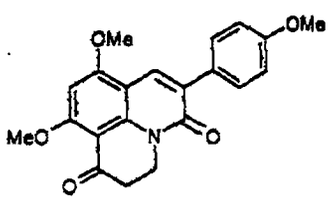
· ^1H NMR (250 MHz, $CDCl_3$): d 2.31 (s, 6H, NCH_3), 2.77 (t, 2H, J = 6.0 Hz, NCH_2), 3.85 (s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 4.62 (t, 2H, J = 6.0 Hz, OCH_2), 6.39 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.81 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.94 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.58 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.25 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 45.7 (2), 55.3, 55.5 (2), 57.8, 63.8, 95.9, 98.5, 112.9, 113.4 (2), 122.0, 129.5, 130.6 (2), 132.3, 147.8, 156.3, 158.9, 160.0, 161.3.

· MS (ionspray): m/z 383 $(M+1)^+$

· *Anal.* calculated for $C_{22}H_{26}NO_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.30; H, 6.70; N, 7.29.

EXAMPLE 22: 8,10-Dimethoxy-6-(4-methoxyphenyl)-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione (compound 24)



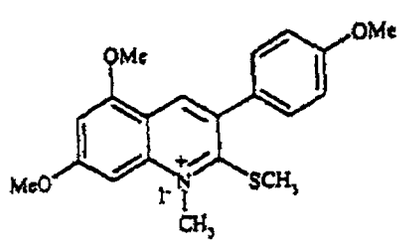
(CRL8285)

63 mg of P_2O_5 and 500 mg of PPA are introduced into a round-bottomed flask and the mixture is then stirred for 1 h at 120°C, under a nitrogen atmosphere. Compound **16** (100 mg, 0.26 mmol) is added and the reaction is then stirred for 45 min at 120°C. After cooling, 2N sodium hydroxide solution is added until a pH = 6-7 is obtained. The crude product is extracted with CH_2Cl_2 (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is purified by chromatography on a column of silica (98/2 CH_2Cl_2/MeOH) to give 62 mg (65%) of compound **24**.

- m.p. 240-241°C (CH_2Cl_2/PE)
- IR (KBr)1678, 1649, 1634 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.83 (t, 2H, J = 7.0 Hz, $COCH_2$), 3.85 (s, 3H, OCH_3), 4.04 (s, 6H, OCH_3), 4.54 (d, 2H, J = 7.0 Hz, NCH_2), 6.32 (s, 1H, H_{Ar}), 6.96 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.68 (d, 2H, J = 7.5 Hz, H_{Ar}), 8.12 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 37.6, 40.3, 55.3, 56.1, 56.5, 88.9, 103.5, 104.8, 113.6 (2), 127.6, 129.0, 129.8, 130.0 (2), 142.9, 159.4, 161.6, 161.7, 163.7, 190.3.
- MS (ionspray): m/z 366 $(M+1)^+$
- *Anal.* calculated for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.80; H, 5.34; N, 4.00.

EXAMPLE 23:

a) 5,7-Dimethoxy-3-(4-methoxyphenyl)-1-methyl-2-(methylsulfanyl)quinolium iodide (compound 25)



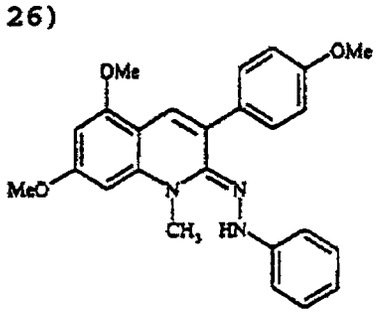
682 mg (2.0 mmol) of compound **10** are dissolved in 30 ml of anhydrous THF, under a nitrogen atmosphere. At room temperature, 3.5 ml of methyl iodide (56 mmol,

28 eq) diluted in 5 ml of THF are added and the reaction is then stirred for 18 h under inert atmosphere. The precipitate observed at the end of the reaction is filtered off on a sinter funnel (washing with THF) to give 761 mg (79%) of compound **25**.

- m.p. 156-157°C (THF wash)
- ^1H NMR (250 MHz, $CDCl_3$): d 2.44 (s, 3H, SCH_3), 3.88 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 5.03 (s, 3H, NCH_3), 6.70 (d, 1H, J = 1.5 Hz, H_{Ar}), 7.03 (d, 2H, J = 8.5 Hz, H_{Ar}), 7.37 (broad s, 1H, H_{Ar}), 7.37 (broad s, 1H, H_{Ar}), 7.45 (d, 2H, J = 8.5 Hz, H_{Ar}), 8.71 (s, 1H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 20.8, 46.5, 55.4, 56.7, 58.5, 92.9, 101.0, 114.4 (2), 117.6, 125.8, 128.9, 130.7 (2), 135.9, 138.8, 144.2, 157.4, 160.3, 167.7.

This compound is rapidly used in the next step.

b) 5,7-Dimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2-dihydro-2-quinolinone-2-phenylhydrazone (compound 26)



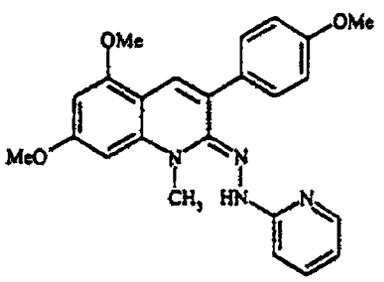
(CRL8270)

200 mg (0.4 mmol) of compound **25** and 0.28 ml (2.8 mmol, 7 eq) of phenylhydrazine are dissolved in 5 ml of anhydrous ethanol, in a sealed tube. The reaction mixture is heated for 18 h at 90°C. After cooling, the ethanol is evaporated off under reduced pressure. The residue is taken up in CH_2Cl_2 and then washed twice with sodium hydrogen carbonate solution. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in methanol, in which the final product

precipitates. This product is isolated by filtration (MeOH wash) to give 102 mg (60%) of compound **26**.

- m.p. 148-149°C (MeOH wash)
- IR (KBr) 3340, 1602, 1599 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.58 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.04 (s, 1H, H_{Ar}), 6.14 (s, 1H, H_{Ar}), 6.48 (broad s, 1H, NH), 6.56-6.67 (m, 3H, H_{Ar}), 6.94 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.11 (t, 2H, J = 7.7 Hz, H_{Ar}), 7.28 (s, 1H, H_{Ar}), 7.28-7.34 (m, 2H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 33.3, 55.4 (2), 55.6, 89.6 (2), 111.6, 113.8 (2), 117.8, 125.9, 128.3, 128.9 (3), 129.5 (2), 130.5, 146.2, 157.2, 159.2 (2), 162.3.
- MS (ionspray): m/z 416 $(M+1)^+$
- *Anal.* calculated for $C_{25}H_{25}N_3O_3$: C, 72.27; H, 6.06; N, 10.11. Found: C, 72.01; H, 5.86; N, 10.02.

EXAMPLE 24: 5,7-Dimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2-dihydro-2-quinolinone-2-(2-pyridyl)hydrazone (compound 27)



(CRL8266)

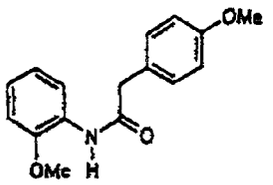
150 mg (0.31 mmol) of compound **25** and 237 mg (2.2 mmol, 7 eq) of 2-hydrazinopyridine are dissolved in 5 ml of anhydrous ethanol, in a sealed tube. The reaction mixture is heated for 18 h at 90°C. After cooling, the ethanol is evaporated off under reduced pressure. The residue is taken up in CH_2Cl_2 and then washed twice with sodium hydrogen carbonate solution. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in methanol, in which the final product

precipitates. This product is filtered off (MeOH wash) to give 75 mg (58%) of the orange-colored compound **27**.

- m.p. 182-183°C (MeOH wash)
- IR (KBr) 3353, 1628, 1593 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.61 (s, 3H, NCH_3), 3.87 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 6.07 (s, 1H, H_{Ar}), 6.17 (s, 1H, H_{Ar}), 6.51-6.55 (m, 1H, H_{pyr}), 6.94-7.01 (m, 3H, H_{Ar} + H_{pyr}), 7.14 (broad s, 1H, NH), 7.32-7.36 (m, 3H, H_{Ar}), 7.48 (t, 1H, J = 7.3 Hz, H_{pyr}), 7.91 (d, 1H, J = 4.3 Hz, H_{pyr}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 33.2, 55.3, 55.4, 55.6, 89.7 (2), 104.7, 105.7, 113.4, 114.1 (2), 122.9, 129.0, 129.2 (2), 130.1, 137.5, 140.7, 143.7, 147.8, 157.3, 157.4, 159.2, 162.4.
- MS (ionspray): m/z 417 $(M+1)^+$
- *Anal.* calculated for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.50; H, 6.04; N, 13.28.

EXAMPLE 25:

a) *N*-(2-Methoxyphenyl)-2-(4-methoxyphenyl)acetamide (compouund 30)

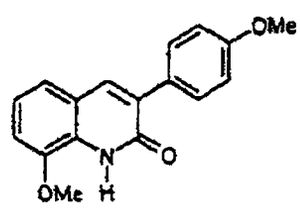


0.46 ml (4.1 mmol) of *o*-anisidine is diluted in toluene (7 ml) at 0°C, under a nitrogen atmosphere. A solution of 4-methoxyphenylacetyl chloride (0.63 ml, 4.1 mmol) in 5 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 1 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is taken up in petroleum ether, which causes precipitation of the desired

product. The crystals thus formed are collected by filtration to give 1.0 g (91%) of compound **30**.

- m.p. 47-48°C (toluene)
- IR (KBr) n 3375, 1667, 1597 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.68 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.79 (dd 1H, J = 1.5, 8.0 Hz, H_{Ar}), 6.89-7.03 (m, 4H, H_{Ar}), 7.25 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.79 (broad s, 1H, NH), 8.33 (dd, 1H, J = 1.5, 8.0 Hz, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.2, 55.3, 55.7, 109.9, 114.4 (2), 119.5, 121.0, 123.6, 126.6, 127.6, 130.7 (2), 147.8, 158.9, 169.3.
- MS (ionspray): m/z 272 $(M+1)^+$

b) 8-Methoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 31)



0.31 ml (4.0 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 1.75 ml (19 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and then 723 mg of amide **30** (2.7 mmol) are added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 1.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with 30% aqueous ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is dissolved in 4.75 ml of glacial acetic acid and 0.15 ml of water and the final solution is then refluxed for 3 h. The acetic acid is evaporated off. The residue is dissolved in water, neutralized with 25% sodium hydroxide solution and then finally extracted with dichloromethane. The

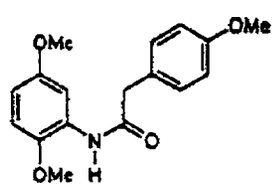
organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which causes precipitation of the final product. The crystals thus obtained are filtered off to give 75 mg (10%) of compound **31**.

The overall yield for the synthesis carried out to obtain compound **31** is 9%.

- m.p. 148-149°C (EtOAc)
- IR (KBr) n 1652, 1625, 1606, 1541 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.79 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.99 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.09-7.15 (m, 2H, H_{Ar}), 7.29 (dd, 1H, J = 3.2, 6.0 Hz, H_{Ar}), 7.74 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.03 (s, 1H, H_{Ar}), 10.90 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 55.2, 56.0, 110.5, 113.4 (2), 119.6, 120.0, 121.8, 127.9, 128.5, 129.9 (2), 131.6, 136.4, 145.3, 159.1, 160.7.
- MS (ionspray): m/z 282 $(M+1)^+$
- *Anal.* calculated for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.50; H, 5.50; N, 4.83.

EXAMPLE 26:

a) *N*-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)acetamide (compound 32)

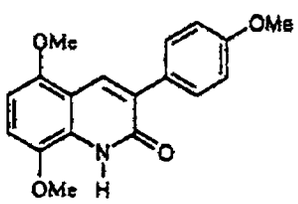


1.0 g (6.5 mmol) of 2,5-dimethoxyaniline is dissolved in toluene (7 ml) at 0°C, under a nitrogen atmosphere. A solution of 4-methoxyphenylacetyl chloride (1.0 ml, 6.5 mmol) diluted in 5 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 1 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice).

The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is taken up in a minimum amount of petroleum ether, which causes precipitation of the final product. The crystals formed are filtered off on a sinter funnel to give 1.83 g (93%) of compound **32**.

- m.p. 89-90°C (toluene)
- ^1H NMR (250 MHz, $CDCl_3$): d 3.67 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.53 (dd, 1H, J = 3.0, 9.0 Hz, H_{Ar}), 6.71 (d, 1H, J = 9.0 Hz, H_{Ar}), 6.92 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.25 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.82 (broad s, 1H, NH), 8.80 (d, 1H, J = 3.0 Hz, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.2, 55.3, 55.7, 56.3, 105.5, 108.6, 110.9, 114.4 (2), 126.4, 128.3, 130.6 (2), 142.0, 153.9, 158.9, 169.3.
- MS (ionspray): m/z 302 $(M+1)^+$

b) 5,8-Dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone (compound 33)



(CRL8336)

0.31 ml (4.0 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 1.75 ml (20 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and 813 mg of amide **32** (2.7 mmol) are then added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 1.5 h. After this period, the solution is poured onto crushed ice, neutralized with aqueous 30% ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is taken up in 4.75 ml of glacial acetic acid and 0.15 ml of water and the final solution is then refluxed for 3 h. The acetic acid is evaporated

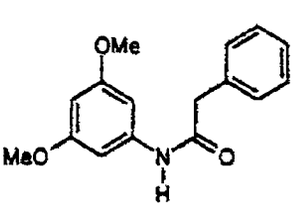
off. The residue is dissolved in water, neutralized with 25% sodium hydroxide solution and then finally extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which causes precipitation of the final compound. The crystals thus obtained are filtered off to give 378 mg (45%) of compound **33**.

The overall yield for the chemical synthesis to obtain compound **33** is 42%.

- m.p. 186-187°C (EtOAc)
- IR (KBr) n 1639, 1571, 1515 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.49 (d, 1H, J = 8.7 Hz, H_{Ar}), 6.84 (d, 1H, J = 8.7 Hz, H_{Ar}), 6.97 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.74 (d, J = 8.8 Hz, H_{Ar}), 8.19 (s, 1H, H_{Ar}), 9.25 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 55.2, 55.8, 56.2, 101.1, 109.7, 111.4, 113.6 (2), 128.7, 128.8, 130.0 (2), 131.4, 131.7, 139.4, 149.8, 159.5, 161.3.
- MS (ionspray): m/z 312 $(M+1)^+$
- *Anal.* calculated for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.71; H, 5.59; N, 4.70.

EXAMPLE 27: 5,7-Dimethyl-3-phenyl-1,2-dihydro-2-quinolinone (compound 34)

a) *N*-(3,5-Dimethoxyphenyl)-2-phenylacetamide (compound 35)

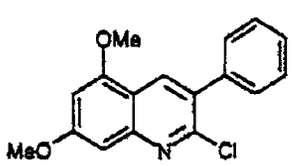


1.0 g (6.5 mmol) of 3,5-dimethoxyaniline is dissolved in toluene (14 ml) at 0°C, under a nitrogen atmosphere. A solution of phenylacetyl chloride (0.86 ml, 6.5 mmol) in 10 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 1 h and the medium is then

hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is crystallized from toluene to give 1.55 g (87%) of compound **35**.

- m.p. 109-111°C (toluene)
- IR (KBr) n 3286, 1657, 1616 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 3.70 (s, 2H, CH_2), 3.74 (s, 6H, OCH_3), 6.21 (t, 1H, J = 2.2 Hz, H_{Ar}), 6.66 (d, 2H, J = 2.2 Hz, H_{Ar}), 7.09 (broad s, 1H, NH), 7.30-7.40 (m, 5H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.9, 55.4 (2), 96.8, 97.9 (2), 127.7, 129.2 (2), 129.5 (2), 134.3, 139.4, 161.0 (2), 169.1.
- MS (ionspray): 272 $(M+1)^+$

b) 2-Chloro-5,7-dimethoxy-3-phenyl-1,2-dihydroquinoline (compound 36)



0.64 ml (8.3 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 3.8 ml (41.0 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and 1.5 g of amide **35** (5.5 mmol) are then added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 2.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with aqueous 30% ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (eluent: 3/7 EtOAc/PE) to give 800 mg (49%) of compound **36**.

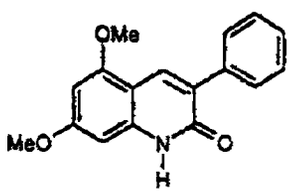
· m.p. 148-150°C

· ^1H NMR (250 MHz, $CDCl_3$): d 3.93 (s, 6H, OCH_3), 6.51 (d, 1H, J = 2.2 Hz, H_{Ar}), 6.97 (d, 1H, J = 2.2 Hz, H_{Ar}), 7.40-7.54 (m, 5H, H_{Ar}), 8.36 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.9 MHz, $CDCl_3$): d 55.6, 55.8, 98.6, 98.8, 115.6, 127.9, 128.1 (2), 129.7 (2), 131.2, 133.9, 138.1, 149.2, 150.2, 156.1, 162.3.

· MS (ionspray): m/z 301 $(M+1)^+$, 303 $(M+3)^+$

c) 5,7-Dimethoxy-3-phenyl-1,2-dihydro-2-quinolinone (compound 34)



I (CRL8330)

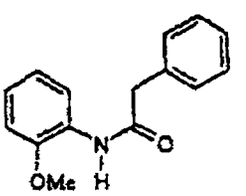
1.52 g (9.9 mmol) of 3,5-dimethoxyaniline and 2.30 g (12 mmol, 1.2 eq) of ethyl α-formylphenylacetate are mixed together in a round-bottomed flask under a nitrogen atmosphere. The medium is stirred for 1 h at room temperature. A solution of trimethylsilyl polyphosphate (PPSE), freshly prepared from 4.56 g (0.03 mol) of P_2O_5, 10.9 ml (0.17 mol) of hexamethyldisiloxane and 50 ml of 1,2-dichloroethane, is added. The final mixture is maintained at 100°C for 2 h. The heating is stopped and ice is then added to the reaction mixture. This mixture is then neutralized by addition of saturated sodium hydrogen carbonate solution (portionwise addition, exothermic reaction). The product is extracted with dichloromethane (large amount to be used). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which causes precipitation of the desired compound. The final product is isolated by filtration through a sinter funnel. After partial concentration of the filtrate, the final product reprecipitates. The solid is reisolated by filtration, this operation being repeated

several times. Compound **34** (444 mg) is obtained in a yield of 16%.

- m.p. 257-258°C (EtOAc)
- IR (KBr) n 1668, 1631, 1569, 1514 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 3.81 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.36 (d, 1H, J = 1.8 Hz, H_{Ar}), 6.45 (d, 1H, J = 1.8 Hz, H_{Ar}), 7.28-7.42 (m, 3H, H_{Ar}), 7.69 (d, 2H, J = 7.0 Hz, H_{Ar}), 8.00 (s, 1H, H_{Ar}), 11.81 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 55.5, 56.0, 90.0, 93.1, 104.5, 126.9, 127.3, 127.9 (2), 128.4 (2), 131.4, 136.7, 140.8, 156.8, 161.4, 162.2.
- MS (ionspray): m/z 282 $(M+1)^+$
- *Anal.* calculated for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.29; H, 5.20; N, 5.10.

EXAMPLE 28:

a) *N*-(2-Methoxyphenyl)-2-phenylacetamide (compound 37)



1.37 ml (0.01 mmol) of *o*-anisidine are dissolved in toluene (14 ml) at 0°C, under a nitrogen atmosphere. A solution of phenylacetyl chloride (1.62 ml, 0.01 mmol) in 5 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 1 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue obtained is dissolved in a minimum amount of toluene, which causes precipitation of the final product. After filtration through a sinter funnel, 2.7 g (92%) of compound **37** are isolated.

3-(3,4-Dimethoxyphenyl)-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}propanoic acid dihydrochloride (CRL42590)

Starting material: compound 12

Yield = 80%

MS-Cl: *m/z*: 547 $(M + H)^+$

^{1}H-NMR (400MHz, CD_3OD): δ 1.15-1.65 (m, 14H), 1.8 (m, 4H), 2.25 (m, 1H), 2.85 (m, 6H), 3.3 (bs, 4H), 3.78 (s, 3H), 3.8 (s, 3H), 3.85 (m, 2H), 5.25 (t, 1H), 6.85 (d, 2H), 6.95 (d, 1H).

EXAMPLE 9:

3-[(3-Carboxymethoxy)phenyl]-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}-propanoic acid dihydrochloride (CRL42639)

Starting material: compound 13

Yield = 79%

^{1}H-NMR (400MHz, CD_3OD): δ 1.2-1.65 (m, 14H), 1.85 (m, 4H), 2.25 (m, 1H), 2.7-3.0 (m, 6H), 3.3 (bs, 4H), 3.78 (d, 2H), 4.68 (s, 2H), 5.3 (t, 1H), 6.82 (d, 1H), 6.95 (m, 2H), 7.25 (t, 1H).

EXAMPLE 10:

3-(3-Methoxyphenyl)-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}propanoic acid dihydrochloride (CRL42660)

Starting material: compound 14

Yield = 81%

MS (ES) : *m/2* 517 $(M + H)^+$

^{1}H-NMR (400MHz, CD_3OD): δ 1.4 (m, 8H), 1.55 (m, 2H), 1.68 (m, 4H), 1.95 (bs, 4H), 2.3 (m, 1H), 2.9 (dd, 2H), 3.0 (m, 4H), 3.4 (m, 4H), 3.86 (s, 3H), 3.95 (s, 2H), 5.4 (m, 1H), 6.9 (m, 1H), 7.0 (m, 2H), 7.3 (t, 1H).

EXAMPLE 11:

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}propanoic acid dihydrochloride (CRL42718)

Starting material: compound 15

Yield = 84%

MS(ES): *m/z* 545 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6 + D_2O): δ 1.1 (m, 4H), 1.25 (m, 6H), 1.4 (m, 4H), 1.7 (m, 4H), 2.15 (m, 1H), 2.6 (t, 2H), 2.75 (m, 4H), 3.15 (bd, 4H), 3.7 (s, 2H), 4.05 (s, 4H), 5.05 (m, 1H), 6.72 (s, 1H), 6.78 (d, 2H).

EXAMPLE 12:

3-(3-Pyridyl)-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}propanoic acid trihydrochloride (CRL42722)

Starting material: compound 16

Yield = 95%

MS(ES): *m/z* 488 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.1 (m, 4H), 1.25 (m, 6H), 1.4 (m, 4H), 1.65 (m, 4H), 2.15 (m, 1H), 2.85 (m, 4H), 2.9 (bd, 2H), 3.15 (m, 4H), 3.7 (m, 2H), 5.25 (m, 1H), 8.1 (bs, 1H), 8.25 (bs, 2H), 8.65 (d, 1H), 8.85 (bs, 1H), 8.95 (m, 4H), 9.2 (bs, 2H).

EXAMPLE 13:

3-{[2-({4-(4-Piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}propanoic acid dihydrochloride (CRL43040)

Starting material: compound 17

Yield = 100%

MS(ES): *m/z* 411 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.3 (m, 6H), 1.45 (m, 4H), 1.75 (bd, 4H), 2.15 (m, 1H), 2.35 (t, 2H), 2.75 (bq, 4H), 3.15 (bd, 4H), 3.25 (q, 2H), 3.65 (d, 2H), 7.9 (t, 1H), 8.15 (t, 1H), 8.85 (bq, 2H), 9.15 (bd, 2H).

EXAMPLE 14:

3-{[2-({4-(4-Piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}butanoic acid dihydrochloride (CRL43041)

Starting material: compound 18

Yield = 100%

MS(ES): *m/z* 425 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.1 (d, 3H), 1.15 (m, 4H), 1.3 (m, 6H), 1.4 (m, 4H), 1.7 (bd, 4H), 2.15 (m, 1H), 2.25 (q, 1H), 2.45 (q, 1H), 2.75 (bq, 4H), 3.15 (bd, 4H), 3.6 (m, 2H), 4.05 (m, 1H), 7.85 (d, 1H), 8.1 (t, 1H), 8.8 (bq, 2H), 9.1 (bd, 2H).

EXAMPLE 15:

5-Phenyl-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}pentanoic acid dihydrochloride (CRL43042)

Starting material: compound 19

Yield = 100%

MS(ES): *m/z* 515 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.25 (m, 6H), 1.45 (m, 4H), 1.75 (m, 6H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (m, 1H), 2.65 (m, 1H), 2.75 (bq, 4H), 3.15 (bd, 4H), 3.7 (bq, 2H), 4.05 (m, 1H), 7.2 (m, 3H), 7.25 (t, 2H), 7.95 (d, 1H), 8.2 (t, 1H), 8.8 (bs, 2H), 9.15 (bd, 2H).

EXAMPLE 16:

(3S)-4-(1-Adamantylamino)-4-oxo-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}butanoic acid dihydrochloride (CRL42592)

Starting material: compound 20

Yield = 94%

MS(ES): *m/z* 588 $(M + H)^+$

^{1}H-NMR (400MHz, CD_3OD): δ 1.25 (m, 10H), 1.5 (m, 4H),1.6 (s, 6H), 1.82 (bd, 4H), 1.9 (bs, 9H), 2.2 (m, 1H), 2.6 (m, 2H), 2.86 (bt, 4H), 3.25 (bd, 4H), 3.7 (d, 2H), 4.5 (t, 1H).

EXAMPLE 17:

(3S)-4-{[2-(1H-Indol-4-yl)ethyl]amino)-4-oxo-3-{[2-({4-(4-piperidyl)-2-[2-(4-

piperidyl)ethyl]butanoyl}amino)acetyl]amino}butanoic acid dihydrochloride (CRL42678)

Starting material: compound 21

Yield = 100%

MS(ES): *m/z* 597 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.3 (m, 6H), 1.45 (m, 4H), 1.75 (m, 4H), 2.2 (m, 1H), 2.55 (m, 2H), 2.75 (m, 6H), 3.15 (m, 4H), 3.35 (m, 2H),3.75 (bs, 2H), 4.6 (m, 1H), 6.98 (t, 1H), 7.08 (t, 1H), 7.16 (s, 1H), 7.35 (m, 1H), 7.55 (d, 1H), 8.1 (d, 1H), 8.2 (bs, 2H), 8.9 (bs, 2H), 9.2 (bs, 2H), 10.9 (bs, 1H).

EXAMPLE 18:

(3S)-4-[(4-Methoxyphenyl)ethylamino]-4-oxo-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}butanoic acid dihydrochloride (CRL42694)

Starting material: compound 22

Yield = 97%

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.25 (m, 6H), 1.45 (m, 4H), 1.8 (bd, 4H), 2.15 (m, 1H), 2.5 (m, 2H), 2.65 (t, 2H), 2.75 (bd, 4H), 3.15 (bd, 6H), 3.7 (s, 5H), 4.55 (m, 1H), 6.85 (d, 2H), 7.15 (d, 2H), 8.1 (d, 1H), 8.15 (m, 2H), 8.95 (bd, 2H), 9.2 (bd, 2H).

EXAMPLE 19:

(3S)-4-(3-Phenylpropylamino)-4-oxo-3-{[2-({4-(4-piperidyl)-2-[2-(4-piperidyl)ethyl]butanoyl}amino)acetyl]amino}butanoic acid dihydrochloride (CRL42719)

Starting material: compound 23

Yield = 100%

MS(ES): *m/z* 572 $(M + H)^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.3 (m, 6H), 1.4 (m, 4H), 1.7 (m, 6H), 2.15 (m, 1H), 2.55 (m, 4H), 2.75 (bd, 4H), 3.05 (m, 2H), 3.2 (bd, 4H), 3.7 (d, 2H), 4.55 (m, 1H), 7.2 (m, 5H), 8.15 (m, 3H), 8.9 (bs, 2H), 9.15 (bs, 2H).

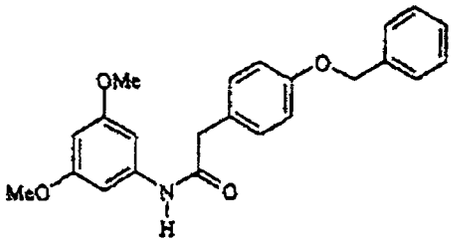
119.5, 122.0, 129.5, 130.5 (2), 132.8, 147.9, 156.4, 159.1, 159.7, 161.6.

· MS (ionspray): m/z 379 (M^++1)

· *Anal.* calculated for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.99; H, 5.72; N, 7.60.

EXAMPLE 31:

a) *N*-(3,5-Dimethoxyphenyl)-2-(4-benzyloxyphenyl)-acetamide (compound 41)



238 mg (1.6 mmol) of 3,5-dimethoxyaniline are dissolved in toluene (7 ml) at 0°C, under a nitrogen atmosphere. A solution of 4-benzylphenylacetyl chloride (0.5 ml, 1.7 mmol) in 5 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 2 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (4/6 EtOAc/PE) to give 300 mg (81%) of compound **41**.

· m.p. 122-123°C (EtOAc/PE)

· IR (KBr) n 291, 1659, 1610, 1595, 1513 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 3.66 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.08 (s, 2H, CH_2), 6.21 (t, 1H, J = 2.2 Hz, H_{Ar}), 6.65-6.66 (m, 2H, J = 2.2 Hz, H_{Ar}), 7.00 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.08 (s, 1H, NH), 7.24 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.33-7.46 (m, 5H, H_{Ar}).

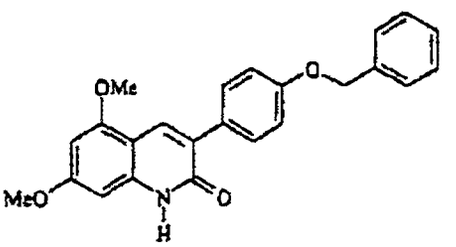
· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 44.2, 55.5 (2), 70.2, 96.9, 98.0 (2), 115.7 (2), 126.6, 127.6 (2), 128.2,

128.8 (2), 130.8 (2), 136.9, 139.6, 158.4, 161.1 (2), 169.7.

· MS (ionspray): 378 (M^++1)

· *Anal.* calculated for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 72.87; H, 5.97; N, 3.85.

b) 5,7-Dimethoxy-3-(4-benzyloxyphenyl)-1,2-dihydro-2-quinolinone (compound 42)



0.31 ml (4.0 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 1.75 ml (19 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and 1.02 g of amide **41** (2.7 mmol) are then added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 1.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with aqueous 30% ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is dissolved in 4.75 ml of glacial acetic acid and 0.15 ml of water and the final solution is then refluxed for 3 h. The acetic acid is evaporated off. The residue is dissolved in water, neutralized with 25% sodium hydroxide solution and then finally extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which causes precipitation of the final product. The crystals thus obtained are filtered off to give 200 mg (20%) of compound **42**.

· m.p. 234-235°C (EtOAc)

· IR (KBr): n 1629, 1608, 1569, 1515 cm^{-1}

· ^{1}H NMR (250 MHz, DMSO-d_6): d 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 6.37 (s, 1H, H_{Ar}), 6.45 (s, 1H, H_{Ar}), 7.04 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.31-7.49 (m, 5H, HAr), 7.69 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.97 (s, 1H, H_{Ar}), 11.76 (broad s, 1H, NH).

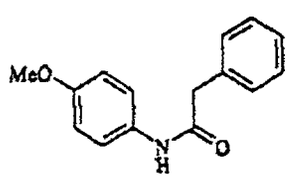
· ^{13}C NMR (62.90 MHz, DMSO-d_6): d 55.4, 55.9, 69.2, 90.0, 93.0, 104.6, 114.3 (2), 126.4, 127.6 (2), 127.8, 128.4 (2), 129.2, 129.6 (2), 130.2, 137.1, 140.5, 156.6, 157.7, 161.5, 161.9.

· MS (ionspray): m/z 388 (M^++1)

· *Anal.* calculated for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.26; H, 5.67; N, 3.52.

EXAMPLE 32:

a) *N*-(4-Methoxyphenyl)-2-phenylacetamide (compound 43)



1.5 g (12.0 mmol) of *p*-anisidine are dissolved in toluene (7 ml) at 0°C, under a nitrogen atmosphere. A solution of phenylacetyl chloride (1.61 ml, 12.2 mmol) in 20 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 2 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (3/7 EtOAc/PE) to give 2.6 g (89%) of compound **43**.

· m.p. 118-119°C (EtOAc/PE)

· IR (KBr): n 3290, 1650, 1603, 1545, 1513 cm^{-1}

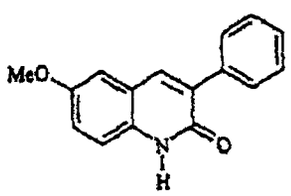
· ^{1}H NMR (250 MHz, $CDCl_3$): d 3.72 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.81 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.00 (broad s, 1H, NH), 7.28-7.43 (m, 7H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): dδ. 44.8, 55.6, 114.2 (2), 121.9 (2), 127.7, 129.3 (2), 129.7 (2), 130.8, 134.7, 156.7, 169.1.

· MS (ionspray): 242 (M^++1)

· *Anal.* calculated for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.79; H, 6.14; N, 5.95.

b) 6-Methoxy-3-phenyl-1,2-dihydro-2-quinolinone (compound 44)



0.96 ml (12.4 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 5.4 ml (58 mmol, 7.5 eq) of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and 2.0 g of amide **43** (8.3 mmol) are then added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 1.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with aqueous 30% ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is dissolved in 12.2 ml of glacial acetic acid and 0.4 ml of water and the final solution is then refluxed for 3 h. The acetic acid is evaporated off. The residue is dissolved in water, neutralized with 25% sodium hydroxide solution and then finally extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which causes precipitation of the final product. The crystals thus obtained are filtered off to give 585 mg (28%) of compound **44**.

· m.p. 243-244°C (EtOAc)

· IR (KBr) n 1645, 1618, 1569, 1503 cm^{-1}

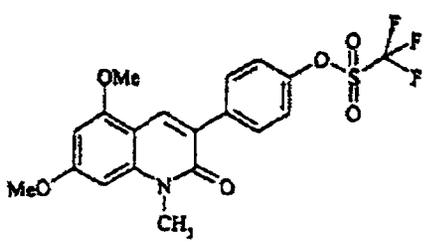
· ^1H NMR (250 MHz, DMSO-d_6): d 3.80 (s, 3H, OCH_3), 7.16 (dd, 1H, J = 2.5, 8.9 Hz, H_{Ar}), 7.28 (d, 1H, J = 8.9 Hz, H_{Ar}), 7.29 (d, 1H, J = 2.5 Hz, H_{Ar}), 7.34-7.47 (m, 3H, H_{Ar}), 7.76 (d, 2H, J = 6.8 Hz, H_{Ar}), 8.06 (s, 1H, H_{Ar}), 11.85 (broad s, 1H, NH).

· ^{13}C NMR (62.90 MHz, DMSO-d_6): d 55.4, 109.4, 116.0, 119.5, 120.1, 127.8, 127.9 (2), 128.7 (2), 131.9, 132.9, 136.4, 137.2, 154.2, 160.6.

· MS (ionspray): m/z 252 (M^++1)

· *Anal.* calculated for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.16; H, 5.11; N, 5.66.

EXAMPLE 33: 5,7-Dimethoxy-3-(4-trifluoromethane-sulfonylphenyl)-1,2-dihydro-2-quinolinone (compound 45)



170 mg (0.55 mmol) of compound **8** are dissolved in triflic anhydride and pyridine (8 ml, v/v) at 0°C, under a nitrogen atmosphere. The reaction mixture is stirred at room temperature for 2 h. The medium is hydrolyzed by addition of water (10 ml) and is then extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (1/9 EtOAc/CH_2Cl_2) to give 194 mg (80%) of compound **45**.

· m.p. 144-145°C (EtOAc)

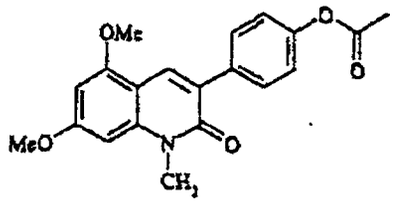
· IR (KBr): n 1646, 1618, 1602, 1504 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 3.75 (s, 3H, NCH_3), 3.94 (s, 6H, CH_3), 6.32 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.39 (d, 1H, J = 2.0 Hz, H_{Ar}), 7.30 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.82 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.19 (s, 1H, H_{Ar}).

· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 30.5, 55.8, 56.0, 90.4, 93.0, 106.0, 121.0 (2), 125.3, 130.9 (3), 132.1, 138.1, 148.9, 158.0, 161.8, 163.2.

· MS (ionspray): m/z 444 (M^++1)

EXAMPLE 34: 5,7-Dimethoxy-3-(4-acetylphenyl)-1,2-dihydro-2-quinolinone (compound 46)



200 mg (0.64 mmol) of compound **8** are dissolved in acetic anhydride and pyridine (8 ml, v/v) at 0°C, under a nitrogen atmosphere. The reaction mixture is stirred at room temperature for 18 h. The medium is hydrolyzed by addition of water (10 ml) and is then extracted with dichloromethane (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (1/9 EtOAc/CH_2Cl_2) to give 165 mg (73%) of compound **46**.

· m.p. 148-149°C (EtOAc/PE)

· IR (KBr): n 1751, 1639, 1601, 1508 cm^{-1}

· ^1H NMR (250 MHz, $CDCl_3$): d 2.31 (s, 3H, CH_3), 3.72 (s, 3H, NCH_3), 3.90 (s, 6H, CH_3), 6.28 (d, 1H, J = 2.0 Hz, H_{Ar}), 6.34 (d, 1H, J = 2.0 Hz, H_{Ar}), 7.13 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.75 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.15 (s, 1H, H_{Ar}).

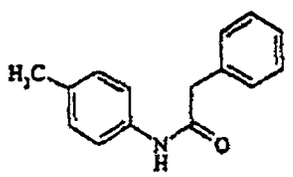
· ^{13}C NMR (62.90 MHz, $CDCl_3$): d 21.3, 30.4, 55.7, 55.9, 90.3, 92.7, 106.0, 121.1 (2), 126.3, 130.1 (3), 131.4, 142.1, 150.1, 157.8, 162.0, 162.7, 169.6.

· MS (ionspray): m/z 354 (M^++1)

· *Anal.* calculated for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.23; H, 5.56; N, 3.79.

EXAMPLE 35:

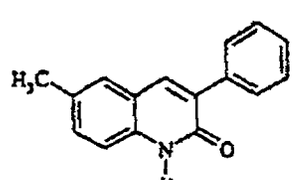
a) *N*-(4-Methylphenyl)-2-phenylacetamide (47)



1.0 g (9.3 mmol) of 4-methylaniline is dissolved in toluene (10 ml) at 0°C, under a nitrogen atmosphere. A solution of phenylacetyl chloride (1.25 ml, 9.4 mmol) in 20 ml of toluene is added dropwise to the medium. The reaction mixture is stirred at room temperature for 2 h and the medium is then hydrolyzed with cold sodium hydrogen carbonate solution. The two-phase system is stirred vigorously for 30 min and the organic phase is then collected. The aqueous phase is extracted with ethyl acetate (twice). The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is purified by chromatography on a column of silica (3/7 EtOAc/PE) to give 1.9 g (92%) of compound **47**.

- m.p. 119-120°C (EtOAc)
- IR (KBr) n 3310, 1657, 1604, 1536, 1514 cm^{-1}
- ^1H NMR (250 MHz, $CDCl_3$): d 2.28 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 7.06 (d, 1H, J = 8.5 Hz, H_{Ar}), 7.25-7.38 (m, 9H, H_{Ar}).
- ^{13}C NMR (62.90 MHz, $CDCl_3$): d 21.0, 44.9, 120.1 (2), 127.7, 129.3 (2), 129.5 (2), 129.6 (2), 134.2, 134.7, 135.2, 169.2.
- MS (ionspray): 226 (M^++1)
- *Anal.* calculated for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.23; H, 6.87; N, 6.11.

b) 6-Methyl-3-phenyl-1,2-dihydro-2-quinolinone (48)



0.41 ml (5.3 mmol, 1.5 eq) of *N,N*-dimethylformamide is added dropwise to 3.3 ml (25 mmol, 7 eq)

of $POCl_3$, under a nitrogen atmosphere and at -30°C. The medium is stirred for 15 min at -30°C and 800 mg of amide **47** (3.5 mmol) are then added. The reaction mixture is warmed to room temperature with stirring and the reaction is then heated at 75°C for 1.5 h. At the end of the reaction, this solution is poured onto crushed ice, neutralized with aqueous 30% ammonia solution and then extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated. The residue obtained is dissolved in 5.4 ml of glacial acetic acid and 0.2 ml of water and the final solution is then refluxed for 3 h. The acetic acid is evaporated off. The residue is dissolved in water, neutralized with 25% sodium hydroxide solution and then finally extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and then evaporated under reduced pressure. The residue is taken up in ethyl acetate, which brings about precipitation of the final product. The crystals thus obtained are filtered off to give 80 mg (10%) of compound **48**.

- m.p. 212-213°C (EtOAc)
- IR (KBr): n 1657, 1570 cm^{-1}
- ^1H NMR (250 MHz, DMSO-d_6): d 2.35 (s, 3H, CH_3), 7.25 (d, 1H, J = 8.5 Hz, H_{Ar}), 7.33-7.48 (m, 5H, H_{Ar}), 7.51 (broad s, 1H, H_{Ar}), 7.76 (d, 2H, J = 8.9 Hz, H_{Ar}), 8.02 (s, 1H, H_{Ar}), 11.87 (broad s, 1H, NH).
- ^{13}C NMR (62.90 MHz, DMSO-d_6): d 20.5, 114.6, 119.5, 127.6, 127.8, 127.9 (2), 128.7 (2), 130.8, 131.5 (2), 136.4 (2), 137.4, 160.9.
- MS (ionspray): m/z 236 (M^++1)
- *Anal.* calculated for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.78; H, 5.39; N, 6.11.

Results of pharmacological tests demonstrating the properties of the compounds of formula I and Ia, either alone or in combination with cytotoxic agents, will be given below.

1 - Interaction (stimulation or inhibition of proliferation) with the generation of clonogenic cells (clonogenic test)

The test used is that described by Hamburger et al. (Science, 1977; 197, 461-463) and Salmon et al. (New England J. Med., 298, 1321-1327). A cell is considered clonogenic if it has the capacity to proliferate and to give rise to a cell colony. "Human tumor stem cells" are the cells which are the source of the neoplastic cells which constitute a given tumor. These tumor stem cells are responsible for the relapse processes which may be observed after surgical resection of primary tumors and are also responsible for the formation of metastases. In a tumor or a tumor cell line, these clonogenic stem cells differ from the other cells of the tumor or from the neoplastic cell line under consideration in that they conserve their capacity to proliferate in the absence of any solid support.

In this test, the tumor cells are cultured on a semi-solid support consisting of agar. Only the cells which do not require a solid support on which to grow (i.e. the highly tumorigenic cells know as "anchorage-independent cells" by M.I. Dawson et al., Cancer Res. 1995; 55: 4446-4451; also known as clonogenic cells with reference to "clonal growth") are capable of growing on such an agar-based support. Specifically, on such a medium, the normal cells - which grow in "adherent mode" ("anchorage-dependent cells" according to the terminology by M.I. Dawson) - such as, for example, the fibroblasts, do not survive. In a tumor cell population, cultured on such a support, it is these clonogenic cells (associated with an unlimited number of cell divisions and whose proliferation is referred to by M.I. Dawson as "anchorage-independent [clonal] growth") which are capable of growing. The percentage of these clonogenic cells in a tumor or a cell line ranges between 0.1% and 0.001%. The non-clonogenic cells (associated with a limited number of

cell divisions) do not grow in this test since they require a solid support on which to grow, which must take place in "adherent mode" ("anchorage-dependent [adherent] growth" according to M.I. Dawson et al., Cancer Res. 1995; 55: 4446-51).

The influence of the compounds of formulae (I) and (Ia) on the growth of the cell colonies obtained by culturing, for example, the mammalian tumor lines MCF7 and MXT and the colorectal line HT-29 on the semi-liquid culture medium known as "soft agar" was measured. On such a medium, only the clonogenic cells referred to by M.I. Dawson as "anchorage-independent (clonal) cells" survive and grow. The growth of these cells in such a "non-adherent" mode bears witness to their degree of tumorigenicity. The inhibition of the growth of the size of a tumor in which a larger number of clonogenic cells has developed then becomes the evidence of reinforced cytotoxic activity.

Conversely, this test can also reveal that a compound is capable of inhibiting the generation/proliferation of clonogenic cells, thus making the tumor less able to grow and thus reducing the population of tumor cells.

The tumor cell lines studied are maintained in culture in 25 cm^2 falcon dishes. They are then trypsinized and the cells are fully dissociated from each other. The percentage of live cells is determined after staining with trypan blue. A cell suspension at a concentration of from $5 \cdot 10^4$ to $15 \cdot 10^4$ cells/ml (depending on the cell type under consideration) is prepared in a 0.3% agar solution. Next, 200 μl of this suspension are inoculated in Petri dishes 35 mm in diameter, in which are placed 3 ml of a base layer consisting of a 0.5% agar solution. The 200 μl of cell suspension are in turn covered with 1.8 ml of an upper layer consisting of a 0.3% agar solution. The dishes are then placed in an incubator at 37°C, 5% CO_2 and 70% humidity until the treatment. This treatment is carried out about 1 to 2 hours after the inoculation. The test

compounds are prepared at a concentration 100 times greater than the desired concentration and 50 μl of these treating solutions are placed over the upper layer of agar in the corresponding dishes. In the present study, the final concentration of the test products is 10^{-5}, 10^{-7} and 10^{-9} M. The dishes are then kept in an incubator for 21 days. On the 21st day the dishes are treated by depositing on the upper layer 100 μl of a 1 mg/ml solution of MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolinium bromide prepared with RPMI 1640 medium) for 3 h at 37°C. After this period, the cell colonies are fixed by adding 2 ml of formalin per dish. After fixing for 24 hours, the formalin is evaporated off and the number of stained cell colonies, thus consisting of metabolically active cells, and whose surface area is greater than 100 μm^2, is determined using an inverted microscope.

The average number of clones of clonogenic cells determined for each experimental condition studied is expressed as a percentage relative to the average number of clones of clonogenic cells counted under the control conditions set equal to 100%. These values, expressed as a percentage relative to the control condition for all of the test products, are given in Table I.

TABLE I

CLONOGENIC TESTS

CELL LINES	CRL8315			CRL8316		
	10^{-5}	10^{-7}	10^{-9}	10^{-5}	10^{-7}	10^{-9}
MCF7	119.6 ± 5.6 *	127 ± 8.8 *	157.1 ± 12.2 **	23.2 ± 1.8 ***	84 ± 5 *	83.4 ± 4.6 *
HT-29	103.5 ± 4.5 NS	111.9 ± 5.4 NS	112.9 ± 2.4 *	50.6 ± 1.8 ***	80.1 ± 2.9 **	101.6 ± 3.2 NS
MXT	76 ± 2.3 **	103.9 ± 4.3 NS	102.4 ± 3.9 NS	10.8 ± 0.5 ***	89.1 ± 3.7 NS	95.3 ± 3.8 NS

CELL LINES	CRL8246			CRL8256		
	10^{-5}	10^{-7}	10^{-9}	10^{-5}	10^{-7}	10^{-9}
MCF7	126.8 ± 9.9 *	145.7 ± 8.9 **	139.1 ± 6.6 **	51.6 ± 3.7 ***	83.8 ± 3.4 *	97.9 ± 5.6 NS
HT-29	70.9 ± 2.8 **	103.3 ± 3.6 NS	104 ± 2.7 NS	97.1 ± 4.3 NS	100.5 ± 4.1 NS	107.5 ± 3.7 NS
MXT	96.7 ± 7.2 NS	97.7 ± 9.3 NS	95.2 ± 6.8 NS	53 ± 1.9 ***	103.8 ± 3.9 NS	104.5 ± 4.7 NS

CELL LINES	CRL8247			CRL8283		
	10^{-5}	10^{-7}	10^{-9}	10^{-5}	10^{-7}	10^{-9}
MCF7	51.5 ± 2.8 ***	81.9 ± 1.2 **	98.3 ± 4.2 NS	56.5 ± 4.9 ***	106.2 ± 4.8 NS	97.4 ± 5.8 NS
HT-29	72.7 ± 3.6 **	98.3 ± 4.9 NS	104.5 ± 2.7 NS	88.9 ± 0.2 **	90.9 ± 3.1 NS	106.1 ± 1.4 NS
MXT	65.7 ± 1.7 ***	89.6 ± 4.9 NS	98.4 ± 2.6 NS	23.7 ± 1.4 ***	81.2 ± 3 **	91.4 ± 4 NS

- Concentrations expressed in $mol.l^{-1}$
- The results summarized in this table represent the average values ± standard error of mean (SEM) established on at least 6 cupules
- Control condition = 100%
- (NS: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$).

Thus, since they act on the clonogenic behavior of the tumor, the compounds of formulae (I) and (Ia):

- either increase (e.g.: CRL 8315) - relative to the reference situation [culture media not supplemented with the compounds of formula (I) or (Ia)] - the average number of clones of clonogenic cells, consequently making a larger number of the tumor cells sensitive to the cytotoxic agent (since the clonogenic cells are more sensitive to cytotoxic agents during their proliferation phase),
- or reduce (e.g.: CRL 8283) the number of clonogenic cells by direct toxicity (resulting, here also, in regression of the tumor).

2 - Cytotoxic activity on non-clonogenic cells: "MTT test"

The influence of the compounds of formulae (I) and (Ia) on non-clonogenic cells was evaluated with the aid of the MTT colorimetric test.

The principle of the MTT test is based on the mitochondrial reduction, by the metabolically active live cells, of the yellow-colored product MTT (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.

The cell lines are maintained as a monolayer culture at 37°C in stoppered culture dishes containing MEM 25 MM HEPES (Minimum Essential Medium) base medium. This medium is suited to the growth of a range of various mammalian diploid or primary cells. This medium is then supplemented with:

- an amount of 5% of FCS (Foetal Calf Serum) decomplemented at 56°C for 1 hour,
- 0.6 mg/ml of L-glutamine,
- 200 UI/ml of penicillin,
- 200 µg/ml of streptomycin,
- 0.1 mg/ml of gentamicin.

The 12 human cancer cell lines which were used were obtained from 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 astrocytoma,
- A549 (code ATCC: CCL-185) and A-427 (code ATCC: HTB-53) which are two non-small-cell lung cancers,

- HTC-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,
- 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.

Experimentally: 100 µl of a cell suspension containing 20 000 to 50 000 (depending on the cell type used) cells/ml of culture medium are inoculated in 96-well flat-bottomed multi-well plates and are incubated at 37°C, under an atmosphere comprising 5% CO_2 and 70% humidity. After incubation for 24 hours, the culture medium is replaced with 100 µl 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 condition). After incubation for 72 hours under the above conditions, the culture medium is replaced with 100 µl 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 are then centrifuged for 10 minutes at 400×g. The yellowish solution of MTT is removed and the blue formazan crystals formed in the cell are dissolved in 100 µl of DMSO. The microplates are then shaken for 5 minutes. The intensity of the resulting blue coloration, and thus of the conversion of the yellow product MTT 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, respectively, to the maximum absorption wavelengths of formazan and to the background noise. Software incorporated in the spectrophotometer calculates the average optical density values and the standard deviation (SD) and standard error of mean (SEM) values.

By way of example, the results of the average optical density, expressed as a percentage relative to the average optical density measured under the control condition (set equal to 100%), obtained at a concentration of 10^{-5} M on the 12 abovementioned tumor cell lines are given in Table II.

TABLE II a

2-QUINOLONES	CELL LINES											
	U-87MG	U-373MG	SW1088	T24	J82	HCT-15	LoVo	MCF7	T-47D	A549	A-427	PC-3
CRL8246	92.1 ± 1.5 *	96.6 ± 1.2 NS	107.6 ± 1.1 **	109.4 ± 3.5 NS	87.6 ± 2.2 **	97.2 ± 5.1 NS	108.8 ± 7 NS	98.1 ± 1.4 NS	96 ± 2.6 NS	113 ± 2.1 ***	101 ± 0.9 NS	121.7 ± 1.7 ***
CRL8284	88.1 ± 2.2 *	87.7 ± 1.4 ***	78.3 ± 1.6 ***	68.5 ± 0.9 ***	48.8 ± 0.7 ***	77.3 ± 1.8 ***	101.7 ± 1.3 NS	66.6 ± 2.7 ***	89.9 ± 1.9 *	91.7 ± 1.6 **	96 ± 2.0 NS	83.8 ± 1 ***
CRL8311	91.8 ± 1.3 NS	113.3 ± 2.5 **	80.7 ± 1.7 ***	90 ± 1.9 **	127 ± 1.9 ***	101.2 ± 3.6 NS	77.9 ± 1.7 ***	98.8 ± 2.3 NS	107.6 ± 6.6 NS	106.1 ± 2.4 NS	89.7 ± 2.0 **	122.1 ± 3.5 **
CRL8271	78.5 ± 1.7 ***	96.2 ± 1.6 NS	102.2 ± 0.5 NS	107.4 ± 2.3 *	75.9 ± 1.3 ***	87.2 ± 2.8 **	94.2 ± 2.8 NS	105.5 ± 2.3 NS	90.9 ± 1.7 **	94.2 ± 4.7 NS	84.1 ± 1.9 **	107 ± 2.7 NS
CRL8244	97 ± 1 NS	69 ± 0.9 ***	81.3 ± 1.1 ***	88.7 ± 2.9 ***	88.5 ± 2.1 **	76.8 ± 3.0 ***	78.2 ± 1.8 ***	75.9 ± 3.8 ***	105 ± 3 *	98 ± 0.9 NS	93.6 ± 2.3 NS	83.2 ± 3.6 **
CRL8321	96.5 ± 1.2 NS	97.1 ± 2.4 NS	97.2 ± 1.8 NS	103.1 ± 1.7 NS	88.6 ± 0.9 ***	118.3 ± 1.6 ***	107.8 ± 1.1 **	96.6 ± 0.9 *	91.5 ± 1.2 **	99.4 ± 1.3 NS	107 ± 1.4 **	102.2 ± 3.1 NS
CRL8245	58.6 ± 1.7 ***	63.7 ± 2.7 ***	75.1 ± 2 ***	51.1 ± 1.9 ***	31.1 ± 0.6 ***	35.8 ± 1.2 ***	65.5 ± 1.1 ***	46.9 ± 1 ***	59.6 ± 2.9 ***	74.1 ± 2.1 ***	69 ± 1.9 ***	74.4 ± 1.9 ***

2-QUINOLONES	CELL LINES											
	U-87MG	U-373MG	SW1088	T24	J82	HCT-15	LoVo	MCF7	T-47D	A549	A-427	PC-3
CRL8314	74.5 ± 3.4 ***	89.2 ± 2 **	85.4 ± 2.5 ***	61.9 ± 2.5 ***	33.2 ± 1.2 ***	116.5 ± 4.4 *	82.9 ± 2.5 **	72.2 ± 2 ***	113.5 ± 2.3 *	85.2 ± 1.4 ***	104.4 ± 3.1 NS	88.6 ± 1.4 ***
CRL8318	78.1 ± 2.4 ***	89.9 ± 1.3 **	75.2 ± 3 ***	81.8 ± 1.4 ***	72.8 ± 1.2 ***	113 ± 1.7 ***	75.2 ± 2.3 ***	105 ± 2.4 NS	100.3 ± 3.9 NS	86.6 ± 2.5 **	74 ± 3 ***	79.2 ± 2.8 ***
CRL8317	91 ± 4.1 NS	91.2 ± 1.9 **	103.4 ± 2.3 NS	91.4 ± 4.3 NS	83.6 ± 1.8 ***	103.6 ± 2.6 NS	86.8 ± 2.8 **	96 ± 2.1 NS	95 ± 2.5 NS	94.7 ± 2.2 NS	91.3 ± 2 **	97.9 ± 1.1 NS
CRL8319	115 ± 2.9 *	101.7 ± 1.5 NS	89.8 ± 2.7 NS	89.6 ± 2.1 **	80.9 ± 1 ***	96.7 ± 1.6 NS	79.7 ± 2.7 **	101.5 ± 2 NS	104.5 ± 2.5 NS	97.3 ± 1.2 NS	79.1 ± 2.5 ***	90.7 ± 3.6 NS
CRL8283	69.9 ± 3.4 ***	93.4 ± 1.5 NS	84.7 ± 3.1 **	72.9 ± 0.9 ***	71.6 ± 2.2 ***	58.2 ± 4.3 ***	97.3 ± 3.6 NS	76.2 ± 0.9 ***	81 ± 3.1 ***	63.6 ± 4.2 ***	73.1 ± 1.7 ***	92.4 ± 1.7 *

x ± y = average value ± standard error of mean

Control condition = 100%

(NS: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$)

TABLE II b

2-QUINOLONES	CELL LINES											
	U-87MG	U-373MG	SW1088	T24	J82	HCT-15	LoVo	MCF7	T-47D	A549	A-427	PC-3
CRL8315	87.6 ± 4.5 *	68.9 ± 2.2 ***	89.1 ± 0.6 ***	89.6 ± 2.1 **	65.9 ± 1.3 ***	87.9 ± 3.3 *	78.9 ± 2.1 ***	96.2 ± 1.7 NS	101.3 ± 2.5 NS	76.1 ± 2.4 ***	92.6 ± 2.1 *	93.6 ± 3 NS
CRL8254	105.1 ± 3.6 NS	7.6 ± 1.3 ***	128.3 ± 2.2 ***	102.6 ± 2.9 NS	87.8 ± 1 ***	94.4 ± 3.5 NS	91.8 ± 2.7 *	81.9 ± 0.6 ***	55.2 ± 4.1 ***	96.9 + 1.5 NS	20.2 ± 2.3 ***	97.9 ± 1.2 NS
CRL8255	72.5 ± 1.1 ***	68.5 ± 2.7 ***	67.5 ± 1.5 ***	79.5 ± 2.2 ***	36.2 ± 0.5 ***	58.7 ± 3 ***	56.9 ± 1.1 ***	71.5 ± 1.4 ***	73.7 ± 3.3 ***	79.1 ± 2.1 ***	76.3 ± 1.5 **	77.7 ± 1.2 ***
CRL8247	59 ± 2.3 ***	68.7 ± 2.8 ***	85.8 ± 3.6 **	77.8 ± 2.7 ***	55 ± 2.3 ***	87.4 ± 2.5 *	66.4 ± 2.5 ***	78.9 ± 1.1 ***	58.3 ± 1.4 ***	81.3 ± 1.9 ***	57 ± 1.5 ***	70.5 ± 4.6 ***
CRL8256	84.7 ± 1.7 ***	76.1 ± 2.6 ***	72.1 ± 3.3 ***	78.2 ± 2.6 ***	77.8 ± 0.8 ***	73.9 ± 3.6 ***	93 ± 2.3 NS	81.8 ± 1.6 ***	77.5 ± 3.6 **	56.5 ± 3.7 ***	81.1 ± 2.9 ***	86 ± 2.3 ***
CRL8316	74.3 ± 1.4 ***	89.8 ± 2.9 *	106.6 ± 2 *	94 ± 3.2 NS	26.9 ± 0.9 ***	79.8 ± 2.9 **	73.9 ± 2.1 ***	78.9 ± 4.0 ***	68.8 ± 2.4 ***	84.2 ± 1.9 ***	79.1 ± 4.8 **	84.8 ± 2.3 **
CRL8285	85.1 ± 2 **	96.9 ± 1.6 NS	89.8 ± 2.7 *	72.7 ± 1.8 ***	68.7 ± 2.9 ***	90.6 ± 1.6 *	102.8 ± 3.1 NS	83.7 ± 2.3 ***	89.3 ± 1.7 **	92.5 ± 3.5 NS	78.4 ± 1.6 ***	93.4 ± 1.8 *

2-QUINOLONES	CELL LINES											
	U-87MG	U-373MG	SW1088	T24	J82	HCT-15	LoVo	MCF7	T-47D	A549	A-427	PC-3
CRL8270	75.6 ± 0.9 ***	52.2 ± 3.2 ***	50.7 ± 1.8 ***	51.1 ± 3.8 ***	42.5 ± 0.8 ***	58.8 ± 1.8 ***	80 ± 3.2 ***	51.5 ± 2.4 ***	22.9 ± 4.3 ***	52.2 ± 2.4 ***	30.8 ± 2.1 ***	49.4 ± 1.1 ***
CRL8366	64.4 ± 1.2 ***	66.3 ± 1.6 ***	68.4 ± 1.6 ***	84.6 ± 3 *	31.2 ± 0.7 ***	76.1 ± 1.5 ***	71.3 ± 4.5 ***	46.3 ± 2.6 ***	25 ± 4 ***	61.6 ± 3.5 ***	45.2 ± 2.2 ***	67.2 ± 0.9 ***
CRL8336	82.3 ± 1.8 ***	82.3 ± 1.6 ***	101.1 ± 4.3 NS	88.2 ± 1.4 ***	90.9 ± 0.9 **	93.1 ± 3.2 NS	92.6 ± 3.4 NS	73.9 ± 0.7 ***	96.2 ± 2.9 NS	114.2 ± 1.9 **	87.9 ± 3.1 **	91.7 ± 1.5 ***
CRL8330	86.6 ± 0.7 ***	75.5 ± 3.7 ***	73.3 ± 1.8 ***	57.4 ± 2.3 ***	70.5 ± 2.4 ***	94.7 ± 2.1 NS	59.9 ± 4.2 ***	87.2 ± 3 **	77.6 ± 3 ***	76.3 ± 2.4 ***	59.8 ± 1 ***	48.5 ± 2.1 ***
CRL8339	69.1 ± 2.1 ***	73.6 ± 1.8 ***	87.1 ± 2.6 **	87.4 ± 2 **	83.7 ± 0.6 ***	65.5 ± 2.2 ***	74.4 ± 1.8 ***	82.7 ± 3.5 **	81 ± 2.8 **	49.6 ± 2.2 ***	52.3 ± 2.3 ***	84.3 ± 1.8 ***

x ± y = average value ± standard error of mean

Control condition = 100%

(NS: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$)

It appears that several of the compounds induce a weak inhibition which can be up to 20-30% of the overall cell proliferation of the tumor lines under consideration and that these compounds do not appear to have any tissue specificity.

3. - 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 graduating from 2.5 to 160 mg/kg. The value of the MTD (expressed in mg/kg) is determined from the observation of the survival rate of the animals over a 14-day period after a single administration of the product under consideration. The weight change of the animals is also monitored during this period. When the value of the MTD is greater than 160 mg/kg, the MTD value is likened to 160 mg/kg by default.

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

TABLE III

Maximum tolerated doses

CRL compounds	MTD (mg/kg)
CRL8246 (Example 1)	> 160
CRL8284 (Example 2)	> 160
CRL8311 (Example 3)	> 160
CRL8271 (Example 4)	> 160
CRL8244 (Example 5)	> 160
CRL8321 (Example 7)	> 160
CRL8245 (Example 8)	> 160
CRL8314 (Example 9)	> 160
CRL8318 (Example 10)	> 160
CRL8317 (Example 12)	> 160
CRL8319 (Example 14)	> 160
CRL8283 (Example 15)	> 160
CRL8315 (Example 16)	> 160
CRL8255 (Example 17)	> 160
CRL8247 (Example 18)	> 160
CRL8256 (Example 19)	> 160
CRL8254 (Example 20)	> 160
CRL8316 (Example 21)	> 160
CRL8285 (Example 22)	> 160
CRL8270 (Example 23)	> 160
CRL8266 (Example 24)	> 160
CRL8336 (Example 26)	> 160
CRL8330 (Example 27)	> 160
CRL8339 (Example 28)	> 160

The products of this family show no direct toxicity and can thus be used *in vivo* at high tissue concentrations, and thus at high doses.

4. - in vivo Antitumor activity in combination with a cytotoxic agent

The tests were carried out on models of:

- hormone-sensitive mouse mammary adenocarcinoma MXT (HS-MXT),

- lymphoma P 388,

in the presence or absence of cytotoxic agents such as cyclophosphamide, etoposide, doxorubicin or vincristine.

When the MTD value of a product was determined, its *in vivo* antitumor activity was characterized at doses of MTD/2, MTD/4 and MTD/8 on the model of mouse mammary adenocarcinoma HS-MXT and on the model of lymphoma P 388. The dose which showed the best antitumor activity on these various models was selected and used in the context of combined treatments with the cytotoxic agents.

In all the examples presented below, irrespective of the model (mammary adenocarcinoma HS-MXT or lymphoma P 388), the control condition is represented by a batch of 9 mice to which is administered for 5 consecutive weeks and at a rate of 5 administrations (Monday, Tuesday, Wednesday, Thursday and Friday) per week a volume of 0.2 ml of physiological saline containing the solvent used to dissolve the various compounds of formulae (I) and (Ia) used.

The following parameters were determined in these tests:

i)- <u>The survival rate of the mice</u>

This survival rate was calculated in the form of a ratio T/C:

$$T = \frac{\text{(Number of days of survival of the median mouse in the batch of mice tested)}}{\text{(Median mouse treated)} - \text{(Number of mice which died in the days preceding that of the median mouse treated)}} + \frac{}{\text{(Number of mice which died on the same day as the median mouse treated)}}$$

$$C = \frac{\text{(Number of days of survival of the median mouse in the batch of control mice)} - \text{(Median mouse treated)}}{\text{(Number of mice which died in the days preceding that of the median mouse treated)}} + \frac{}{\text{(Number of mice which died on the same day as the median control mouse)}}$$

This ratio represents the average survival time of the median mouse from the batch of treated mice relative to the average survival time of the median mouse from the batch of control mice. Thus, a molecule induces a significant ($P < 0.05$) increase in the survival of the animals when the index T/C exceeds 130%. Conversely, it has a toxic effect when this value of T/C is less than 70%.

ii)- The tumor growth [lacuna] by measuring the area of the grafted HS-MXT or P 388 tumors twice a week (Monday and Friday). This area is calculated by multiplying the values of the largest two perpendicular axes of the tumor. The value of these axes is measured using a sliding caliper.

4.1. Mouse mammary adenocarcinoma (HS-MXT)

The model of hormone-sensitive MXT (HS-MXT) mouse mammary adenocarcinoma grafted onto 4- to 6-week-old B6D2F1/JIco mice is derived from the milk ducts of the mammary gland (Watson C. *et al.* Cancer Res. 1977; 37: 3344-48).

The results obtained using compounds 1 and 20, either alone or in combination with the cytotoxic agents, will be given by way of example.

A - Compound 1 or CRL 8246:

Treatments 1 and 1a

Compound 1 is administered alone. The first injection of the product is carried out on the seventh day post-grafting (D7) for four consecutive weeks at a rate of 5 injections per week (Monday, Tuesday,

Wednesday, Thursday and Friday) and at a dose of 20 mg/kg.

Treatment 2

Cyclophosphamide (CPA) is administered alone. The first injection of the product is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) and at a dose of 10 mg/kg.

Treatment 3

Compound 1 is co-administered with cyclophosphamide. In this case, the first injection of compound 1 is carried out on the seventh day post-grafting (D7) for four consecutive weeks at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) at a dose of 20 mg/kg, and the first injection of cyclophosphamide is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) at a dose of 10 mg/kg.

Treatment 4

Etoposide (ETO) is administered alone. The first injection of the product is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) and at a dose of 10 mg/kg.

Treatment 5

Doxorubicin (DOX) is administered alone. The first injection of the product is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) and at a dose of 5 mg/kg.

Treatment 6

Compound 1 is co-administered with etoposide. In this case, the first injection of compound 1 is carried out on the seventh day post-grafting (D7) for four consecutive weeks at a rate of 5 injections per

week (Monday, Tuesday, Wednesday, Thursday and Friday) at a dose of 20 mg/kg and the first injection of etoposide is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) at a dose of 10 mg/kg.

Treatment 7

Compound 1 is co-administered with doxorubicin. In this case, the first injection of compound 1 is carried out on the seventh day post-grafting (D7) for four consecutive weeks at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) at a dose of 20 mg/kg, and the first injection of adriamycin is carried out on the fourteenth day post-grafting (D14) for three consecutive weeks at a rate of 3 injections per week (Monday, Wednesday and Friday) at a dose of 5 mg/kg.

The results obtained regarding the survival time for compound 1 are given in Tables IV and V:

TABLE IV

Treatments	T/C (expressed as %)
1 (Compound 1)	100
2 (CPA)	122
3 (Compound 1 + CPA)	135

TABLE V

Treatments	T/C (expressed as %)
1a (Compound 1)	95
4 (ETO)	130
5 (DOX)	92.5
6 (Compound 1 + ETO)	150
7 (Compound 1 + DOX)	145

These results show that the co-administration of compound 1 with the cytotoxic agents: cyclophosphamide, etoposide or doxorubicin, significantly increases the average survival time of the median mouse from the various batches of mice thus treated, relative

to the average survival time of the median mouse from the batch of control mice. Furthermore, this increase in the average survival time of the median mouse from the various batches of mice treated with these co-administrations is significantly longer than that obtained with the treatments involving these cytotoxic agents used alone.

The study of the tumor growth moreover revealed the following results for compound 1. Table VI below indicates, in percentages, the reductions (-) or increases (+) of the area of the HS-MXT tumors induced with the various treatments 1, 2 and 3 of Example 1, compared with the control condition on the 31st day after the tumor graft, i.e. after 19 administrations of compound 1 and 8 administrations of cyclophosphamide, used in co-administration or otherwise. On the 31st day post-grafting, 89% of the control animals are still alive (i.e. 8 out of the 9 animals).

TABLE VI

Treatments	Tumor area (expressed as %)
1 (Compound 1)	-19.5
2 (CPA)	-23.6
3 (Compound 1 + CPA)	-49.6

The results show that the co-administration of compound 1 with cyclophosphamide induces a highly significant reduction in the growth of the HS-MXT tumors, which is greater than the reduction induced by the treatments involving compound 1 or cyclophosphamide used alone.

B - Compound 21 or CRL 8256:

Another example, relating to compound 21 used alone or in combination with etoposide.

Treatment 10

Compound 21 is administered alone. The first injection of the product is carried out on the 7th day post-grafting (D7) at a rate of 5 injections per week

(Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks and at a dose of 40 mg/kg.

Treatment 20

Etoposide (ETO) is administered alone. The first injection of the product is carried out on the 7th day post-grafting (D7) at a rate of 3 injections per week (Monday, Wednesday and Friday) for three consecutive weeks and at a dose of 10 mg/kg.

Treatment 30

Compound 21 is co-administered with etoposide. In this case, the first injection of compound 21 is carried out on the 7th day post-grafting (D7) at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks at a dose of 40 mg/kg, and the first injection of etoposide is carried out on the 7th day post-grafting (D7) at a rate of 3 injections per week (Monday, Wednesday and Friday) for three consecutive weeks at a dose of 10 mg/kg.

Table VII gives the survival time results obtained with compound 21.

TABLE VII

Treatments	T/C (expressed as %)
10 (Compound 21)	110
20 (ETO)	124
30 (Compound 21 + ETO)	138

These results show that the co-administration of compound 21 with etoposide induces a significant increase in the average survival time of the median mouse from the batch of mice thus treated, compared with the average survival time of the median mouse from the batch of control mice. Furthermore, this increase in the average survival time of the median mouse from the batch of mice treated with this co-administration is significantly longer than that obtained with the treatments involving this 2-quinolone or this cytotoxic agent used alone.

4.2. Lymphoma P 388:

4- to 6-week-old CDF1 mice are grafted with a piece of P 388 tumor (from a tumor bank maintained in the laboratory) subcutaneously into the right flank on day D0. In order to be under conditions close to clinical reality, we waited until the 5th day post-grafting (D5) before starting the treatment. The reason for this was that, after this period of time, the subcutaneous P 388 tumors are palpable.

By way of example, the results obtained with compounds 1 (CRL 8246) and 20 (CRL 8247), alone or in combination with vincristine, are given below.

Treatment 1

Compound 1 is administered alone. The first injection of the product is carried out on the 5th day post-grafting (D5) at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks and at a dose of 40 mg/kg.

Treatment 2

Compound 20 is administered alone. The first injection of the product is carried out on the fifth day post-grafting (D5) at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks and at a dose of 40 mg/kg.

Treatment 3

Vincristine (VCR) is administered alone. The first injection of the product is carried out on the fifth day post-grafting (D5) at a rate of 3 injections per week (Monday, Wednesday and Friday) for three consecutive weeks and at a dose of 0.63 mg/kg.

Treatment 4

Compound 1 is co-administered with vincristine. In this case, the first injection of compound CRL8246 is carried out on the fifth day post-grafting (D5) at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks at a dose of 40 mg/kg, and the first injection of vincristine is carried out on the fifth day post-

grafting (D5) at a rate of 3 injections per week (Monday, Wednesday and Friday) for three consecutive weeks at a dose of 0.63 mg/kg.

Treatment 5

Compound 20 is co-administered with vincristine. In this case, the first injection of compound CRL8247 is carried out on the fifth day post-grafting (D5) at a rate of 5 injections per week (Monday, Tuesday, Wednesday, Thursday and Friday) for five consecutive weeks at a dose of 40 mg/kg, and the first injection of vincristine is carried out on the fifth day post-grafting (D5) at a rate of 3 injections per week (Monday, Wednesday and Friday) for three consecutive weeks at a dose of 0.63 mg/kg.

Table IX shows the results obtained with treatments 1 to 5 mentioned above, on the survival time of the mice.

TABLE IX

Treatments	T/C (expressed as %)
1 (Compound 1)	120
2 (Compound 20)	125
3 (VCR)	122
4 (Compound 1 + VCR)	144
5 (Compound 20 + VCR)	164

These results show that the co-administration of compounds 1 and 20 with vincristine produces a highly significant increase in the average survival time of the median mouse from the various batches of mice thus treated, compared with the average survival time of the median mouse from the batch of control mice. Furthermore, this increase in the average survival time of the median mouse from the various batches of mice treated with these co-administrations is significantly longer than that obtained with the treatments involving these two compounds 1 and 20 or vincristine used alone.

Examples of the method for using the compounds of formulae (I) and (Ia) in mono- or polychemotherapy protocols with cytotoxic agents will be given below. In these protocols, the compounds of formulae (I) and (Ia) will be referred to for simplicity as "2-quinolone".

A. Solid tumors

1/ Lung cancers

1.1. To non-small cells (advanced stage):

- to the recommended protocol (T. Le Chevalier et al., J. Clin. Oncol. 1994; 12: 360-367) are added intravenous infusions of a 2-quinolone:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1, D_8, D_{15}, D_{22}, D_{29} and D_{36}
• navelbine	30 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}, D_{29} and D_{36}
• cisplatin	120 mg/m^2	i.v.	D_1 and D_{29}

This cure is to be repeated 8 times.

1.2. To small cells (advanced stage):

- to the recommended protocol CAV or VAC (B.J. Roth et al., J. Clin. Oncol.1992; 10: 282-291) are added infusions of 2-quinolone:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1
• cyclophosphamide	1000 mg/m^2 bolus	i.v.	D_1

	Dose	Route	Days
• doxorubicin	40 to 50 mg/m^2 bolus	i.v.	D_1
• vincristine	1 to 1.4 mg/m^2 bolus (max 2 mg)	i.v.	D_1

This cure is to be repeated 6 times every 21 days.

- To the recommended Pt-E protocol (B.J. Roth et al., J. Clin. Oncol. 1992; 10: 282-291) are added infusions of 2-quinolone.

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cisplatin	20 mg mg/m^2/day infusion for 20 to 60 minutes	i.v.	D_1-D_5
• etoposide	80 mg/m^2/day infusion for 60 minutes	i.v.	D_1-D_5

Each cycle is repeated every 21 days and the cure comprises 6 cycles.

1.3. Non-small-cell bronchial cancer, locally advanced or metastatic:

• monochemotherapy:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1, D_8, D_{15} and then 1 week/rest

• gemcitabine	1000 mg/m^2/day infusion for 0.5 hour	i.v.	D_1, D_8, D_{15} and then 1 week/rest

the cure being able to comprise repetition of this 4-week cycle.

• gemcitabine/cisplatin combination:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{15}
• gemcitabine	1000 mg/m^2/day infusion for 0.5 hour	i.v.	D_1, D_8, D_{15}
• cisplatin	20 mg/m^2/day infusion for 20-60 minutes	i.v.	D_1

the cure comprising the repetition of this cycle every 21 days.

2/ <u>Breast cancers</u>

- CMF protocol as auxiliary treatment for operable breast cancer (G. Bonnadonna et al., N. Engl. J. Med.; 1976; 294: 405-410):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1 to D_{14}
• cyclophosphamide	100 mg/m^2/day	oral	D_1 to D_{14}
• methotrexate	40 mg/m^2 bolus	i.v.	D_1 and D_8
• 5-FU	600 mg/m^2	i.v.	D_1 and D_8

each cycle is repeated every 28 days and the cure comprises 6 cycles.

- AC protocol (B. Fisher et al., J. Clin. Oncol.; 1990; 8: 1483-1496) as an auxiliary treatment:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1
• doxorubicin	60 mg/m^2 bolus	i.v.	D_1
• cyclophosphamide	600 mg/m^2 bolus	i.v.	D_1

each cycle is repeated every 21 days and the cure comprises 4 cycles.

- Breast cancers with metastasis:

- in the FAC protocol (A.U. Buzdar et al., Cancer 1981; 47: 2537-2542) and its various adaptations, the infusions of 2-quinolone are added according to the following (non-limiting) scheme:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 and D_8-D_{12} or D_1-D_5
• 5-FU	500 mg/m^2/day	oral	D_1 and D_8 or D_1-D_2
• doxorubicin	50 mg/m^2 bolus	i.v.	D_1 or D_1 and D_2
• cyclophosphamide	500 mg/m^2	bolus i.v. or oral	D_1 D_1

each cycle is repeated every 3 weeks until a new progression of the disease is diagnosed.

- in the CAF protocol (G. Falkson et al., Cancer 1985; 56: 219-224):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_{14}
• cyclophosphamide	100 mg/m^2/day	oral	D_1-D_{14}
• doxorubicin	30 mg/m^2 bolus	i.v.	D_1 and D_8
• 5-FU	500 mg/m^2 bolus	i.v.	D_1 and D_8

each cycle is repeated every 21 days until new progression of the disease is diagnosed.

- in the CMF protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 and D_8-D_{12}
• cyclophosphamide	600 mg/m^2/day bolus	i.v.	D_1 and D_8
• methotrexate	40 mg/m^2/day bolus	i.v.	D_1 and D_8
• 5-FU	600 mg/m^2/day bolus	i.v.	D_1 and D_8

this cycle is to be repeated every 3 to 5 weeks and the cure comprises 6 cycles.

- In the CMF-VP protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{12} D_{15}-D_{19} D_{22}-D_{26}
• cyclophosphamide	2 to 2.5 mg/kg/day	oral	daily
• methotrexate	25 to 50 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}
• 5-FU	300 to 500 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}
• vincristine	0.6 to 1.2 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}
• prednisone	30 mg/m^2/day	oral	from D_1 to D_{10}

this cure is to be repeated every 4 weeks.

- In the FEC protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 and D_8-D_{12}
• 5-FU	600 mg/m^2/day	i.v.	D_1 and D_8
• epirubicin	50 mg/m^2	i.v.	D_1
• cyclophosphamide	600 mg/m^2	i.v.	D_1

this cure is to be repeated every 3 weeks.

- in the MMC-VBC protocol (C. Brambilla et al., Tumori, 1989; 75: 141-144):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 and D_{15}-D_{19}
• mitomycin C	10 mg/m^2 bolus	i.v.	D_1
• vinblastine	50 mg/m^2/day bolus	i.v.	D_1 and D_{15}

this cure is to be repeated every 28 days until a progression of the disease is diagnosed.

- in the NFL protocol (S.E. Jones et al., J. Clin. Oncol. 1991; 9: 1736-1739):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• mitoxantrone	10 mg/m^2 bolus	i.v.	D_1
• 5-FU	1000 mg/m^2 infusion for 24 hours	i.v.	D_1-D_3
• leucovorin	100 mg/m^2 bolus	i.v.	D_1

the cure comprises two cycles with an interval of 21 days and then requires an evaluation.

The infusions of 2-quinolone can also be combined with the treatment of breast cancers with metastases when a taxoid is used, for example:

- with paclitaxel (F.A. Holmes et al., J. Natl Cancer Inst. 1991; 83: 1797-1805) in the treatment of the forms with metastases which may be resistant to anthracyclins:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• paclitaxel	175 mg/m^2 infusion for 3 to 24 hours	i.v.	D_1

this cycle is repeated every 21 days until a new progression of the disease is diagnosed.

- with docetaxel (C.A. Hudis et al., J. Clin. Oncol. 1996; 14: 58-65), in locally advanced or metastatic breast cancer, resistant or in relapse after cytotoxic chemotherapy (having comprised an anthracyclin) or in relapse during an auxiliary treatment:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• docetaxel	100 mg/m^2 or 60-100 mg/m^2 infusion for 1 hour (or 24 hours)	i.v.	D_1

this cycle is repeated every 21 days for a cure of two cycles or until a progression of the disease appears.

- in dose intensification protocols, combining a transplantation of autologous medullary cells and of

peripheral blood stem cells, in consolidation of the primary treatment, for example:

- CPB protocol (W.P. Peters et al., J. Clin. Oncol. 1993; 11: 132-1143), in which the i.v. infusion of stem cells takes place on days D_{-1}, D_0 and D_1:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-6}-D_{-1}
• cyclophosphamide	1875 mg/m² infusion for 1 hour	i.v.	D_{-6} to D_{-4}
• cisplatin	55 mg/m²/day continuous infusion for 24 hours	i.v.	D_{-6} to D_{-4}
• carmustin (BCNU)	600 mg/m²/day infusion for 2 hours	i.v.	D_{-3}

- CTCb protocol (K. Antman et al., J. Clin. Oncol. 1992; 10: 102-110), in which the i.v. infusion of stem cells takes place on D_0:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-7}-D_{-1}
• cyclophosphamide	1500 mg/m² continuous infusion for 24 hours (4 doses)	i.v.	D_{-7} to D_{-3}

	Dose	Route	Days
• thiotepa	125 mg/m^2 continuous infusion for 24 hours (4 doses)	i.v.	D_{-7} to D_{-3}
• carboplatin	200 mg/m^2 continuous infusion for 24 hours (4 doses)	i.v.	D_{-7} to D_{-3}

- CTM protocol (L.E. Damon et al., J. Clin. Oncol. 1989; 7: 560-571 and I.C. Henderson et al., J. Cellular Biochem. 1994 (Suppl 18B): 95) in which the i.v. infusion of hematopoietic stem cells takes place on D_0

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-6}-D_{-1}
• cyclophosphamide	1500 mg/m^2/day infusion for 1 hour	i.v.	D_{-6} to D_{-3}
• thiotepa	150 mg/m^2/day infusion for 2 hours	i.v.	D_{-6} to D_{-3}
• mitoxantrone	10-15 mg/m^2 infusion for 1 hour	i.v.	D_{-6} to D_{-3}

3/ Gynecological cancers

3.1 Ovarian cancer:

- for the treatment of ovarian carcinomas, in particular metastatic ones:

i) **PAC protocol** (G.A. Omura et al. J. Clin. Oncol. 1989; 7: 457-465): the infusions of 2-quinolones are administered according to the following scheme:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cisplatin	50 mg/m^2 (or 40-90 mg/m^2) infusion for 1 to 2 hours	i.v.	D_1
• doxorubicin	50 mg/m^2 bolus (or 30 to 50 mg/m^2)	i.v.	D_1
• cyclophosphamide	1000 mg/m^2 infusion for 1 to 2 hours (or 200 to 600 mg/m^2)	i.v.	D_1

this cycle is repeated every 21 to 28 days and the cure comprises 8 cycles.

ii) **Altretamine protocol**, according to A. Marietta et al. (Gynecol. Oncol. 1990; 36: 93-96):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{12}
• altretamine	200 mg/m^2/day divided into 4 doses	oral	D_1-D_{15}

the cure comprising two cycles, with an interval of 28 days.

ii) **Paclitaxel protocol**: the 2-quinolones can be added to the paclitaxel protocol as described by W.P. McGuire et al. (Ann. Intern. Med. 1989; 111: 273-279):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• paclitaxel	135 mg/m^2 infusion for 3 hours or 24 hours	i.v.	D_1

the cure comprising two of these cycles, with an interval of 28 days (with evaluation at the end).

- for the treatment of metastatic and refractory ovarian carcinomas, the 2-quinolones may be added to the secondary protocol, based on topotecan:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• topotecan	1.5 mg/m^2/day infusion for 0.5 hours	i.v.	D_1-D_5

the cure comprising two cycles, with an interval of 21 days (with evaluation at the end) according to A.P. Kudelka et al. (J. Clin. Oncol. 1996; 14: 1552-1557).

3.2 Trophoblastic tumors:

- in patients at low risk, the 2-quinolones may be combined with the protocol described by H. Takamizawa et al. (Semin. Surg. Oncol. 1987; 3: 36-44):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• methotrexate (MTX)	20 mg/day	i.m.	D_1-D_5
• dactinomycin (DACT)	0.5 mg/day as bolus	i.v.	D_1-D_5

(MTX-DATC protocol).

3.3 Uterine cancers:

- the 2-quinolones may also be combined with the CAV (or VAC) protocol according to the scheme below:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• cyclophosphamide	750-1200 mg/m^2 infusion	i.v.	D_1
• doxorubicin	45-50 mg/m^2 infusion	i.v.	D_1
• vincristine	1.4 mg/m^2	i.v.	D_1

the cure comprising the repetition of this cycle every 21 days.

- in the FAP protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• fluorouracil (5-FU)	600 mg/m^2/day	i.v.	D_1, D_8
• doxorubicin	30 mg/m^2	i.v.	D_1
• cisplatin	75 mg/m^2	i.v.	D_1

the cure comprising the repetition of this cycle every 21 or 28 days.

4/ Testicular cancers

- The 2-quinolones may also be combined with testicular cancer protocols:

BEP protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• bleomycin	30 mg/m^2 infusion	i.v.	D_1
• etoposide	100 mg/m^2/day infusion	i.v.	D_1-D_5
• cisplatin	20 mg/m^2/day	i.v.	D_1-D_5

the cure comprising 3 cycles, at a rate of 1 cycle every 21 days.

5/ Bladder cancers

- The 2-quinolones may be combined with the CISCA2 (also known as PAC) protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cisplatin	50 mg/m^2	i.v.	D_1
• cyclophosphamide	600 mg/m^2 infusion	i.v.	D_1
• doxorubicin	75 mg/m^2 infusion	i.v.	D_1

the cycle being repeated every 3 weeks.

- In the MVAC protocol (according to C.N. Sternberg et al., J. Urol. 1988; 139: 461-469):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 D_{15}-D_{18} D_{22}-D_{25}
• methotrexate	30 mg/m^2 bolus	i.v.	D_1, D_{15}, D_{22}
• vinblastine	3 mg/m^2	i.v.	D_2 or D_2, D_{15}, D_{22}
• doxorubicin	30 mg/m^2 bolus	i.v.	D_2
• cisplatin	70-100 mg/m^2 infusion for 1 h	i.v.	D_1 or D_2

this cycle being repeated every 4 to 5 weeks, for a minimum of 2 cycles.

6/ Nasopharyngeal carcinomas/head and neck cancers

- The 2-quinolones may be viably combined with polychemotherapy protocols used in the treatment of these cancers:

6.1 Nasopharyngeal cancers:

- ABVD protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 D_8-D_{10} or D_{15}-D_{17}
• doxorubicin	30 mg/m^2/day	i.v.	D_1 and D_8 or D_{15}
• bleomycin	10 mg/m^2/day	i.v.	D_1 and D_8 or D_{15}
• vinblastine	6 mg/m^2/day	i.v.	D_1 and D_8 or D_{15}
• dacarbazine	200 mg/m^2/day	i.v.	D_1 and D_8 or D_{15}

the cure comprising 1 to 6 cycles repeated at a rate of 1 cycle every 4 weeks.

6.2 Head and neck cancers with metastases:

- in the Pt-FU protocol (e.g.: for pharyngeal cancers): according to the DVAL Study Group (New Engl. J. M. 1991; 324: 1685-1690):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5

	Dose	Route	Days
• cisplatin	100 mg/m^2 infusion for 1 hour	i.v.	D_1
• fluorouracil (5-FU)	1000 mg/m^2/day continuous infusion	i.v.	D_1-D_5

the cure comprising two cycles, at a rate of 1 cycle every 3 weeks.

7/ <u>Soft-tissue sarcomas</u>

- The 2-quinolones may be introduced into a protocol such as the CYVADIC protocol:
- according to H.M. Pinedo et al. (Cancer 1984; 53: 1825):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day <u>or</u> 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{10} D_{15}-D_{17}
• cyclophosphamide (Cy)	500 mg/m^2 bolus	i.v.	D_2
• vincristine (V)	1.5 mg/m^2/day bolus	i.v.	D_1, D_8, D_{15}
• doxorubicin (A)	50 mg/m^2 bolus	i.v.	D_2
• dacarbazine (DIC)	250 mg/m^2/day infusion for 15 minutes	i.v.	D_1-D_5

the cure comprising the repetition of this cycle every 4 weeks, first for 2 cycles.

8/ Hormono-refractory prostate cancer, with metastases

- In the VBL-estramustine protocol, according to G.R. Hudis et al. (J. Clin. Oncol. 1992; 10: 1754-1761):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3, D_8-D_{10} D_{15}-D_{17}, D_{22}-D_{24} D_{29}-D_{31}, D_{36}-D_{38}
• vinblastine	4 mg/m^2/day bolus	i.v.	D_1, D_8, D_{15}, D_{22}, D_{29}, D_{36}
• estramustine	200 mg/m^2 tid (600 mg/m^2/day)	oral	every day for 6 weeks

a treatment cycle lasting 6 weeks and being followed by a 2-week free interval.

9/ Germinal cell cancers

i) For tumors of favorable prognosis:

- Pt-E protocol, according to G.J. Bosl et al. (J. Clin. Oncol. 1988; 6: 1231-1238)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cisplatin (Pt)	20 mg/m^2/day infusion for 20 to 60 minutes	i.v.	D_1-D_5
• etoposide (E)	100 mg/m^2/day infusion for 1 hour	i.v.	D_1-D_5

the cure comprising 4 cycles, at a rate of 1 cycle every 21 or 28 days.

ii) For tumors with metastases:

- PEB protocol, according to S.D. Williams et al. (N. Eng. J. Med. 1987; 316: 1435-1440):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_9-D_{11} D_{16}-D_{18}
• cisplatin (P)	20 mg/m^2/day infusion for 20 to 60 minutes	i.v.	D_1-D_5
• etoposide (E)	100 mg/m^2/day infusion for 1 hour	i.v.	D_2, D_9, D_{16}
• bleomycin (B)	30U (or mg)day bolus	i.v.	D_1-D_5

the cure comprising 4 cycles, at a rate of 1 cycle every 21 days.

10/ Kidney cancers

- **Metastatic renal carcinoma:** the 2-quinolones may be introduced into the protocol described by M.J. Wilkinson et al. (Cancer 1993; 71: 3601-3604):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{18}
• floxuridine	0.075 mg/kg/day continuous infusion	i.v.	D_1-D_{14}

the cure comprising 2 cycles with an interval of 28 days.

- **Nephroblastoma:** the 2-quinolones may be introduced into the DAVE protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 D_8-D_{10}
• dactinomycin	0.6 mg/m²/day	i.v.	D_1, D_8
• doxorubicin	30 mg/m²/day	i.v.	D_1, D_8
• cyclophosphamide	200 mg/m²/day infusion for 1 hour	i.v.	D_1, D_8

at a rate of one cycle every 3 to 4 weeks.

11/ Cancers of the digestive tract

11.1 Esophageal cancers:

- the 2-quinolones may be introduced into the FAP protocol according to:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 D_8-D_{10}
• 5-fluorouracil (5-FU)	600 mg/m²	i.v.	D_1, D_8
• doxorubicin	30 mg/m²	i.v.	D_1
• cisplatin	75 mg/m²	i.v.	D_1

this cycle being repeated every 3 to 4 weeks.

11.2 Stomach cancers:

- in gastric carcinomas that are advanced and/or with metastases:

- EAP protocol (according to P. Preusser et al., J. Clin. Oncol. 1989; 7: 1310):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{10}
• etoposide	120 mg/m^2/day infusion for 1 hour	i.v.	D_3, D_4, D_5 or D_4-D_6
• doxorubicin	20 mg/m^2/day bolus	i.v.	D_1, D_7
• cisplatin	40 mg/m^2/day infusion for 1 hour	i.v.	D_2, D_8

at a rate of 1 cycle every 28 days.

- FAMtx protocol: according to J.A. Wils et al. (J. Clin. Oncol. 1991; 89: 827):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• fluorouracil (5-FU) (F)	1500 mg/m^2 bolus 1 hour near [sic] methotrexate	i.v.	D_1
• doxorubicin (A)	30 mg/m^2 bolus	i.v.	D_{15}
• methotrexate (Mtx)	1500 mg/m^2 infusion for 30 minutes	i.v.	D_1

the cure first comprising two cycles, with an interval of 28 days.

- in certain patients, this protocol or its variant (epirubicin replacing doxorubicin) may be used according to the following scheme:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• fluorouracil (5-FU)	1500 mg/m^2	i.v.	D_1
• doxorubicin (A) or • epirubicin	30 mg/m^2 bolus 60 mg/m^2 bolus	i.v. i.v.	D_1 = FAMTx D_1 = FEMTx
• methotrexate (to be infused before 5-FU)	1500 mg/m^2	i.v.	D_1
• leucovorine	15 mg/m^2/day	oral	D_2-D_4

12/ Colorectal cancers

- the 2-quinolones may be introduced into the FU-Levamizole auxiliary treatment protocol for colorectal cancer (according to C.G. Moertel et al., N. Eng. J. Med. 1990; 322: 352):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_{29}-D_{31}
• 5-fluorouracil	450 mg/m^2/day bolus	i.v.	D_1-D_5
• 5-fluorouracil	450 mg/m^2 bolus	i.v.	D_{29}
• levamisole	50 mg tid	oral	3 days/week one week in two

the treatment in bolus with 5-FU being repeated every week after the induction phase D_1-D_5, for 52 weeks; the treatment with a 2-quinolone being repeated at the same rhythm, on the day of the bolus of 5-FU and then on the following 2 days.

- for the treatment of colorectal cancer, which is resistant to treatment with 5-fluorouracil (5-FU) and with metastases:

- according to M.L. Rothenberg et al. (J. Clin. Oncol. 1996; 14: 1128-1135):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3, D_8-D_{10}, D_{15}-D_{17}, D_{22}-D_{24}
• irinotecan	125 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}

the cure comprising two cycles with an interval of 42 days.

13/ Kaposi's sarcomas

- the 2-quinolones may be combined with the two protocols using antracyclines formulated as liposomes:

i) protocol described by P.S. Gill et al. (J. Clin. Oncol. 1995; 13: 996-1003) and C.A. Presant et al. (Lancet 1993; 341: 1242-1243):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 and D_{15}-D_{17}
• liposomal daunorubicin	20 mg/m^2/day infusion for 1 h	i.v.	D_1, D_{15}

the cure comprising two cycles repeated with an interval of 28 days before evaluating the effects.

ii) protocol of M. Harrison et al. (J. Clin. Oncol. 1995; 13: 914-920):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• liposomal doxorubicin	20 mg/m^2 infusion for 30 minutes	i.v.	D_1

the cure comprising two cycles repeated with an interval of 28 days before evaluating the effects.

14/ Metastatic melanomas

- the 2-quinolones may also be incorporated into combination protocols for treating metastatic malignant melanomas:

- DTIC/TAM protocol: according to G. Cocconi et al. (N. Eng. J. Med. 1992; 327: 516), the cure comprising the repetition of 4 cycles, at a rate of 1 cycle every 21 days, according to the scheme below:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• dacarbazine (DTIC)	250 mg/m^2/day infusion [15 to 30 min if central catheter] or [30 min if peripheral infusion in 250 ml]	i.v.	D_1-D_5
• tamoxifen (TAM)	20 mg/m^2/day	oral	D_1-D_5

the cure comprising 4 cycles at a rate of 1 cycle every 21 days.

15/ Neuroendocrine carcinoma

- 2-Quinolones may be combined with the protocol described by C.G Moertel et al. (Cancer 1991; 68: 227):
- Pt-E protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• etoposide	130 mg/m^2/day infusion for 1 hour	i.v.	D_1-D_3
• cisplatin	45 mg/m^2/day infusion for 1 hour	i.v.	D_2, D_3

the cure comprising two cycles repeated every 28 days.

16/ Pancreatic cancer

- **Advanced pancreatic adenocarcinoma:** the 2-quinolones may be combined with the treatment with

gemcitabine, according to the protocol of M. Moore et al. (Proc. Am. Soc. Clin. Oncol. 1995; 14: 473):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3, D_8-D_{10}, D_{15}, D_{22}, D_{29}, D_{36}, D_{43}, D_{57}
• gemcitabine	1000 mg/m^2 infusion for 0.5 hour	i.v.	D_1, D_8, D_{15}, D_{22}, D_{29}, D_{36}, D_{43}, and then D_{57} and then once/week for 3 weeks followed by 1 week of rest and evaluation

B. Onco-hematology

1/ Acute adult leukemias

1.1. Acute lymphoblastic leukemia

1.1.1. Linker protocol

The 2-quinolones may be added to the linker protocols-induction chemotherapy and consolidation chemotherapy (see C.A. Linker et al. Blood 1987; 69: 1242-1248 and C.A. Linker et al. Blood 1991; 78: 2814-2822) according to the following schemes:

i) Induction chemotherapy:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}, D_{15}-D_{19}
• daunorubicin	50 mg/m^2 bolus every 24 hours (30 mg/m^2 in the	i.v.	D_1, D_2, D_3

	Dose	Route	Days
	patients > 50 years old)		
• vincristine	2 mg bolus	i.v.	D_1, D_8, D_{15}, D_{22}
• prednisone	60 mg/m^2/day	oral	D_1-D_{28}
• L-asparaginase	6000 U/m^2	i.m.	D_{17}-D_{28}

ii) Consolidation chemotherapy (regimen A):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}
• daunorubicin	50 mg/m^2 bolus every 24 hours	i.v.	D_1, D_2
• vincristine	2 mg bolus	i.v.	D_1, D_8
• prednisone	60 mg/m^2/day divided into 3 doses	oral	D_1-D_{14}
• L-asparaginase	12 000 U/m^2	i.m.	D_2, D_4, D_7, D_9 and D_{14}

the consolidation cure A comprises 4 consecutive cycles such as that described above = cycles 1, 3, 5 and 7.

iii) Consolidation chemotherapy (regimens B and C):
the regimens described below correspond to the consolidation cycles 2, 4, 6 and 8 (regimen B) and 9 (regimen C), described by C.A. Linker et al.:

Regimen B:	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}
• Ara-C	300 mg/m^2 infusion for 2 hours	i.v.	D_1, D_4, D_8, D_{11}
• teniposide	165 mg/m^2 infusion for 2 hours (4 cycles)	i.v.	D_1, D_4, D_8, D_{11}

Regimen C:	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5,
• methotrexate	690 mg/m^2 continuous infusion for 42 hours	i.v.	D_1-D_2
• leucovorin	15 mg/m^2 every 6 hours	oral	D_2-D_5

1.1.2. Hoelzer protocol

The products claimed may be added to the cytotoxic agents of this polychemotherapy protocol (D. Hoelzer et al., Blood 1984; 64: 38-47, D. Hoelzer et al., Blood 1988; 71: 123-131) according to the following scheme:

i) Induction chemotherapy/Phase 1:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}, D_{15}-D_{19}

	Dose	Route	Days
• daunorubicin	25 mg/m^2	i.v.	D_1, D_8, D_{15}, D_{22}
• vincristine	1.5 mg/m^2 (maximum 2 mg)	i.v.	D_1, D_8, D_{15}, D_{22}
• prednisone	60 mg/m^2	oral	D_1-D_{28}
• L-asparaginase	5000 U/m^2 (maximum 2 mg)	i.m.	D_1-D_{14}

ii) Induction chemotherapy/Phase 2:
Phase 2 of the induction may be carried out as follows:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{29}-D_{33}, D_{36}-D_{40}, D_{43}-D_{47}
• cyclosphosphamide	650 mg/m^2 (maximum 1000 mg)	i.v.	D_{29}, D_{43}, D_{57}
• cytarabine	75 mg/m^2/day infusion for 1 hour	i.v.	D_{31}-D_{34}, D_{38}-D_{41}, D_{45}-D_{48}, D_{52}-D_{55}
• mercaptopurine	60 mg/m^2	oral	D_{29}-D_{57}
• methotrexate	10 mg/m^2/day (maximum 15 mg)	i.v.	D_{31}, D_{38}, D_{45}, D_{52}

iii) Re-induction chemotherapy/Phase 1:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}, D_{15}-D_{19}, D_{22}-D_{26}
• doxorubicin	25 mg/m^2/day	i.v.	D_1, D_8, D_{15}, D_{22}

	Dose	Route	Days
• dexamethasone	10 mg/m^2/day	i.v.	D_1-D_{28}
• vincristine	1.5 mg/m^2/day (maximum 2 mg)	oral	D_1, D_8, D_{15} and D_{22}

iv) Re-induction chemotherapy/Phase 2:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{31}-D_{35}, D_{38}-D_{42}
• cyclophosphamide	650 mg/m^2 (maximum: 1000 mg)	i.v.	D_{29}
• cytarabine	75 mg/m^2	i.v.	D_{31}-D_{34}, D_{38}-D_{41}
• thioguanine	60 mg/m^2	oral	D_{29}-D_{42}

1.2. Acute myeloid leukemias:

1.2.1. Treatment of adults of any age

The 2-quinolones may be added, according to the scheme below, to the treatment incorporating the standard dose of cytarabine described previously by R.O. Dilleman et al. (Blood, 1991; 78: 2520-2526), Z.A. Arlin et al. (Leukemia 1990; 4: 177-183) and P.H. Wiernik et al. (Blood 1992; 79: 313-319):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_{12}
• cytarabine	100-200 mg/m^2/day in continuous infusion	i.v.	D_1-D_7

	Dose	Route	Days
• daunorubicin	45 mg/m²/day in bolus (30 mg/m²/day if ≥ 60 years old)	i.v.	D_1-D_3 or D_8-D_{10}
or			
• mitoxantrone	12 mg/m² as daily bolus	i.v.	D_1-D_3
or			
• idarubicin	13 mg/m² as daily bolus	i.v.	D_1-D_3

1.2.2. Treatment of adults less than 60 years old

i) Induction chemotherapy:

This induction cycle incorporates the administration of cytarabine at high dose according to the following scheme:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_{10}
• Ara-C (cytarabine)	2000 mg/m²/day infusion for 2 hours, every 12 hours	i.v.	D_1-D_6
• daunorubicin	60 mg/m²/day in continuous infusion for 24 hours	i.v.	D_4-D_6
or			
• cytarabine	3000 mg/m²/day infusion for 1 hour, every 12 hours	i.v.	D_1-D_6
• daunorubicin	45 mg/m² bolus every 24 hours	i.v.	D_7-D_9

(in order to reduce the risk of C.N.S. toxicity, in the event of renal insufficiency, adjust the dosage of

cytarabine to the creatinine clearance) according to L.E. Damon et al. (Leukemia 1994; 8: 535-541), G.L. Phillips et al. (Blood 1991; 77: 1429-1435) and G. Smith et al. (J. Clin. Oncol. 1997; 15: 833-839).

ii) Consolidation chemotherapy:
The cycle described below will be repeated 8 times, at a rate of 1 cycle every 4 to 6 weeks (according to R.J. Mayer et al., N. Engl J. Med. 1994; 331: 896-903):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cytarabine	3000 mg/m^2 infusion for 3 hours, every 12 hours (4 cycles)	i.v.	D_1, D_3, D_5
and then			
• cytarabine	100 mg/m^2/day every 12 hours	s.c.	D_1-D_5
• daunorubicin	45 mg/m^2 bolus (4 cycles)	i.v.	D_1

iii) Consolidation chemotherapy (with strong dose of cytarabine):
The cycle described below will have to be repeated twice and is suitable according to G.L. Phillips et al. (Blood 1991; 77: 1429-1435); S.N. Wolff et al. (J. Clin. Oncol. 1989; 7: 1260-1267); R.J. Mayer et al. (N. Engl J. Med. 1994; 331: 896-903):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_{10}
• cytarabine	3000 mg/m^2 1 hour every 12 hours	i.v.	D_1-D_6
• daunorubicin	30-45 mg/m^2/day bolus once/day	i.v.	D_7-D_9

1.2.3. Treatment of adults 60 years old or more

The substances claimed may be added to the consolidation chemotherapy protocols below:

i) according to R.O. Dilman et al. (Blood 1991; 78; 2520-2526), Z.A. Arlin et al. (Leukemia 1990; 4: 177-183), P.H. Wiernik et al. (1992; 79: 313-319):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_6
• cytarabine (Ara-C)	100-200 mg/m^2 continuous infusion for 24 hours	i.v.	D_1-D_5
• daunorubicin	30-45 mg/m^2/day bolus	i.v.	D_1, D_2
or			
• mitoxantrone	12 mg/m^2/day bolus	i.v.	D_1, D_2
or			
• idarubicin	13 mg/m^2/day bolus	i.v.	D_1, D_2

ii) According to R.J. Mayer et al. (N. Engl. J. Med. 194; 331: 896-903):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_6
• cytarabine	100 mg/m^2 continuous infusion for 24 hours (4 cycles)	i.v.	D_1-D_2
and then • cytarabine	100 mg/m^2 every 12 hours	s.c.	D_1, D_5
• daunorubicin	45 mg/m^2/day bolus (4 cycles)	i.v.	J_1

iii) According to C.A. Linker et al. (Blood 1993; 81: 311-318), N. Chao et al. (Blood 1993; 81: 319-323) and A.M. Yeager et al. (N. Eng. J. Med. 1986; 315: 145-147):
This protocol comprises an autologous bone marrow transplantation (performed on day D_0):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-7}-D_{-2}
• busulfan	1 mg/kg qid (16 doses in total)	oral	D_{-7} to D_{-4}
• etoposide	60 mg/kg/day infusion for 10 hours	i.v.	D_{-3}

or

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-9}-D_{-1}
• busulfan	1 mg/kg qid	oral	D_{-9} to D_{-6}
• cyclophosphamide	50 mg/kg/day infusion for 1 hour	i.v.	D_{-5} to D_{-2}

iv) In the case of HLA-compatible allogenic bone marrow transplantation, according to:
P.J. Tutscha et at. Blood 1987; 70: 1382-1388,
F.R. Applebaum et al., Ann. Int. Med. 1984; 101: 581-588:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_{-7}-D_{-1}
• busulfan	1 mg/kg qid (16 doses in total)	oral	D_{-7} to D_{-4}
• cyclophosphamide	60 mg/kg/day infusion for 1 hour	i.v.	D_{-3} to D_{-2}

2/ Chronic adult leukemias

2.1 Chronic myeloid leukemia

In the myeloblast phase, the 2-quinolones may be added to the HU-Mith treatment described by C.A. Koller et al. (N. Engl. J. Med. 1986; 315: 1433-1438):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{12} D_{15}-D_{19} D_{22}-D_{26}
• hydroxyurea	500 mg/day	oral	every day
• mithramycin	25 µg/kg/day infusion for 2-4 hours	i.v.	daily for 3 weeks and then 3 times/week

2.2. Chronic lymphocytic leukemia

2.2.1 FCG-CLL protocol

The 2-quinolones may be added to the "pulsed chlorambucil" combinations as described by E. Kimby et al. (Leuk. Lymphoma 1991; 5 (Suppl.) 93-96) and by FCGCLL (Blood 1990; 75: 1422-1425):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}, D_{15}-D_{22}
• chlorambucil	0.1 mg/kg/day	oral	once/day
or			
• chlorambucil	0.4 mg/kg/day every 14 days	oral	D_1
and			
• prednisone	75 mg/day	oral	D_1-D_3

2.2.2 Fludarabine-CdA protocol

According to H.G. Chun et al. (J. Clin. Oncol. 1991; 9: 175-188), M.J. Keating et al. (Blood 1989; 74: 19-25/ J. Clin. Oncol. 1991; 9: 44-49) and A. Saven et al. (J. Clin. Oncol. 1995; 13: 570-574):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_8 (once/month for 6 to 12 cycles)
• fludarabine	25-30 mg/m^2/day infusion for 30 minutes [every 4 weeks for 6 to 12 cycles]	i.v.	D_1-D_5
or			
• cladibrine	0.09 mg/kg/day in continuous infusion [1 cycle every 28 to 35 days for 1 to 9 cycles (median: 4 cycles)]	i.v.	D_1-D_7

3/ Lymphoproliferative diseases

3.1 Hodgkin's disease

The 2-quinolones may be incorporated into the polychemotherapy protocols used conventionally for treating Hodgkin lymphoma:

3.1.1 AVDB protocol

According to G. Bonnadonna et al. (Cancer Clin. Trials 1979; 2: 217-226) and G.P. Canellos et al. (N. Engl. J. Med. 1993; 327: 1478-1484):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3, D_{15}-D_{18}
• doxorubicin (A)	25 mg/m^2 bolus	i.v.	D_1, D_{15}
• bleomycin (B)	10 U/m^2 bolus	i.v.	D_1, D_{15}

	Dose	Route	Days
• vinblastine (V)	6 mg/m^2 bolus	i.v.	D_1, D_{15}
• dacarbazine (D)	375 mg/m^2 bolus	i.v.	D_1, D_{15}

the cure comprising 6 to 8 cycles, at a rate of 1 cycle every 28 days.

3.1.2 MOPP/ABVD protocol

According to G. Bonnadonna et al. (Ann. Intern. Med. 1986; 104: 739-746) and G.P. Canellos et al. (N. Engl. J. Med. 1993; 327: 1478-1484):

the MOPP protocol should be alternated with the ABVD protocol (cf. § 3.1.1) every 28 days, and the cure comprises 6 cycles:

MOPP protocol:	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3, D_8-D_{11} and D_{14}-D_{17}
• mechlorethamine (M)	6 mg/m^2 bolus	i.v.	D_1, D_8
• vincristine (O)	1.4 mg/m^2 bolus (no maximum)	i.v.	D_1, D_8
• procarbazine (P)	100 mg/m^2/day	oral	D_1-D_{14}
prednisone (P)	40 mg/m^2/day	oral	D_1-D_{14}

3.1.3 Stanford V protocol

According to N.L. Bartlett et al. (J. Clin. Oncol. 1995; 13: 1080-1088):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 D_8-D_{12} D_{15}-D_{19} D_{22}-D_{26}
• doxorubicin	25 mg/m^2	i.v	D_1, D_{15}
• vinblastine	6 mg/m^2 bolus (4 mg/m^2 during cycle 3 if ≥ 50 years old)	i.v.	D_1, D_{15}
• mechlorethamine (M)	6 mg/m^2 bolus	i.v.	D_1
• vincristine	1.4 mg/m^2 bolus (max. dose: 2 mg) [1 mg/m^2 during cycle 3 if ≥ 50 years old)	i.v.	D_1, D_{22}
• bleomycin	5 U/m^2	i.v.	D_8, D_{22}
• etoposide	60 mg/m^2	oral	D_{15}, D_{16}
• prednisone	40 mg/m^2/day	oral	once/week (weeks 1-9)

the cure comprising 3 cycles at a rate of 1 cycle every 28 days.

3.1.4 EVA protocol

According to G.P. Canellos et al. (Proc. Am. Soc. Clin. Oncol. 1991; 10: 273):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• etoposide (E)	100 mg/m^2 infusion for 2 hours	oral	D_1, D_2, D_3
• vinblastine (V)	6 mg/m^2 bolus	i.v.	D_1
• doxorubicin (A)	50 mg/m^2 bolus	i.v.	D_1

the cure comprising 6 cycles at a rate of 1 cycle every 28 days.

3.1.5 B-CAVe protocol

According to W.G. Harker et al. (Ann. Intern. Med. 1984; 101: 440-446):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3
• bleomycin (B)	5 U/m^2 bolus	i.v.	D_1
• lomustine (CCNU)	100 mg/m^2	oral	D_1
• doxorubicin (A)	60 mg/m^2 bolus	i.v.	D_1
• vinblastine (Ve)	5 mg/m^2 bolus	i.v.	D_1

the cure comprising 8 cycles, at a rate of 1 cycle every 28 days.

3.2. Non-Hodgkin lymphomas

3.2.1. With a low degree of malignance

i)- CVP protocol

- According to C.M. Bagley et al. (Ann. Intern. Med. 1972; 76: 227-234) and C.S. Portlock et al. (Blood 1976; 47: 747-756)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cyclophosphamide (c)	300-400 mg/m^2/day	oral	D_1, D_5
• vincristine (V)	1.4 mg/m^2 bolus (max. 2 mg)	i.v.	D_1
• prednisone (P)	100 mg/m^2/day	oral	D_1, D_5

this cycle is repeated every 21 days up to the maximum response.

ii)- I-COPA protocol

- According to R.V. Smalley et al. (N. Eng. J. Med. 1992; 327: 1336-1341)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cyclophosphamide (C)	600 mg/m^2 day	i.v.	D_1
• vincristine (O)	1.2 mg/m^2 bolus (max. 2 mg)	i.v.	D_1
• prednisone (P)	100 mg/m^2/day	i.v.	D_1-D_5
• doxorubicin (A)	50 mg/m^2 bolus	i.v.	D_1
• interferon-alpha (I)	6 MU/m^2	i.m.	D_{22}-D_{26}

the cure comprises 8 to 10 cycles, at a rate of 1 cycle every 28 days.

iii)- Fludarabine-CdA protocol

- According to P. Solol-Celigny et al. (Blood 1994; 84

(Supp. 1): 383a), H. Hoeschster et al.; (Blood 1994; 84 (Suppl. 1): 564a and A.C. Kay (J. Clin. Oncol. 1992; 10: 371-377)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_7
• fludarabine	25 mg/m^2 day infusion for 0.5 hour	i.v.	D_1-D_5
or			
• fludarabine	20 mg/m^2/day	i.v.	D_1-D_5
and cyclophosphamide	600-1000 mg/m^2/day	i.v.	D_1
or cladribine	0.1 mg/m^2/day infusion for 24 hours	i.v.	D_1-D_7

for fludarine, each cycle is repeated every 28 days; For cladribine, each cycle is repeated every 35 days.

3.2.2. With an intermediate degree of malignance

i)- CHOP or CNOP protocol

- According to EM McKelvey et al. (Cancer 1976; 38: 1484-1493), J.O. Armitage et al. (J. Clin. Oncol. 1984; 2: 898-902), S. Paulovsky et al. (Ann. Oncol. 1992; 3: 205-209)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cyclophosphamide (C)	750 mg/m^2 day	i.v.	D_1
• doxorubicin (H)	50 mg/m^2 bolus	i.v.	D_1

	Dose	Route	Days
• vincristine (O)	1.4 mg/m^2 bolus (max: 2 mg)	i.v.	D_1
• prednisone (P)	100 mg/m^2/day (as 1 dose/day)	oral	D_1-D_5

for the CHOP protocol

Mitoxantrone (N) may be used to replace (CNOP protocol) doxorubicin in patients over 60 years old (dose: 12 mg/m^2 as i.v. bolus on day D1 of each cycle).

The cure with the CHOP or CNOP protocol comprises 6 to 8 cycles at a rate of 1 cycle every 21 days.

ii)- MACOP-B protocol

- According to P. Klimo et al. (Ann. Intern. Med. 1985; 102: 596-602) and I.A. Cooper et al. (J. Clin. Oncol. 1994; 12: 769-778)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12} D_{15}-D_{22}, D_{29}-D_{33} D_{43}-D_{47}, D_{57}-D_{61}, D_{71}-D_{75}
• methotrexate (M)	100 mg/m^2 bolus then 300 mg/m^2 infusion for 4 hours	i.v.	D_8, D_{36}, D_{64}
• leucovorin	15 mg qid	oral	D_9, D_{37}, D_{65}
• doxorubicin (A)	50 mg/m^2 bolus	i.v.	D_1, D_{15}, D_{29}, D_{43}, D_{57}, D_{71}
• cyclophosphamide (c)	350 mg/m^2 bolus	i.v.	D_1, D_5, D_{29}, D_{43}, D_{57}, D_{71}

	Dose	Route	Days
• vincristine (O)	1.4 mg/m^2 bolus (max: 2 mg)	i.v.	$D_8, D_{22}, D_{36}, D_{50}, D_{64}, D_{78}$
• prednisone (P)	75 mg/day	oral	every day for 12 weeks
• bleomycin (B)	10 U/m^2 bolus	i.v.	D_{22}, D_{50}, D_{78}

this treatment protocol spreads over 12 weeks and corresponds to 1 cycle.

iii)- VACOP-B protocol

- According to J.M. Connors et al. (Proc. Am. Soc. Clin. Oncol. 1990; 9: 254):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12} D_{15}-D_{22}, D_{29}-D_{34}D D_{43}-D_{47}, D_{57}-D_{61}, D_{71}-D_{75}
• etoposide (V)	50 mg/m^2	i.v.	D_{15}, D_{43}, D_{71}
• etoposide	100 mg/m^2	oral	$D_{16}, D_{17}, D_{44}, D_{45}, D_{72}, D_{73}$
• doxorubicin (A)	50 mg/m^2 bolus	i.v.	$D_1, D_{15}, D_{29}, D_{43}, D_{57}, D_{71}$
• cyclophosphamide (c)	350 mg/m^2/day bolus	i.v.	$D_8, D_{22}, D_{36}, D_{50}, D_{64}, D_{78}$
• vincristine (O)	1.2 mg/m^2 bolus	i.v.	$D_8, D_{22}, D_{36}, D_{50}, D_{64}, D_{78}$
• prednisone (P)	45 mg/m^2/day	oral	1/day for 1 week, then 4/day for the next 11 weeks

each cycle lasting 12 weeks.

iv)- m-BACOD/M-BACOD protocol

- According to M.A. Shipp et al. (Ann. Int. Med. 1986; 140; 757-765) and A.T. Skarin et al. (J. Clin. Oncol. 1983; 1: 91-98)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12} D_{15}-D_{19}
• methotrexate (m)	200 mg/m² infusion for 4 hours	i.v.	D_8, D_{15}
or			or
(M)	3000 mg/m² infusion for 4 hours	i.v.	D_{15}
• leucovorin	10 mg/m² qid (6 doses in total)	oral	D_9, D_{16} or D_{16}
• bleomycin (B)	4 U/m² bolus	i.v.	D_1
• doxorubicin (A)	45 mg/m² bolus	i.v.	D_1
• cyclo-phosphamide (C)	600 mg/m² bolus	i.v.	D_1
• vincristine (O)	1 mg/m² bolus	i.v.	D_1
• dexamethasone (D)	6 mg/m²/day	oral	D_3-D_5

the cure comprising 10 cycles, at a rate of 1 cycle every 21 days.

v)- ProMACE/CytaBOM protocol

- According to D.L. Longo et al. (J. Clin. Oncol. 1991; 9: 25-38):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}
• cyclophosphamide (C)	650 mg/m^2 infusion for 0.5 hour	i.v.	D_1
• doxorubicin (A)	25 mg/m^2 bolus	i.v.	D_1
• etoposide	120 mg/m^2 infusion for 1 hour	i.v.	D_1
• prednisone (P)	60 mg/day	oral	D_1-D_{14}
• cytarabine	300 mg/m^2 bolus	i.v.	D_8
• bleomycin (B)	5 U/m^2 bolus	i.v.	D_8
• vincristine (O)	1.4 mg/m^2 bolus	i.v.	D_8
• methotrexate	120 mg/m^2 bolus	i.v.	D_8
• leucovorin	25 mg/m^2 qid (4 doses in total)	oral	D_9

the cure comprising 6 to 8 cycles, at a rate of 1 cycle every 14 days.

3.2.3. With a low or intermediate degree of malignance

i)- ESHAP rescue protocol

- In the event of a relapse or of a failure of the first line treatment, according to W.S. Velasquez et al. (J. Clin. Oncol. 1994; 12: 1169-1176)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5

	Dose	Route	Days
• etoposide (E)	40 mg/m^2 infusion for 2 hours	i.v.	D_1-D_4
• methyl-prednisolone (S)	500 mg/day infusion for 15 minutes	i.v.	D_1,D_4
• cytarabine (HA)	2000 mg/m^2 infusion for 3 hours	i.v.	D_5
• cisplatin (P)	25 mg/m^2/day bolus continuous infusion for 24 hours	i.v.	D_1-D_4

the cure comprising 6 cycles, at a rate of 1 cycle every 28 days.

ii)- MINE rescue protocol

- In the event of a relapse or of a failure of the first line treatment, according to F. Cabanillas et al. (Semin. Oncol. 1990; 17 (suppl. 10): 28-33)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• ifosfamide (I)	1330 mg/m^2 infusion for 1 hour	i.v.	D_1-D_3
• mesna (M)	1330 mg/m^2 in the infusion of ifosfamide and then 266 mg/m^2 bolus 4 and 8 hours after each dose of ifosfamide	i.v.	D_1-D_3

	Dose	Route	Days
• mitoxantrone (M)	8 mg/m^2 infusion for 15 minutes	i.v.	D_1
• etoposide (E)	65 mg/m^2/day infusion for 1 hour	i.v.	D_1-D_3

this cycle being repeated every 21 days.

3.3. Non-Hodgkin lymphomas: Burkitt's lymphoma, small-cell lymphoma, lymphoblast lymphoma

3.3.1. Magrath protocol

- the products claimed may be combined with the Magrath protocols according to the following schemes:

i)- cycle 1

- according to I.T. Magrath et al. (Blood 1984; 63: 1102-1111)

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{12}
• cytarabine	30 mg/m^2	intra-thecal	D_1, D_2, D_3, D_7
• cyclophosphamide	1200 mg/m^2 bolus	i.v.	D_1
• methotrexate	12.5 mg/m^2 (max: 12.5 mg)	intra-thecal	D_{10}
• methotrexate	300 mg/m^2/day infusion for 1 hour and then 60 mg/m^2/h infusion for 41 hours	i.v.	D_{10}-D_{11}

	Dose	Route	Days
• leucovorin	15 mg/m^2 bolus qid (8 successive doses)	i.v.	to be started 42 hours after the start of the administration of methotrexate

ii)- Cycles 2 to 15

- According to I.T. Magrath et al. (1984) also.

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_3 D_{10}-D_{11}
• cytarabine	45 mg/m^2	intra-thecal	D_1,D_2 (cycles 2 and 3) D_1 (cycles 4 and 6)
• cyclophosphamide	1200 mg/m^2 bolus	i.v.	D_1
• doxorubicin	40 mg/m^2 bolus	i.v.	D_1
• vincristine	1.4 mg/m^2 bolus (max: 2 mg)	i.v.	D_1
• methotrexate	12.5 mg/m^2 (max: 12.5 mg)	intra-thecal	D_3,D_{10} (cycles 2 and 3) D_{10} (cycles 4, 5, 6)

	Dose	Route	Days
• methotrexate	300 mg/m^2 infusion for 1 hour and then 60 mg/m^2 continuous infusion for 41 hours	i.v.	D_{10}, D_{11} (cycles 2 and 6) D_{14}, D_{15} (cycles 7-15)
• leucovorin	15 mg/m^2 bolus qid (8 consecutive doses)	i.v.	start at the 42nd hour of the treatment with methotrexate

the cure comprising 14 cycles, at a rate of 1 cycle every 28 days.

3.4 Waldenström's macroglobulinaemia

3.4.1 CVP protocol

according to the CVP protocol described by M.A. Dimopoulous et al. (Blood 1994; 83: 1452-1459) and C.S. Portlock et al. (Blood 1976; 47: 747-756):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• cyclophosphamide (C)	300-400 mg/m^2/day	oral	D_1-D_5
• vincristine (V)	1.4 mg/m^2/day bolus (max: 2 mg)	i.v.	D_1
• prednisone (P)	100 mg/m^2/day	oral	D_1-D_5

the cure being continued indefinitely (1 cycle every 21 days).

3.4.2 Fludarabine-CdA protocol

According to H.M. Kantarjian et al. (Blood 1990; 75: 1928-1931) and M.A. Dinopoulous et al. (Ann. Intern. Med. 1993; 118: 195-198):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• fludarabine	25-30 mg/m^2 infusion for 0.5 hour	i.v.	D_1-D_5

or

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_7
• cladribine (CdA)	0.09 mg/m^2/day continuous infusion	i.v.	D_1-D_7

the cure comprising 6 to 12 cycles with an interval of 28 days in the case of fludarabine and 2 cycles with an interval of 28 days also in the case of cladribine.

3.5 Multiple myeloma

3.5.1 MP protocol

According to R. Alexanian et al. (JAMA 1969; 208: 1680-1685), A. Belch et al. (Br. J. Cancer 1988; 57: 94-99) and F. Mandelli et al. (N. Engl. J. med. 1990; 322: 1430-1434):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• melphalan (M)	0.25 mg/kg/day	oral	D_1-D_4
• prednisone (P)	100 mg/day	oral	D_1-D_4

or

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• melphalan (M)	9 mg/m^2/day	oral	D_1-D_4
• prednisone (P)	100 mg/day	oral	D_1-D_4

the cure comprising at least 12 cycles, at a rate of 1 cycle every 4 to 6 weeks.

3.5.2 VAD protocol

According to B. Barlogie et al. (N. Engl. J. Med. 1984; 310: 1353-1356):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m^2/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• vincristine (V)	0.4 mg/day continuous 24-hour infusion	i.v.	D_1-D_4
• doxorubicin (A)	9 mg/m^2/day continuous 24-hour infusion	i.v.	D_1-D_4

	Dose	Route	Days
• dexamethasone (D)	40 mg/day	i.v.	D_1-D_4, D_9-D_{12}, D_{17}-D_{20}

3.5.3 MP-interferon α protocol
according to O. Osterborg et al. (Blood 1993; 81: 1428-1434):

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• melphalan (M)	0.25 mg/kg/day	oral	D_1-D_4
• prednisone (P)	2 mg/kg/day	oral	D_1-D_4
• interferon-alpha	7 MU/kg/day	s.c.	D_1-D_5 and D_{22}-D_{26}

the cure comprising the indefinite repetition of this cycle, at a rate of 1 cycle every 42 days.

3.5.4 VCAP or VBAP protocol
According to S.E. Salmon et al. (J. Clin. Oncol. 1983; 1: 453-461):
VCAP protocol:

	Dose	Route	Days
• 2-quinolone	200-2000 mg/m²/day or 5-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5
• vincristine (V)	1 mg/m² bolus (max: 1.5 mg)	i.v.	D_1
• doxorubicin (A)	30 mg/m² bolus	i.v.	D_1
• prednisone (P)	60 mg/m²/day	oral	D_1-D_4

	Dose	Route	Days
• cyclophosphamide (C)	125 mg/m^2 infusion for 1 hour	oral	D_1-D_4

VBAP protocol: the cyclophosphamide is replaced with carmustine (BCNU), the remainder being identical:

	Dose	Route	Days
• carmustine	30 mg/m^2 infusion for 1 hour	i.v.	D_1

C. TUMORS IN CHILDREN - Pediatric oncology

The isoflavones can also be incorporated into poly-chemotherapy protocols for treating pediatric tumors in order to improve the antitumor efficacy while at the same time reducing the severity of the side effects by virtue of the action on the recruitment and mobilization of the clonogenic cells and by virtue of the possibility of reducing the active doses.

1/ Ewing's sarcoma/primitive neuroectodermal tumor

The 2-quinolones may be introduced into the VCR-Doxo-CY-Ifos-Mesna-E protocol (E.D. Berger et al., J. Clin. Oncol. 1990; 8: 1514-1524; W.H. Meyer et al., J. Clin. Oncol. 1992; 10: 1737-1742):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day <u>or</u> 2-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5 and D_{22}-D_{27} and D_{43}-D_{48} and D_{63}-D_{66}
• vincristine	2 mg/m^2 bolus (maximum dose = 2 mg)	i.v.	D_1, D_8, D_{15}, D_{43}

	Dose	Route	Days
• doxorubicin	30 mg/m^2/day in infusion for 24 hours	i.v.	D_1-D_3, D_{43}-D_{45}
• cyclophosphamide	2.2 g/m^2 in infusion for 0.5 hour	i.v.	D_1, D_{43}
• ifosfamide	1800 mg/m^2/day in infusion for 1 hour	i.v.	D_{22}-D_{26} D_{63}-D_{67}
• mesna	360 mg/m^2 in infusion for 15 minutes at a rate of 5 doses every 3 hours	i.v.	administered with cyclophosphamide and ifosfamide
• etoposide	100 mg/m^2 in infusion for 1 hour	i.v.	D_{22}-D_{26} D_{63}-D_{67}

the cure comprises 6 to 10 of these cycles depending on the initial severity of the sarcoma and the amplitude of the response.

2/ Acute pediatric lymphoblast leukemia

2.1. Induction chemotherapy (days D_1-D_{30})

The 2-quinolones may be added to the recommended protocols (P.S. Gaynon et al., J. Clin. Oncol., 1993, 11, 2234-2242; J. Pullen et al., J. Clin. Oncol. 1993; 11: 2234-2242; J. Pullen et al., J. Clin. Oncol. 1993; 11: 839-849; V.J. Land et al., J. Clin. Oncol. 1994; 12: 1939-1945):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_8-D_{11}, D_{15}-D_{18}, D_{22}-D_{27}
• vincristine	1.5 mg/m^2 bolus (maximum dose ≈ 2 mg)	i.v.	D_1, D_8, D_{15}, D_{22}
• L-asparaginase	6000 IU/m^2	i.m.	3 times/week for 3 weeks
• prednisone	60 mg/m^2 in 3 doses/day	oral	D_1 to D_{28}
• daunorubicin	25 mg/m^2/day in infusion for 15 minutes	i.v.	D_1, D_8, D_{15} and D_{22}
• methotrexate	depending on the age	intra-thecal	D_{15}, D_{28}
• cytarabine	depending on the age	intra-thecal	D_1

depending on the result of the bone marrow examination, passage to the consolidation phase takes place on day D_{28} of the treatment protocol.

2.2. Consolidation/maintenance chemotherapy

The 2-quinolones may be introduced into the maintenance protocol (P.S. Gaynon et al., J. Clin. Oncol., 1993, 11, 2234-2242; J. Pullen et al., J. Clin. Oncol. 1993; 11: 839-849; V.J. Land et al., J. Clin. Oncol. 1994; 12: 1939-1945) according to the following scheme:

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 h	i.v.	D_1-D_5, D_{15}-D_{20} and D_{94}-D_{99}, D_{101}-D_{106} D_{108}-D_{113}, D_{122}-D_{127}
• cyclophos-phamide	1000 mg/m^2 in infusion for 0.5 hour	i.v.	D_1, D_{15}, D_{122}
• L-asparaginase	6000 U/m^2	i.m.	3 times/week between D_{97} and D_{122}
• cytarabine	75 mg/m^2/day in infusion for 15 minutes	i.v./ s.c.	a sequence of 4 days starting D_2, D_9, D_{16}, D_{23}, D_{123}, D_1
• doxorubicin	25 mg/m^2/day in infusion for 15 minutes	i.v.	D_{94}, D_{101}, D_{108}
• mercaptopurine	60 mg/m^2/day	oral	D_1-D_{93}, D_{143} to the end of the treatment
• methotrexate	20 mg/m^2/day	oral	once/week between D_{36} and D_{72} and between D_{143} and the end of the treatment
• prednisone	40 mg/m^2/day (divided into 3 doses/day)	oral	5 consecutive days per month between D_{143} and the end of the treatment
• thioguanine	60 mg/m^2/day	oral	D_{122}-D_{135}

	Dose	Route	Days
• vincristine	1.5 mg/m^2 bolus (maximum dose = 2 mg)	i.v.	D_{94}, D_{101}, D_{108}, then once/month between D_{143} and the end of the treatment
• methotrexate	depending on the age	intra-thecal	D_1, D_8, D_{15}, D_{22}, D_{123}, D_{130} then once/3 months between D_{143} and the end of the treatment

3/ Acute pediatric myeloid leukemia

The 2-quinolones are added to the induction and consolidation/maintenance protocols according to the following schemes:

3.1. Induction chemotherapy

According to Y. Ravindranath et al., J. Clin. Oncol. 1991; 9: 572-580; M.E. Nesbit et al., J. Clin. Oncol. 1994; 12: 127-135; R.J. Wells et al., J. Clin. Oncol. 1994; 12: 2367-2377):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_{10}-D_{13}
• cytarabine	depending on the age	intra-thecal	D_1
• daunorubicin	20 mg/m^2/day in infusion for 24 hours	i.v.	D_1-D_4, D_{10}-D_{13}

	Dose	Route	Days
• cytarabine	200 mg/m^2/day in infusion for 24 hours	i.v.	D_1-D_4, D_{10}-D_{13}
• thioguanine	100 mg/m^2/day divided into 2 doses/day	oral	D_1-D_4, D_{10}-D_{13}
• etoposide	100 mg/m^2/day in infusion for 24 hours	i.v.	D_1-D_4, D_{10}-D_{13}
• dexamethasone	6 mg/m^2 divided into 3 doses/day	i.v./ oral	D_1-D_4, D_{10}-D_{13}

this cycle being repeated from D_{28}.

3.2. Consolidation/maintenance chemotherapy

According to Y. Ravindranath et al., J. Clin. Oncol. 1991; 9: 572-580; M.E. Nesbit et al., J. Clin. Oncol. 1994; 12: 127-135; R.J. Wells et al., J. Clin. Oncol. 1994; 12: 2367-2377):

	Dose	Route	Days
• cytarabine	depending on the age	intra-thecal	D_1, D_{28}, D_{56}
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_8-D_{13}, D_{28}-D_{33}, D_{56}-D_{61} D_{89}-D_{94}
• cytarabine	3000 mg/m^2 in infusion for 3 hours every 12 hours	i.v.	D_1-D_2, and D_8-D_9

	Dose	Route	Days
• L-asparaginase	6000 IU/m^2 3 hours after cytarabine	i.m.	D_2, D_9
• vincristine	1.5 mg/m^2 bolus (maximum dose = 2 mg)	i.v.	D_{28}, D_{56}
• thioguanine	75 mg/m^2/day	oral	D_{28}-D_{84}
• cytarabine	75 mg/m^2/day bolus	i.v.	D_{28}-D_{31}, D_{56}-D_{59}
• cyclophos-phamide	75 mg/m^2/day in infusion for 0.5 hour	i.v.	D_{28}-D_{31}, D_{56}-D_{59}
• cytarabine	25 mg/m^2/day bolus	sc/i.v.	D_{89}-D_{93}
• thioguanine	50 mg/m^2/day	oral	D_{89}-D_{93}
• etoposide	100 mg/m^2/day in infusion for 1 hour	i.v.	D_{89}, D_{92}
• dexamethasone	2 mg/m^2/day	oral	D_{89}-D_{92}
• daunorubicin	30 mg/m^2 in infusion for 15 minutes	i.v.	D_{89}

4/ Pediatric Hodgkin's disease

The 2-quinolones may be added to the MOPP-ABVD protocol according to E.A. Gehan et al. (Cancer 1990; 65: 1429-1437), S.P. Hunger et al. (J. Clin. Oncol. 1994; 12: 2160-2166) and M.M. Hudson et al. (J. Clin. Oncol. 1993; 11: 100-108):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5 and D_8-D_{12}
• mechlorethamine (M)	6 mg/m^2 bolus	i.v.	D_1, D_8
• vincristine (O)	1.5 mg/m^2 bolus (maximum 2 mg)	i.v.	D_1, D_8
• procarbazine (P)	100 mg/m^2/day	oral	D_1-D_{14}
• prednisone (P)	40 mg/m^2/day (divided into 3 doses/d)	oral	D_1-D_{14}
• doxorubicin (A)	25 mg/m^2/day in infusion for 15 minutes	i.v.	D_{29}, D_{43}
• bleomycin (B)	10 U/m^2 in infusion for 15 minutes	i.v.	D_{29}, D_{43}
• vinblastine (V)	6 mg/m^2 bolus (maximum 2 mg)	i.v.	D_{29}, D_{43}
• dacarbazine (D)	375 mg/m^2 in infusion for 15 minutes	i.v.	D_{29}, D_{43}

this cycle should be repeated 6 times at a rate of 1 cycle every 8 weeks, the cure comprising 6 cycles.

If an autologous bone marrow transplant (auto-graft) is prescribed, the CVB protocol described by R. Chopra et al. (Blood 1993; 81: 1137-1145), C. Wheeler et al. (J. Clin. Oncol. 1990; 8: 648-656) and R.J. Jones et al. (J. Clin. Oncol. 1990, 8, 527-537) may be used according to the following scheme (the allograft taking place on day D_0):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_{-7}, D_{-1}
• cyclophosphamide	1800 mg/m^2/day in 2 infusions for 1 hour	i.v.	D_{-7}, D_{-6} D_{-5}, D_{-4}
• carmustine (BCNU)	112 mg/m^2/day in infusion for 0.5 hour	i.v.	D_{-7}, D_{-6} D_{-5}, D_{-4}
• etoposide	500 mg/m^2/day in 2 infusions for 1 hour	i.v.	D_{-7}, D_{-6} D_{-5}, D_{-4}

5/ Pediatric lymphoblast lymphoma

The compounds claimed may also be combined with the induction chemotherapy protocols (A.T. Meadows et al., J. Clin. Oncol. 1989; 7: 92-99-C. Patte et al., Med. Ped. Oncol. 1992; 20: 105-113 and A. Reiter et al., J. Clin. Oncol. 1995; 13: 359-372) and the maintenance chemotherapy protocols:

5.1 Induction chemotherapy

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_{17}-D_{22}, D_{24}-D_{29}
• cyclophosphamide	1200 mg/m^2 in infusion for 0.5 hour	i.v.	D_1
• cytarabine	depending on the age	intra-thecal	D_1

	Dose	Route	Days
• vincristine	1.5 mg/m^2 bolus (maximum 2 mg)	i.v.	D_3, D_{10}, D_{17}, D_{24}
• prednisone	60 mg/m^2/day divided into 3 doses/day	oral	D_3-D_{28}
• daunorubicin	60 mg/m^2 in infusion for 15 minutes	i.v.	D_{17}
• L-asparaginase	6000 U/m^2/day in infusion for 15 minutes	im	D_{17}-D_{35} 3 times/ week
• methotrexate	depending on the age	intra-thecal	D_{17}, D_{31}

5.2 Maintenance chemotherapy:
according to the following scheme

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_{15}-D_{20}, D_{29}-D_{34}
• cyclophos-phamide	1000 mg/m^2 in infusion for 0.5 hour	i.v.	D_1
• vincristine	1.5 mg/m^2 bolus (maximum 2 mg)	oral	D_1, D_5 (from cycles 2 to 10)
• methotrexate	300 mg/m^2/day (60% in infusion for 15 minutes and 40% in infusion for 4 hours)	i.v.	D_{15}

	Dose	Route	Days
• leucovorin	10 mg/m^2/every 4 h	oral	D_{16}
• daunorubicin	30 mg/m^2 in infusion for 0.5 hour	i.v.	D_{29}
• methotrexate	depending on the age	intra-thecal	D_1, D_8, D_{15} (cycle 1) and then once/ month (cycles 2 to 10)

the cure comprising 10 cycles.

6/ Pediatric neuroblastoma

The recommended polychemotherapy protocol Doxo-E-Cy-Pt is adapted from R.P. Castleberry et al. (J. Clin. Oncol. 1992; 10: 1299-1304), A. Garaventa et al. (J. Clin. Oncol. 1993; 11: 1770-1779) and D.C. West et al. (J. Clin. Oncol. 1992; 11: 84-90):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_{28}-D_{35}, D_{58}-D_{65}
• doxorubicin	25 mg/m^2/day in infusion for 15 minutes	i.v.	D_2, D_{30}, D_{58}
• etoposide	100 mg/m^2 in infusion for 1 hour	oral/ naso-gastric	D_2, D_5, D_{30}, D_{33}, D_{58}, D_{61}
• cyclophos-phamide	1000 mg/m^2 in infusion for 0.5 hour	i.v.	D_3, D_4, D_{31}, D_{32}, D_{59}, D_{60}

	Dose	Route	Days
• cisplatin	60 mg/m^2 in infusion for 6 hours	i.v.	D_1, D_{28}, D_{56}

the evaluation of the therapeutic response is carried out after 9 weeks in order to determine the approach: surgical resection, radiotherapy or new chemotherapy.

7/ Pediatric osteosarcoma

The 2-quinolones may be added to the Doxo-Pt-Mtx-Lcv protocol as described by M. Hudson et al. (J. Clin. Oncol. 1990; 8: 1988-1997), P.A. Meyers (J. Clin. Oncol. 1992; 10: 5-15) and V.H.C. Bramwell et al. (J. Clin. Oncol. 1992; 10: 1579-1591):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_{21}-D_{26}, D_{28}-D_{33}
• doxorubicin	25 mg/m^2/day in infusion for 24 hours	i.v.	D_1-D_3
• cisplatin	120 mg/m^2 in infusion for 6 hours	i.v.	D_1
• methotrexate	12 mg/m^2/day in infusion for 1 hour	i.v.	D_{21}, D_{28}
• leucovorin	100 mg/m^2 every 6 hours	oral	D_{22}, D_{29}

8/ Pediatric rhabdomyosarcoma

The Vcr-Dact-CY-Mesna protocol (H. Maurer et al., Cancer 1993; 71: 1904-1922 and L.R. Mandell et al., Oncology 1993; 7: 71-83) may include the i.v. infusion of the compounds claimed according to the following scheme:

	Dose	Route	Days
• 2-quinolone	100-200 mg/m^2/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_8-D_{12}, D_{22}-D_{27}, D_{43}-D_{47}
• vincristine	1.5 mg/m^2 bolus (max. 2 mg)	i.v.	D_1, D_8, D_{15}, D_{22}, D_{29}, D_{36}, D_{43}, D_{50} and D_{57}
• dactinomycin	0.015 mg/kg bolus (max. daily dose: 0.5 mg)	i.v.	D_1-D_5, D_{22}-D_{27}, D_{43}-D_{47}
• cyclophos-phamide	2.2 g/m^2 in infusion for 1 hour	i.v.	D_1, D_{22}, D_{43}
• mesna	360 mg/m^2 in infusion for 1 hour every 3 hours for 5 doses	i.v.	D_1, D_{22}, D_{43}

At the end of the 9th week of treatment, the efficacy should be evaluated to decide the follow-up treatment (surgery, radiotherapy, continuation of the chemo-therapy).

9/ Wilms' tumor in children

In the Vcr-Dact protocol as described by G.J. D'Angio et al. (Cancer, 1989; 64: 349-360) and D.M. Green et al. (J. Clin. Oncol. 1993; 11: 91-95):

	Dose	Route	Days
• 2-quinolone	100-200 mg/m²/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_1-D_5, D_8-D_{12} and then every week
• vincristine	2 mg/m² bolus (max. dose: 2 mg)	i.v.	D_7 and then every week
• dactinomycin	0.045 mg/kg bolus (P ≤ 30 kg) 1.35 mg/m² (P > 30 kg) (max. dose: 3 mg)	i.v.	D_1 and then every 3 weeks

this protocol being started after the surgical resection.

In the event of autologous bone marrow transplants (auto-graft) according to A. Garaventar et al. (Med. Pediatr. Oncol. 1994; 22: 11-14), the E-Thio-Cy protocol may be modified as follows:

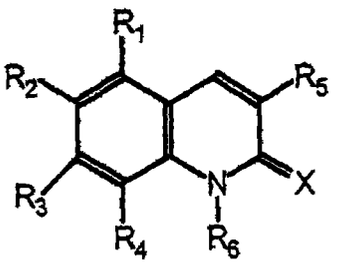
	Dose	Route	Days
• 2-quinolone	100-200 mg/m²/day or 2-50 mg/kg/day infusion for 1 hour	i.v.	D_{-8}-D_{-1}
• etoposide	1800 mg/m² (infusion for 24 hours)	i.v.	D_{-8}

	Dose	Route	Days
• thiotepa	300 mg/m^2/day in infusion for 2 hours	i.v.	D_{-7}, D_{-6}, D_{-5}
• cyclophosphamide	50 mg/kg/day in infusion for 1 hour	i.v.	D_{-4}, D_{-3}, D_{-2}, D_{-1}

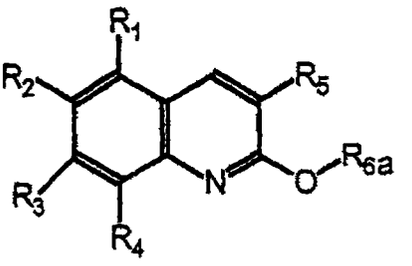
The bone marrow transplant taking place on day D_0.

CLAIMS

1. Use of a compound chosen from the compounds of formulae:



(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group -OCOR_8, a phenyl (C_1-C_4 alkoxy) group, a group -O-SO_2-R'_8, R'_8 being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_{6a} is chosen from a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_9 being a C_1-C_4 alkyl group,

A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group -$COOR_{11}$, -$CONR_{12}R_{13}$, a group -$NR_{14}R_{15}$ and a group -$COOR_{16}$ [sic],

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R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a $-CO-CH_2-CH_2-$ group,

for the manufacture of a medicine for interfering with the generation of clonogenic cells in tumors during a treatment of these tumors with at least one cytotoxic agent.

2. Use according to Claim 1, in which the compound is a compound of formula (I) in which:

- R_1 is a C_1-C_4 alkoxy group
- R_2 is a hydrogen atom
- R_3 is a C_1-C_4 alkoxy group
- R_4 is a hydrogen atom.

3. Use according to Claim 2, in which the compound is a compound of formula (I) in which:

- R_5 is a 4-(C_1-C_4 alkoxy)phenyl group.

4. Use according to Claim 3, in which:

- R_1 is a methoxy group,
- R_3 is a methoxy group, and
- R_5 is a 4-methoxyphenyl group.

5. Use according to Claim 4, in which the compound is 5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone.

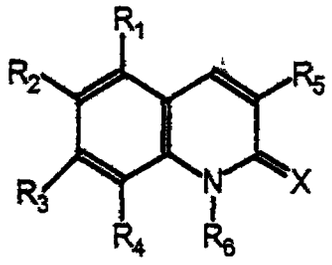
6. Use according to Claim 4, in which the compound is 3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanenitrile.

7. Use according to Claim 4, in which the compound is 1-[2-(1H-1,2,3,4-tetrazol-5-yl)ethyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone.

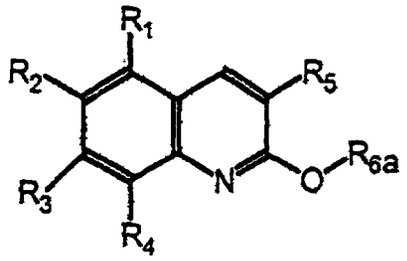
8. Use according to Claim 4, in which the compound is N,N-diethyl-3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanamide.

9. Pharmaceutical composition having activity on the proliferation of clonogenic cells in tumors and which comprises an effective amount of a compound chosen from the compounds of formulae:

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(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group -OCOR_8, a phenyl (C_1-C_4 alkoxy) group, a group -O-SO_2-R'_8, R'_8 being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group -CO-R_9 and a group -A-R_{10},

R_{6a} is chosen from a group -CO-R_9 and a group -A-R_{10},

R_9 being a C_1-C_4 alkyl group,

A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group -$COOR_{11}$, -$CONR_{12}R_{13}$, a group -$NR_{14}R_{15}$ and a group -COR_{16},

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a -CO-CH_2-CH_2- group.

10. Composition according to Claim 9, in which the compound is a compound of formula (I) in which:

- R_1 is a C_1-C_4 alkoxy group
- R_2 is a hydrogen atom

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- R_3 is a C_1-C_4 alkoxy group
- R_4 is a hydrogen atom.

11. Composition according to Claim 10, in which the compound is a compound of formula (I) in which:

- R_5 is a 4-(C_1-C_4 alkoxy)phenyl group.

12. Composition according to Claim 11, in which the compound is a compound of formula (I), R_1 is a methoxy group, R_3 is a methoxy group and R_5 is a 4-methoxyphenyl group.

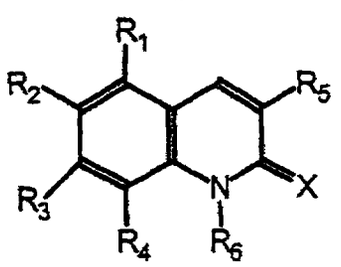
13. Composition according to Claim 12, in which the compound is 5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone.

14. Composition according to Claim 12, in which the compound is 3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanenitrile.

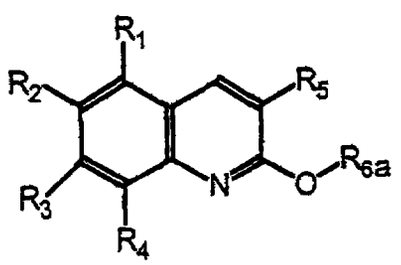
15. Composition according to Claim 12, in which the compound is 1-[2-(1*H*-1,2,3,4-tetrazol-5-yl)ethyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone.

16. Composition according to Claim 12, in which the compound is *N*,*N*-diethyl-3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanamide.

17. Compounds of formulae:



(I) and



(Ia)

in which:

X is chosen from =O, =S and =N-NH-R_7, R_7 being a phenyl or pyridyl group,

R_1, R_2, R_3 and R_4 are chosen, independently of each other, from H, OH, a C_1-C_4 alkyl group, a C_1-C_4 alkoxy group, a group -OCO-R_8, R_8 being a C_1-C_4 alkyl group, and a group derived from a saccharide, at least one of the substituents R_1, R_2, R_3 or R_4 being other than H, and R_2 and R_3 together possibly forming a methylenedioxy group,

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R_5 is a phenyl group or a phenyl group substituted 1 to 3 times with groups chosen from H, OH, a C_1-C_4 alkoxy group, a group $-OCOR_8$, a phenyl (C_1-C_4 alkoxy) group, a group $-O-SO_2-R'_8$, R'_8 being a C_1-C_4 alkyl group or a CF_3 group, and a group derived from a saccharide,

R_6 is chosen from H, a C_1-C_4 alkyl group, a group $-CO-R_9$ and a group $-A-R_{10}$,

R_{6a} is chosen from a group $-CO-R_9$ and a group $-A-R_{10}$,

R_9 being a C_1-C_4 alkyl group,

A being a C_1-C_4 alkylene group,

R_{10} being chosen from 5- or 6-membered heterocyclic groups containing 1 to 4 hetero atoms chosen from oxygen, sulfur and nitrogen, the CN group, a group $-COOR_{11}$, $-CONR_{12}R_{13}$, a group $-NR_{14}R_{15}$ and a group $-COR_{16}$,

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} being chosen independently from a hydrogen atom, a C_1-C_4 alkyl group and a phenyl(C_1-C_4 alkyl) group,

R_4 and R_6 together also possibly forming a $-CO-CH_2-CH_2-$ group,

with the exclusion of the compounds in which X = O, R_6 = H and two of the substituents R_1, R_2, R_3 and R_4 are OH or OCH_3.

18. Compound according to Claim 17, which is 3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanenitrile.

19. Compound according to Claim 17, which is 1-[2-(1*H*-1,2,3,4-tetrazol-5-yl)ethyl]-5,7-dimethoxy-3-(4-methoxyphenyl)-1,2-dihydro-2-quinolinone.

20. Compound according to Claim 17, which is *N*,*N*-diethyl-3-[5,7-dimethoxy-3-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1-quinolinyl]propanamide.

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