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Y BENZIMIDAZOLES DE LACTAMA TRICICLICA

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CANCER RESEARCH TECHNOLOGY LIMITED

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3

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4

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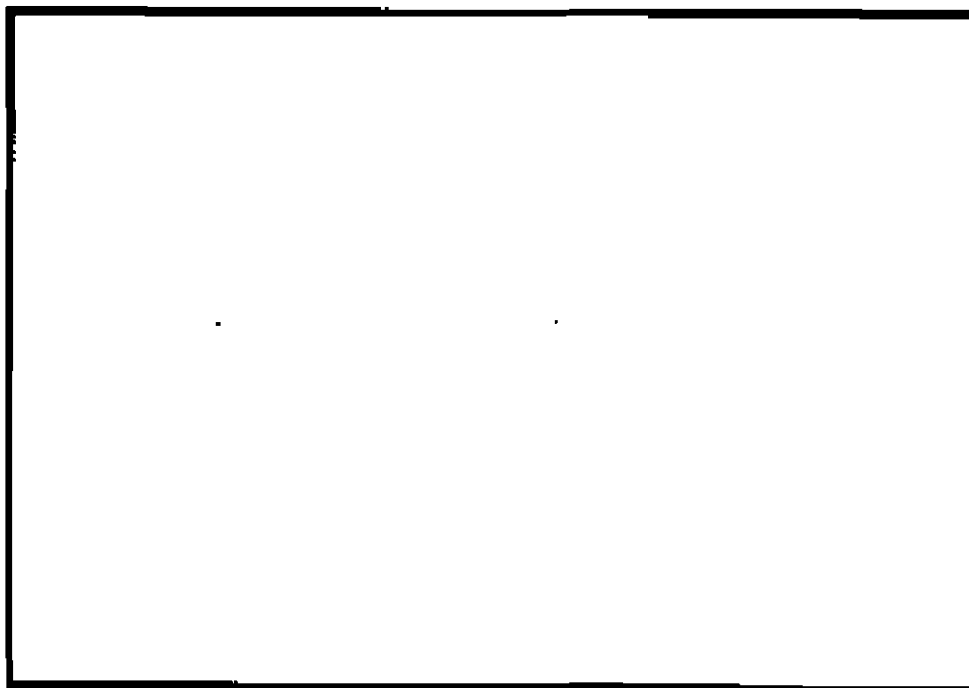
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$463.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso. Fotocopia autenticada
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA
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- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
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11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

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(54) Title: THERAPEUTIC COMPOUNDS

(57) Abstract: The invention relates to tricyclic heteron indole derivatives and tricyclic heteron benzimidazole derivatives and their use in inhibiting the activity of PARP enzyme. The invention also relates to the use of these compounds in the preparation of pharmaceuticals.

WO 2005/012305 A2

Therapeutic Compounds

This invention relates to a series of compounds derived which are derivatives of tricyclic lactam indoles and tricyclic lactam benzimidazoles and which inhibit poly (ADP-ribose) polymerase (PARP) and their use in the treatment of cancer, in particular breast cancer.

Homologous recombination (HR) has been shown to play an important role in repair of damage occurring at DNA replication forks in mammalian cells (2). Thus, cells deficient in HR show retarded growth and exhibit higher levels of genetic instability. It is believed that genetic instability due to loss of HR repair in human cancer significantly contributes to the development of cancer in these cells (1).

Post transcriptional modification of nuclear proteins by poly (ADP-ribosylation) in response to DNA strand breaks plays an important role in DNA repair, regulation of apoptosis, and maintenance of genomic stability.

Poly (ADP-ribose) polymerase (PARP-1) is the principal member of the PARP enzyme family and is an abundant nuclear protein in mammalian cells. PARP-1 catalyses the formation of poly (ADP-ribose) (PAR) polymers using NAD⁺ as substrate. Upon DNA damage, PARP-1 binds rapidly to a DNA single-strand break (SSB) and catalyses the addition of negatively charged PAR chains to itself (automodification) and other proteins [see (3,4) for reviews]. The binding of PARP-1 to SSBs is believed to protect DNA lesions from further processing until PARP-1 is

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dissociated from the break by the accumulated negative charge resulting from PAR polymers (5, 6).

Although PARP-1 has been implicated in several nuclear processes, such as modulation of chromatin structure, DNA-replication, DNA repair and transcription, PARP-1 knockout mice develop normally (7). Cells isolated from these mice exhibit a hyper-recombination phenotype and genetic instability in the form of increased levels of sister chromatid exchanges (SCE) micronuclei and tetraploidy (8, 10). Genetic instability may also occur in these PARP-1 knockout mice through telomere shortening, increased frequency of chromosome fusion and aneuploidy (11), although all these results could not be repeated in another set of PARP-1 knockout mice (12).

In the former mice knockout, PARP-1 null mutation rescued impaired V (D) J recombination in SCID mice (13).

These results support the view suggested by Lindahl and co-workers that PARP-1 has

a protective role against recombination (5). It was proposed that binding of PARP-1 to ssDNA breaks prevents the recombination machinery from recognising and processing DNA lesions or, alternatively that the negative charges accumulated following poly (ADP-ribosylation) repel adjacent recombinogenic DNA sequences. Only the latter model is consistent with inhibition of PARP-1 itself and expression of a dominant negative mutant PARP-1, including SCE, gene amplification and homologous recombination (14-18).

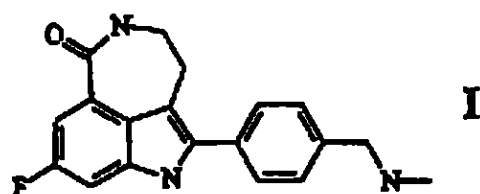
Studies based on treating cells with inhibitors of PARP-1 or cells derived from PARP-1 knockout mice indicate that the suppression of PARP-1 activity increases cell susceptibility to DNA damaging agents and inhibits strand break rejoining (3, 4, 8 - 11, 19, 20).

Inhibitors of PARP-1 activity have been used in combination with traditional cancer treatment regimes such as radio-therapy and chemotherapy (21). When the inhibitors were used in combination with methylating agents, topoisomerase poisons and ionising radiations they were found to enhance the effectiveness of these forms of treatment. However, such treatments are non-selective and as such cause damage and death to non-cancerous or 'healthy' cells. Furthermore, such treatments are known to give rise to unpleasant side effects.

Therefore, it is highly desirable to provide a treatment for cancer that is both effective and selective in the killing of cancer cells and which does not need to be administered in combination with radio-therapy or chemotherapy treatments.

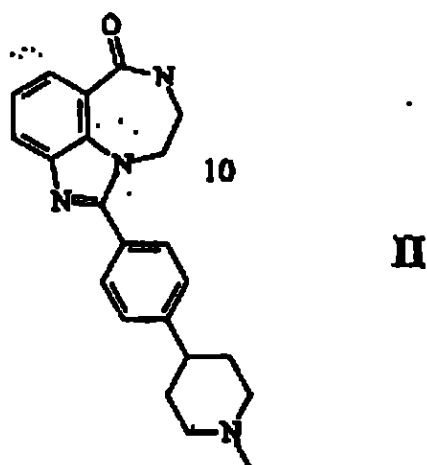
Surprisingly it has been found that cells deficient in homologous recombination (HR) are hypersensitive to PARP inhibitors relative to wild type cells.

Thus, according to a first aspect of the present invention there is provided a compound for inhibiting the activity of PARP having formula I:



and pharmaceutically acceptable salts thereof.

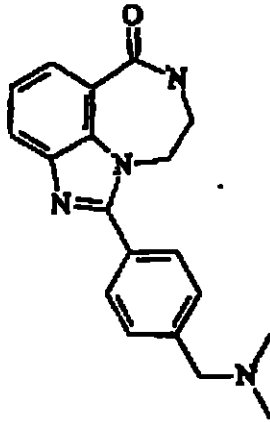
According to a second aspect of the present invention there is provided a compound for inhibiting the activity of PARP having formula II:



and pharmaceutically acceptable salts thereof.

According to a third aspect of the present invention there is provided a compound for inhibiting the activity of PARP having formula III:

b5 c1



III

and pharmaceutically acceptable salts thereof.

The compounds described herein can be prepared by synthetic routes based on those disclosed in WO 00/42040 and WO 01/16136.

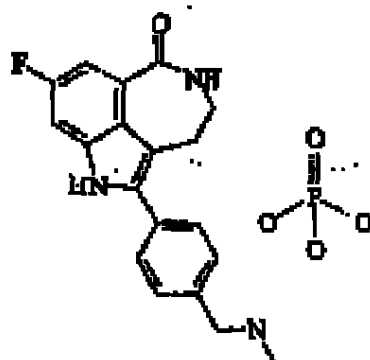
It will be understood that where reference is made in this specification to compounds of formulas I to III the reference should be construed as extending also to their pharmaceutically acceptable salts and to other pharmaceutically acceptable bioprecursors (prodrug forms) where relevant. The term "prodrug" is used in the present specification to denote modified forms or derivatives of a pharmacologically active compound which biodegrade or are modified in vivo so as to become converted into said active compound after administration, especially oral or intravenous administration, in the course of therapeutic treatment of a mammal. Such prodrugs are commonly chosen because of an enhanced solubility in aqueous media which helps to overcome formulation problems, and also in some cases to give a relatively slow or controlled release of the active agent.

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As referred to herein pharmaceutically acceptable salts include metal salts, phosphates and quaternary amines. The metal salts may be formed with alkali metals such as lithium, sodium or potassium.

Preferably, formula I, above, is administered in the form of a pharmaceutically acceptable phosphate salt having the following formula:

Formula I - phosphate



The present invention also relates to the therapeutic utility of the compounds described herein.

Thus, according to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula I, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula I, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

According to a further aspect of the present invention there is provided the use of a compound of formula II in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

According to a further aspect of the present invention there is provided the use of a compound of formula III in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

Diseases and conditions which are caused by a genetic defect in a gene that mediates homologous recombination include, but are not limited to cancer, in particular breast cancer.

As referred herein "cancer" or "tumour" includes, but is not limited to, cancers of the lung, colon, pancreas, stomach, ovary, cervix, breast, prostate bone, brain or skin.

The use of PARP inhibitors is particularly suitable in the treatment of cancer which is caused by a genetic defect in a gene wherein the said gene mediates homologous recombinations. Cancer cells of this type tend to be HR defective.

The specific sensitivity of HR defective tumours to PARP inhibition means that normally dividing "healthy" cells in patients which have adequate amounts of HR will be largely unaffected by the treatment.

A further advantage of treatment using PARP inhibitors is that the PARP inhibitors do not need to be administered as a combination therapy along with conventional radiotherapy or chemotherapy treatments thereby avoiding the side effects associated with these conventional forms of treatment.

A defect in a gene that mediates homologous recombination may be due to a mutation in, the absence of, or defective expression of, a gene encoding a protein involved in HR.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula I in the manufacture of a medicament for inducing apoptosis in HR defective cells.

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According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula II in the manufacture of a medicament for inducing apoptosis in HR defective cells.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula III in the manufacture of a medicament for inducing apoptosis in HR defective cells.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula I in the manufacture of a medicament for the treatment of cancer.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula II in the manufacture of a medicament for the treatment of cancer.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula III in the manufacture of a medicament for the treatment of cancer.

Cancer cells suitable for treatment with the compounds described herein may be partially or totally deficient in HR. Preferably, the cells are totally deficient in HR.

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The compounds described herein may be used to treat an inherited form of cancer wherein the patient to be treated has a familial predisposition to the cancer. However the said compounds are particularly suitable for the treatment of gene-linked hereditary cancer, and most particularly gene-linked hereditary breast cancer.

In a preferred aspect, the PARP inhibitor is useful in the treatment of cancer cells defective in the expression of a gene involved in HR. Genes with suggested function in HR include XRCC1, ADPRT (PARP-1), ADPRTL2, (PARP02) CTPS, RPA, RPA1, RPA2, RPA3, XPD, ERCC1, XPF, MMS19, RAD51, RAD51B, RAD51C, RAD51D, DMCI, XRCC2, XRCC3, BRCA1, BRCA2, RAD52, RAD54, RAD50, MRE11, NBS1, WRN, BLM, KU70, KU80, ATM, ATR, CHK1, CHK2, FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, RAD1, RAD9 [See (2, 3, 5, 22-28) for reviews].

A gene involved in HR may be a tumour suppressor gene. The invention thus provides for the treatment of cancer cells defective in the expression of a tumour suppressor gene. Preferably, the tumour suppressor gene is BRCA1 or BRCA2.

Breast cancer is the most common type of cancer among women in the Western World. Certain families have a strong predisposition for breast cancer, which is often owing to an inherited mutation in one allele of either BRCA1 or BRCA2. However, one functional allele is maintained. Thus, individuals possessing the said mutation develop normally and have no phenotypic consequence from this mutation. However,

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in one cell, the functional allele might be lost, making this cell cancerous and at the same time deficient in HR. This step is critical for the onset of a tumour (1).

Therefore, according to a still further aspect of the invention there is provided the use of a therapeutic amount of a compound of formula I in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula II in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

According to a further aspect of the present invention there is provided the use of a therapeutic amount of a compound of formula III in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

The cancer cells to be treated may be partially or totally deficient in BRCA1 or BRCA2 expression. Such deficiencies can be identified using multiplex PCR techniques array techniques (29, 30) or using other screens known to the skilled person. Particularly useful techniques include real-time quantitative RT-PCR, Northern blot, immunohistochemistry and Western Blot (31, 32).

H 16

Accordingly, the compounds of the present invention are of particular interest for the treatment of a range of selected cancer tumours, and the invention further provides a method for the treatment of a patient suffering from cancer.

The compounds described herein may be administered in a therapeutically effective non-toxic amount via any suitable route for effectively targeting cancer cells. Suitable administration routes include, but are not limited to, any of the following: oral, intravenous, intramuscular, intradermal, intranasal, or topical.

A therapeutically effective amount of the compounds described herein is typically one which is sufficient to achieve the desired effect and may vary according to the nature and severity of the disease condition, and the potency of the compound. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of an active disease.

For administration to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0.01 to 50 mg/kg in mice and 0.01 mg/m² to 50 mg/m² body surface area in humans. Ultimately, however, the amount of active ingredient administered and the frequency of administration will be at the discretion of a physician.

Advantageously, only very low doses of PARP inhibiting compounds are needed to have a therapeutic effect in treating cancer thereby reducing systemic build up of the compounds and thus minimising any associated toxic effects.

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While it may be possible for the compounds described herein to be administered alone as the 'raw' compound, it is preferable to present the compounds in a pharmaceutical composition.

All methods of formulation in making up such pharmaceutical compositions will generally include the step of bringing one of the compounds described herein into association with a carrier which constitutes one or more accessory ingredients. Usually, the formulations are prepared by uniformly and intimately bringing the compound of formula I into association with a liquid carrier or with a finely divided solid carrier or with both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of one of the compounds describe herein; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught. Any one of the compounds described herein may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tables may be prepared by compressing, in a suitable machine, any one of the compounds described herein to a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent,

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surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of any one of the powdered compound described herein with any suitable carrier.

A syrup may be made by adding any one of the compounds described herein to a concentrated, aqueous solution of a sugar, for example sucrose, to which may be added any desired accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol.

Formulations for rectal administration may be prepared as a suppository with a usual carrier such as cocoa butter.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of any one of the compounds describe herein which is preferably isotonic with the blood for the recipient.

In addition to the aforementioned ingredients, formulations of this invention, for example ointments, creams and the like, may include one or more accessory ingredients, for example a diluent, buffer, flavouring agent, binder, surface active agent, thickener, lubricant and/or a preservative (including an antioxidant) or other pharmaceutically inert excipient.

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The compounds of this invention may also be made up for administration in liposomal formulations which can be prepared by methods well-known in the art.

Thus, according to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula I, or pharmaceutically acceptable salt thereof, as an active agent.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula II, or pharmaceutically acceptable salt thereof, as an active agent.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula III, or pharmaceutically acceptable salt thereof, as an active agent.

The pharmaceutical composition may further comprise at least one other ingredient providing a compatible pharmaceutically acceptable additive, carrier diluent carrier or excipient and may be presented in unit dosage form.

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

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The possible formulations include those suitable for oral, rectal, topical and parenteral (including subcutaneous, intramuscular and intravenous) administration or for administration to the lung or another absorptive site such as the nasal passages.

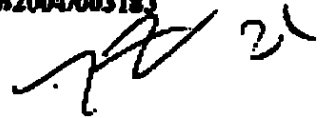
The compounds referred to herein may be administered in combination with other anti-cancer compounds.

The present invention also includes a method of treating cancer in mammals by administering the compounds described herein and their pharmaceutically acceptable salts.

Thus, according to a further aspect of the present invention there is provided a method for the treatment of cancer in mammals comprising administering a compound of formula I, or a pharmaceutically acceptable salt thereof.

Thus, according to a further aspect of the present invention there is provided a method for the treatment of cancer in mammals comprising administering a compound of formula II, or a pharmaceutically acceptable salt thereof.

Thus, according to a further aspect of the present invention there is provided a method for the treatment of cancer in mammals comprising administering a compound of formula III, or a pharmaceutically acceptable salt thereof.



The present invention will now be described by way of example only with reference to the accompanying figures wherein:

Figure 1 is a graph showing cell survival in the presence of PARP inhibitor of formula III in AA8 cell line, IslISF cell line and CxR3 cell line;

Figure 2 is a graph showing cell survival in the presence of PARP inhibitor of formula III in V79 cell line, VC8 cell line and VC8B2 cell line;

Figure 3 is a graph showing cell survival in the presence of PARP inhibitor of formula I in V79 cell line, VC8 cell line and VC8B2 cell line;

Figure 4 is a bar chart showing PARP activity in VC8, V79, VC8#13 and VC8, VC8#13 and VC8+B2 cell lines in the presence of PARP inhibitor of formula III;

Figure 5 is a pair of graphs showing inhibition of cellular PARP activity in the presence of PARP inhibitor of formula I and III in permeabilised (upper graph) and intact (lower graph) L1210 cells;

Figure 6 is a pair of bar charts showing the blood and tumour pharmacokinetics and pharmacodynamics with formula I-phosphate at 1 mg/kg (upper) and 10 mg/kg (lower) in mice bearing SW620 xenografts;

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Figure 7 is a bar chart showing the pharmacokinetics and pharmacodynamics with formula III in mice bearing SW620 xenografts;

Figure 8 is a graph showing the tumour growth (median relative tumour volume) in mice bearing SW620 xenografts following treatment with formula III in combination with temozolomide (TMZ) and with TMZ alone;

Figure 9 is a graph showing the tumour growth (median relative tumour volume) of mice bearing SW620 xenografts following treatment with formula I-phosphate in combination with temozolomide (TMZ) and with formula I-phosphate and TMZ alone;

Fig. 1 shows the percentage survival of A48, IrS ISF and CxR3 cell lines when treated with various concentrations of the compound of formula III. Formula III was found to be most active against IrS ISF, which lacks XRCC3, having an LC₅₀ (the concentration of the active component that kills 50% of the cells) of 100 nM.

Fig. 2 shows the percentage survival of V79-Z, VC8 and VC8B2 cell lines when treated with various concentrations of the compound of formula III. Formula III was found to be most effective against the VC8 cell line, which lacks BRCA2, having an LC₅₀ value of 43 nM and an LC₉₀ (concentration of active component that kills 90% of the cells) was 1200 nM.

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Fig. 3 shows the percentage survival of V79-Z, VC8 and VC8B2 cell lines when treated with various concentrations of the compound of formula I. Formula I was found to be most effective against the VC8 cell line, which lacks BRCA2, having an LC_{50} value of 12 nM, LC_{25} was 27 nM.

Fig. 4 shows PARP activity of various cell lines when treated with various concentrations of the compound of formula III. The graph of Fig. 3 is divided into four result sets for each respective cell line. The first bar of each set shows the background PARP activity (no oligo present, so PARP activity is dependent upon endogenous DNA breaks), the second bar is total stimutable (by oligo) PARP activity and the third and fourth bars show the PARP activity in the presence of the compound of formula III.

Fig. 5 shows the effect of Compounds Formula I and III on PARP activity.

Cells used to obtain the results shown in Fig. 5 were either permeabilised with digitonin and then assayed for total stimutable (by oligo) PARP activity in the presence and absence of PARP inhibitor of formula I and formula III or exposed to one of said PARP inhibitors for 20 minutes prior to permeabilisation and assayed for total stimutable PARP activity.

There was no difference in the PARP inhibitory activity of the compounds of formula I and formula III when the cells were permeabilised prior to adding the inhibitor.

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compound but the compound of formula I was more potent in intact cells, possibly because it accumulates within cells to a higher degree.

Fig. 6 shows the plasma and tumour concentrations of the compound of formula I, and its pharmacokinetic effect on mouse peripheral blood lymphocytes (pbl pcrp) and SW620 xenografts (tumour PARP), at various times following intraperitoneal administration of the phosphate salt of compound of formula I. The phosphate salt of the compound of formula I increases the solubility of formula I. However, on administration to an animal (including human) plasma phosphatases break the phosphate salt of formula I (formula I-phosphate) down to the parent compound i.e. formula I.

It is evident from fig. 6 that thirty minutes after administration of formula I-phosphate at 10 mg/kg high levels of the parent compound were detected in both plasma and tumour. The concentration of formula I decreased with time more rapidly in the plasma than in the tumour and at 24 hr after administration significant levels were detectable in the tumour but none could be detected in the plasma. There was a profound and sustained inhibition of PARP activity in both pbls and tumour, <50% control up to 24 hr.

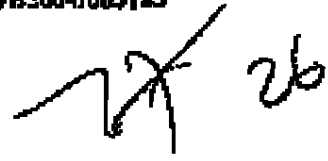
After administration of formula I-phosphate at 1 mg/kg lower levels of the compound of formula I can be found in both the plasma and tumour and consequently there was a less pronounced effect on PARP activity.

JP 25

Fig. 7 shows the plasma and tumour concentrations of the compound of formula III, and its pharmacokinetic effect on SW620 xenografts (tumour PARP act), at various times following intraperitoneal administration of the 10 mg/kg of compound of formula III. This compound also distributes well to the tumour and is preferentially retained with time and similarly inhibits PARP activity in the tumour.

Fig. 8 shows that for 20 days from administration of temozolomide (68 mg/kg daily x5) the tumour xenograft has progressively reduced in size. However, shortly after this time the tumour size begins to increase. When a compound of formula III (5 mg/kg daily x 5) is administered in conjunction with temozolomide the tumour shrinks significantly for around 15 days, to an undetectable size, the tumour size remains undetectable for a further 50 days thereafter when it begins to increase in size. When a larger dose of formula III (15 mg/kg daily x 5) is administered the tumour size remains undetectable for a further 80 days until the end of the experiment when no tumour was detectable at autopsy i.e. complete tumour regression.

Fig.9 shows a similar pattern to that seen in fig. 8 following the administration of formula I-phosphate (at 0.1 mg/kg and 1.0 mg/kg) in combination with temozolomide.


Table 1. Genotype and origin of cell lines used in this study.

Cell line	Genotype	Defect	Origin	Reference	Comments
AA8	wt	wt	CHO	[41]	Chinese hamster ovary cell line
irs1SF	<i>XRCC3</i>	<i>XRCC3</i> , deficient in HR	AA8	[41]	Radiation-sensitive cell line derived from AA8 which lacks <i>XRCC3</i> a component of HR pathway
CXR3	<i>XRCC3</i> - +h <i>XRCC3</i>	wt	irs1SF	[41]	irs1SF transfected with h <i>XRCC3</i> gene
V79-Z	wt	wt	V79	[42]	V79 are hamster lung fibroblasts
VC8	<i>BRCA2</i>	<i>BRCA2</i> , deficient in HR	V79-Z	[42]	VC8 are radiation sensitive derivatives of V79 which are deficient in <i>BRCA2</i>
VC8#13	<i>BRCA2</i> , +h <i>BRCA2</i>	wt	VC8	[42]	VC8 with chromosome 13 containing h <i>BRCA2</i>
VC8#B2	<i>BRCA2</i> +h <i>BRCA2</i>	wt	VC8	[42]	VC8 transfected with h <i>BRCA2</i>

Materials and Methods**Cytotoxicity of PARP inhibitors to cells deficient in HR, *XRCC3* or *BRCA2*****Cell culture**

The AA8, irs1SF and CXR3 cell lines were provided by Larry Thompson [41].

The VC-8, VC-8+B2, VC-8#13 were a gift from Malgorzata Zdienicka [42]. All cell lines in this study were grown in Dulbecco's modified Eagle's Medium (DMEM) with 10% Fetalbovine serum and penicillin (100 U/ml) and streptomycin sulphate (100 µg/mL) at 37°C under an atmosphere containing 5% CO₂.

Toxicity assay – clonogenic survival assay

Exponentially growing cells in 6-well plates were exposed to the compound of formula III at the concentrations indicated in Fig 2 in 1% DMSO or 1% DMSO alone in medium for 24 hours.

The cells were harvested by trypsinisation, counted and seeded at varying densities in 10 cm dishes in fresh medium in the absence of drug for colony formation.

7-10 days later the dishes were fixed with methanol:acetic acid 3:1 and stained with 0.4% crystal violet.

Colonies were counted and the survival relative to 1%DMSO control treated cells calculated.

PARP activity assay

Exponentially growing cells were exposed to 1% DMSO in culture medium (control) or a compound of formula I or III in 1% DMSO at the concentrations indicated in Fig. 4 to cells permeabilised with digitonin, or intact cells for 20 minutes prior to washing and digitonin-permeabilization. PARP activity was measured by incorporation of a

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[³²P] labelled NAD⁺ substrate into TCA precipitable polymers after stimulation by the addition of a blunt-ended oligonucleotide and compared with non-oligonucleotide-stimulated cells. PARP activity in tumour homogenates (1 in 40 in isotonic buffer) from formula III-treated mice was measured in the same way. PARP activity in pbls and tumour homogenates from formula I-phosphate treated mice was measured by immunological detection of polymer using the 10H antibody. Briefly, tumour homogenates diluted to up to 1:1000 in isotonic buffer were incubated with 350 μ M NAD for 6 min and blotted onto nitrocellulose membranes. The poly(ADP-ribose) (PAR) polymer formation was quantified by chemiluminescence detection using a Fuji LAS3000 UV Illuminator by reference to serial dilutions of a PAR standard, following incubation with 10H antibody to PAR and a secondary anti-mouse antibody. The results were standardised by reference to the measured protein content of the homogenate.

It is of course to be understood that the invention is not intended to be restricted to the details of the above embodiments which are described by way of example only.

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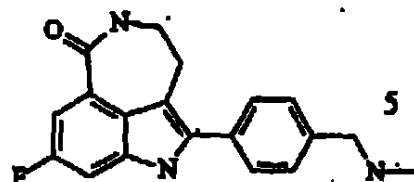
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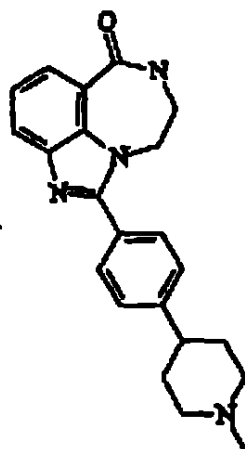
Claims

1. A compound for inhibiting the activity of PARP having formula I:



and pharmaceutically acceptable salts thereof.

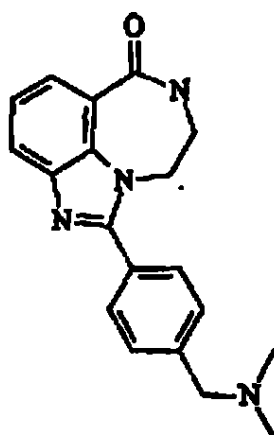
2. A compound for inhibiting the activity of PARP having formula II:



and pharmaceutically acceptable salts thereof.

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3. A compound for inhibiting the activity of PARP having formula

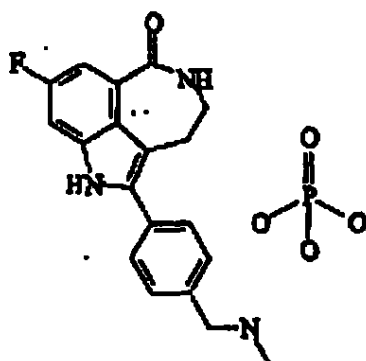


III

and pharmaceutically acceptable salts thereof.

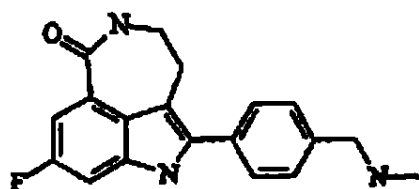
4. A compound according to claim 1, wherein the compound is in the form of a phosphate salt of the following formula:

Formula I - phosphate



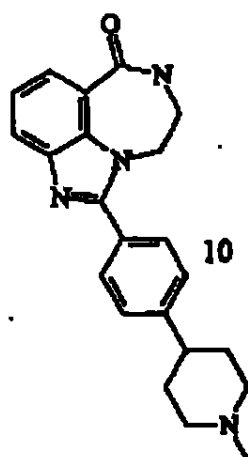
5. The use of a therapeutic amount of a compound of formula I, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.

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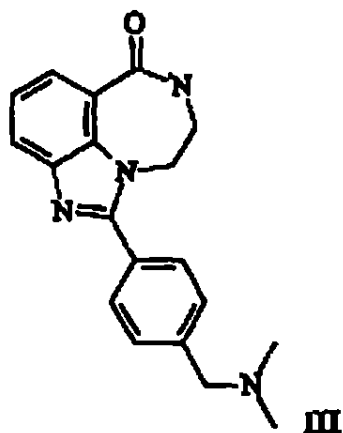
I

6. The use of a therapeutic amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.



II

7. The use of a therapeutic amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament.



III

8. The use of a therapeutic amount of a compound of formula I, and

pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

9. The use of a therapeutic amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

10. The use of a therapeutic amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a disease or condition that is caused by a genetic defect in a gene that mediates homologous recombination.

11. The use as claimed in any one of claims 8 to 10, wherein the defect is a gene encoding a protein involved in HR.

12. The use as claimed in any one of claims 8 to 10, wherein the defect is the absence of a gene encoding a protein involved in HR.

13. The use as claimed in any one of claims 8 to 10, wherein the defect is in the expression of a gene encoding a protein involved in HR.

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14. The use of a therapeutically effective amount of a compound of formula I and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for inducing apoptosis in HR defective cells.

15. The use of a therapeutically effective amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for inducing apoptosis in the defective cells.

16. The use of a therapeutically effective amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for inducing apoptosis in the defective cells.

17. The use of a therapeutically effective amount of a compound of formula I, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer.

18. The use of a therapeutically effective amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer.

19. The use of a therapeutically effective amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer.

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20. The use of a compound according to any one of claims 15 to 17, wherein the cancer is gene-linked hereditary cancer.

21. The use of a therapeutically effective amount of a compound of formula I, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

22. The use of a therapeutically effective amount of a compound of formula II, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

23. The use of a therapeutically effective amount of a compound of formula III, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of cancer cells defective in BRCA1 and/or BRCA2 expression.

24. The use of a compound according to any one of claims 21 to 23, wherein the cancer cells to be treated are partially or totally deficient in BRCA1 and/or BRCA2 expression.

25. A pharmaceutical composition comprising a compound of formula I, and a pharmaceutically acceptable salt thereof, as an active ingredient.

26. A pharmaceutical composition comprising a compound of formula II, a pharmaceutically acceptable salt thereof, as an active ingredient.

CH 40

27. A pharmaceutical composition comprising a compound of formula III and a pharmaceutically acceptable salt thereof, as an active ingredient.

28. A pharmaceutical composition according to any one of claims 25 to 27, wherein the composition further comprises at least one diluent and/or carrier together with at least one bulking agent.

29. A pharmaceutical composition according to claim 28, wherein the carrier and/or diluent is selected from any of the following either alone or in combination, saline, buffered saline, dextrose, water, glycerol and ethanol.

30. A method for the treatment of cancer in mammals comprising administering a compound of formula I as described in claim 1; or a pharmaceutically acceptable salt thereof.

31. A method for the treatment of cancer in mammals comprising administering a compound of formula II as described in claim 2, or a pharmaceutically acceptable salt thereof.

32. A method for the treatment of cancer in mammals comprising administering a compound of formula III as described in claim 3, or a pharmaceutically acceptable salt thereof.

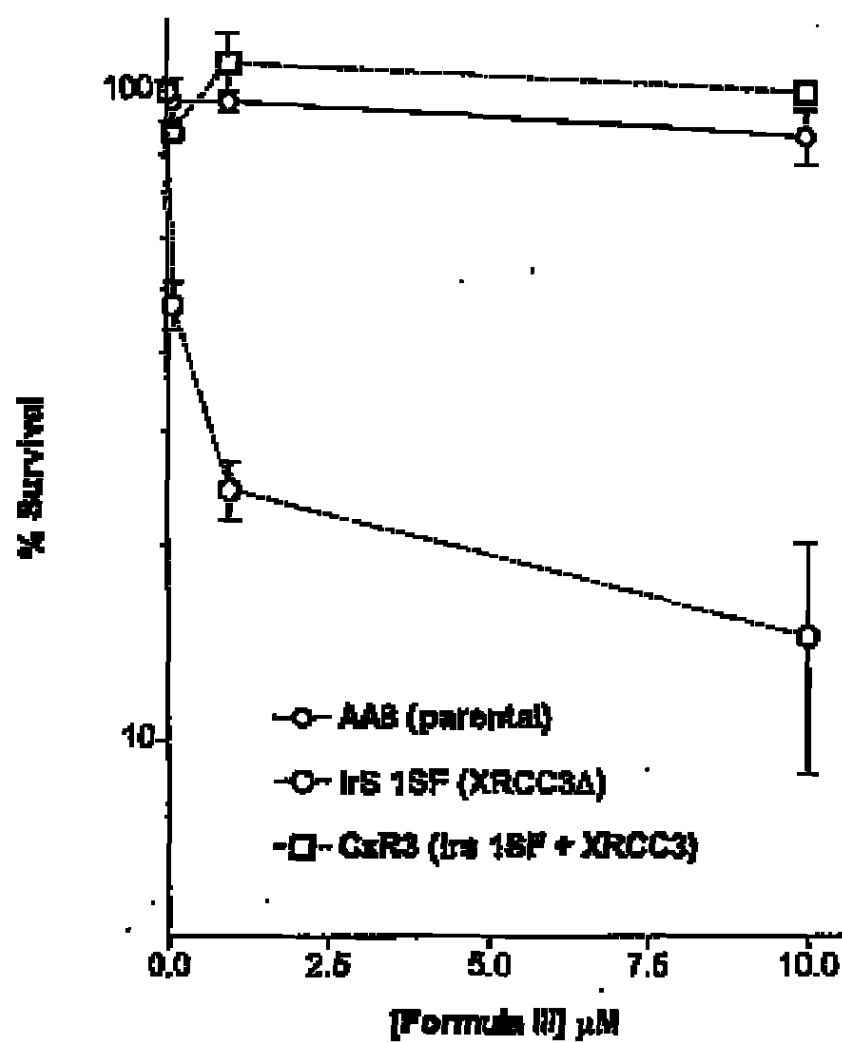


Fig. 1

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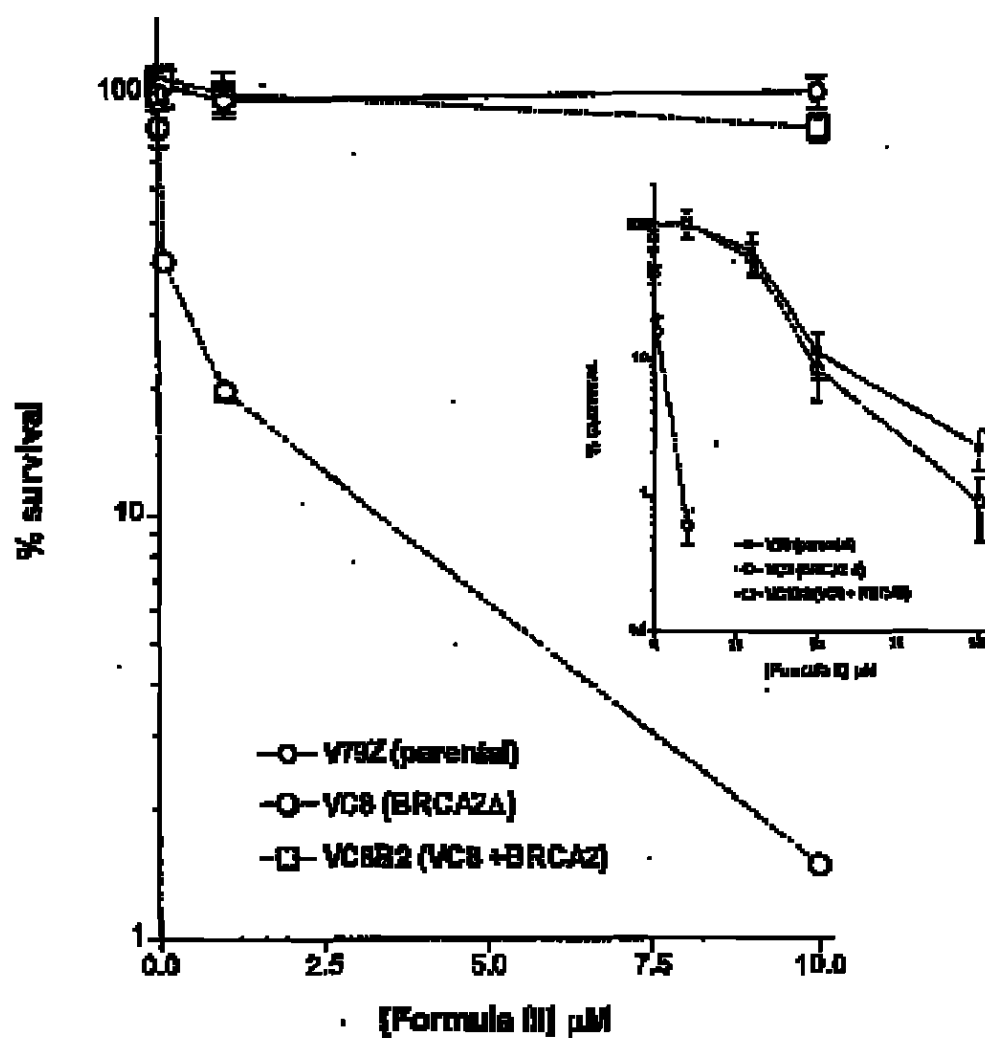


Fig. 2

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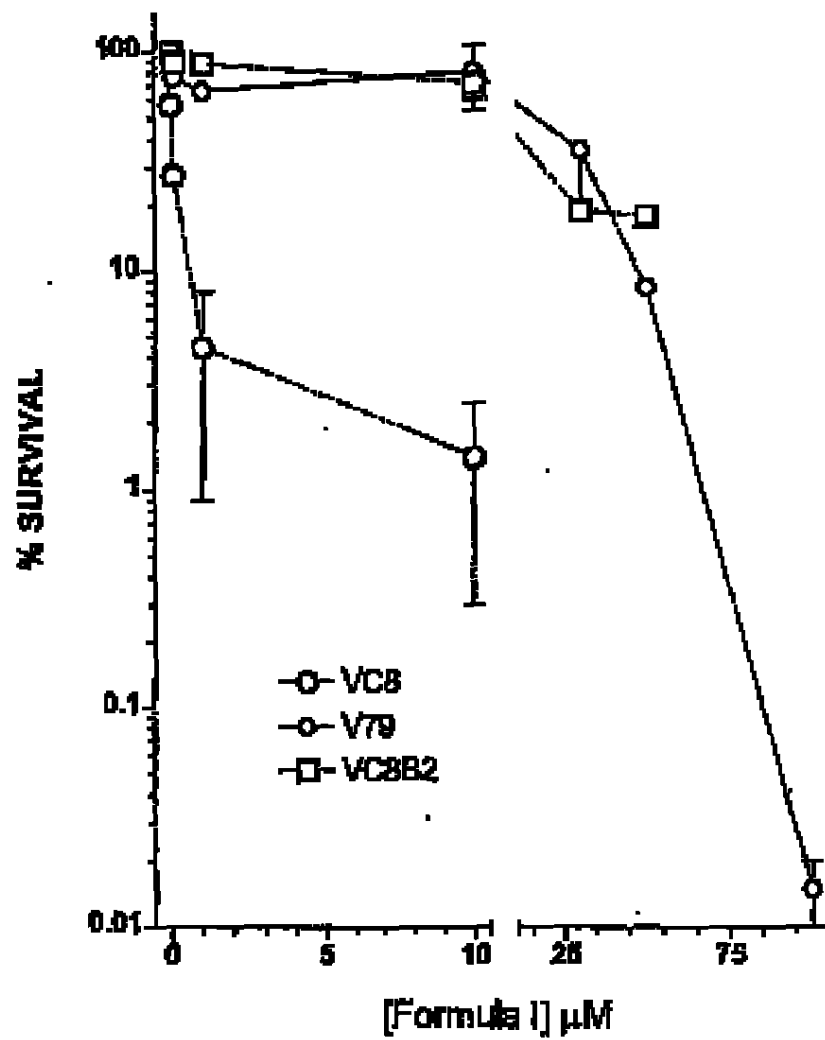


Fig. 3

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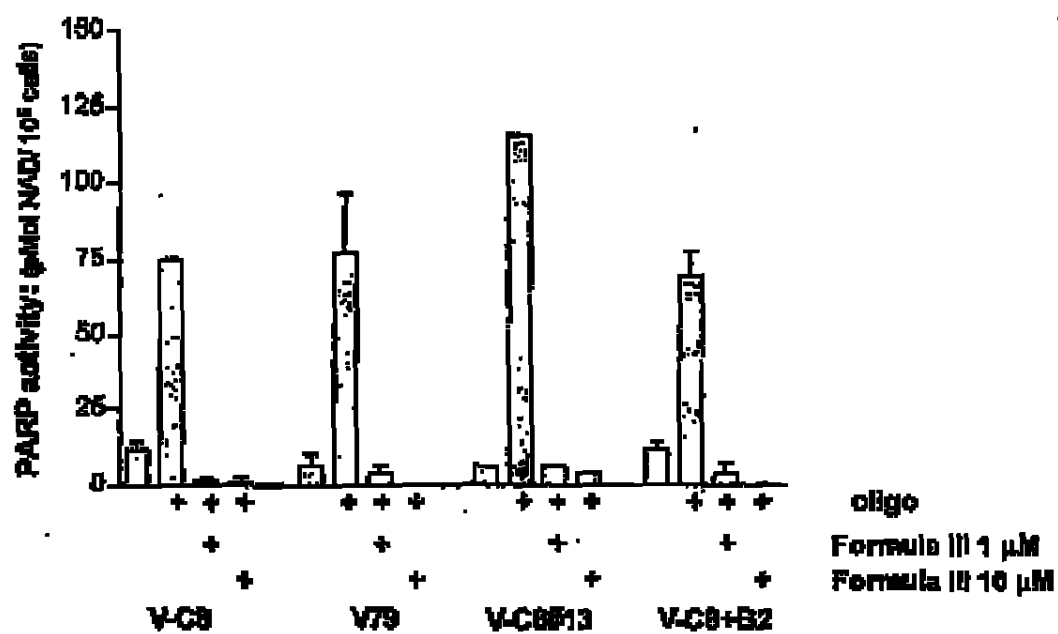


Fig. 4

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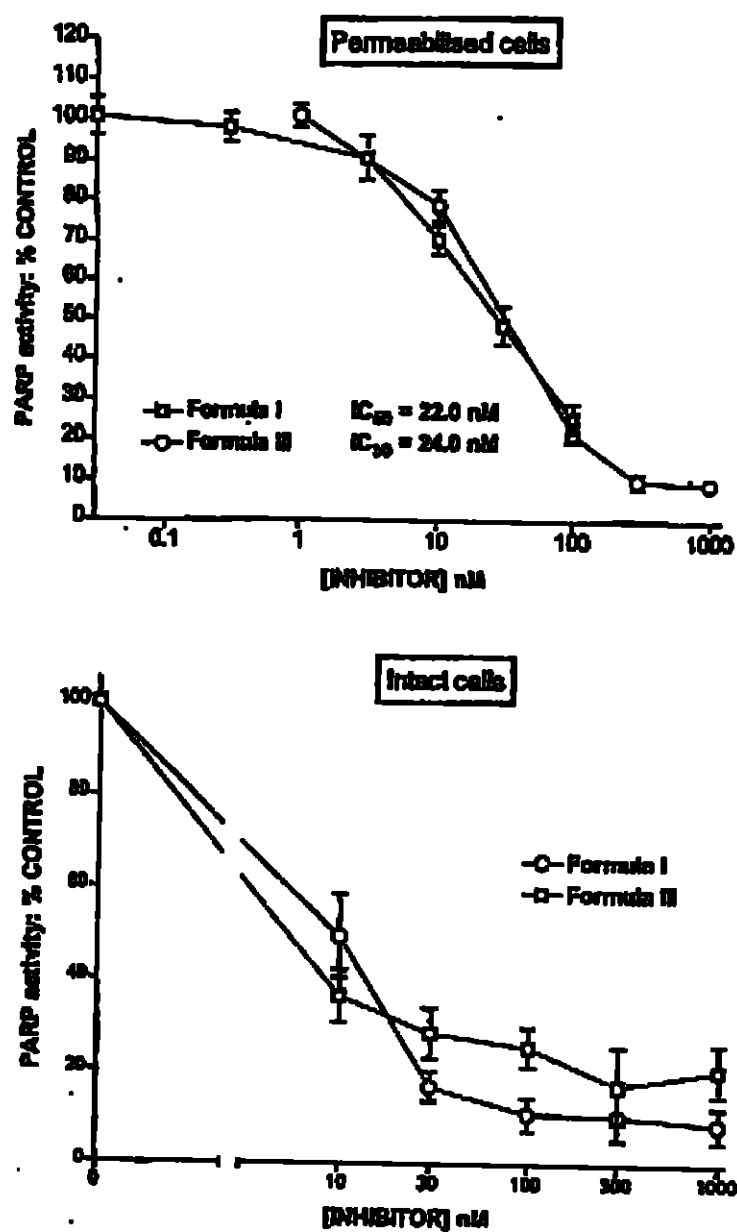


Fig 5

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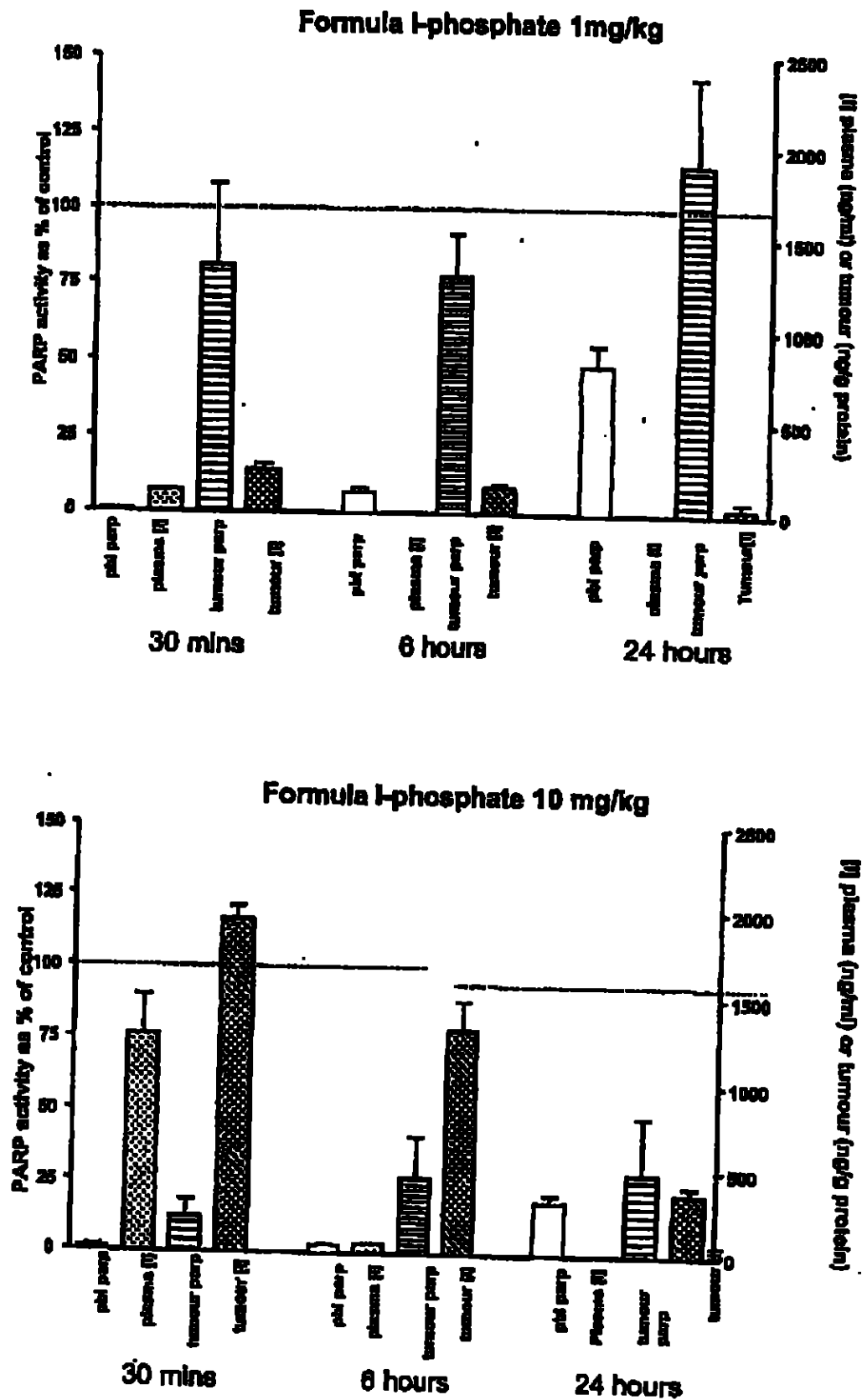


Fig. 6

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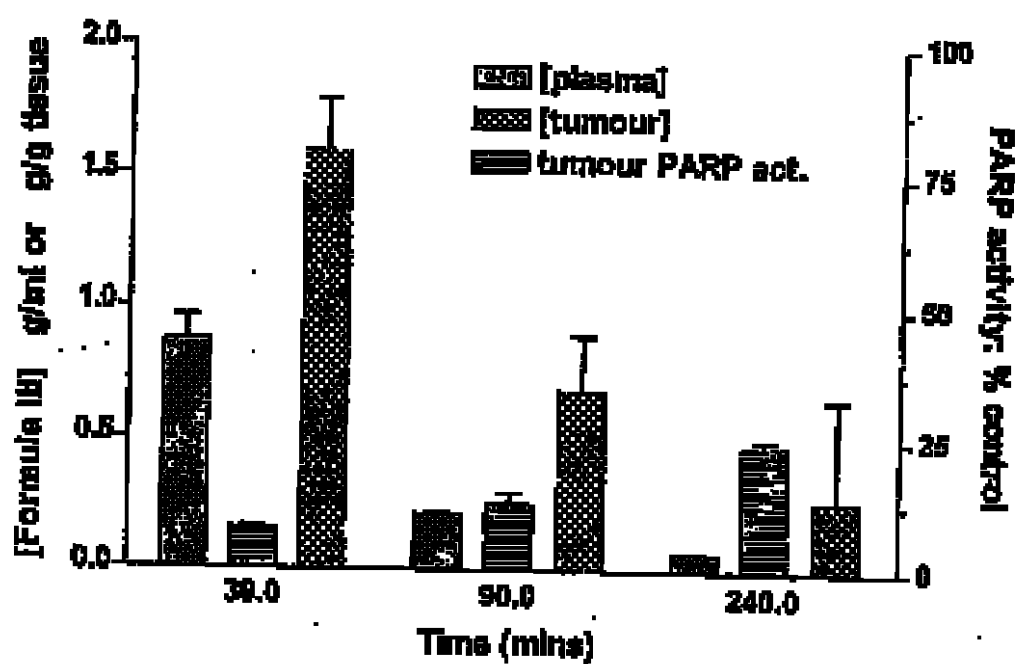


Fig 7

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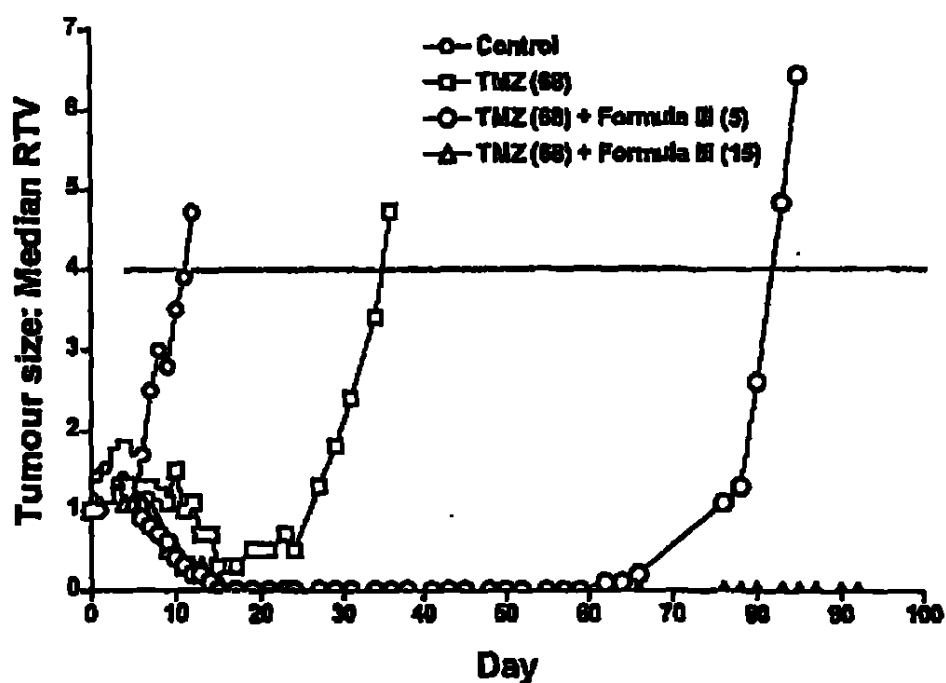


Fig. 8

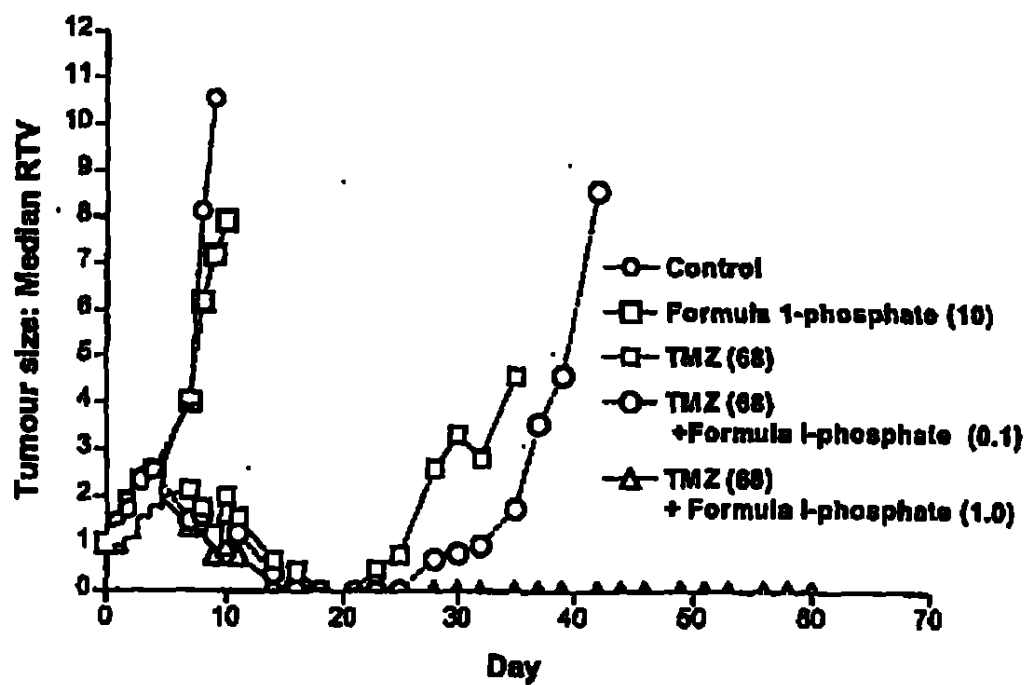
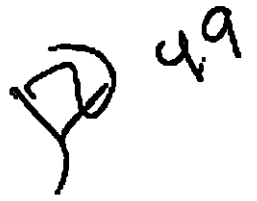


Fig 9



Sequence Listings

Sequence 1 – Human cDNA sequence of PARP-1

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 181 gctacaant gacattaagg aaaaaggcgg aaagtcttc tticgttaa atctcagtg
 241 cacacatata atcttagata atgtatnigt tctgagtcag taccantga attotatcca
 301 aaagaaccac gttatattg caaacccaga ttatatag aaatctatca gaaaaagag
 361 actctaggat gtaagaait atgaccca taagccctg gacatcacac cactctcga
 421 tcagaaggcg agcagttcig aagtgaaac agaaggctca tgcgcggaca gtgcacaga
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 541 tctcaagat ttgaagtg caaatataa cacttgag aaagtggaa tggaggagg
 601 ocaggaaagt gtgtgtgtg agcttcagtg tgcgcggag tcaaggagct gtcttctt
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 721 gaaacctct gaagtgcac gtgaactct tgaattac atgaagaac tgaagaaca
 781 aggtattca ctagaaga atctacac tgaagcaac caatagcat ctgaacat
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50

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52

Sequence 2 – Human cDNA sequence of PARP-2

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Sequence 4 – Human gDNA sequence of Tankyrase 1

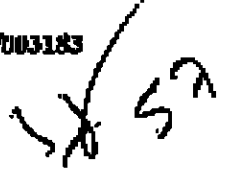
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53

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Sequence 5 – Human mRNA sequence of Tankyrase 2

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 2581 taatgagt gtaatgca cggcaaat ggttcaaa ccttggag agcagcca



2641 aaggggaga acacgotti gicottit getagccot ggagctgacc cganotlra
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 4201 acagacaa ttactat accacaggt gttcttca accacaggt tctctgaat
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53

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Sequence 6— Human mRNA sequence of VPARP

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 301 aaagaactac gttcatatg caaaccaga tttatatg aaatotala gagaaaagag
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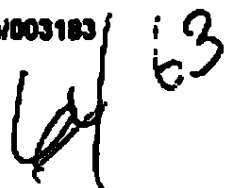
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(54) Título: COMPUESTOS TERAPÉUTICOS

(57) Extracto: La invención se refiere a derivados de indol lactama tríciclica y derivados de benzimidazol de
lactama tríciclica y su uso en inhibir la actividad de la enzima PARP. La invención concierne igualmente al uso
de estos compuestos en la preparación de medicamentos.

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Compuestos Terapéuticos

Esta invención se refiere a una serie de compuestos derivados, que son derivados de indoles de lactama tricíclica y benzimidazoles de lactama tricíclica, los cuales inhiben poli (ADP-ribosa) polimerasa (PARP) y su uso en el tratamiento de cáncer, en particular cáncer de mama.

Se ha demostrado que la recombinación homóloga (HR) juega un papel importante en la reparación de daño que ocurre en las horquillas de replicación del ADN en células de mamífero (2). Por consiguiente, las células deficientes en HR evidencian un crecimiento retardado y exhiben niveles más altos de inestabilidad genética. Se cree que la inestabilidad genética, debida a la pérdida de reparación HR en neoplasias malignas humanas contribuye significativamente al desarrollo de cáncer en estas células (1).

La modificación pos-transcripción de proteínas nucleares por poli (ADP-ribosil)ación en respuesta a rupturas de la hebra de ADN juega un papel importante en la reparación de ADN, regulación de apoptosis y mantenimiento de la estabilidad genómica.

Poli (ADP-ribosa) polimerasa (PARP-1) es el miembro principal de la familia de enzimas PARP y es una proteína nuclear abundante en células de mamífero. PARP-1 cataliza la formación de poli (ADP-ribosa) (PAR) polímeros usando NAD^+ como sustrato. Al ocurrir el daño de ADN, PARP-1 se fija rápidamente a una ruptura de hebra única de ADN (SSB) y cataliza la adición de cadenas PAR cargadas negativamente a ella misma (automodificación) y otras proteínas [véase (3,4) para reseñas]. Se cree que la fijación de PARP-1 a SSBs protege las lesiones de ADN de un ulterior procesamiento hasta que PARP-1 se disocia de la ruptura por la carga negativa acumulada resultante de polímeros PAR (5, 6).

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Aunque PARP-1 ha estado implicada en varios procesos nucleares, tales como modulación de la estructura de cromatina, replicación de ADN; reparación y transcripción de ADN, ratones con inactivación de PARP-1 se desarrollan normalmente (7). Células aisladas de estos ratones exhiben un fenotipo de hiper-recombinación e inestabilidad genética en la forma de niveles aumentados de micronúcleos de intercambios de cromátidas hermanas (SCE) y tetraploidismo (8, 10). La inestabilidad genética puede ocurrir asimismo en estos ratones con inactivación de PARP-1 mediante recortes de telómeros, mayor frecuencia de fusión de cromosomas y aneuploidia (11), aunque todos estos resultados podrían no repetirse en otro conjunto de ratones con deficiencia de PARP-1 (12). En la inactivación de los ratones anteriores, la mutación carente de PARP-1 ("*PARP-1 null mutation*") salvó la recombinación V (D) J alterada en ratones SCID (con inmunodeficiencia combinada grave) (13).

Estos resultados respaldan el punto de vista sugerido por Lindahl y colaboradores de que PARP-1 tiene un papel protector contra la recombinación (5). Se propuso que la fijación de PARP-1 a rupturas de ssADN evita que la maquinaria de recombinación reconozca y procese lesiones de ADN o, alternatively, que las cargas negativas acumuladas a raíz de la poli (ADP-ribosil)ación repelan secuencias de ADN recombinogénicas adyacentes. Solamente el último modelo es consistente con la inhibición de PARP-1 misma y la expresión de una PARP-1 mutante negativa dominante, incluida SCE, amplificación génica y recombinación homóloga (14-18).

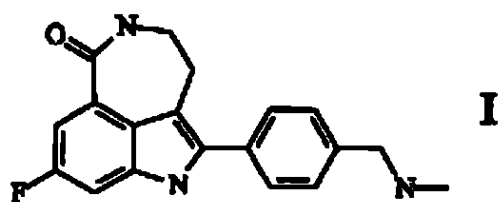
Estudios basados en tratar células con inhibidores de PARP-1 ó células derivadas de ratones con inactivación de PARP-1 indican que la supresión de la actividad PARP-1 aumenta la susceptibilidad de la célula a agentes nocivos al ADN e inhibe la reunión de la ruptura de las hebras (3, 4, 8 -11, 19, 20).

Los inhibidores de la actividad de PARP-1 se han usado en combinación con regímenes tradicionales de tratamiento de cáncer tales como radioterapia y quimioterapia (21). Cuando los inhibidores se usaron en combinación con agentes de metilación, tóxicos de topoisomerasa y radiaciones ionizantes, se descubrió que mejoran la efectividad de estas formas de tratamiento. No obstante, tales tratamientos son no selectivos y, como tales, ocasionan daño y muerte a células no cancerosas o 'sanas'. Más aún, tales tratamientos son conocidos por dar lugar a efectos secundarios indeseables.

Por lo tanto, es altamente deseable proveer un tratamiento para el cáncer que sea tanto efectivo como selectivo en eliminar las células cancerosas y que no necesite administrarse en combinación con tratamientos de radioterapia o quimioterapia.

Sorpresivamente se ha descubierto que las células deficientes en recombinación homóloga (HR) son hipersensibles a los inhibidores de PARP en relación con las células tipo natural.

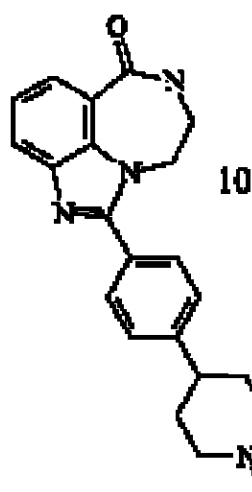
Por consiguiente, de acuerdo con un primer aspecto de la presente invención se provee un compuesto para inhibir la actividad de PARP que tiene la fórmula I:



y sus sales farmacéuticamente aceptables.

De acuerdo con un segundo aspecto de la presente invención se provee un compuesto para inhibir la actividad de PARP que tiene la fórmula II:

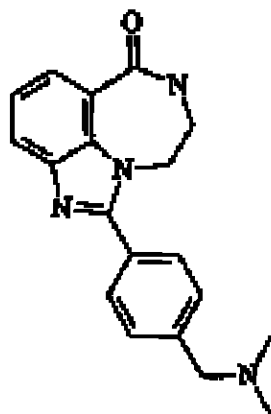
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II

y sus sales farmacéuticamente aceptables.

De acuerdo con un tercer aspecto de la presente invención se provee un compuesto para inhibir la actividad de PARP que tiene la fórmula III:



III

y sus sales farmacéuticamente aceptables.

Los compuestos descritos aquí pueden prepararse por vías sintéticas basados en los divulgados en WO 00/42040 y WO 01/16136.

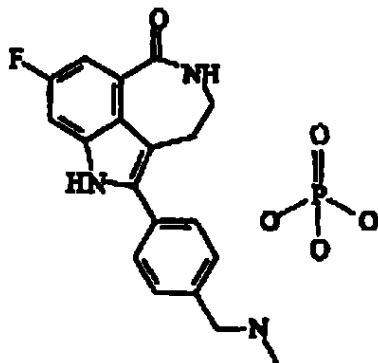
Se entenderá que donde se hace referencia en esta especificación a compuestos de fórmulas I a III la referencia debe interpretarse como extensiva también a sus sales farmacéuticamente aceptables y a otros bioprecursores farmacéuticamente aceptables (formas de profármacos) donde sea relevante. El término "profármaco" se usa en la presente especificación para denotar formas modificadas o derivados de un compuesto activo farmacológicamente aceptable que se biodegradan o se

modifican *in vivo* de modo que se convierten en dicho compuesto activo luego de la administración, especialmente administración oral o intravenosa, en el ciclo del tratamiento terapéutico de un mamífero. Tales profármacos se eligen comúnmente debido a una mayor solubilidad en medios acuosos que contribuye a superar problemas de formulación y, además, en algunos casos para facilitar una liberación controlada o relativamente lenta del agente activo.

Como se menciona aquí, sales farmacéuticamente aceptables incluyen sales de metal, fosfatos y aminas cuaternarias. Las sales de metal pueden formarse con metales alcalinos tales como litio, sodio o potasio.

Preferiblemente, el compuesto de fórmula I, ya mencionado, se administra en la forma de una sal de fosfato farmacéuticamente aceptable que tiene la siguiente fórmula:

Formula I - Fosfato



La presente invención se refiere además a la utilidad terapéutica de los compuestos descritos aquí.

Así, de acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula II, y sus sales

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farmacéuticamente aceptables, en la manufactura de un medicamento.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de un compuesto de fórmula II en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de un compuesto de fórmula III en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

Enfermedades y afecciones que se causan por un defecto genético en un gen que media recombinación homóloga incluyen, pero no se limitan a cáncer, en particular cáncer de mama.

Como se menciona aquí, "cáncer" o "tumor" incluye, pero no se limita a, cáncer del pulmón, colon, páncreas, estómago, ovario, cuello uterino, mama, próstata, hueso, cerebro o piel.

El uso de inhibidores de PARP es particularmente apropiado en el tratamiento de cáncer que se causa por un defecto genético en un gen en

donde el dicho gen media recombinaciones homólogas. Las células cancerosas de este tipo tienden a ser deficientes en HR.

La sensibilidad específica de tumores defectuosos en HR a la inhibición de PARP significa que células "sanas" que se dividen normalmente en pacientes, que poseen cantidades adecuadas de HR, quedarán ampliamente no afectadas por el tratamiento.

Una ventaja adicional del tratamiento que usa inhibidores de PARP es que los inhibidores de PARP no necesitan administrarse como una terapia de combinación junto con tratamientos de radioterapia convencional o quimioterapia, evitando así los efectos secundarios asociados con estas formas convencionales de tratamiento.

Un defecto en un gen que media la recombinación homóloga puede deberse a una mutación en, la ausencia de, o expresión defectuosa de, un gen que codifica una proteína involucrada en la HR.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula I en la manufactura de un medicamento para inducir apoptosis en células deficientes en HR.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula II en la manufactura de un medicamento para inducir apoptosis en células deficientes en HR.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula III en la manufactura de un medicamento para inducir apoptosis en células deficientes en HR.

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De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula I en la manufactura de un medicamento para el tratamiento de cáncer.

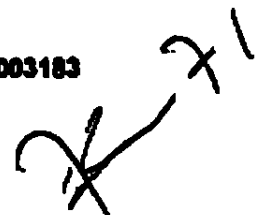
De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula II en la manufactura de un medicamento para el tratamiento de cáncer.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula III en la manufactura de un medicamento para el tratamiento de cáncer.

Células cancerosas apropiadas para tratamiento con los compuestos descritos aquí pueden ser parcial o totalmente deficientes en HR. Preferiblemente, las células son totalmente deficientes en HR.

Los compuestos descritos aquí pueden utilizarse para tratar una forma heredada de cáncer en donde el paciente a tratarse tiene una predisposición familiar al cáncer. Sin embargo los dichos compuestos son particularmente apropiados para el tratamiento de cáncer hereditario asociado con un gen y, muy particularmente, cáncer de mama asociado con un gen.

En un aspecto preferido, el inhibidor de PARP es útil en el tratamiento de células cancerosas deficientes en la expresión de un gen involucrado en HR. Genes con función sugerida en HR incluyen XRCC1, ADPRT (PARP-1), ADPRTL2, (PARP02) CTPS, RPA, RPA1, RPA2, RPA3, XPD, ERCC1, XPF, MMS19, RAD51, RAD51 β , RAD51C, RAD51D, DMC1, XRCCR, XRCC3, BRCA1, BRCA2, RAD52, RAD54, RAD50, MRE11, NB51, WRN, BLM KU70, RU80, ATM, ATR CHK1, CHK2, FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, RAD1, RAD9



[véase (2, 3, 5, 22-28) para reseñas].

Un gen involucrado en HR puede ser un gen supresor de tumores. La invención posibilita así el tratamiento de células cancerosas deficientes en la expresión de un gen supresor de tumores. Preferiblemente, el gen supresor de tumores es BRCA1 ó BRCA2.

El cáncer de mama es el tipo de cáncer más común entre las mujeres en el mundo occidental. Ciertas familias tienen una fuerte predisposición al cáncer de mama, el cual se debe a menudo a una mutación heredada en un alelo de cualquiera de BRCA1 ó BRCA2.

Sin embargo, se mantiene un alelo funcional. Por consiguiente, individuos que poseen la dicha mutación desarrollan normalmente y no tienen consecuencia fenotípica de esta mutación. No obstante, en una célula, el alelo funcional podría perderse, haciendo esta célula cancerosa y, al mismo tiempo, deficiente en HR. Este paso es crítico para la iniciación de un tumor (1).

Por consiguiente, de acuerdo con todavía un aspecto adicional de la invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula I en la manufactura de un medicamento para el tratamiento de células cancerosas deficientes en expresión de BRCA1 y/o BRCA2.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula II en la manufactura de un medicamento para el tratamiento de células cancerosas deficientes en expresión de BRCA1 y/o BRCA2.

De acuerdo con un aspecto adicional de la presente invención se provee el uso de una cantidad terapéutica de un compuesto de fórmula III en la manufactura de un medicamento para el tratamiento de células cancerosas

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deficientes en expresión de BRCA1 y/o BRCA2.

Las células cancerosas a tratarse pueden ser parcial o totalmente deficientes en expresión de BRCA1 ó BRCA2. Tales deficiencias pueden identificarse usando técnicas de PCR múltiple, técnicas de arreglo (29, 30) o utilizando otros cribados conocidos por la persona experta. Técnicas particularmente útiles incluyen RT-PCR cuantitativa en tiempo real, Northern blot, inmunohistoquímica y Western Blot (31, 32).

En consecuencia, los compuestos de la presente invención son de interés particular para el tratamiento de una gama de tumores cancerosos seleccionados, y la invención contempla además un método para el tratamiento de un paciente que sufre de cáncer.

Los compuestos descritos aquí pueden administrarse en una cantidad atóxica, terapéuticamente efectiva por cualquier vía apropiada para reconocer efectivamente células cancerosas ("*for effectively targeting cancer cells*"). Vías apropiadas de administración incluyen, pero no se limitan a, cualquiera de las siguientes: oral, intravenosa, intramuscular, intradérmica, intranasal, o tópica.

Una cantidad terapéuticamente efectiva de los compuestos descritos aquí es típicamente una que es suficiente para alcanzar el efecto deseado y puede variar de acuerdo con la naturaleza y gravedad de la enfermedad, y la potencia del compuesto. Se observará que pueden emplearse diferentes concentraciones para profilaxis que para tratamiento de una enfermedad activa.

Para administración a mamíferos y, particularmente, humanos se espera que el nivel de posología diaria del agente activo irá desde 0.01 a 50 mg/kg en ratones y 0.01 mg/m² a 50 mg/m² de área de superficie corporal en humanos. En última instancia, sin embargo, la cantidad de ingrediente

activo administrado y la frecuencia de administración estarán a discreción de un facultativo.

Ventajosamente, tan sólo se necesitan dosis muy bajas de compuestos inhibidores de PARP para tener un efecto terapéutico en tratar cáncer, reduciendo así la acumulación sistémica ("*systemic build up*") de los compuestos y, por consiguiente, minimizar cualesquiera efectos tóxicos asociados.

Aunque puede ser posible que los compuestos descritos aquí se administren solos como el compuesto 'natural', es preferible presentar los compuestos en una composición farmacéutica.

Todos los métodos de formulación en la elaboración de tales composiciones farmacéuticas incluirán generalmente el paso de asociar uno de los compuestos, descritos aquí, con un excipiente que constituya uno o más ingredientes adicionales. Usualmente, las formulaciones se preparan asociando de manera íntima y uniforme el compuesto de fórmula I con un excipiente líquido o con un excipiente sólido finamente dividido o con ambos y luego, si fuera necesario, moldear el producto en las formulaciones deseadas.

Formulaciones de la presente invención apropiadas para administración oral pueden presentarse como unidades discretas tales como cápsulas, sellos ("*cachets*"- *cápsulas amiláceas*), tabletas o pastillas para chupar ("*lozenges*"), que contienen, cada una, una cantidad predeterminada de uno de los compuestos descritos aquí; como un polvo o gránulos; o una suspensión en un líquido acuoso o un líquido no acuoso tal como un jarabe, un elixir, una emulsión o una poción. Cualquiera de los compuestos descritos aquí puede presentarse también como inyección intravenosa rápida ("*bolus*"), electuario o pasta.

Una tableta puede elaborarse por compresión o moldeo, opcionalmente con uno o más ingredientes adicionales. Tabletas comprimidas pueden prepararse comprimiendo, en una máquina apropiada, cualquiera de los compuestos descritos aquí en una forma de flujo libre tal como un polvo o gránulos, mezclados opcionalmente con un aglutinante, lubricante, diluyente inerte, agente tensioactivo o dispersante. Tabletas moldeadas pueden elaborarse moldeando, en una máquina apropiada, una mezcla de uno cualquiera de los compuestos en polvo descritos aquí con cualquier excipiente apropiado.

Un jarabe puede prepararse agregando uno cualquiera de los compuestos descritos aquí a una solución acuosa, concentrada, de un azúcar, por ejemplo sacarosa, a la cual puede añadirse cualquier ingrediente adicional deseado. Tal(es) ingrediente(s) adicional(es) puede(n) incluir saborizantes, un agente para retardar la cristalización del azúcar o un agente para aumentar la solubilidad de cualquier otro ingrediente, tal como un alcohol polihídrico, por ejemplo glicerol o sorbitol.

Formulaciones para administración rectal pueden presentarse como un supositorio con un excipiente usual, tal como manteca de cacao.

Formulaciones apropiadas para administración parenteral comprenden convenientemente una preparación acuosa estéril de uno cualquiera de los compuestos descritos aquí, el cual es preferiblemente isotónico con la sangre del receptor.

Además de los ingredientes ya mencionados, formulaciones de esta invención, por ejemplo ungüentos, cremas y similares, pueden incluir uno o más ingredientes adicionales, por ejemplo un diluyente, tampón, agente saborizante, aglutinante, agente tensioactivo, espesante, lubricante y/o un preservante (incluido un antioxidante) u otro excipiente inerte farmacéuticamente inerte.

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Los compuest s de esta invención pueden elaborarse también para administración en formulaciones liposómicas las cuales pueden prepararse por métodos bien conocidos en el arte.

Así, de acuerdo con un aspecto adicional de la presente invención se provee una composición farmacéutica que comprende un compuesto de fórmula I, o su sal farmacéuticamente aceptable, como un agente activo.

De acuerdo con un aspecto adicional de la presente invención se provee una composición farmacéutica que comprende un compuesto de fórmula II, o su sal farmacéuticamente aceptable, como un agente activo.

De acuerdo con un aspecto adicional de la presente invención se provee una composición farmacéutica que comprende un compuesto de fórmula III, o su sal farmacéuticamente aceptable, como un agente activo.

La composición farmacéutica puede comprender además por lo menos un otro ingrediente que provea un aditivo compatible farmacéuticamente aceptable, vehículo, diluyente o excipiente, y puede presentarse en una forma farmacéutica unitaria.

El(los) vehículo(s) tiene(n) que ser farmacéuticamente aceptable(s) en el sentido de ser compatibles con los demás ingredientes de la formulación e inocuo al receptor del mismo.

Las posibles formulaciones incluyen aquellas apropiadas para administración oral, rectal, tópica y parenteral (incluidas subcutánea, intramuscular e intravenosa) o para administración al pulmón o cualquier otro sitio de absorción tal como las fosas nasales.

Los compuestos mencionados aquí pueden administrarse en combinación

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con otros compuestos antineoplásicos.

La presente invención incluye asimismo un método de tratar cáncer en mamíferos administrando los compuestos descritos aquí y luego sales farmacéuticamente aceptables.

Así, de acuerdo con un aspecto adicional de la presente invención se provee un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula I, o su sal farmacéuticamente aceptable.

Así, de acuerdo con un aspecto adicional de la presente invención se provee un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula II, o su sal farmacéuticamente aceptable.

Así, de acuerdo con un aspecto adicional de la presente invención se provee un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula III, o su sal farmacéuticamente aceptable.

La presente invención se describirá ahora a manera de ejemplo únicamente con referencia a las figuras acompañantes en donde:

Figura 1 es una gráfica que muestra la supervivencia de células en la presencia de un inhibidor de PARP de fórmula III en estirpe celular AA8, estirpe celular IspSF y estirpe celular CxR3;

Figura 2 es una gráfica que muestra la supervivencia de células en la presencia de un inhibidor de PARP de fórmula III en estirpe celular V79, estirpe celular VC8 y estirpe celular VC8B2;

- Figura 3** es una gráfica que muestra la supervivencia de células en la presencia de un inhibidor de PARP de fórmula I en estirpe celular V79, estirpe celular VC8 y estirpe celular VC8B2;
- Figura 4** es un histograma ("*a bar chart*") que muestra actividad PARP en estirpes celulares VC8; V79, VC8#13 y VC8, VC8#13 y VC8+B2 en la presencia de un inhibidor de PARP de fórmula III;
- Figura 5** es un par de gráficas que muestran la inhibición de actividad PARP celular en la presencia de un inhibidor de PARP de fórmula I y III en células permeabilizadas (gráfica superior) y células intactas (gráfica inferior) L1210;
- Figura 6** es un par de histogramas que muestran la farmacocinética y farmacodinámica sanguínea y tumoral con fórmula I-fosfato con 1 mg/kg (superior) y 10 mg/kg (inferior) en ratones que portaban xenoinjertos SW620;
- Figura 7** es un histograma que muestra la farmacocinética y farmacodinámica con fórmula III en ratones que portaban xenoinjertos SW620;
- Figura 8** es una gráfica que muestra el crecimiento del tumor (volumen de tumor relativo mediano) en ratones que portaban xenoinjertos SW620 luego del tratamiento con fórmula III en combinación con temozolomida (TMZ) y con TMZ sola;
- Figura 9** es una gráfica que muestra el crecimiento del tumor (volumen del tumor relativo mediano) de ratones que portaban xenoinjertos SW620 luego del tratamiento con fórmula I - fosfato en combinación con temozolomida (TMZ) y con

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fórmula I-fosfato y TMZ sola.

Fig. 1 muestra la supervivencia porcentual de estirpes celulares AA8, IrS ISF CxR3 cuando se tratan con diferentes concentraciones del compuesto de fórmula III. Se descubrió que fórmula III era la más activa contra IrS ISF, que carece de XRCC3, con una IC_{50} (la concentración del componente activo que elimina 50% de las células) de 100 nM.

Fig. 2 muestra la supervivencia porcentual de estirpes celulares V79-Z, VC8 y VC8B2 cuando se tratan con diferentes concentraciones del compuesto de fórmula III. Se descubrió que la fórmula III era la más efectiva contra la estirpe celular VC8, que carece de BRCA2, con un valor LC_{50} de 43 nM y una IC_{90} (concentración de componente activo que elimina 90% de las células) fue de 1200 nM.

Fig. 3 muestra la supervivencia porcentual de estirpes celulares V79-Z, VC8 y VC8B2 cuando se tratan con diferentes concentraciones del compuesto de fórmula I. Se descubrió que Fórmula I era la más efectiva contra la estirpe celular VC8, que carece de BRCA2, con un valor LC_{50} de 12 nM; LC_{90} fue de 27 nM

Fig. 4 muestra la actividad PARP de varias estirpes celulares cuando se tratan con diferentes concentraciones del compuesto de fórmula III. La gráfica de Fig. 4 se divide en cuatro conjuntos de resultados para cada estirpe celular respectiva. La primera barra de cada conjunto muestra la actividad de fondo de PARP (sin presencia de oligo, de modo que la actividad PARP depende de rupturas de ADN endógeno), la segunda barra es la actividad total PARP, estimulable (por oligo) y las barras tercera y cuarta muestran la actividad PARP en la presencia del compuesto de fórmula III.

Fig. 5 muestra el efecto de Compuestos de Fórmula I y III sobre la actividad

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PARP.

Las células utilizadas para obtener los resultados indicados en Fig. 5 se permeabilizaron o bien con digitonina y luego se analizaron para detectar la actividad total PARP, estimulable (por oligo) en la presencia y ausencia del inhibidor PARP de fórmula I y fórmula III, o bien se expusieron a uno de dichos inhibidores de PARP durante 20 minutos antes de la permeabilización y se analizaron para detectar la actividad total PARP estimulable.

No hubo diferencia en la actividad inhibidora PARP de los compuestos de fórmula I y fórmula III cuando las células se permeabilizaron antes de agregar el compuesto inhibidor, pero el compuesto de fórmula I fue más potente en células intactas, posiblemente debido a que se acumula en las células en un grado más alto.

Fig. 6 muestra las concentraciones, en el plasma y el tumor, del compuesto de fórmula I, y su efecto farmacocinético sobre los linfocitos de sangre periférica de ratón (pbl parp) y xenoinjertos SW620 (PARP de tumor), en diferentes momentos luego de la administración intraperitoneal del la sal de fosfato del compuesto de fórmula I. La sal de fosfato del compuesto de fórmula I aumenta la solubilidad de fórmula I. No obstante, con la administración a un animal (incluido un humano) las fosfatasas del plasma descomponen la sal de fosfato de fórmula I (fórmula I-fosfato) en el compuesto precursor, es decir, fórmula I.

Es evidente de Fig. 6 que treinta minutos después de la administración de fórmula I-fosfato a 10 mg/kg, se detectaron altos niveles del compuesto precursor tanto en el plasma como en el tumor. La concentración de fórmula I disminuyó con el tiempo más rápidamente en el plasma que en el tumor y, 24 horas después de la administración, fueron detectables niveles significativos en el tumor, pero ninguno pudo detectarse en el plasma.

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Hubo una inhibición profunda y sostenida de la actividad PARP tanto en pbls como en el tumor: <50% control hasta 24 horas.

Luego de la administración de fórmula I-fosfato a 1 mg/kg, se pueden encontrar niveles más bajos del compuesto de fórmula I tanto en el plasma como en el tumor y, en consecuencia, hubo un efecto menos pronunciado sobre la actividad PARP.

Fig. 7 muestra las concentraciones en el plasma y el tumor del compuesto de fórmula III, y su efecto farmacocinético sobre xenoinjertos SW620 (actividad PARP en el tumor), en varios momentos luego de la administración intraperitoneal de 10 mg/kg de compuesto de fórmula III. Este compuesto se distribuye igualmente bien al tumor y se retiene preferencialmente con el tiempo e inhibe de manera análoga la actividad PARP en el tumor.

Fig. 8 muestra que durante 20 días a partir de la administración de temolozomida (68 mg/kg diarios x 5) el xenoinjerto del tumor se había reducido progresivamente en tamaño. No obstante, poco después de este tiempo, el tamaño del tumor empieza a aumentar. Cuando un compuesto de fórmula III (5 mg/kg diarios x 5) se administra en conjunción con temozolomida, el tumor se reduce significativamente durante alrededor de 15 días, a un tamaño indetectable, el tamaño del tumor permanece indetectable durante otros 50 días a partir de entonces cuando comienza a aumentar en tamaño. Cuando se administra una dosis mayor de fórmula III (15 mg/kg diarios x 5), el tamaño del tumor permanece indetectable durante unos 80 días más hasta el final del experimento, cuando ningún tumor fue detectable en la autopsia, es decir, regresión completa del tumor.

Fig. 9 muestra un patrón similar al observado en Fig. 8 luego de la administración de fórmula I-fosfato (con 0.1 mg/kg y 1.0 mg/kg) en combinación con temolozomida.

Tabla I. Genotipo y origen de estirpes celulares usadas en este estudio.

Estirpe celular	Genotipo	Defecto	Origen	Referencia	Comentarios
AA8	wt	wt	CHO	[41]	Estirpe celular de ovario de hamster chino
Irs1SF	<i>XRCC3</i>	<i>XRCC3</i> ⁻ , Deficiente en HR	AA8	[41]	Estirpe celular, sensible a la radiación, derivada de AA8, que carece de <i>XRCC3</i> , un componente de la ruta de HR
CXR3	<i>XRCC3</i> +h <i>XRCC3</i>	wt	Irs1SF	[41]	Irs1SF transfectado con el gen h <i>XRCC3</i>
V79-Z	wt	wt	V79	[42]	V79 son fibroblastos de pulmón de hamster
VC8	<i>BRCA2</i> ⁻	<i>BRCA2</i> ⁻ , Deficiente en HR	V79-Z	[42]	VC8 son derivados, sensibles a la radiación, de V79 los cuales deficientes en <i>BRCA2</i>
VC8#13	<i>BRCA2</i> ⁻ +h <i>BRCA2</i>	wt	VC8	[42]	VC8 con cromosoma 13 que contiene h <i>BRCA2</i>
VC8+B2	<i>BRCA2</i> ⁻ +h <i>BRCA2</i>	wt	VC8	[42]	VC8 transfectado con h <i>BRCA2</i>

Materiales y Métodos

Citotoxicidad de inhibidores de PARP a células deficientes en HR (*XRCC3* ó *BRCA2*)

Cultivo de células

Las estirpes celulares AA8, Irs1SF y CXR3 se proporcionaron por Larry Thompson [41].

Las VC-8, VC-8+B2, VC-8#13 fueron un regalo de Malgorzata Zdienicka [42]. Todas las estirpes celulares en este estudio se cultivaron en Dulbecco's modified Eagle's Medium (DMEM) con 10% de suero bovino

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fetal y penicilina (100 U/ml) y sulfato de estreptomycin (100 [μ g/mL]) a 37°C bajo una atmósfera que contenía 5% CO₂.

Análisis de toxicidad — análisis de supervivencia clonogénica

Células que crecían exponencialmente en placas de 6 pocillos se expusieron al compuesto de fórmula III con las concentraciones indicadas en Fig. 2 en 1% DMSO ó 1% DMSO solo en medio durante 24 horas.

Las células se cosecharon por tripsinización, se contaron y sembraron con densidades variables en cajas de 10 cm en medio fresco en la ausencia de fármaco para formación de colonias.

7-10 días más tarde las cajas se fijaron con metanol:ácido acético 3:1 y se tñieron con 0.4% cristal violeta.

Se contaron las colonias y se calculó la supervivencia relativa a células tratadas con control 1% DMSO.

Análisis de actividad PARP

Células que crecían exponencialmente se expusieron a 1% DMSO en medio de cultivo (control) o un compuesto de fórmula I ó III en 1% DMSO con las concentraciones indicadas en Fig. 4 a células permeabilizadas con digitonina, o células intactas durante 20 minutos antes del lavado y permeabilización con digitonina. La actividad PARP se cuantificó por incorporación de un sustrato NAD⁺ marcado con [³²P] en polímeros precipitables TCA luego de la estimulación por la adición de un oligonucleótido de extremo despuntado y se comparó con células estimuladas con no-nucleótico. La actividad PARP en homogenatos de tumor (1 en 40 en tampón isotónico) procedentes de ratones tratados con fórmula III se cuantificó en la misma forma. La actividad PARP en pbls y homogenados de tumor procedentes de ratones tratados con fórmula I – fosfato se cuantificó por detección inmunitaria de polímero utilizando el

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anticuerpo 10H. Brevemente, homogenados de tumor diluidos hasta 1:1000 en tampón isotónico se incubaron con 350 μ M NAD durante 6 minutos y se transfirieron ("were blotted") en una membrana de nitrocelulosa. La formación del polímero poli(ADP-ribosa) (PAR) se cuantificó por detección de quimioluminiscencia usando un Iluminador UV Fuji LAS3000 por referencia a diluciones en serie de un estándar PAR, luego de la incubación con anticuerpo 10H a PAR y un anticuerpo anti-ratón secundario. Los resultados se estandarizaron por referencia al contenido de proteína cuantificado del homogenado.

Naturalmente se entenderá que la invención no pretende restringirse a los detalles de las incorporaciones anteriores, las cuales se describen a modo de ejemplo únicamente.

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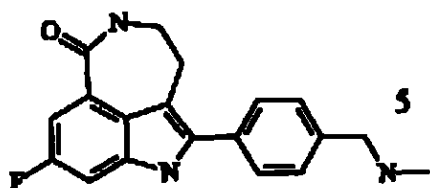
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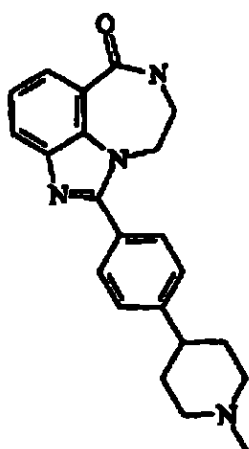
42
89**Reivindicaciones**

1. Un compuesto para inhibir la actividad de PARP que tiene la fórmula I

**I**

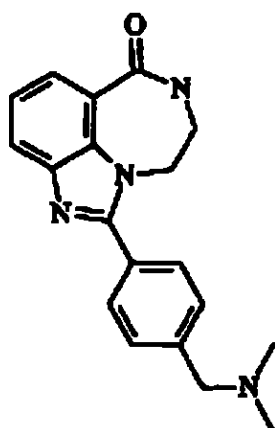
y sus sales farmacéuticamente aceptables.

2. Un compuesto para inhibir la actividad de PARP que tiene la fórmula II:

**II**

y sus sales farmacéuticamente aceptables.

3. Un compuesto para inhibir la actividad de PARP que tiene la fórmula

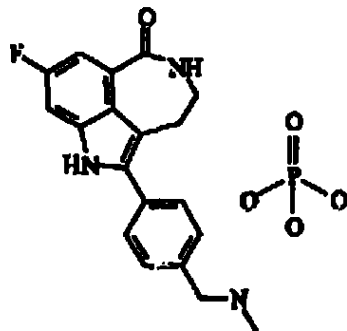
**III**

y sus sales farmacéuticamente aceptables.

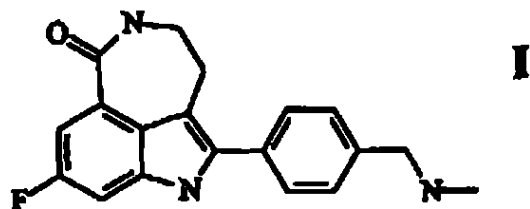
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4. Un compuesto de acuerdo con la reivindicación 1, en donde el compuesto está en la forma de una sal de fosfato de la siguiente fórmula:

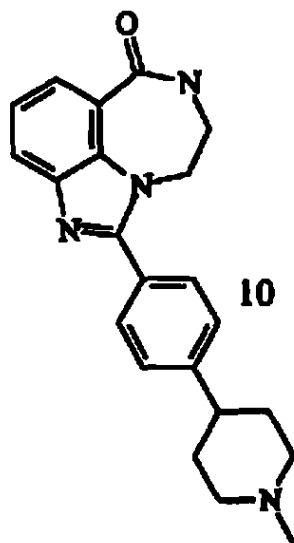
Fórmula I - Fosfato



5. El uso de una cantidad terapéutica de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento

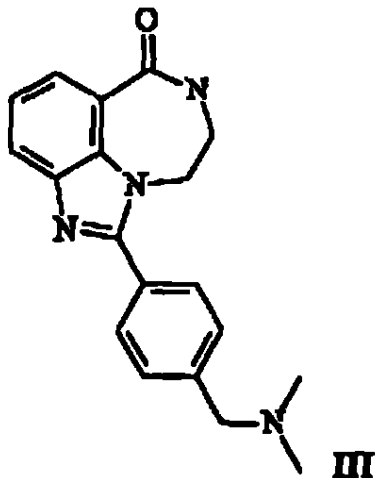
**I**

6. El uso de una cantidad terapéutica de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento.

**II**

CZ
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7. El uso de una cantidad terapéutica de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento.



8. El uso de una cantidad terapéutica de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

9. El uso de una cantidad terapéutica de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

10. El uso de una cantidad terapéutica de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de una enfermedad o afección que es causada por un defecto genético que media recombinación homóloga.

11. El uso como se reivindica en una cualquiera de las reivindicaciones 8 a 10, en donde el defecto es un gen que codifica una proteína involucrada en HR.

12. El uso como se reivindica en una cualquiera de las reivindicaciones 8

a7 92

a 10, en donde el defecto es la ausencia de un gen que codifica una proteína involucrada en HR.

13. El uso como se reivindica en una cualquiera de las reivindicaciones 8 a 10, en donde el defecto es la expresión de un gen que codifica una proteína involucrada en HR.

14. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula I y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para inducir apoptosis en las células deficientes en HR.

15. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para inducir apoptosis en las células deficientes.

16. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para inducir apoptosis en las células deficientes.

17. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de cáncer.

18. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de cáncer.

19. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de cáncer.

20. El uso de un compuesto de acuerdo con una cualquiera de las

af 93

reivindicaciones 15 a 17, en donde el cáncer es un cáncer hereditario asociado a un gen.

21. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de células cancerosas deficientes en expresión BRCA1 y/o BRCA2.

22. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de células cancerosas deficientes en expresión BRCA1 y/o BRCA2.

23. El uso de una cantidad terapéuticamente efectiva de un compuesto de fórmula III, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento para el tratamiento de células cancerosas deficientes en expresión BRCA1 y/o BRCA2.

24. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 21 a 23, en donde las células cancerosas a tratar son parcial o totalmente deficientes en expresión in BRCA1 y/o BRCA2.

25. Una composición farmacéutica que comprende un compuesto de fórmula I y su sal farmacéuticamente aceptable, como un ingrediente activo.

26. Una composición farmacéutica que comprende un compuesto de fórmula II y su sal farmacéuticamente aceptable, como un ingrediente activo.

27. Una composición farmacéutica que comprende un compuesto de fórmula III y su sal farmacéuticamente aceptable, como un ingrediente activo.

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28. Una composición farmacéutica de acuerdo con una cualquiera de las reivindicaciones 25 a 27, en donde la composición comprende además por lo menos un diluyente y/o excipiente junto con por lo menos un agente de relleno.

29. Una composición farmacéutica de acuerdo con la reivindicación 28, en donde el vehículo y/o diluyente se selecciona de cualquiera de los siguientes, solos o en combinación, solución salina, solución salina tamponada, dextrosa, agua, glicerol y etanol.

30. Un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula I como se describe en la reivindicación 1; o su sal farmacéuticamente aceptable.

31. Un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula II como se describe en la reivindicación 2, o su sal farmacéuticamente aceptable.

32. Un método para el tratamiento de cáncer en mamíferos que comprende administrar un compuesto de fórmula III como se describe en la reivindicación 3, o su sal farmacéuticamente aceptable.

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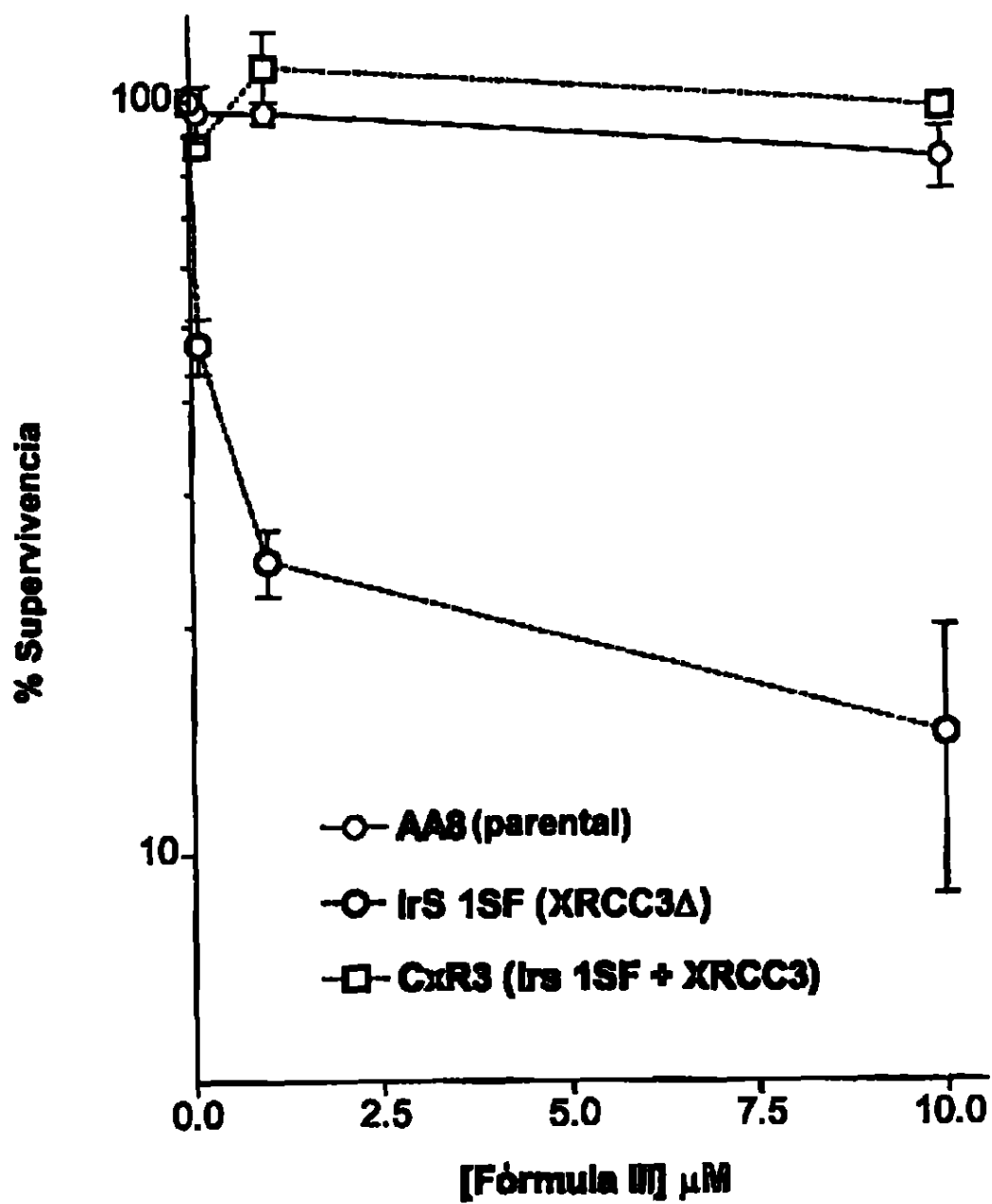


Fig. 1

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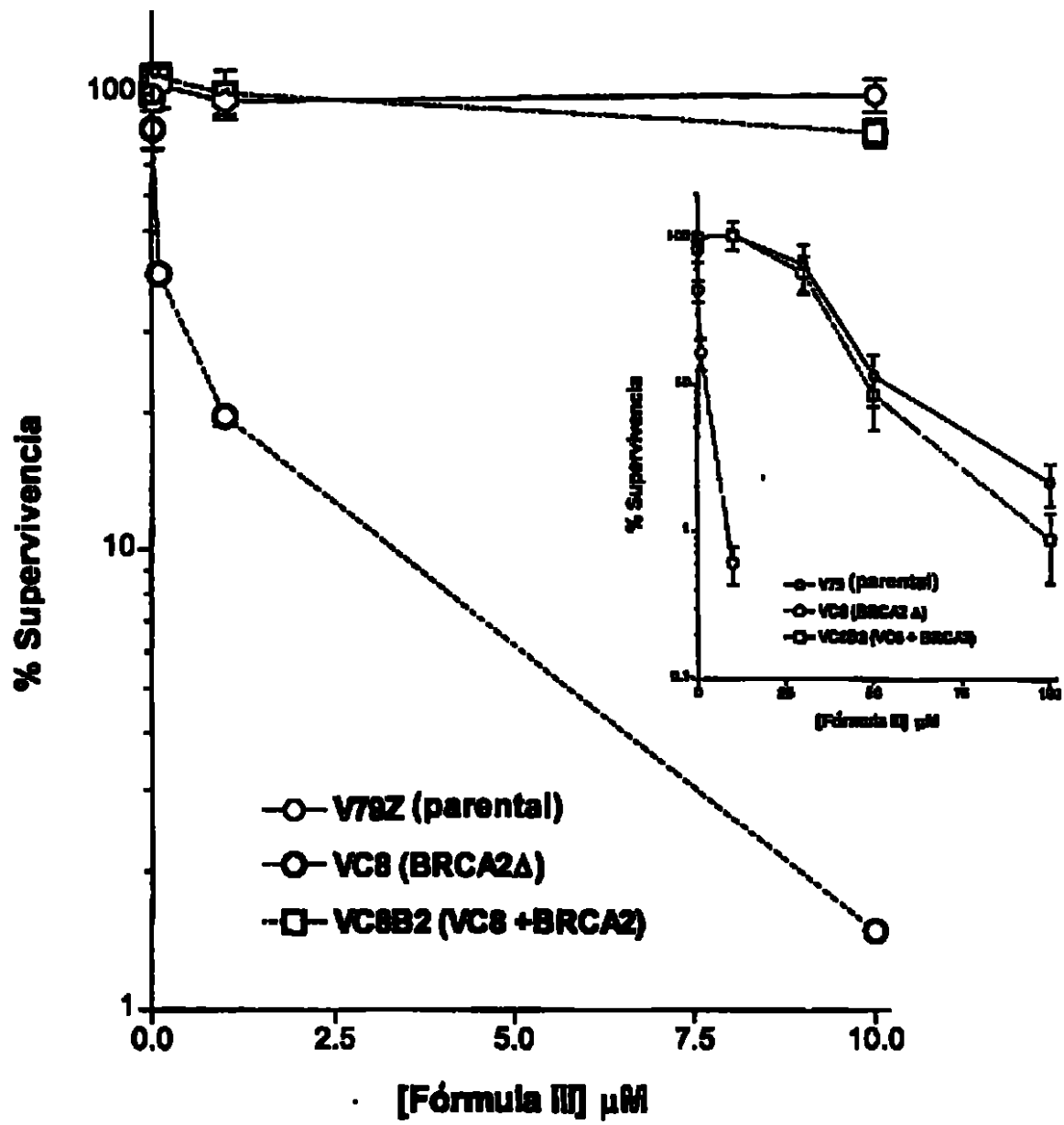


Fig. 2

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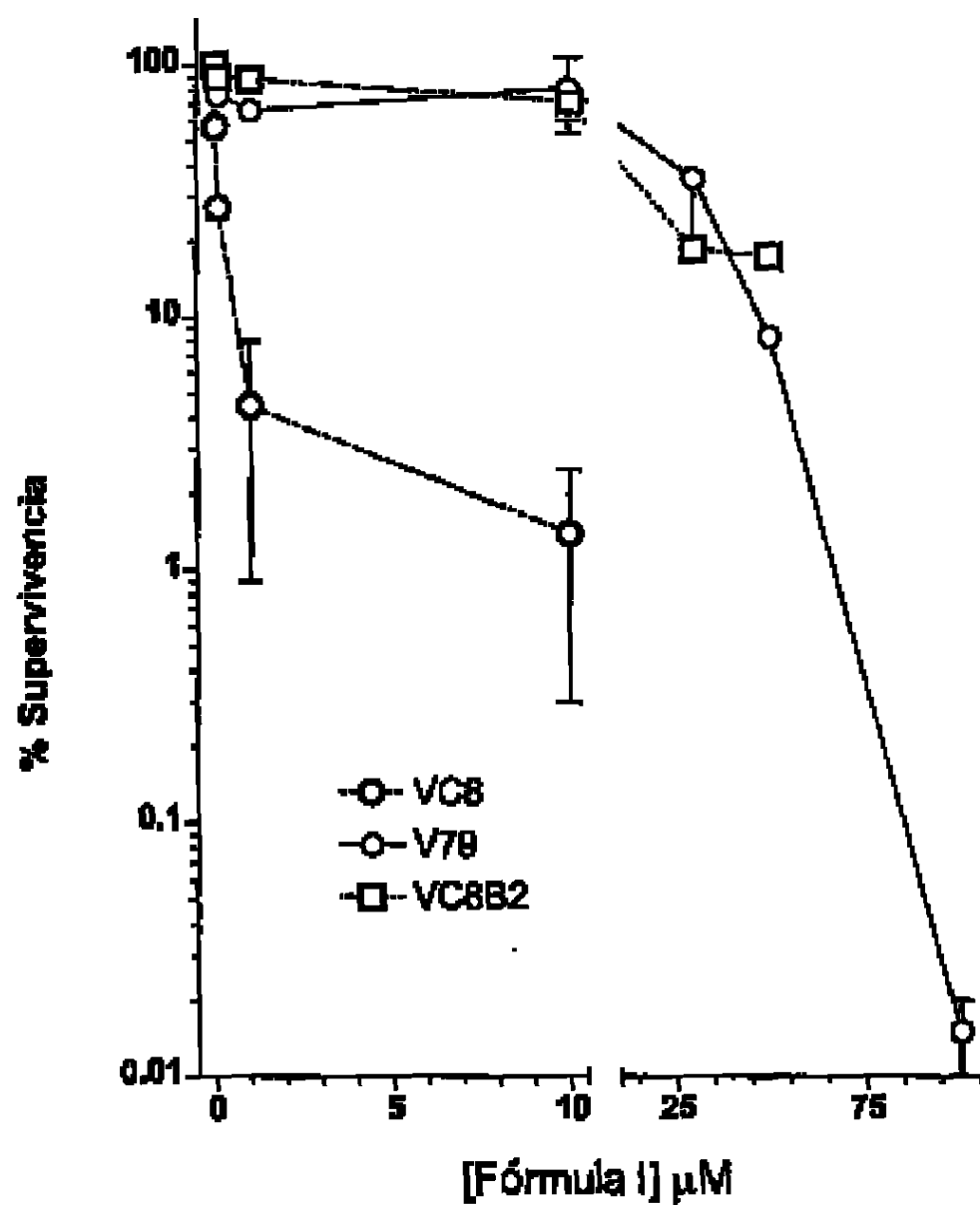


Fig. 3

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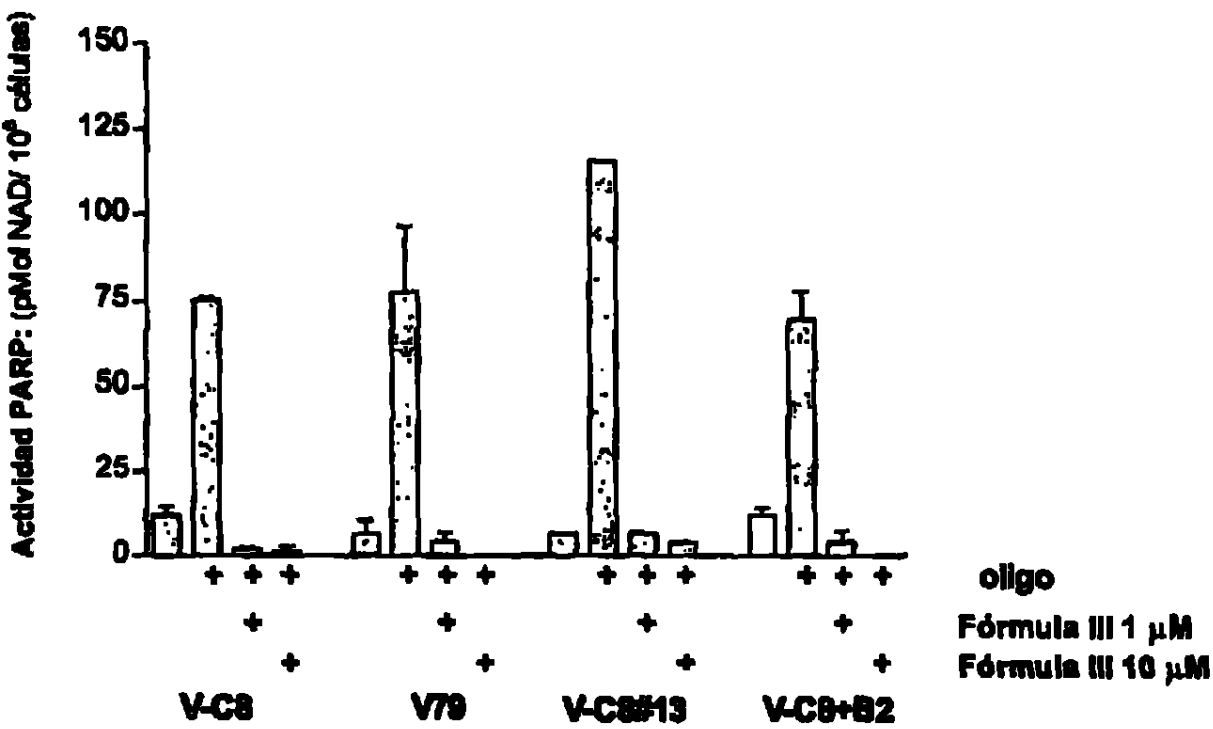


Fig. 4

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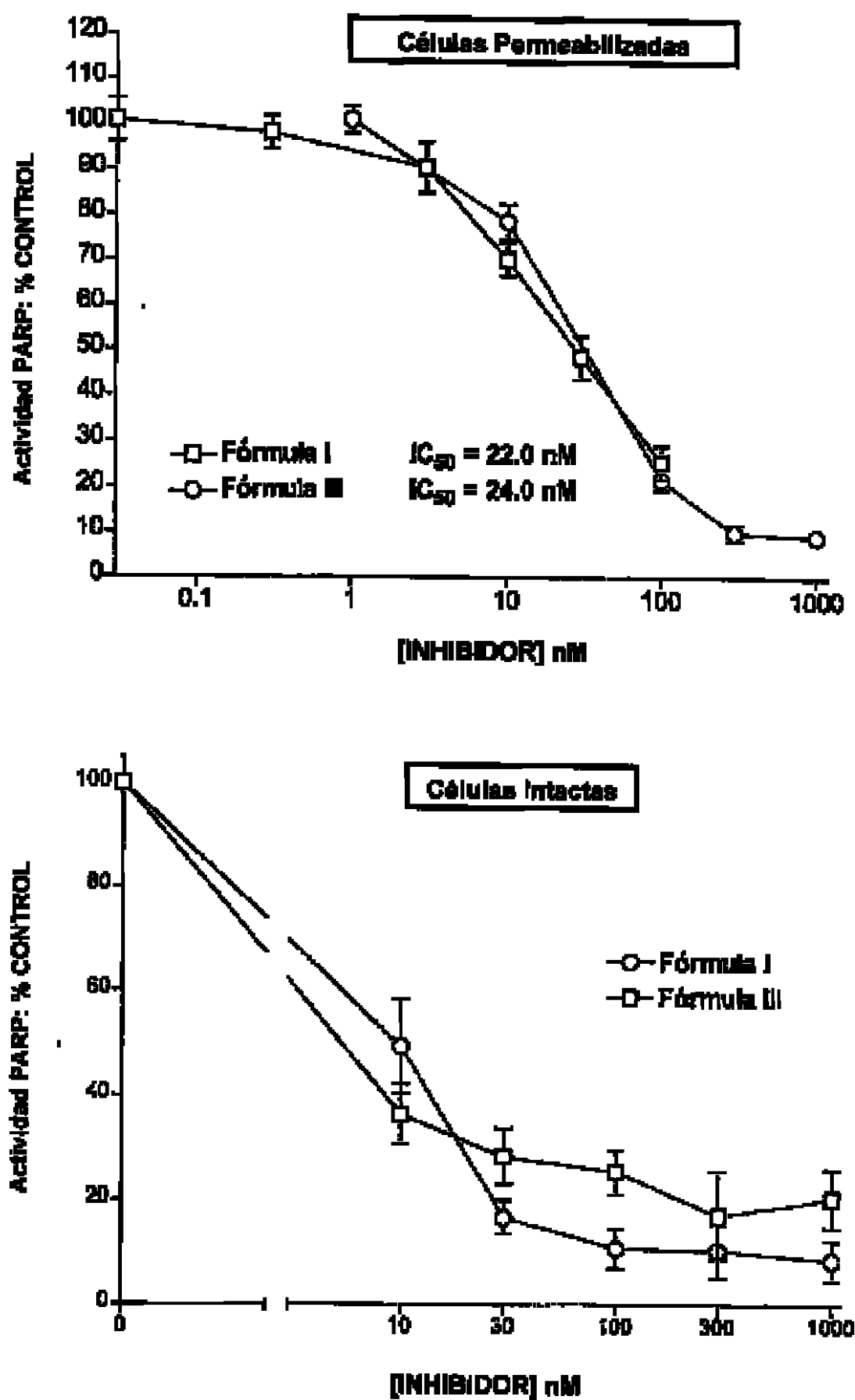
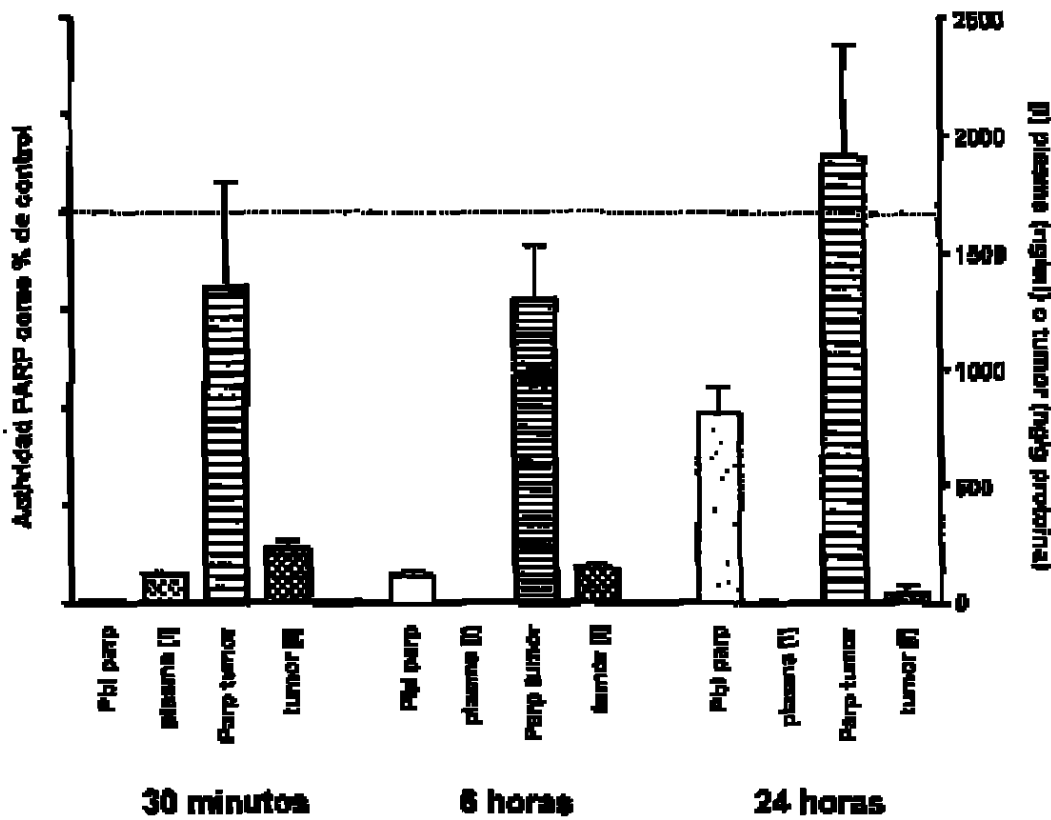


Fig 5

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Fórmula I-Fosfato 1mg/kg



Fórmula I-Fosfato 10 mg/kg

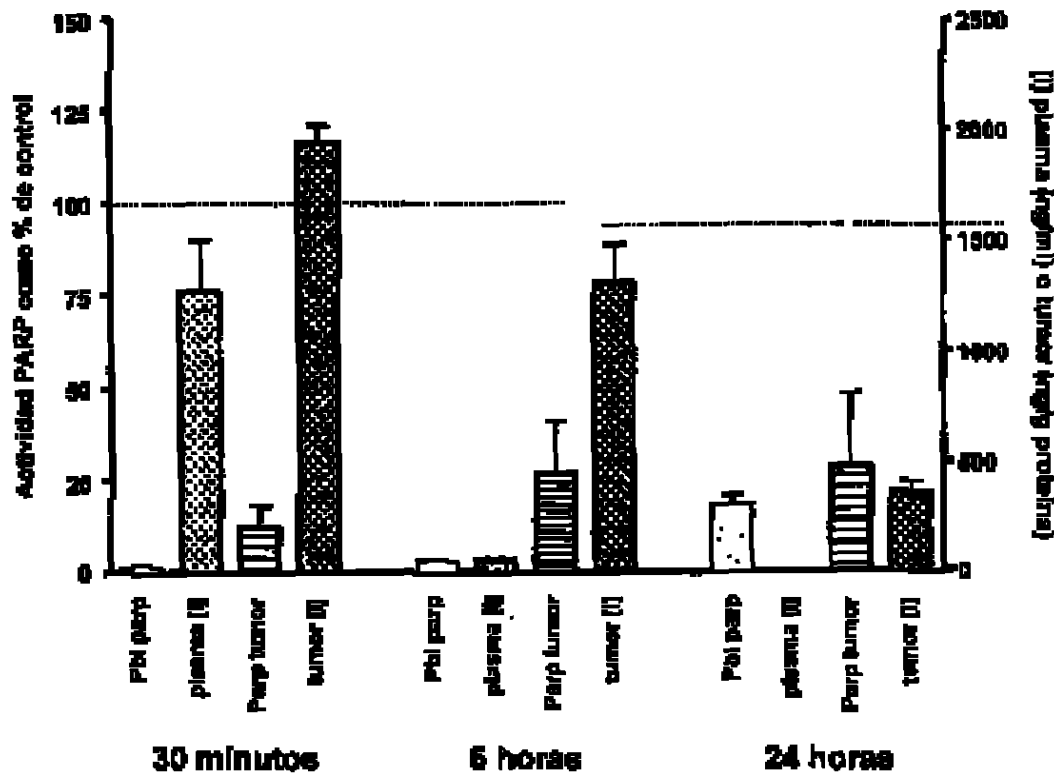


Fig. 6

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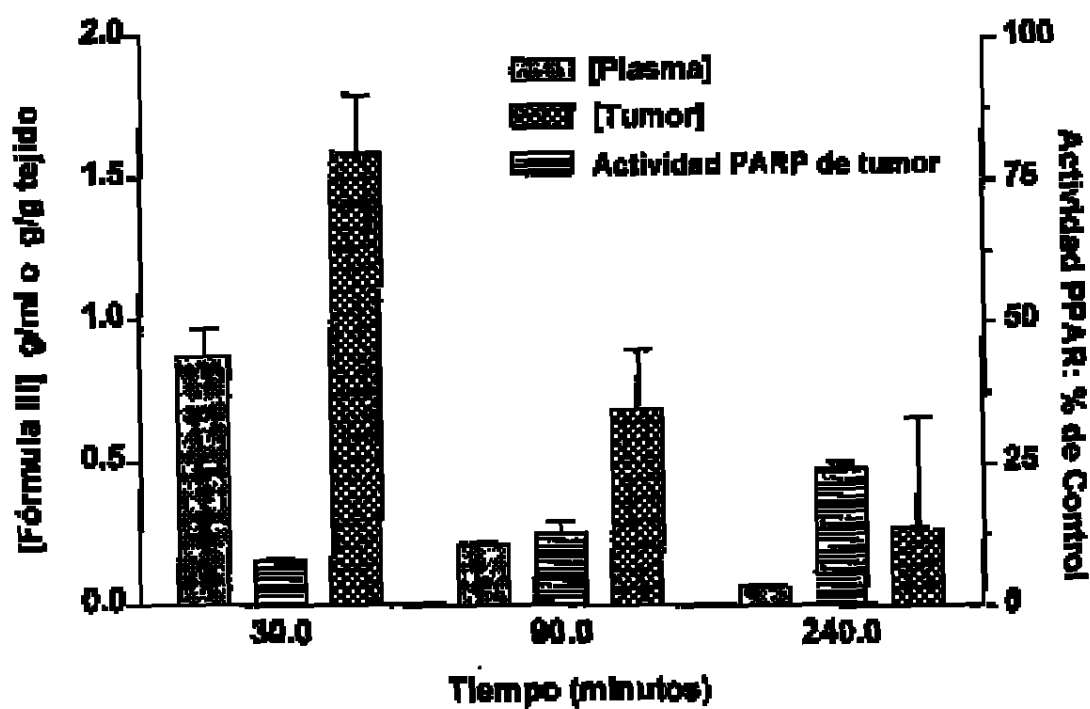


Fig 7

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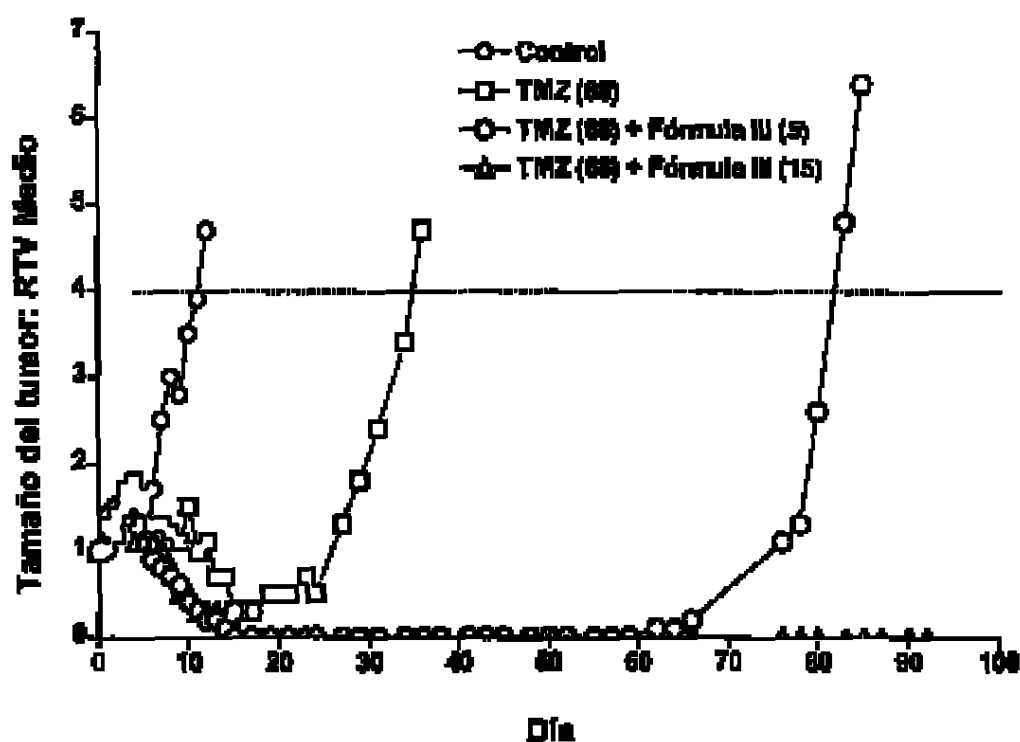


Fig. 8

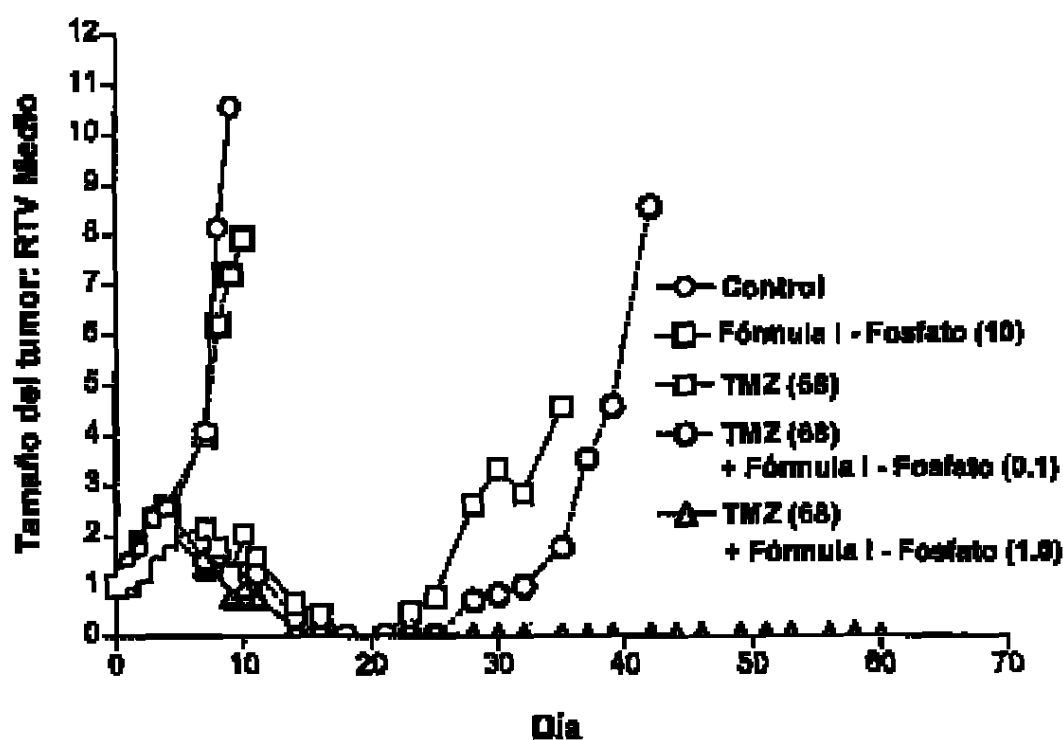


Fig 9

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Listados de Secuencias**Secuencia 1 – Secuencia cADN Humano de PARP-1**

1 cgcgcgcga gcccgggggc cagggaagc ctaaattaag gaattacaga gaggaggag
 61 cggggatag gggagcgtcc gggagtagct ggaicctcta ggcaggatag tgatgggat
 121 cttgcaaat tgtatctct gttgaaagt gaagtaacta otcagagac agagaaaaa
 181 gctacaaat gaoattaagg aaatggcgg aagttttcc ttctgtta atctcagtg
 241 cacacataa atctagata atctgagtg tctgagtcag taccaactga attatacca
 301 aaagaaccac gticatatg caaacccaga ttatatatg aaatctatca gagaagaag
 361 actcttggt gtaagaatt atgacctta taagccctg gacacacac cactctcga
 421 tcagaaggcg agcagttctg aagtgaaaac agaaggtola tggccggaca gtccacaga
 481 ggaggagac actgtggac tactgagtg tggatgcag aatgttgaat tctctatct
 541 tctcaagat ttgagtg caaatataa cactctgag aaagtcggaa tggaggagg
 601 ccaggagct gttgtgggg agctcagtg ttgcgggac tccaggagct gtctttct
 661 gatactcca cactctcc tggatgagtg catggagact agaagacgt ttgccttaa
 721 gaataacta gaagatgaa gtgaatact tgaatttac attgaagaa tgaagaaca
 781 aggatttca ctagagaaac attacacc tgaagcaac caattagcat ctgaacaat
 841 gcaagcattg ctltggagg aagtcagaa ttaagcaat ctgagccag agtgagaga
 901 tttagtagag atgatttgg cagaggccct gggccacctg gaacacatgc ttcaagcc
 961 agtgaacagg attagctca agatgtgag caaggcagag gggatctcc ttctagtaa
 1021 ggaagcaatg aaaaatggag aaacagcaga gcaattgaa agatgagta cagatttla
 1081 cagactgata cctacaaag gcacatgac caagaagtg aacctggac ttctggtaa
 1141 gaagcagac ctctgcaga taataagaa catggtaat gtctgtgaa ctatttgc
 1201 caaoccaa ccaactccc tggcaata cggagcttg aggtgcaaa ttgagcatg
 1261 tgaacagant atgaagaat tttaaggtg tgaagaag gtttcaga atcatcag
 1321 taagagcca gttgagtg tgcagatct tagagttggc agagtgatg aaaccacaga
 1381 gttttgagc aaacttgta atgtgagga ctgttgatg ggttctctg tacaaacat
 1441 cgtgggagt ttgtgagag gtttcttt acccaagta gtgaagatc gttgtgtca
 1501 aagaaagac gtgggaacc ttgaagtg gatttttc agtgattgo taagtcag
 1561 taaagtagc taacaccgg gagagacaga tggcaccaga ctctgctca ttgtgagc
 1621 agccctcga aagtgtatg actaacatga gaaggactt tcttaactg aagcaccac
 1681 aggtacagac agtgagatg gatttcaca aacagccct gtcaccacag acttgagga
 1741 tgatgaatt gtgtctata aaacactca ggttaaatg aaatataa ttaatttc
 1801 catgctgga gacagataa agaatctca tctagtgt catctgaa taaggaata
 1861 caactgag tttaaat ttcaaatg tgaagattc cagtaccag atgcacaa
 1921 tccagcagc accaaggccg gctccagga tcttttggg aatttggtc ctctggaga
 1981 tgtccaatc aaaggagaa tcatagacac tctagccag gcaatgtt tcaagata
 2041 caaataaa agtcacgtg ccattgagg aatataatc ttcccttg atgacagga
 2101 cgtgtgtgt ggttcgaag cctcatcaa tgggaagac atagttggag agattaaga
 2161 gaaggagaa gccagcaag agtaactaga agcctgacc caggccatg gcgctaat
 2221 gatgagcag gatgtcagg aggttttac tgaagtggt ggaacttac cccaaagg
 2281 taagttctt aaaaataa cctacatcag aagatcagc atctggga ctgtgtgt
 2341 ctctcagc ccgcccag tagcaccctg gcaacaggac aaggtttga atgaanaat
 2401 tcaggataa ghagagaa ttgtataa agaatagga acaaagaaa gcttcttt

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2461 gaoratytot atgagatgo cgtacgtgt tgaatcatt ttagtgata ototgaact
2521 gaaacanaag cgtacagact gcaagctgt catagcacc atggaagga gctcttga
2581 cagcagtga tttototo acatcgttt gtctgtgco tatotocaa gaatgtggt
2641 lgaanaacat ccagaaaaag aaagcagggc ttgatgtt gtotthaac ccgatctga
2701 tgtogaccto cctgacctag ccaatgagag cgnagtgtt attgtotig actgtccag
2761 ttcattgag ggtgtgacat tottgaagc caagaaatc gcttgcctg cgtgtcct
2821 ggtgggtgag aagcagaag taatatat cagttcggc aonggttca aggagctat
2881 ttgtatctt aagcatatc caagcaatc cgcggcagca gaggatca tgtctgcc
2941 aotacatg aggaacacag actctgga aucttcca tatctagct tatgtacc
3001 tctctgaggt tcatggaac totctctgt gtctgtgag caotocagg atgagatct
3061 gacattacag ctotggaag ggagccgcc gcacacagg taticgctt ggggtatcg
3121 ttctacagca atctgtcag tottaagat ttgtocag tgggtgccc gattattga
3181 atatttat gcaaatoca agcatagt gagaacacg atagaagoo aatgaccg
3241 gctagtctt ccagttgc actctgtc cgtcaatgg cagcaatca atcagatg
3301 gccagagcc ctgcagccc cagccaggt gcttctgt ttctcattg atgactct
3361 tgtatgga thotctc acttccaca ggcactct tgtcactaa ticanagaa
3421 agattttgt acaatgtgt cgtatctg gcttgaag acaatggaa ctatgata
3481 caagctgga gcccgagct taatagga tatgaagat gctatctc acgaaatga
3541 aaccagtat gatatgaa acaacactt gaattctg atataaac tcatgaag
3601 aaactotc aiaauctat tcaagctt tggcaggt gagaagag atgagatga
3661 gtcacttt ccttatct caaagttt tgaactat gcaagag atgtagct
3721 cctgcctac atgagctgc agggggaac caagagcc gtaaggaac agtctctt
3781 agcatctt ggtggccag aattcgtt atcaaaaga aaatagga aattcatt
3841 thcaaaaga aaatggat tatctagcc agagttct gaagattg aagagatgc
3901 ctatgtgt ataccagt tcatcaaa ttggaactt ggcgtgtg aaagtatt
3961 ggtttagt tgaagagt catgaac aacagcaat gaacatct tgaagat
4021 cagtcatgg gaacatct ctctagct tttctatt ttgtctcg cgttggtc
4081 ctatctac cgtctacc ggcctacag totgtctc ttgtttg cctatctg
4141 toaggtagt agttcgtt cagctgctc tccagacag ttgatgat otatctag
4201 caagggcct ggtctgga ctgtctga ctgaacca cagctgggt ctgtccac
4261 aggacotcc agaaocac ctctgccc ctattgtgc attgtttt caggagot
4321 atagctat gcaagctc ctactgca aatctgga gcttacta ccaggtct
4381 tgtggcac tccctgag ttgattcc cagcttct ttctctc ctacagccc
4441 tgaacctc agagtttg ggttacta tctctgtt tctctct ttacttca
4501 acctccga gctotlga ctgcaact laggctgca atggctcty ctatctga
4561 ggtctttg agtactcc ggtacccc agtagctc tgtctctag aagaatagt
4621 aggcagctc gaaggagtc gatgtctt ctgtctt caagtttg acaagaaag
4681 tcatgacta tcagaagac ttaagacag ctgtttt caataaant gtagaaca
4741 agtagaagt atccgtgt ttctgaagt aaagagag gatgaatag tgtcaaca
4801 acatggcag gatgtgtc ctggaaga actctcagt ctacagac aggtatgt
4861 ctgaactt aacacagac tgggactat attactct aataaant gttccacag
4921 ctctttaa caaagagca ttaatctt aggttaaa ggaagagat gtctctga
4981 octattgao caatgtgt tactacagt ttctgccc aggttgaaa agaggaat
5041 agttgcaa tcatgata aatgtatg cctctat tcatgaat ttctgtggc
5101 ttgtgga atagagag caagtatg gtagaaga actgaagao agtaccatc
5161 tatctgcca cagcttgc tgggaaga ctggactt gccacagc agtctgtg
5221 actcagcc atagactg tctccctt tcatagag ctacttca gcaagcta

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5281 agtcaaatga aactgaattt taaactttt gcctgcttct atgtagaaa taatcaatg
5341 ataatagata ctataatga aacttcatia aggtttcatt cagtgtagca attactgtct
5401 ttaaaaata agtggaagaa gaattacttt aatcaactaa caagcaataa taanaatgaaa
5461 cttaaaat

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Secuencia 2 – Secuencia de cADN Humano de PARP-2

1 ctagaattca gcggccgcig aattctaggg ggccgcggcgg cgacggagca ccggcggcgg
61 cagggcgaga gcattaatg aaagcaaaag agttaataat ggaacacagg ctccagaaga
121 ctctccctt gccaaagaaa ctctagatg ccagagacag gagicgaaa agatgcctgt
181 ggctggagga aaagctaata aggacaggac agaagacaag caagatgga tgccaggaag
241 gtcattggcc agcaaaaggg tctctgaatc tgtgaaggcc ttgcgttaa agggcaaacg
301 tctgtggac ccagagtga cagccaagg ggggaaggct catgtgtatt gtaaggaaa
361 tgatgtctat gatgtcatg taaatcagac caatctccag ttcaacaaca acaagtacta
421 tctgattcag ctattagaag atgatgccca gaggaacttc agtgtttga tgagatggg
481 ccagttggg aaatgggac agcacagcct ggtggctgt tcaggcaatc tcaacaaggc
541 caaggaaatc ttcaagaaga aatccttga caaacgaaa acaattggg aagatcgaga
601 aaagttagg aaggtgctg gaaatatga tatctacag atggactatg ccaccaatc
661 tcaggatga gaggaacaa aaaagagga atctcttaa tctccctga agccagagtc
721 acagctagat ctctgggtac aggtgtaat aaagttagc tgaatgttc agyccatgga
781 agaatgatg atggaaatga agtataatc caagaaagcc ccactggga agctgacgt
841 ggcacaaatc aaggcagggt accagtctt taagaagatt gaggattga ttccggctgg
901 ccagcatgga cgagctctc tgaagcatg caatgaatio tacaccagga ttccgcaiga
961 cttaggactc cgtactctc cactaatccg gacacagaag gaactgtcag aaaaaatca
1021 attactagag gcttgggag acattgaat tgcattaa ctggtgaaa cagagctaca
1081 aagccagaa caccatigg accaacata tagaaacct cattgtgct tgcgcccc
1141 tgaccatgaa agttacaggt tcaagtgat ttccagtag ctacaatca ccatgctcc
1201 cacacacagc gactatacca tgacctgct ggattgtt gaagtggga aggatggga
1261 gaaagaagcc ttcagagagg accttcaaa caggatgct ctatggcatg gtccaggat
1321 gagtaactgg gtgggaatc tgagccatg gcttcgaat gccaccctg aagctccat
1381 cacaggttac atgttggga aaggaatca ctgtctgac atgtctcca agagtccaa
1441 ttactgctt gccctcggc taagaatc aggactgct ctctatcag aggtagctt
1501 aggtcagtgt aatgaactc tagaggcaa tctaaggcc gaaggatgc tcaaggtaa
1561 acatagcacc aaggggctg gcaagatgc tccagtct gccacttcg taccctgaa
1621 tggagtaca gtgccattg gaccagcaag tgacacagga attctgaatc cagatggta
1681 taccctaac taatgaat atattgata taacccaac caggtccga tgggtacct
1741 tttaaagggt cagtttaatt tcttcagct gtggtaatg ttgatctaa ataaaccaga
1801 gatctgatct tcaagcaaga aaataagcag tgtgtactt gtaatttg tgatattta
1861 tgtaataaaa actgtacagg tctaaaaaa aaaaaaaaa aaaaaaaaa

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Secuencia 3 – Secuencia de cADN Humano de PARP-3

1 tgggaactggt agcctgaetc ggcctgcccc agcctctgct tcaccccaact ggtagcgaan
 61 tagccgatgt ctaatcccc acacaagctc atccccgggc tcctgggattg ttgggaattc
 121 tctccctaatt tcacgcctga ggcctcatgga gacttgctag accctgggaot gccctgggag
 181 ggcacacaa ccaggccggg ttgcagocag gacctctcc atgtccctgc ttctctgac
 241 cttggctcca aagccgaagc cctgggtaca gactgagggc cctgagaaga agaaagggccg
 301 gcaggcagga agggaggagg acccttccg ctccacccgt gaggccctca aggcataacc
 361 cgcagagaag cgcataatcc gctgggatac aacatgtcca ctacgcagca accccgggac
 421 ccagggtgat gaggatata actgcacct gaacacagaa aacatcgaga acacacaaa
 481 caagtctac atcatcaga tgcctcaga cagcaaccgc ttctcaact gctgggaaccg
 541 ctggggcgtt gggggaggg ttggccagtc aaagatcaac cacttcaca ggctagaaga
 601 tgcagaagag gacttgaga agaatctcg ggaagagcc aagaacaact gggcagagcg
 661 ggaccacttt ggtctcacc ogggcaagta cacactatc gaagtacaga cagaggatga
 721 ggccaggaa gctggtgta aggtgacag agggccagtg aggactctga ctaggcgggt
 781 gcaaccctgc tccctggacc cagccacgca gaagctcacc actaacatct tcagcaagga
 841 gatgicag aacacatgg cctctatgga cctggatgt agaaagtgc cctgggaaa
 901 gctgagcaag caacagattg caggggttt cagggcctg gaggcctga aggagccct
 961 gaaagggccc accgaagggt gcaaaagcc ggaaggagtg tctacact ttacaccgt
 1021 catccggac aattcggc acagccagcc ccggccatc attccctg agctctga
 1081 ggcaagaag gacatgctc tgggtctggc ggaatcgag ctggccagg ccctcaggg
 1141 agtctctgag caggagaaga cggtagga ggtagcaca cccctggaa gagaacaa
 1201 gcttctcag tccagctgc agctctaga ctctggaga cctgagtaca aggtatata
 1261 gacatccta gaacagctg gcagcaacca caggtgcct acatcaac acatctgaa
 1321 agtaaccaa gaaggagg agacagatt ccaggccac tcaaatgg gtataggaa
 1381 gctgctgag catggacca acatggcct ggtggcgc atctcacta gtggctccg
 1441 catatgcca catctggg ggcgtgtg caagggcacc tacttgct cagagacag
 1501 caagtaagt ggaatgta ttggatga gttggggcc caccatgct gctacatgt
 1561 cctgggtgag gtggccctg gcagagagca ccatatcaac acggacac ccagcttga
 1621 gagccacct cctggcttc aagtgcat tggccaggc cacacagag ctgacagac
 1681 ccaggacact gatgggagc tggatggca gaagtggtg ghuuacagg gcaagcctgt
 1741 gccctgcca gatgcaga gctccacti ctccagagc gactccta tctaccagga
 1801 gagccaggt agctggct accgtctga ggtcacctc tggtagccg cctgtccc
 1861 cgggtctct caaggtgga ctgtatcti caatcatct gcoantcti ggtacccca
 1921 tatcactct tttttaa gatacaaac gttgtgta actatagta ccagtgta
 1981 caagatccct gaactatgc ctctaactg aaatttga ttcttgca catctgcca
 2041 gtcctctcc tccagacca tggtaaccag catctgact ttacttga taaggagga
 2101 tttataggt tccatgta agtagatca tgcagtgtt gtcttctgt gctgggta
 2161 ttacatag cataatgac accggttca ccatgttti caaaatgac aagattcti
 2221 ccttaaaa aaaaaaaa aaaaaaaa aaaaaaaa aaa

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Secuencia 4 – Secuencia de gADN Humano de Tankirasa 1

1 cgaagatggc ggctgcgct cgtctcagc atcatatca uulcatcaa caacagctcc
 61 agcccgcccc aggggttca ggcgggcgc eguacctcc tccccactc agccctggcc
 121 tggcccgga gacacccca gctcttcaa oggocaggg cctggcccc ttgccttccc
 181 cggggcagg cctagcgtc cggggggg atggcagtc ggtccggcc gacaggccc
 241 gatcccgga cgggttga ggtaccagc gttgcagtc caccagcaa atctgtacc
 301 tggccgggc tcccggttc cagcggtt ctactcctc tggcgctgg gtcgttcaa
 361 accagcggc cgtggcagc acaattcac cgtgtctc ttctcccg actcttct
 421 catctctc tcatctcc cctggatga gctggcgga gggcccgag gctggcgag
 481 ttgcagcac agcaccctc gggcctggg cagcaggac tgggacagg gtcacagc
 541 tggcggggc cctacggga ctgcggag cctgttcaa tgggagcgt uggggtaa
 601 agggctggt ggcgggga aagtaattc caaggacat ggcggcgg agtctctc
 661 cctgcactt ogctcaggt ttggaagg aagatgtt agaaccta ctacagtc
 721 gtctaatgt ccagcgtt gatgatgg gtcctccc gttcattt gctgtctt
 781 ttggcatgc tgaattgt agctgtat tggcagg agtgatca atgcccgg
 841 ataactgaa ctatacct ctgcagag ctgtattt agggagac gatgtgtca
 901 ttgtctgt gggccgga gctgacaa acattcgaa cctgctgg aatcagcc
 961 tggacctgg agatctta gaaagctc tcttaccg tgaataag aagaggaac
 1021 tctagaagc tctaggagt ggtatgag aaaaactat ggtttact actcttca
 1081 atgtgattt cctgcagt gatggcga agtcactc ttacatca gcagcggct
 1141 acaacagat tgaatgtt cagctctc ttacatag tctgtatt catgaaag
 1201 acaagggtg acttgtct ctctaatg cgtgtata tggcattt gattcacg
 1261 aactgtact aagcagga gctgtgtt atgcatga tcttggcag ttactcac
 1321 tgcagagac tcttcaa aacgtgtg agtctgct ttgttatt agcatggc
 1381 ctgtctac gtatgac tgcattgca aagtgctt ggtatggt ccaactcgg
 1441 agctaggga ggtatgct tatgattt aggtcatt ttactaca gacgcagc
 1501 aagcagctt agctaat aaaaaaac tgccttga aatcttat tcaaacac
 1561 cgcagctca tgaacgca ctgcctgt ctgtgctc tctcatcc aacgtaac
 1621 aagtcagc attgtact agaaaggc caatgtta tgaanaat aagattca
 1681 tgaatccc gctgtgca ggcgaagc ccaatatg tgcattgaa gtttgcata
 1741 agcatgggc cagatgat gacatgga ccttggca gctgtctt catagagc
 1801 cctagcag cactgag aactgggc tctgtgag ttatgtct gacctcca
 1861 tcatctct aacggctc acagcagc agatggca tgaagcgt cagcagtc
 1921 tgaatgag ttacgtct gaccccca tcatctct aacggctc acagcagc
 1981 agatggca tgaagcgt cagcagtc tgaatgca ttatgata gttatc
 2041 tactcagc ttatgtga tctgagag ggaatata gagggaat tatccagat
 2101 gttcactg tcaatgaa gattacact atcgtact ctgtgtga ttatgact
 2161 ttgaggcat cttaagtg agattgga actgtgag aacttgcg ctctcaat
 2221 gttatgta gacattga gggcggca tccacgct tacattgc agcaggct
 2281 aacagagac acctatct acttctgt ttattatg actttagc gcatctag
 2341 ctggagatt ggaactgt agcaactt gcagctca aatgtgat tgaagact
 2401 tagaggcgc gcatccag ccttacct tgcagcag ctacaacgc gttctgtg
 2461 tagatact gctacacc ggtgcgat tcatgcaa agcaagggt gcttggtc
 2521 ccttctaa tgcctgca tatggact atgagtgga tgaattta gtaaggat
 2581 ggtctctt cactgggc gattatga aattcccc tctcatga gcagcagc

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2641 aeggaagta tgaastetge aagtoctit taaacatgy agcagatcca actaaaangu
2701 acagagatgg aaatacaoot tiggaittgy taaaggaagg agcacagat atcaggact
2761 tactgaaury ggalgclgc. itgiggaig ctgccaagaa gggotgcotg ecnagagtgn
2821 agaagctctg tccccagag aatitcaoot goagagacac ccagggcaga aaticaacc
2881 otctgonoot ggcagcagge taataaoo tggangtagc tgaatctct ctagagontg
2941 gagctgatgt taatccccag gacaaaggtg gttantoc tctacaaat gggcatct
3001 atgggcagt tgaahagug gctttatga taaataosa cacgtgcta aatgaacag
3061 atagtgagg gttatccc ctuatgaag cagcccagaa aggaaggag cagctgtgog
3121 cctccctct aggcctagt gcagaccca cctgagaa coaggaggc cagacgcto
3181 tggatctggc aacagctgac gatacagag ctigctga agatgcctg cccacaggg
3241 cctaacac ctgtttaa octaggcta ctgtagtga tgcctctg atctaacag
3301 catcaccoc ctctgcctc tggotgcca gcagcataga caoctcaot ggcotliag
3361 cagagtggc cgtaggaga gctccaatg caggagatg cgcggaggga acagaaagga
3421 aggaaggaga agtgcctgt ctgacatga atctagaca attotaaa agocttygc
3481 tgaacaot tgggatac tgaanag aacagatc actagatg tggctgata
3541 tggctatga agagt/gaa gaataagca tcaatgata tgggcacgc oacaaata
3601 kaaaggagt agaaagatc taagtggac aacaggaco caatcctat tgaacttc
3661 actagttaa tcaaggagc atthctg atctgctoc agagataa gaatatcgt
3721 caglggaag agagt/gca agtacttc gagaacag agatgtgtt aatgtgoc
3781 gaocttcaa cagatacant gctatgaa tcaaaaat tgaacaag aagttaggg
3841 agogttotg ccaccagag aaggaagtgt ctgaggagaa kaonaccat cacaatgagc
3901 gcatgtgtt tcatgttct ccttata atgcaat tcaaaaggg ttigtgao
3961 gaaatgata cataggaga atgttgggg cgggatta ttigtgaa aactctoa
4021 aaagcaaaa atagttaa ggaatggag gaggaaagg utgcccaca cacaaggca
4081 ggaatgata tatgtgac agacaaatg tctctgag agtgacctt gggaaatct
4141 tctgaagt tagcaccatg aaatggccc agcgcctoc agggcaccac tgaicattg
4201 gtagacggag ctcaatgg ctgcatatg ctgaalatg catcacaga gagaacagg
4261 calaccaga gtabatc actaacaga tontgaagc agaaacctt tccagacc
4321 caacagccc agagagag acciatgaa tgcctgolg tgaaggcag atcagatc
4381 aactgggc tggattacag aggaatgti otaaacaa catcaat ctgaagtc
4441 ctgacacct agaaataagc tgttgtcti ctataagca tgcctatg g

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Secuencia 5 – Secuencia de mRNA Humano de Tankirasa 2

1 cggcgccgcct cgtctagccga aacctggcca gccgggtgcc gccactgag uacggcgagg
 61 acgacgtcac gtgogctccc gggcctggac ggaagctggca gggggggcct tgcacgttc
 121 cggcgccgcg tcgttcagg acccggaacg cggatcgcc cgtgctccg cggcgccggg
 181 cagccggggg gcaaggagcc cagcgaggga cggcgtgag cagggccatg ggaatgcgc
 241 ggatccgggt acagcaggga gccaaaggcc cggggccgt agcgcgtctt ctcgggggg
 301 cctggccctc ctgctggcg ggcggggcct cctgctccg ttgctggcg tttgctggc
 361 tgtggggggg gcaaggatca tgtgggctc ccgctggcc ggggggggag cggcctggc
 421 gaggcgccg gccgaggccg tggagccgc cggcgagag ctgttgagg cgtggcgca
 481 cgggacgtg gaacgagta agaggtcgt gacgctgag aagtgaca gccgcgaca
 541 gggggcagg aaatccccc cgtgacat cgcgcagg ttggggga aagacgtgt
 601 tgaattttg cttagaatg gtgcattgt ccaagcagt gatgatggg gccatccc
 661 tctcatat gcatctct tggctatg tgaatgag aatctctt tggacatg
 721 tgcagaccc aatgctcg ataatggaa ttactcct ctcatgag ctgcattaa
 781 aggaagatt gatgttga ttgtctgt acagatgga gctgagcaa cctccgaaa
 841 tacagatga aggaagcat tggattgag agatcattt gcaagcag tcttactgg
 901 tgaatatag aaagtgaac tctagaaag tgcaggat ggaattgag aaaaatgat
 961 ggcctactc acacattaa atgtaactg ccacgcaat gatgcagaa agtcaactc
 1021 attacattg gacgaggat aatcagagt aagattgta cagctgtac tgaacatgg
 1081 agotgatgc catgttaag ataaaggta tctggatca ttacaaatg cctgtctta
 1141 ttgtattat gaagtaactg aactttgt caagcattgt gctgtgaa atgcaatga
 1201 cttgtggaa ttactctc ttatggag agctctaa gacagggtg aagtatgt
 1261 tctctctta agtatgtg cagaccaa acgtctcat tgcacata aagtctat
 1321 agattggct ccaacacc agttaaaga aagattgca tatgattt aagccactc
 1381 gttgtgona gctgcagag aagctgat tactgcat aaaaacatc tctcttga
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212 112

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6121 accctcattt aattcttaat aaaactgttc acttgtaaaa aaaaaaaaaa aaaaaaaaaa
6181 aaaaaaaaaa

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Secuencia 6 – Secuencia de mARN Humano de VPARP

1 cgcgcgccca gccccggggg cagggaagc cttaattacg gaattacgc gagcaaggag
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5401 ~~taaaatta agggagaa gaattctt aatcaactaa caagcaataa taatatgaaa~~
5461 ~~cttaaaataa aaaaaaaana aaaaaaaana~~

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) LAT/P/76397.WOBox No. I TITLE OF INVENTION
THERAPEUTIC COMPOUNDS

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

CANCER RESEARCH TECHNOLOGY LIMITED
Sardinia House,
Sardinia Street,
London
WC2A 3NL

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

HELLEDAY, Thomas, Dr.
Erk Dahlbergsgatan 38,
S-115 32 Stockholm
Sweden

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (if this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

SWEDEN

State (that is, country) of residence:

SWEDEN

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MARK GOODWIN
WILSON GUNN SKERRETT
CHARLES HOUSE, 148/9 GREAT CHARLES STREET
BIRMINGHAM
B3 3HT
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Telephone No.

+44 121 238 1038

Facsimile No.

+44 121 233 2875

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CURTIN, Nicola, Dr
Vale View, Stirling Avenue
Rowlands Gill
Tynā and Wear
NE39 1PU
United Kingdom

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VII(f) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the State indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other parent grant or the date of filing of the parent application (Rules 4.11(a)(20) and 49bis.1(a) or (b)).
3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(c)(iv) and 49bis.1(d)).

CONTINUATION OF BOX N . IV

DOWNEY, WILLIAM GERRARD
 QUEST, BARRY
 HILL, RICHARD
 PHILLIPS, PATRICIA MARIE
 MIDDLEMIST, IAN ALASTAIR
 ROBEY, JAMES EDWARD

OF

WILSON GUNN SKERRETT
 CHARLES HOUSE,
 148/9 GREAT CHARLES STREET,
 BIRMINGHAM, B3 3HT
 UNITED KINGDOM.

Box No. V DESIGNATIONS

The filing of this request constitutes under Article 4.3(a), the designation of all Contracting States bound by the PCT as the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KE Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (or to omit) the designations concerned in order to avoid the covering of the office, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or member of WTO	regional application: regional Office	international application: receiving Office
Item (1) 25/07/2003	0317488.1	GB		
Item (2) 18/04/2004	0408524.7	GB		
Item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☒ all items ☐ Item (1) ☐ Item (2) ☐ Item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Article 4.7(b)(v)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the sup-latter copy may be used):

ISA / EPO

Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosure or exception to lack of novelty | : |

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) in paper form, the following number of sheets:

request (including declaration sheet) : 5
description (including sequence listing and/or tables related thereto) : 29
claims : 7
abstract : 1
drawings : 8

Sub-total number of sheets : 50

sequence listing : 13

tables related thereto :

(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)

Total number of sheets : 63

(b) ☐ only in computer readable form (Section 80 I(a)(ii))

(i) ☐ sequence listing

(ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 80 I(a)(ii))

(i) ☐ sequence listing

(ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the

☐ sequence listing;

☐ tables related thereto;

(Additional copies to be indicated under Item 6(b) and/or 10(i), in right column)

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☐ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ priority document(s) identified in Box No. VI as item(s):
7. ☐ translation of international application into language(s):
8. ☐ separate indications concerning deposited microorganism or other biological material
9. ☐ sequence listing in computer readable form (indicate type and number of carrier(s))
 - (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application);
 - (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter
 - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column
10. ☐ tables in computer readable form related to sequence listing (indicate type and number of carrier(s))
 - (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application)
 - (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater)
 - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column
11. ☒ other (specify): Two Patent Form 23/77 & Assignment document

Figure of the drawings which shows accompany the abstract:

Language of filing of the international application:

ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Mark to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

GOODWIN, Mark
(Authorized Representative)

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 1(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the correct copy by the International Bureau:
--

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121Form 510
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference

see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/GB2004/009183

International filing date (day/month/year)

23.07.2004

Priority date (day/month/year)

25.07.2003

International Patent Classification (IPC) or both national classification and IPC

A61K31.5517, A61P35.00, C07D487.06

Applicant

CANCER RESEARCH TECHNOLOGY LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 56.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80589 Munich
Tel. +49 89 2369-0 Tlx 52365B epon:d
Fax: +49 89 2369-4465

Authorized Officer

Härtinger, S

Telephone No. +49 89 2369-8289



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. **3:22**
PCT/GB2004/003163

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language: , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. **21/23**
PCT/GB2004/003183

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30-32

because:

☒ the said international application, or the said claims Nos. 30-32 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. **PCT/GB2004/003183**

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4
	No: Claims	1-3,5-32
Inventive step (IS)	Yes: Claims	
	No: Claims	1-32
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item III.

- 1 Claims 30-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V.

- 1 The following documents are referred to in this communication:
D1 : WO 01/16136 A (CANCER RES CAMPAIGN TECH ; AGOURON PHARMA (US)) 8 March 2001 (2001-03-08)
D2 : WO 00/42040 A (CANCER RES CAMPAIGN TECH ; CANAN KOCH STACIE S (US); WEBBER STEPHEN EV) 20 July 2000 (2000-07-20)
D3 : CANAN KOCH S S ET AL: "Novel Tricyclic Poly(ADP-ribose) Polymerase-1 Inhibitors with Potent Anticancer Chemopotentiating Activity: Design, Synthesis, and X-ray Cocystal Structure" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, 2002, pages 4961-4974, XP002304613 ISSN: 0022-2623
- 2 The invention relates basically to four independent compounds I, II, III and the phosphate of I according to claims 1-4, with each compound having first and second medical use claims and claims drawn to pharmaceutical compositions comprising the said compounds. Further claims 30-32 relate to methods of the treatment of the human or animal body.
- 2.1 The compound I is already known from example IIII disclosed on pages 97-98 of D2. This compound is said to be a PARP inhibitor, hence, the disclosure of D2 is also considered to take away the novelty of claims 5,8,11-14,17,20-21,24-25, 28-30. These claims do not meet the requirements of Art. 33(2) PCT.

The phosphate salt of compound I is not specifically disclosed in any of the cited documents. Hence, the subject-matter of claim 4 appears to be novel in the sense of Art. 33(2) PCT.

The compounds II and III are already disclosed in D1, examples 141 and 58. Since the compounds of D1 are PARP inhibitors, the subject-matter of present claims 6-7, 9-13, 15-16, 18-20, 22-24, 26-29, 31-32 is not new in the sense of Art. 33(2) PCT.

- 2.2 The present application does not meet the criteria of Art. 33(1) PCT, because the claimed subject matter does not involve an inventive step in the sense of Art. 33(3) PCT.

All of the cited documents relate to the activity of the presently claimed compounds, namely the ability to inhibit PARP. The compounds are therefore useful to treat various forms of cancer. Given the fact that all, but the present phosphate salt of compound I, are already known for this medical utility from the prior art, and taken into consideration, that phosphate salts of the present compound type are explicitly taught by D1 (page 14, line 18) and D2 (page 13, line 19), the skilled person would have expected that the present compounds in salt form are likewise useful to treat cancer. The skilled person would also base his expectation on the established structure-activity for tricyclic compounds, which bear amino groups in para position of the 2-aryl moiety (see D3). From page 4966 of D3, the skilled person was aware that the "PARP-1 binding site appears to be fairly tolerant of a variety of functional groups at each phenyl regioisomer". He was also aware of the beneficial solubilizing effect arising from the introduction of amine groups at the said para position of the phenyl ring (see D3, page 4966, left column). Hence, the provision of the present PARP inhibitors is considered to be an obvious solution to the problem of providing further anticancer agents. Since pharmaceutically acceptable salts thereof are likewise taught, of which the phosphate salt is specifically disclosed in D1 and D2, it is not apparent in how far the phosphate salt should have properties other than the beneficial solubility and medical utility already described in detail for the compounds I, II and III. The requirements of Art. 33(3) PCT are therefore not considered to be met by the present claims.

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

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PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

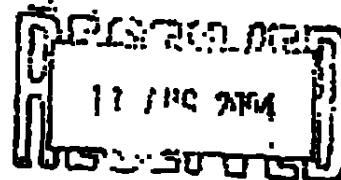
(PCT Rule 20.5(c))

Wilson Gunn Skerrett Charles House 148/9 Great Charles Street Birmingham B3 3HT		Date of mailing <i>(day/month/year)</i> 09 AUG 2004
Applicant's or agent's file reference LAT/P/76397.WO		IMPORTANT NOTIFICATION
International application No. PCT/GB2004/003183	International filing date <i>(day/month/year)</i> 23/07/2004	Priority date <i>(day/month/year)</i> 16/04/2003
Applicant Cancer Research Technology Limited et al		
Title of the invention Therapeutic Compounds		

1. The applicant is hereby notified that the international application has been recorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- ☒ was transmitted to the International Bureau on 09 AUG 2004
- ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:
- ☐ because the necessary national security clearance has not yet been obtained.
- ☐ because (reason to be specified):



* The International Bureau monitors the transmission of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office The Patent Office Cardiff Road, Newport South Wales NP10 8QQ	Authorized officer Laura Francis
Facsimile No.	Telephone No. 01633 814384

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GOODWIN, Mark
Wilson Gunn Skerrett
Charles House
148/9 Great Charles Street
Birmingham B3 3HT
United Kingdom

Date of mailing (day/month/year) 29 September 2004 (29.09.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference LAT/P/76397.WO	
International application No. PCT/GB2004/003183	International filing date (day/month/year) 23 July 2004 (23.07.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 July 2003 (25.07.2003)
Applicant CANCER RESEARCH TECHNOLOGY LIMITED et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 July 2003 (25.07.2003)	0317486.1	GB	27 Augu 2004 (27.08.2004)
16 April 2004 (16.04.2004)	0408524.7	GB	10 Sept 2004 (10.09.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.65	Authorized officer Sylvie SOBEZYNSKI Telephone No. (41-22) 336 8067
--	--

From the INTERNATIONAL BUREAU

PCT

**SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))**

(PCT Rule 47.1(c))

To:

GOODWIN, Mark
Wilson Gunn
Charles House
148/9 Great Charles Street
Birmingham B3 8HT
ROYAUME-UNI

Date of mailing (day/month/year)

01 December 2005 (01.12.2005)

Applicant's or agent's file reference

LAT/P/76397.WO

IMPORTANT NOTICE

International application No.

PCT/GB2004/003183

International filing date (day/month/year)

23 July 2004 (23.07.2004)

Priority date (day/month/year)

25 July 2003 (25.07.2003)

Applicant

CANCER RESEARCH TECHNOLOGY LIMITED et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308 (First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
10 February 2005 (10.02.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SG, SK, SL, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

RECEIVED - 7 DEC 2005

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nora Lindner

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PATENT COOPERATION TREATY

Appointment of Agent or Common Representative

The undersigned Applicants hereby appoint:-

**QUEST, BARRY
DOWNEY, WILLIAM GERRARD
GOODWIN, MARK
HILL, RICHARD
MIDDLEMIST, IAN ALASTAIR
PHILLIPS, PATRICIA MARIE
R BEY, JAMES EDWARD
JOHN BADGER
SIMON JOHN CHURCH**

of

**WILSON GUNN SKERRETT,
Charles House,
148/9 Great Charles Street,
Birmingham. B3 3HT.
England.**

Tel: 0121 236 1038
Telecopier: 0121 233 2875

As Agent to act on their behalf before the competent International Authorities in connection with the International Application concerning:- **Therapeutic Compounds**, has been indicated in the Request filed with the United Kingdom Receiving Office)

Place *London*

Date *08.09.2004*

Carola Lempke

For and on behalf of
Cancer Research Technology Ltd

in respect of designated states
other than United States of America

Name: *Carola Lempke*

Title: *Intellectual Property Manager*

Place *Sheffield*

Date *13/09/04*

Thomas Helled

HELLEDAY, Thomas, Dr.

in respect of the designation
of the United States of America

Place *Newcastle upon Tyne*

Date *08/09/04*

N. Curtin

CURTIN, Nicola, Dr.

in respect of the designation
of the United States of America



Industria y Comercio

SUPERINTENDENCIA

Superintendencia de Industria y Comercio
Radiación: 06099401 00230023
Fecha (MM): 2506-02-01 16:07:59
Trámite : 011 PCI-PATENT 206 PAGE 0001 411 PRESENTAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 132

133
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Delegatura de Propiedad Industrial División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
-Indicación de que se solicita la concesión de una patente.		☒	☐
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.		☒	☐
-Descripción de la invención.		☒	☐
-Dibujos de ser estos pertinentes.		☒	☐
-Comprobante de Pago de las tasas establecidas.		☒	☐
COMPLETA ()	INCOMPLETA ()	()	()

DISEÑO INDUSTRIAL ()

-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()

-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica del Esquema Trazado.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Fecha:

17 Feb / 06

PETITORIO

AS: 100.394

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicación: 8605401 00000000 Folios: 132
Fecha (M/D): 2005-02-03 16:07:55 /
Trámite: PCT-PATENTE 370 FASE NACI 411 PRESENTAC
Observaciones: 2020. TITULO DE INVENCIÓN (OBLIGATORIO)

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 25-01-2006

1 SOLICITUD DE:
☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: CANCER RESEARCH TECHNOLOGY LIMITED Dirección: Sardinia House, Sardinia Street, London WC2A 3NL, Reino Unido Nacionalidad o Domicilio: Reino Unido Lugar de Constitución: Reino Unido Teléfono: Fax E-mail:	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
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3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax 380-2700 E-mail:	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
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4 INVENTOR (ES) (72)	Nombre: Thomas Helleday, Nicola Curcin Dirección: Erik Dahlbergsgatan 38, S-115 32 Stockholm, SE; Vale View, Stirling Avenue, Rowlands Gill, Tyne and Wear NE39 1PU, GB (Respectivamente) Nacionalidad o Domicilio: Suecia, y Reino Unido (Respectivamente)
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5 PCT (86)
Solicitud Internacional No. PCT/GB2004/003183 Fecha 23-07-2004
Publicación Internacional No. WO 2005/012305 A2 Fecha 10-02-2005

Título (54): COMPUESTOS TERAPEUTICOS DERIVADOS DE INDOLES DE LACTAMA TRICICLICA Y BENZIMIDAZOLES DE LACTAMA TRICICLICA

7 Clasificación Internacional (51) C03D 437/00, A61K 31/55, 31/5517, A61P 35/00

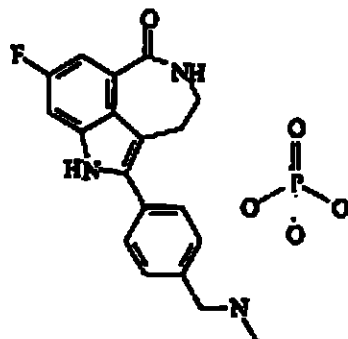
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	GB	25-07-2003	0317486.1
	GB	16-04-2004	0408524.7

9 Comprobante de pago No. 08-1.523 Fecha 31-01-2006

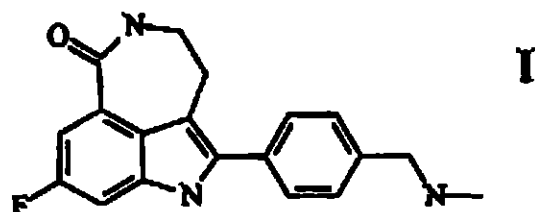
BT
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4. Un compuesto de acuerdo con la reivindicación 1, en donde el compuesto está en la forma de una sal de fosfato de la siguiente fórmula:

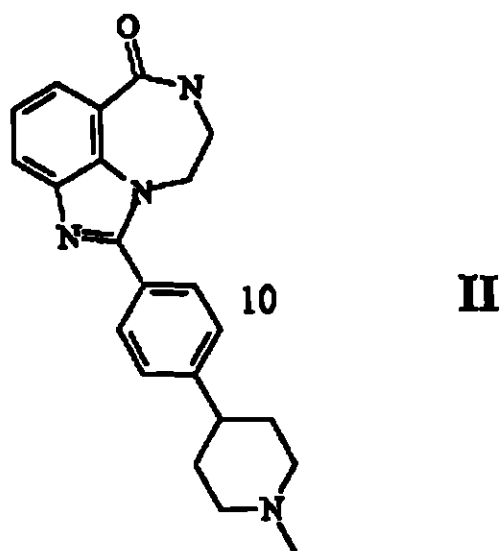
Fórmula I - Fosfato



5. El uso de una cantidad terapéutica de un compuesto de fórmula I, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento



6. El uso de una cantidad terapéutica de un compuesto de fórmula II, y sus sales farmacéuticamente aceptables, en la manufactura de un medicamento.



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REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADERNA SARMIENTO JUAN PABLO

REFERENCIA	Radicación No.	06 9401
	Solicitud internacional	GE2004/003183
	Fecha inicio fase nacional	25/02/2006
	Trámite	11
	Evento	378
	Actuación	436
	Oficio No.	3367

Como resultado del examen de forma, realizado con fundamento en el artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.
2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredite la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
3. En la documentación allegada no se evidencia la existencia y representación de la sociedad solicitante, por lo tanto debe allegar el documento que así lo acredite.

En cumplimiento de lo dispuesto por el artículo 19 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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


ALIX CARMEN CEPEDAZ DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
Fecha 24 MAR. 2006
jrnms