Description

FIELD OF THE INVENTION

This invention relates to certain porphyrins and their use in cancer treatment.

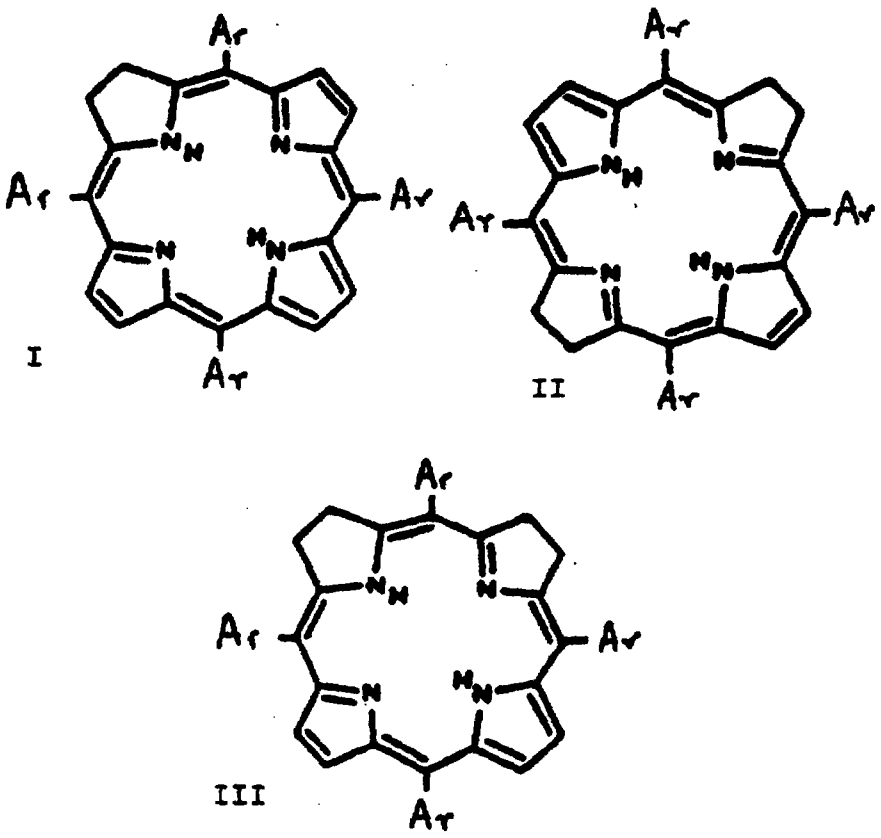
BACKGROUND

Haematoporphyrin derivatives of uncertain specific composition (HpD) have been used in cancer treatment, having been found to locate in tumours and other tissues after injection into the bloodstream, and to sensitise cells to light irradiation (transport in the blood is believed to be largely in association with the serum albumin). Irradiation, with a laser or other source, may be direct or indirect, for example using fibre optics. Irradiated cells, unless deeply pigmented, are rapidly killed to a depth depending on the light penetration. The mechanism of cell killing in phototherapy is believed to be largely by production of singlet oxygen. This is produced by transfer of energy from the light-excited porphyrin molecule to an oxygen molecule. Singlet oxygen is highly reactive. It is believed to oxidise cell membranes so that they are damaged and become incapable of exerting their function of controlling the cell's internal operation. This rapidly leads to cell death.

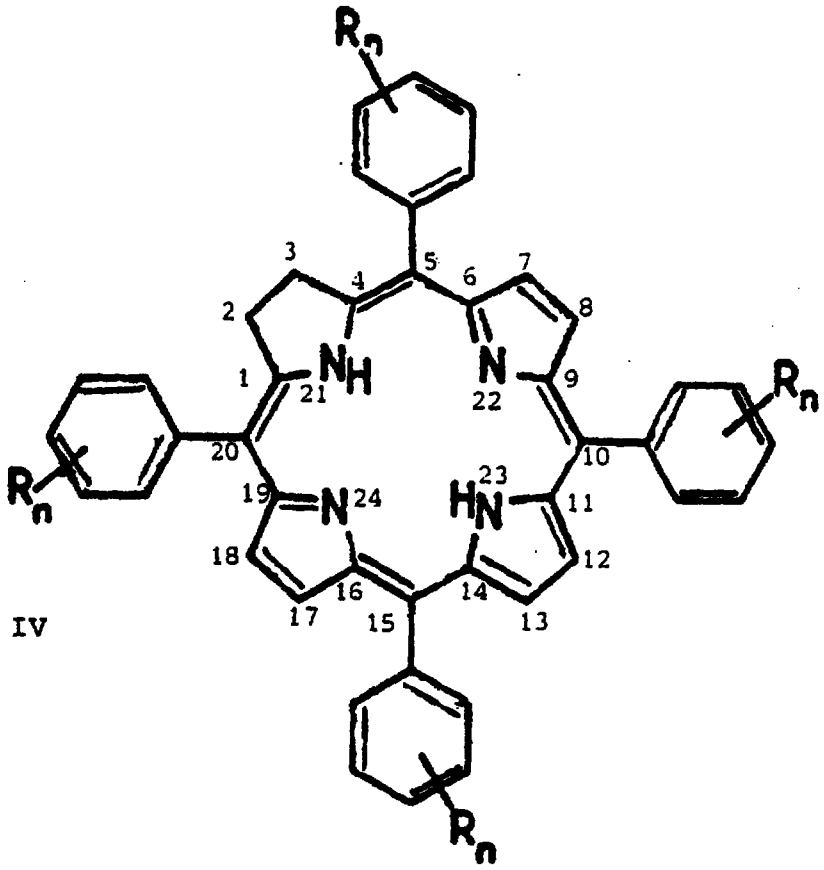
Selectivity of damage for various tissues, including tumours, is governed by a variety of factors, including selective uptake, selective vulnerability and selective ability to repair damage (cf. Albert A.A. "Selective Toxicity" fifth edition, Chapman & Hall, London 1973). In tumours an additional factor is the precarious nature of tumour blood supply and its particular vulnerability to photo-dynamic damage as compared with the robust and well-established blood supply of normal tissues. All the above factors vary from one tissue to another and from one compound to another, so that the pattern of tumour and normal tissue damage may be expected to vary.

In EP-A-0,186,962, the present applicants made proposals to improve on HpD by finding well characterised and thus more exactly controllable compounds. Other aims were to find compounds activated by light at wavelengths longer than those used to activate HpD so as to exploit deeper penetration of longer wavelength radiation, and to increase effectiveness generally, as in many anatomical sites, such as the brain, HpD has been found to sensitise normal cells unduly as well as cancerous cells. The wavelength at which a photo-sensitising compound is activated is one factor in its in vivo effectiveness. Other things being equal, the longer the activating wavelength within the visible range, the greater the tissue penetration of light and therefore the greater the depth of damage. Thus, compounds activated at 650-660nm might be expected to produce greater depths of damage than HpD, which is activated at 625-630nm. Successful photo-therapy depends on the ability to produce severe tumour damage without unacceptable damage to contiguous normal tissues. The compounds used according to EP-A-0,186,962 are porphyrins tetra-meso-substituted by aromatic groups bearing hydroxy, amino or sulphydryl groups, some new as compounds others old.

The present invention also concerns medicaments for therapy of tumours susceptible to necrosis when an appropriate compound is administered to locate in the tumour followed by illumination of the tumour with light of a wavelength absorbed by the compound, but the compounds are now and the invention therefore lies primarily in them. They are dihydro porphyrins (chlorins) I, and corresponding tetra-hydro porphyrins II and III, of the formulae:



wherein each Ar, the same or different, is an aromatic group with one or more hydroxy (-OH) substituent groups. For example, and showing the ring numbering, the dihydro porphyrins (and the tetra-hydro porphyrins correspondingly) may be:-



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wherein each R (one or more in each ring n = 1 to 3) is an ortho, meta or para positioned hydroxy substituent group, particularly to give polyhydroxyphenyl compounds. Said substituent groups may be in the same or different positions on their respective aromatic groups. Any said substituent group may be free or itself substituted by alkyl or acyl groups preferably C_1 to C_4 and the compounds when in such form are within the claims herein.

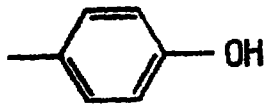
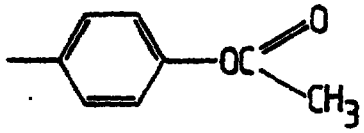
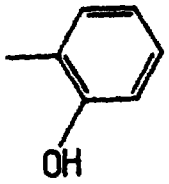
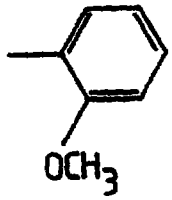
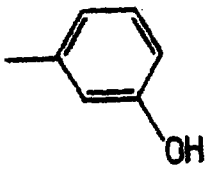
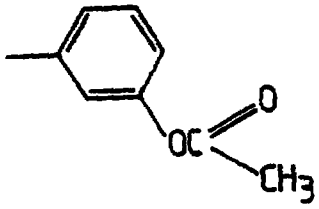
Any of the compounds further may be in the form of derivatives such as salts at acidic or basic centres, metal complexes (e.g. Zn, Ga), or hydrates or other solvates particularly with lower, e.g. C_1 - C_4 aliphatic alcohols and again such derivatives are within the claims.

It is preferred that one or more of the said substituent groups should be of a kind and in a form able to ionise at physiological pH, to increase the absorption in the red part of the spectrum, that is in the portion that most effectively penetrates tissue. Compounds not very soluble in themselves may be solubilised by the presence of suitable groups such as sulphonate groups.

The invention further extends to the medicaments, to their preparation and to the method of therapy itself.

Various specific compounds within the claims are given in Table 1 below:-

TABLE 1

NUMBER	NATURE OF "Ar" IN FORMULA I or II	CODE NAME (DIHYDRO or TETRA-HYDRO FORM OF)
1		HK7
2		acetyl HK7
3		ortho-HK7
4		ortho-HK7 methyl ether
5		meta-HK7
6		acetyl meta-HK7

The invention is illustrated in the following Examples, in which the compounds are made by the reduction of the corresponding porphyrins, without protection of the latter. The general method of reduction is not new (Whitlock et al., J. Amer. Chem. Soc., 1969, 91, 7485) but the products are new. It is unexpected that they can be obtained without prior protection of phenolic hydroxy functions, especially when an oxidative step is

required in the work up.When required, a chloranil dehydrogenation step is included to oxidise tetra-hydro porphyrins formed back to the dihydro form.

EXAMPLE 1

Synthesis of 2,3-dihydro-5,10,15,20-tetra(p-hydroxyphenyl) porphyrin ("Dihydro HK7")

5,10,15,20-Tetra(p-hydroxyphenyl)porphyrin (163mg, 0.24 mmoles), p-toluenesulphonhydrazide (90mg, 0.48 mmoles), anhydrous potassium carbonate (300mg) and anhydrous pyridine (11.25 ml) were stirred with nitrogen flushing for 20 minutes. The mixture was heated (100-105°C) for 6.5 hours under nitrogen: further quantities of p-toluenesulphonhydrazide (97mg in 0.3 ml anhydrous pyridine on each occasion) were added after 2 hours and 4 hours. The reaction mixture was treated with ethyl acetate (75 ml) and distilled water (37.5 ml) and digested on a steam bath for 1 hour. The organic layer was separated and washed in turn with hydrochloric acid (2M, 75 ml), distilled water (75 ml) and saturated sodium bicarbonate solution (75 ml).

o-Chloranil (total 166mg, 0.675 mmoles) was added in portions to the stirred organic solution at room temperature until the absorption peak at 735 nm had disappeared.

The mixture was washed with aqueous sodium bisulphite (5%, 2 x 75 ml), distilled water (75 ml), sodium hydroxide (0.01M, 100 ml) and saturated sodium bicarbonate (80 ml) and dried over anhydrous sodium sulphate. The filtered solution was evaporated to dryness and the residue was crystallised from methanol-distilled water to give 77 mg (middle cut, 47%) of 2,3-dihydro-5,10,15,20-tetra(p-hydroxyphenyl)porphyrin as a purple solid. Mass spectrum (FAB) Found $(M+H)^+$ 681.253 $C_{44}H_{32}N_4O_4$ requires M + 1 = 681.250. Nmr spectrum in accord with structure. Electronic spectrum λ_{max} (MeOH) (ε) 285 (17000), 295 (16900), 418 (143000), 520 (10000), 550 (9000), 597 (5100), and 651 (18600). R_f 0.49 on Merck silica gel irrigated with MeOH:$CHCl_3$ (1:4).

EXAMPLE 2

Synthesis of 2,3-dihydro-5,10,15,20-tetra(m-hydroxyphenyl) porphyrin ("Dihydro meta-HK7")

The method was as described above starting with the following reagents: 5,10,15,20-tetra(m-hydroxyphenyl) porphyrin (160mg, 0.23 mmoles), p-toluenesulphonhydrazide (90mg, 0.48 mmoles), anhydrous potassium carbonate (303mg), anhydrous pyridine (11.25 ml), and o-chloranil (106mg, 0.43 mmoles).

The middle cut from the crystallisation from methanol-distilled water gave 59mg (37%) of 2,3-dihydro-5,10,15,20-tetra(m-hydroxyphenyl)porphyrin as a purple solid. Mass spectrum (FAB) $(M+H)^+$ 681. $C_{44}H_{32}N_4O_4$ requires M 680. Electronic spectrum λ_{max} (MeOH) (ε) 284 (16900), 306 (15600), 415 (146000), 516 (11000) 543 (7300), 591 (4400), and 650 (22400). R_f 0.52 on Merck silica gel irrigated with MeOH:$CHCl_3$ (1:4).

EXAMPLE 3

Synthesis of 2,3-dihydro-5,10,15,20-tetra (o-hydroxyphenyl) porphyrin ("Dihydro ortho-HK7").

The method was as described above starting with the following reagents: 5,10,15,20-tetra (o-hydroxyphenyl) porphyrin (163 mg, 0.24 m moles), anhydrous potassium carbonate (303 mg), anhydrous pyridine (11.25 ml), and o-chloranil (132 mg, 0.54 m moles).

Crystallisation from methanol-distilled water gave 105 mg (64%) of 2,3-dihydro-5,10,15,20 -tetra(o-hydroxyphenyl) porphyrin as a dark purple crystalline solid. It was a mixture of atropisomers (Rf 0.23, 0.29, 0.38 and 0.43 on silica gel irrigated with 1% MeOH in $CHCl_3$. Mass spectrum (FAB) $(M+H)^+$ 681. $C_{44}H_{32}N_4O_4$ requires M 680. Electronic spectrum λ_{max} (MeOH) (ε) 415 (90700), 515 (8400), 542 (5600), 597 (3800), and 651 (16000).

EXAMPLE 4

Synthesis of 7,8,17,18-tetrahydro-5,10,15,20-tetra(m-hydroxyphenyl) porphyrin

5,10,15,20-tetra(m-hydroxyphenyl)porphyrin (109 mg, 0.16 mmoles), p-toluenesulphonylhydrazide (60 mg), anhydrous potassium carbonate (200 mg) and anhydrous pyridine (7.5 ml) were stirred with nitrogen flushing for 20 min. The mixture was heated (100°-105°C) for a total of 12 hours under nitrogen, further quantities of p-toluenesulphonylhydrazide being added every 1.5 hour (60 mg in 0.2 ml pyridine on each occasion). The reaction mixture was treated with ethyl acetate (100 ml) and water 50 ml) and digested on a steam bath for 1

hour. The organic layer was separated, and washed with hydrochloric acid (2M, 50 ml), and then with phosphoric acid (56%, 4 x 50 ml, to remove chlorin). The organic layer was washed in turn with distilled water (50 ml), sodium bicarbonate (50 ml), distilled water (50 ml), hydrochloric acid (2M, 50ml), and distilled water (50 ml), and dried over anhydrous potassium carbonate. After filtration and removal of solvent the residue was crystallised from methanol-water to give the title compound as a green solid (29 mg, 27%). R_f 0.47 on silica gel irrigated with MeOH-$CHCl_3$ (1:4).

λ(MeOH, nm) (ε) 352 (92,000), 361 (114,000), 372 (129,000), 516 (50,000) and 735 (91,000).

δ (d_6-DMSO) (250 MHz):- 9.69 (s, 3.8H, OH); 7.95 (s, 4.OH, β-pyrrole H), 7.47 (t, 5.2H, ArH); 7.21 (d, 4.2H, ArH); 7.18 (s, 4.2H, ArH; 7.04 (d, 4.OH, ArH); 3.95 (s, 7.5H, CH_2); and -1.54 (s, 2.0H, NH).

The activity of the compounds has been demonstrated in tests given in Table 2 below, the dihydro compounds being referred to as chlorins and the tetra-hydro compounds as bacteriochlorins.

TABLE 2

Tumour photo-necrosis with chlorins (C) and a bacteriochlorin (BC) of the meso-tetra(hydroxyphenyl) (THP) series.

Photosensitiser	Dose μM/Kg	Wavelength* (nm)	Depth of Tumour Necrosis mm ± SE**
p-THPC	6.25	653	3.50 ± 0.54 (10)
	3.125	653	2.13 ± 0.50 (10)
m-THPC	0.75	652	5.41 ± 0.39 (19)
	0.375	652	3.79 ± 0.28 (6)
o-THPC	6.25	652	4.16 ± 0.27 (14)
	3.125	652	3.69 ± 0.74 (9)
m-THPBC	0.39	741	5.22 ± 1.21 (8)

* The total energy administered was 10 J cm^{-2} throughout.

** Number of tumours in parenthesis.

The method of testing is that the PC6 plasma cell tumour, obtained initially from the Chester Beatty Research Institute, was grown by inoculating 0.3 - 0.6 x 10^6 cells subcutaneously in female BALB/c mice. It was used about two weeks later, when it was 12 - 13 mm in its longest diameter and 6 - 7 mm deep. Sensitisers were injected in dimethyl sulphoxide intra-peritoneally (2.5 ul g^{-1}) and, twenty four hours later, skin over the tumours was depilated, the mice anaesthetised and tumours exposed to 10 J cm^{-2} light. Wavelengths for illumination were the longest wavelength absorption peaks in the red in solutions of sensitiser in fetal calf serum, and were 652 - 653 nm for the compounds of Examples 1 to 3 and 741 nm for the compound of Example 4. The light source was a copper vapour laser with an output of 10 to 12 watts (Cu 10 laser, Oxford Lasers Ltd) pumping a D2 10K dye laser (Oxford Lasers Ltd). The dye was rhodamine 640 (Applied Photophysics Ltd) for illumination at 652 - 653 nm and LDS-722 for illumination at 741 nm. Light intensity at the tumour surface was kept below 0.3 W cm^{-2}, where thermal effects were undetectable.

Twenty four hours after illumination at 652 - 653 nm and LDS 722 for illumination at 741 nm, 0.2 ml 1% Evans blue (Sigma) in saline was given intravenously and tumours were removed one hour later and fixed in formol-saline. The fixed tumours were sliced at right angles to the surface and the depth of necrosis measured with a dissecting microscope fitted with an eye piece graticule.

In preliminary tests the new compounds have shown similar results as regards skin sensitivity to those given in EP-A-0,186,962. Moreover, the para and meta dihydroxy compounds have been shown specifically, improved properties in other respects which may be expected in all the compounds. The results of a number of experiments are given in Tables 3 and 4 below.

TABLE 3

DEGREE OF TUMOUR NECROSIS OBTAINED AT AN EQUIVALENT MUSCLE DAMAGE LEVEL

Muscle Oedema (% increase in muscle weight)	Tumour Necrosis (mm)	
	Corresponding Compounds of EP-A-0186962	Compounds of Examples 1 and 2 above
	Para	Para
10%	2.25	3.5
20%	3.0	4.0 approx.
	Meta	Meta
10%	3.5	5.5-6
20%	4.0	6.5

TABLE 4

COST IN TERMS OF MUSCLE DAMAGE FOR SPECIFIED DEPTHS OF TUMOUR NECROSIS

Depth of Tumour Necrosis (mm)	Muscle Oedema (% Increase in Weight)	
	Corresponding Compounds of EP-A-0186962	Compounds of Examples 1 and 2 above
	Para	Para
3.0	20	8
3.5	22	10
	Meta	Meta
3.5	10	2
4.0	20	3
5.0	36	5
5.5	49	7

CONCLUSION

Tables 3 and 4 show that, for specified levels of muscle damage, the compounds of Examples 1 and 2 produce more tumour necrosis than the corresponding compounds of EP-A-0,186,962 and, for specified levels

of tumour necrosis, cause considerably less muscle damage than the corresponding compounds of EP-A-0,186,962.

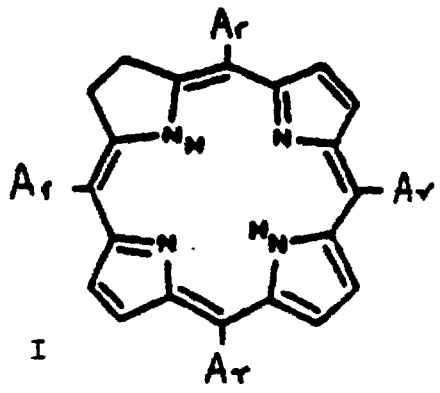
This type of selectivity is particularly important in the photo-therapy of tumours in anatomical sites where muscle is a major constituent, e.g., in cancer of the head and neck, and in cancer of the large intestine and rectum with possible involvement of abdominal wall or pelvis.

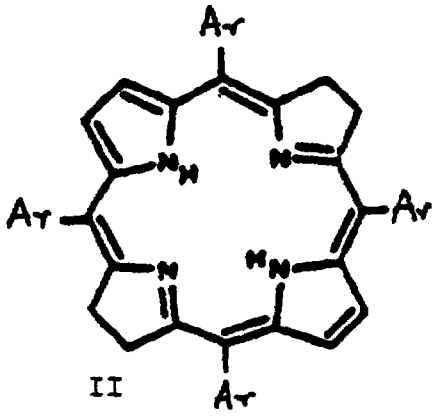
In administration the compounds, as with known tumour sensitisers, will be given intravenously in a blood compatible preparation. Conveniently an aqueous solution is used but if water solubility is limited, a solution in an organic, non-toxic polar solvent such as ethanol or a mixture of such solvents may for example be prepared. A further route to water solubility in the sense of transport in the aqueous environment of the bloodstream is the preparation of liposomes to be administered in aqueous media. Therapy according to the invention is thus administered in suitable form in an amount determined by the general toxicity of the particular compound and its level of necrotic effect, allowing tumour location to take place, and illuminating with light of a wavelength reaching the tumour and exciting the compound, at a dose effecting tumour necrosis without unacceptably damaging normal tissue. All this is in per se known manner, not requiring detailed discussion on its optimisation.

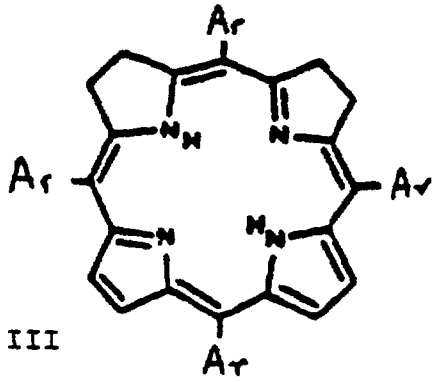
Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Compounds being pharmacologically acceptable tumour locating dihydro or tetra-hydro porphyrins of the formulae:-







wherein each Ar, the same or different, is an aromatic group with one or more hydroxy (-OH) substituent groups each itself free or substituted with an alkyl or acyl group, and salts, metal complexes or hydrates or other solvates thereof

2. Compounds according to claim 1. of the formula:-

of tumour necrosis, cause considerably less muscle damage than the corresponding compounds of EP-A-0,186,962.

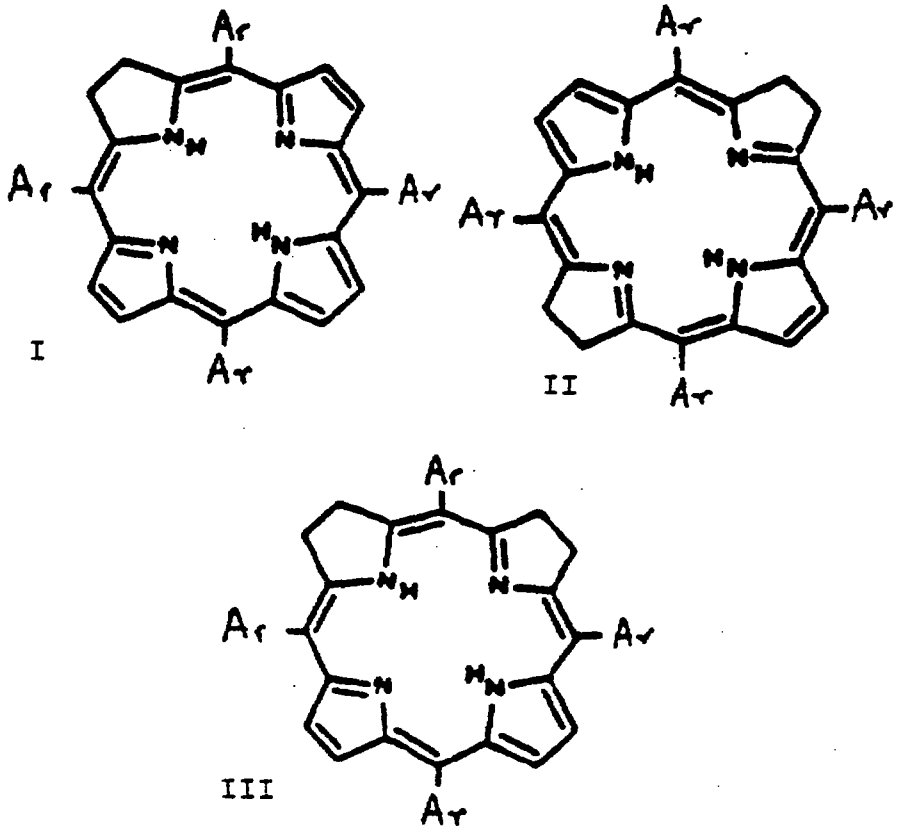
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In administration the compounds, as with known tumour sensitisers, will be given intravenously in a blood compatible preparation. Conveniently an aqueous solution is used but if water solubility is limited, a solution in an organic, non-toxic polar solvent such as ethanol or a mixture of such solvents may for example be prepared. A further route to water solubility in the sense of transport in the aqueous environment of the bloodstream is the preparation of liposomes to be administered in aqueous media. Therapy according to the invention is thus administered in suitable form in an amount determined by the general toxicity of the particular compound and its level of necrotic effect, allowing tumour location to take place, and illuminating with light of a wavelength reaching the tumour and exciting the compound, at a dose effecting tumour necrosis without unacceptably damaging normal tissue. All this is in per se known manner, not requiring detailed discussion on its optimisation.

Claims

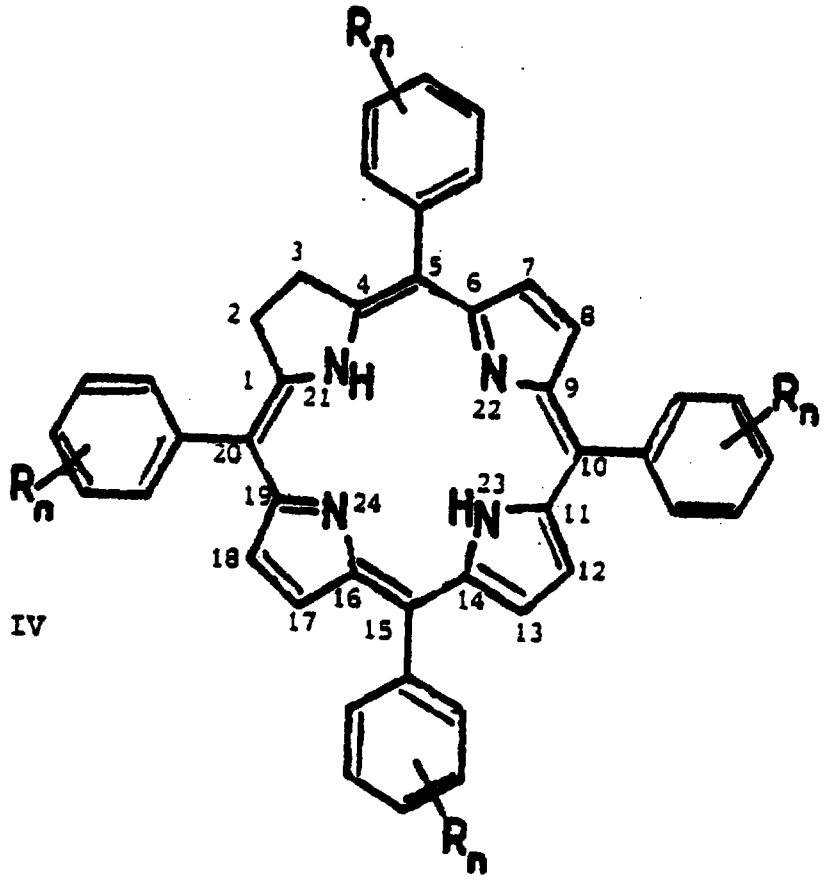
Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Compounds being pharmacologically acceptable tumour locating dihydro or tetra-hydro porphyrins of the formulae:-



wherein each Ar, the same or different, is an aromatic group with one or more hydroxy (-OH) substituent groups each itself free or substituted with an alkyl or acyl group, and salts, metal complexes or hydrates or other solvates thereof

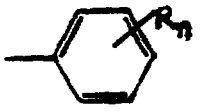
2. Compounds according to claim 1, of the formula:-



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or the corresponding tetra-hydro porphyrins, where each n = 1 to 3 and each substituent R, which may be the same or different, is at the same or different position in its respective substituent phenyl ring, is a hydroxy group itself free or substituted.

3. Compounds according to claim 2 where each substituent



is an o-hydroxyphenyl, m-hydroxyphenyl or p-hydroxyphenyl group.

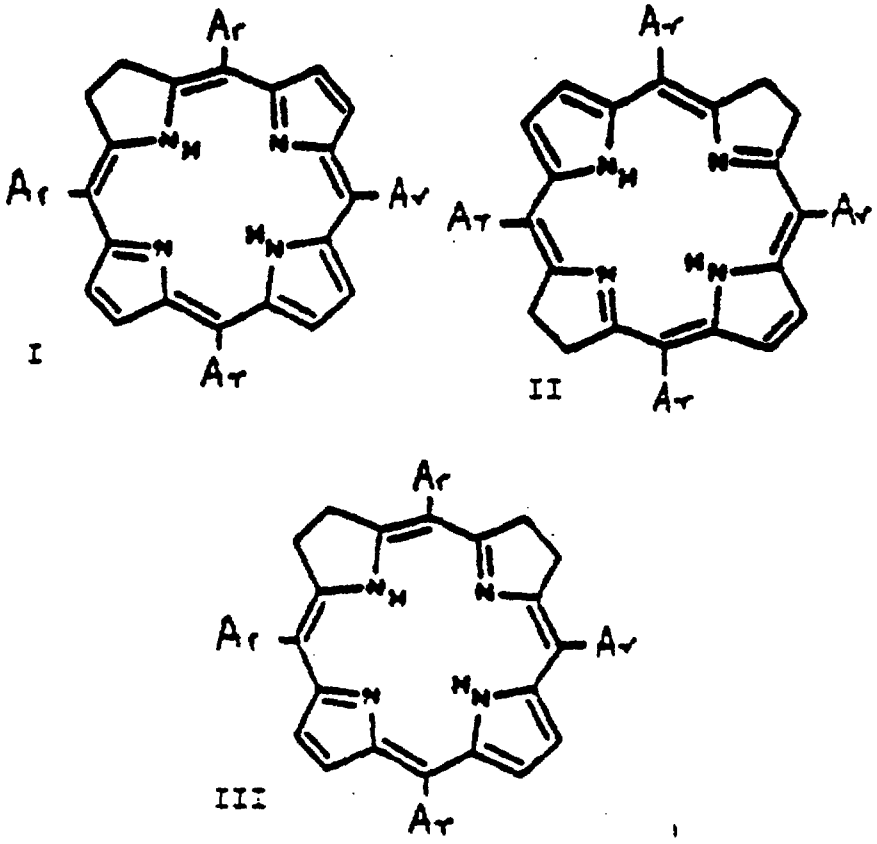
4. Compounds according to claim 1, 2 or 3 wherein each hydroxy group is free rather than in a substituted form.

5. The compound of claims 1, 2, 3 or 4 being 2,3-dihydro-5,10,15,20-tetra(p-hydroxy-phenyl) porphyrin; 2,3-dihydro-5,10,15,20-tetra(m-hydroxy-phenyl) porphyrin; 2,3-dihydro-5,10,15,20-tetra (o-hydroxyphenyl) porphyrin; or 7,8,17,18-tetrahydro-5,10,15,20-tetra(m-hydroxyphenyl) porphyrin.

6. The use of a compound according to any one of claims 1 to 5 in association with a pharmaceutical diluent or carrier, in the preparation of a medicament of use in the therapy of tumours by irradiation.

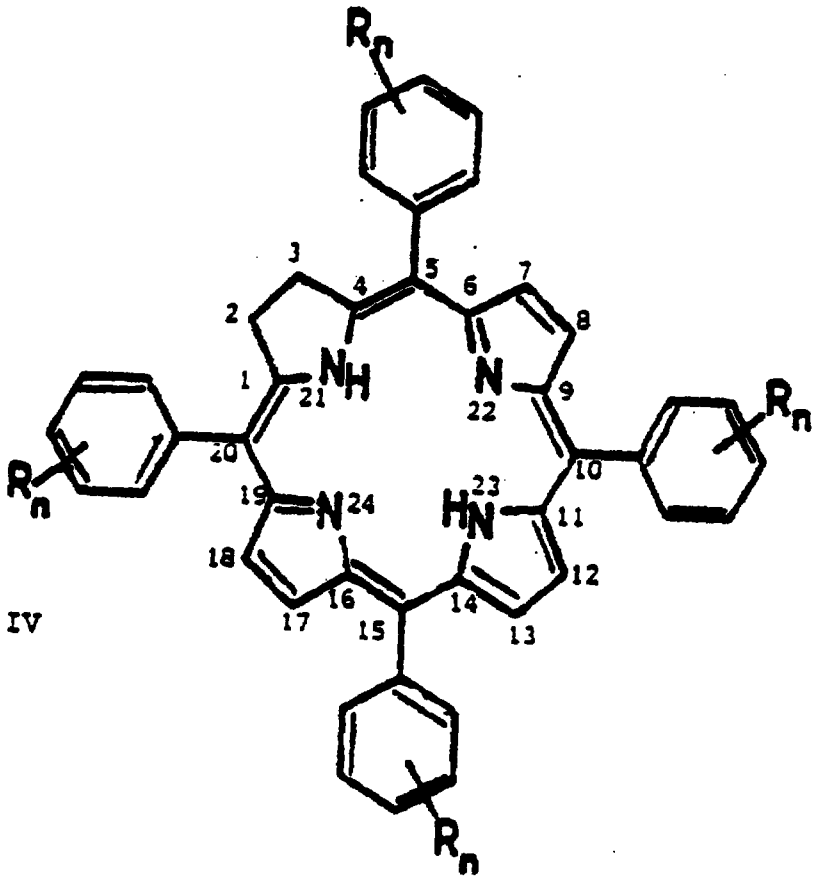
Claims for the following Contracting State : ES

1. Process for the preparation of compounds being pharmacologically acceptable tumor locating dihydro or tetra-hydro porphyrins of the formulae:-



wherein each Ar, the same or different, is an aromatic group with one or more hydroxy (-OH) substituent groups each itself free or substituted with an alkyl or acyl group, and salts, metal complexes or hydrates or other solvates thereof, by reduction of the corresponding porphyrins.

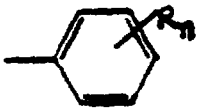
2. Process according to claim 1, wherein the compounds are of the formula:-



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or the corresponding tetra-hydro porphyrins, where each n = 1 to 3 and each substituent R, which may be the same or different, is at the same or different position in its respective substituent phenyl ring, is a hydroxy group itself free or substituted.

3. Process according to claim 2 where each substituent



is an o-hydroxyphenyl, m-hydroxyphenyl or p-hydroxyphenyl group.

4. Process according to claim 1, 2 or 3 wherein each hydroxy group is free rather than in a substituted form.

5. The process of claims 1, 2, 3 or 4 being 2,3-dihydro-5, 10, 15,20-tetra (p-hydroxy-phenyl) porphyrin; 2,3-dihydro-5,10,15,20-tetra(m-hydroxy-phenyl) porphyrin; 2,3-dihydro-5,10,15,20-tetra(o-hydroxy-phenyl); or 7,8, 17, 18-tetrahydro-5, 10, 15,20-tetra(m-hydroxyphenyl) porphyrin.

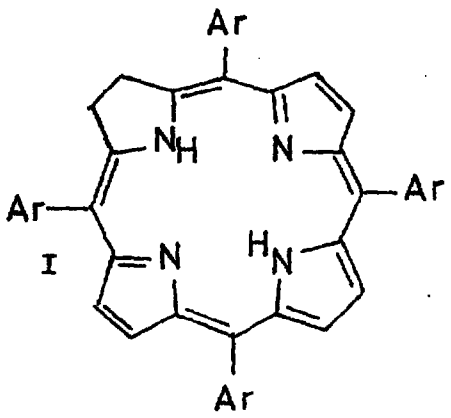
6. The use of a compound according to any one of claims 1 to 5 in association with a pharmaceutical diluent or carrier, in the preparation of a medicament of use in the therapy of tumours by irradiation.

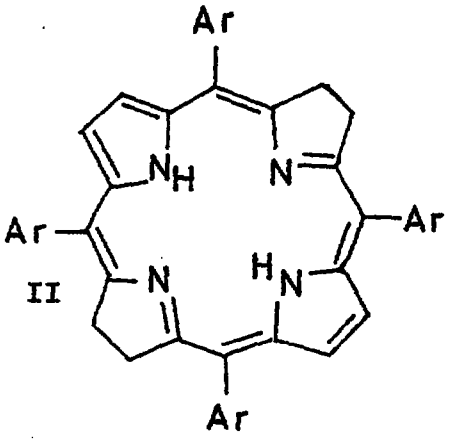
Patentansprüche

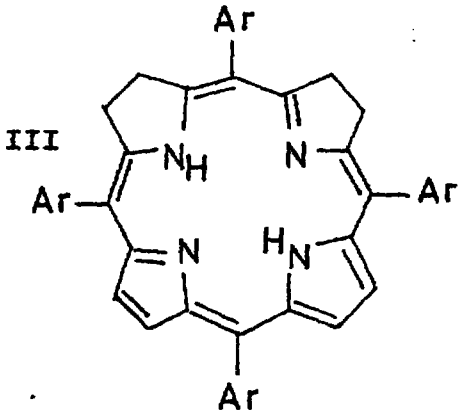
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindungen, die pharmakologisch akzeptable Dihydro- oder Tetrahydroporphyrine zur Lokalisierung

von Tumoren sind, mit den Formeln:

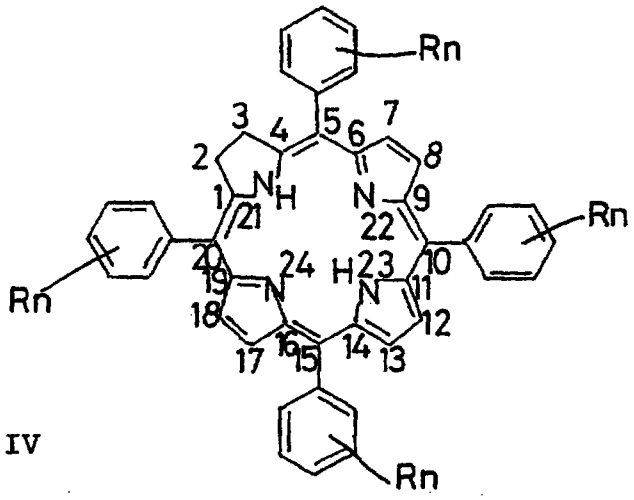






wobei jedes gleiche oder unterschiedliche Ar eine aromatische Gruppe mit einer oder mehr Hydroxy- (OH-) Substituentengruppen ist, von welchen jede selbst ungebunden oder mit einem Alkyl oder einer Azylgruppe und Salzen, Metallkomplexen oder Hydraten oder anderen Solvaten von diesen substituiert ist.

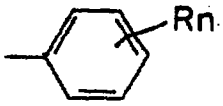
2. Verbindungen gemäß Anspruch 1, der Formel:



IV

oder die entsprechenden Tetrahydroporphyrine, wobei jede n = 1 bis 3 und jeder Substituent R, gleich oder unterschiedlich sein kann, an der gleichen oder unterschiedlichen Position in seinem jeweiligen Substituentenphenylring ist, eine Hydroxygruppe ist, die selbst ungebunden oder substituiert ist.

3. Verbindungen gemäß Anspruch 2, wobei jeder Substituent



eine o-Hydroxyphenyl, m-Hydroxyphenyl oder p-Hydroxyphenylgruppe ist.

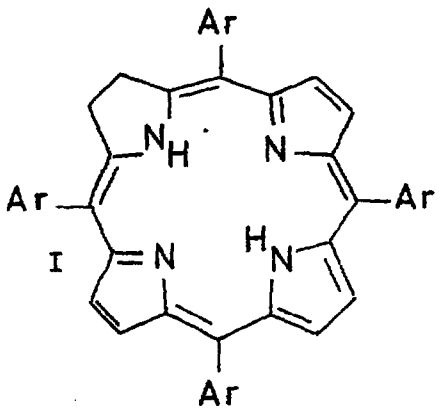
4. Verbindungen gemäß Anspruch 1, 2 oder 3, wobei jede Hydroxygruppe ungebunden und nicht in substituierter Form ist.

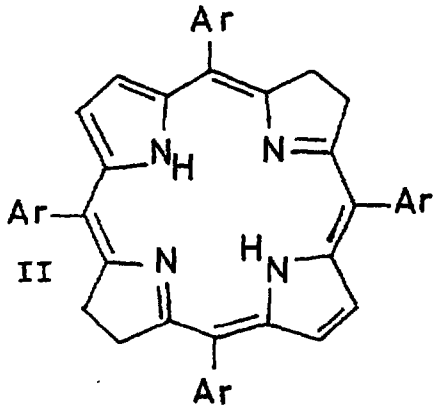
5. Die Verbindung aus Anspruch 1, 2, 3 oder 4, wobei 2,3-Dihydro-5,10,15,20-tetra(p-hydroxyphenyl)porphyrin; 2,3-Dihydro-5,10,15,20-tetra(m-hydroxyphenyl)porphyrin; 2,3-Dihydro-5,10,15,20-tetra(o-hydroxyphenyl)porphyrin oder 7,8,17,18-Tetrahydro-5,10,15,20-tetra (m-hydroxyphenyl)porphyrin ist.

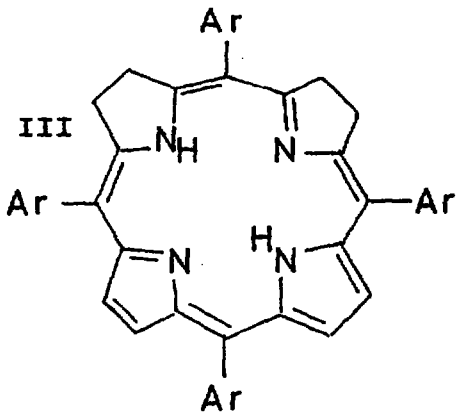
6. Die Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 5 zusammen mit einem pharmazeutischen Verdünner oder Träger bei der Präparation eines Medikamentes zur Verwendung bei der Therapie von Tumoren durch Bestrahlung.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Präparation von pharmakologisch akzeptablen Verbindungen, die Dihydro- oder Tetra-Hydroporphyrine zur Lokalisierung von Tumoren sind, mit der Formel:

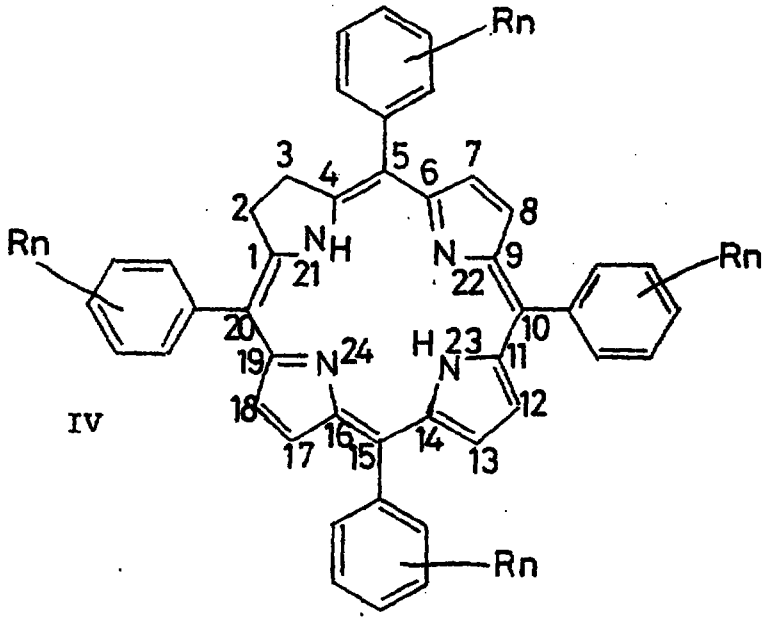






wobei jedes gleiche oder unterschiedliche Ar eine aromatische Gruppe mit einer oder mehr Hydroxy- (OH-) Substituentengruppen ist, von welchen jede selbst ungebunden oder mit einem Alkyl oder einer Azylgruppe und Salzen, Metallkomplexen oder Hydraten oder anderen Solvaten von diesen substituiert ist, durch Reduzierung der entsprechenden Porphyrine.

2. Verfahren gemäß Anspruch 1, wobei die Verbindungen folgende Formel haben:

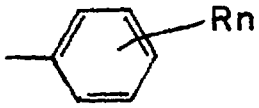


IV

IV

oder die entsprechenden Tetrahydroporphyrine, wobei jede n = 1 bis 3 und jeder Substituent R, gleich oder unterschiedlich sein kann, an der gleichen oder unterschiedlichen Position in seinem jeweiligen Substituentenphenylring ist, eine Hydroxygruppe ist, die selbst ungebunden oder substituiert ist.

3. Verfahren gemäß Anspruch 2, wobei jeder Substituent



eine o-Hydroxyphenyl, m-Hydroxphenyl oder p-Hydroxyphenylgruppe ist.

4. Verfahren gemäß Anspruch 1, 2 oder 3, wobei jede Hydroxygruppe ungebunden und nicht in substituierter Form ist.

5. Das Verfahren aus Anspruch 1, 2, 3 oder 4, wobei 2,3-Dihydro-5,10,15,20-tetra(p-hydroxyphenyl)porphyrin; 2,3-Dihydro-5,10,15,20-tetra(m-hydroxyphenyl)porphyrin; 2,3-Dihydro-5,10,15,20-tetra(o-hydroxyphenyl)porphyrin oder 7,8,17,18-Tetrahydro-5,10,15,20-tetra (m-hydroxyphenyl)porphyrin ist.

6. Die Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 5 zusammen mit einem pharmazeutischen Verdünner oder Träger bei der Präparation eines Medikamentes zur Verwendung bei der Therapie von Tumoren durch Bestrahlung.

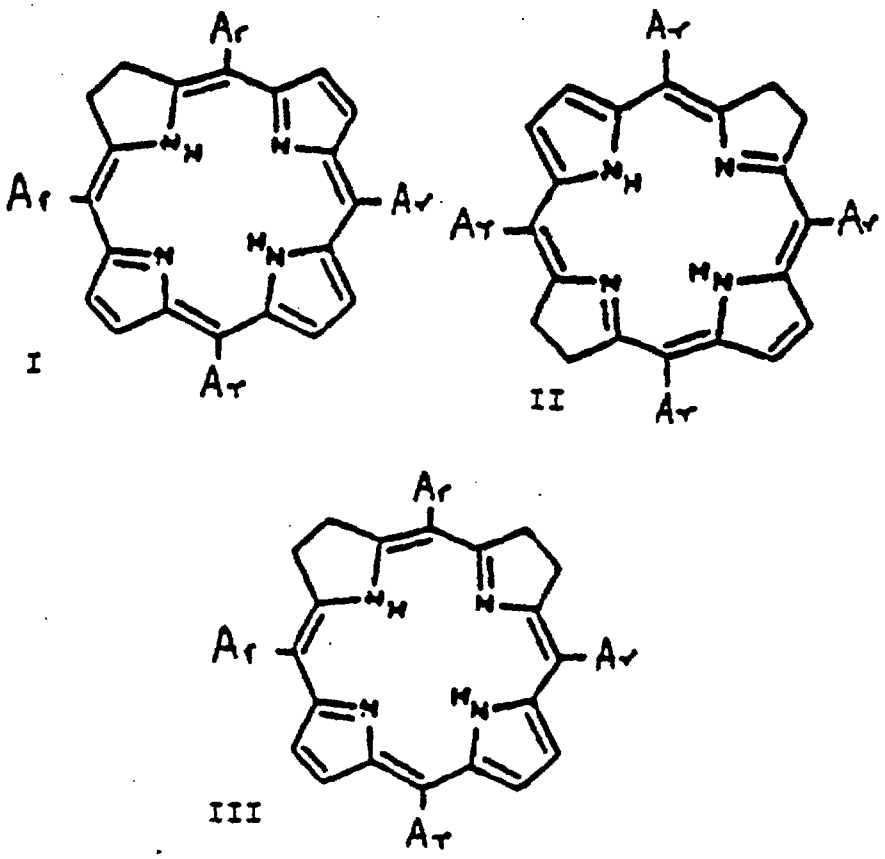
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Composés qui sont des dihydro ou tétra-hydro prophyrines, pharmacologiquement acceptables, permet-

* C L M S *

tant de localiser une tumeur, représentées par les formules :



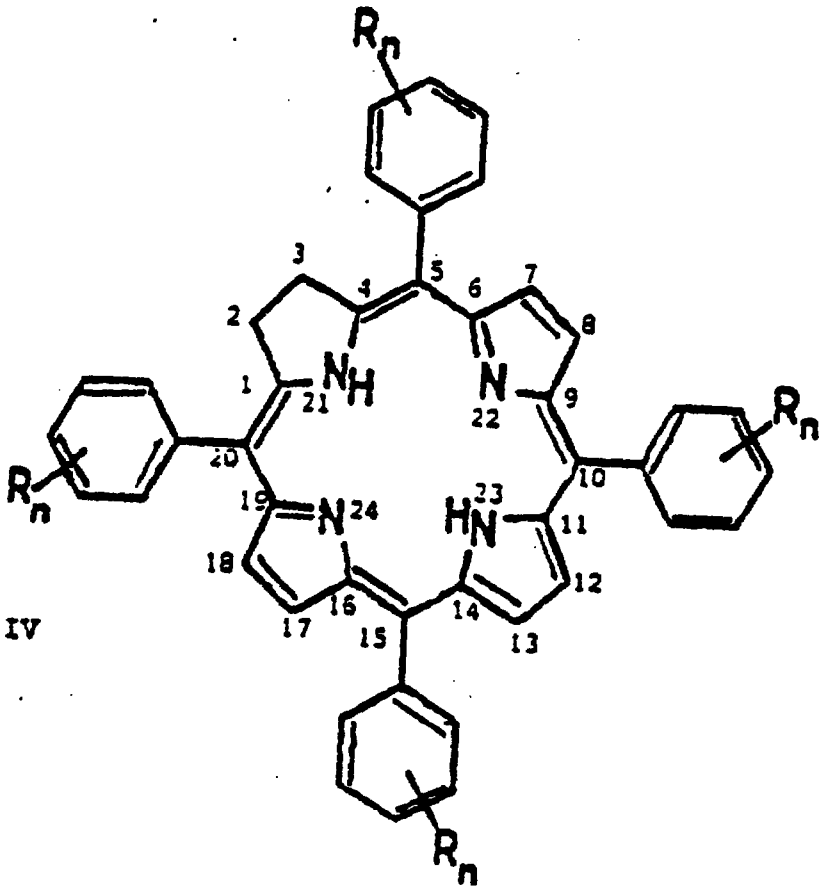
I

II

III

dans lesquelles les Ar, identiques ou différents, représentent chacun un groupe aromatique ayant un ou plusieurs groupes substituants hydroxy (-OH), chacun étant lui-même libre ou substitué par un groupe alkyle ou acyle, et les sels, complexes avec un métal ou hydrates ou autres solvates de ces composés.

2. Composés selon la revendication 1, représentés par la formule :

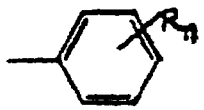


IV

ou les téta-hydro phorphyrines correspondantes, dans laquelle :

- chaque n = 1 à 3 ; et
- les substituants R, qui peuvent être identiques ou différents, se situent chacun dans une position identique ou différente sur leur noyau phényle substituant respectif, et représentent chacun un groupe hydroxy lui-même libre ou substitué.

3. Composés selon la revendication 2, dans lesquels chaque substituant



représente un groupe o-hydroxyphényle, m-hydroxyphényle ou p-hydroxyphényle.

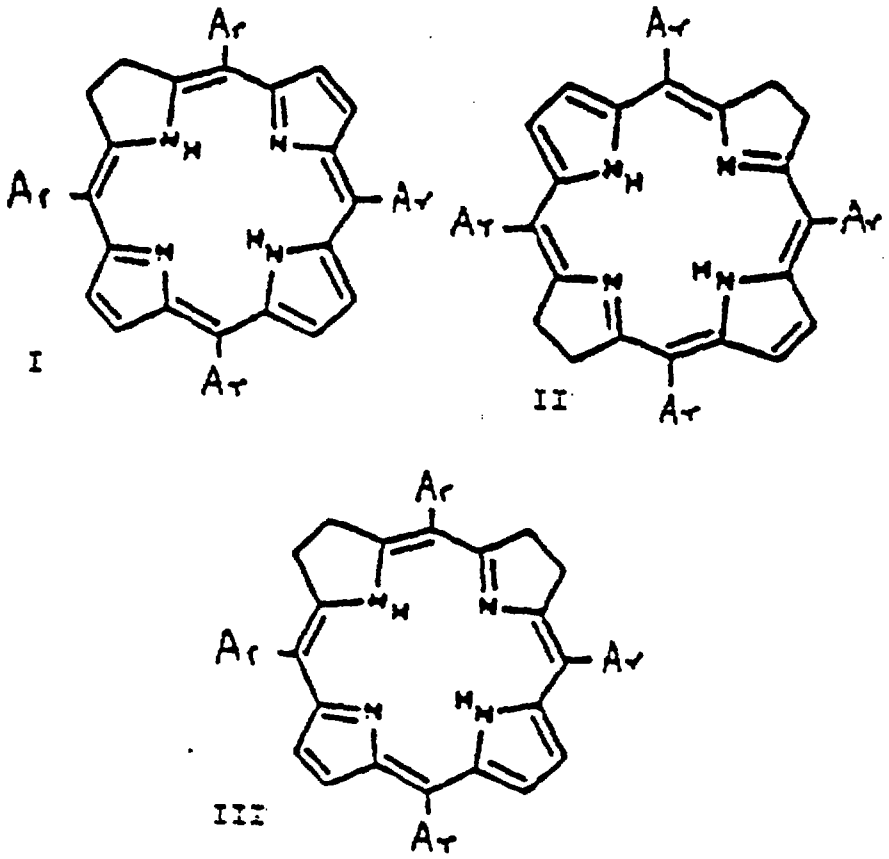
4. Composés selon l'une des revendications 1, 2 ou 1, dans lesquels chaque groupe hydroxy est libre plutôt que sous une forme substituée.

5. Composé selon l'une des revendications 1, 2, 3 ou 4, qui est :
   - la dihydro-2,3 téta(p-hydroxyphényl)-5,10,15,20 porphyrine ;
   - la dihydro-2,3 téta(m-hydroxyphényl)-5,10,15,20 porphyrine ;
   - la dihydro-2,3 téta(o-hydroxyphényl)-5,10,15,20 porphyrine ; ou
   - la tétrahydro-7,8,17,18 téta(m-hydroxyphényl)-5,10,15,20 porphyrine.

6. Utilisation d'un composé tel que défini à l'une quelconque des revendications 1 à 5, en association avec un diluant ou support pharmaceutique, dans la préparation d'un médicament destiné à être utilisé dans la thérapie des tumeurs par irradiation.

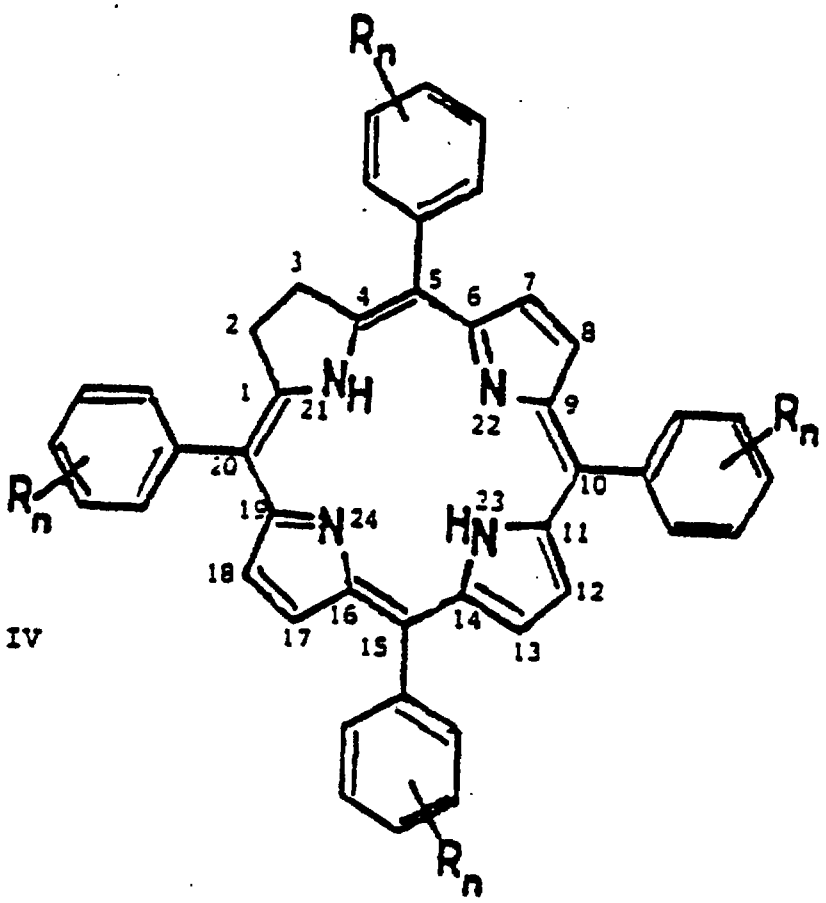
Revendications pour l'Etat contractant suivant : ES

1. Procédé de fabrication de composés qui sont des dihydro ou tétra-hydro prophyrines, pharmacologiquement acceptables, permettant de localiser une tumeur, représentées par les formules :



dans lesquelles les Ar, identiques ou différents, représentent chacun un groupe aromatique ayant un ou plusieurs groupes substituants hydroxy (-OH) chacun étant lui-même libre ou substitué par un groupe alkyle ou acyle, et les sels, complexes avec un métal ou hydrates ou autres solvates de ces composés, par réduction des porphyrines correspondantes.

2. Procédé selon la revendication 1, dans lequel les composés sont représentés par la formule :



IV

ou les téta-hydro phorphyrines correspondantes, dans laquelle :

- chaque n = 1 à 3 ; et
- les substituants R, qui peuvent être identiques ou différents, se situent chacun dans une position identique ou différente sur leur noyau phényle substituant respectif, et représentent chacun un groupe hydroxy lui-même libre ou substitué.

3. Procédé selon la revendication 2, dans lequel chaque substituant



représente un groupe o-hydroxyphényle, m-hydroxyphényle ou p-hydroxyphényle.

4. Procédé selon l'une des revendications 1, 2 ou 3, dans lequel chaque groupe hydroxy est libre plutôt que sous une forme substituée.

5. Procédé selon l'une des revendications 1, 2, 3 ou 4 qui permet de préparer :
   - la dihydro-2,3 téta(p-hydroxyphényl)-5,10,15,20 porphyrine ;
   - la dihydro-2,3 téta(m-hydroxyphényl)-5,10,15,20 porphyrine ;
   - la dihydro-2,3 téta(o-hydroxyphényl)-5,10,15,20 porphyrine ; ou
   - la tétrahydro-7,8,17,18 téta(m-hydroxyphényl)-5,10,15,20 porphyrine.

6. Utilisation d'un composé tel que défini à l'une quelconque des revendications 1 à 5, en association avec un diluant ou support pharmaceutique, dans la préparation d'un médicament destiné à être utilisé dans la thérapie des tumeurs par irradiation.