TUMOUR LOCALISING PHOTOSENSITISING COMPOUNDS

This invention relates to polyether-substituted photosensitising compounds and their use in the treatment of tumours.

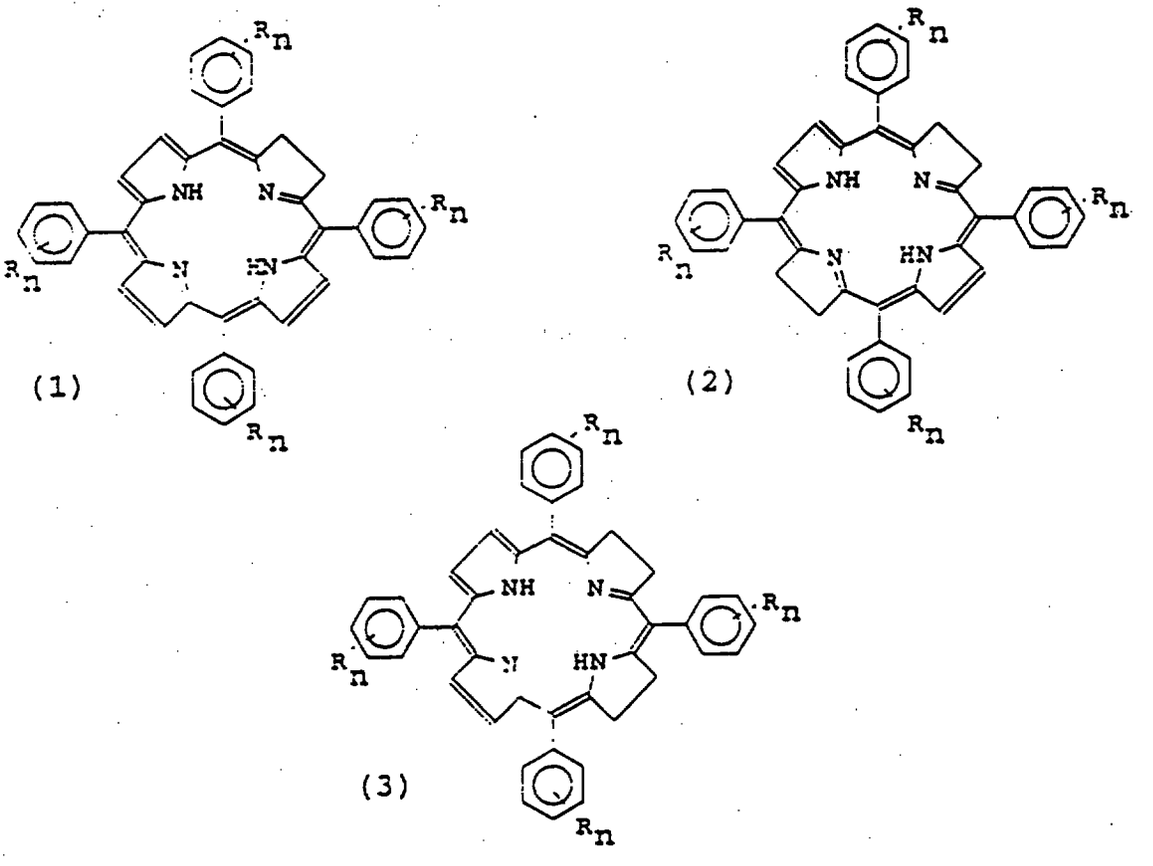
Photodynamic therapy involves the administration of a photosensitising compound followed by irradiation of the tissue containing the compound with visible light of a specific wavelength. The resulting activated compound, with oxygen, forms a reactive radical which causes necrosis of the surrounding tissue.

The success of this modality is dependent on administration of a compound which is selectively retained in tumour tissue as compared to normal tissue and thus on irradiation of the tumour with visible light, the amount of damage caused by necrosis in tumour tissue is proportionally higher than that in normal tissue. However some normal tissue damage may occur and one specific side effect seen with the use of many photosensitisers is redness and swelling (erythema) of the skin on exposure to normal lighting levels, and particularly sunlight. This requires patients to be kept in subdued light for some weeks after treatment which can restrict their quality of life. A more efficient delivery of the photosensitising compound into tumour tissue, thus providing a much higher tumour to normal-skin ratio of drug concentration could dramatically reduce the potential for skin side effects with this treatment.

Such tumour localisation can also be used as a diagnostic tool for determination of tumour position, size etc. and thus of the treatment of choice. Certain photosensitisers can be used as diagnostic tools, if applicable as sources of detectable fluorescence. In addition certain radio-labelled entities can also be incorporated into the tumour localising compounds for the purpose of diagnosis.

A group of photosensitising compounds have previously been the subject of

EP 0 337 601 A1. These compounds are dihydroporphyrins (chlorins) (1) and the corresponding tetrahydro porphyrins (bacteriochlorins) (2) and (3) of the formuiae:



wherein each **R** is a hydroxyl group (one or more in each ring ie., **n = 1 to 3**) and is in an ortho, meta or para position relative to the position of attachment of the phenyl ring to the nucleus.

Said substituent groups may be in the same or different positions on their respective phenyl groups and may be free, substituted, or partly substituted, for example with alkyl or acyl groups containing 1 to 4 carbon atoms. The nucleus or the phenyl rings may be substituted further, provided pharmacological tolerability, appreciable

solubility in water-based pharmacologically acceptable solutions (required so that the drug may be administered intravenously to ensure rapid distribution to the tumour), absorption of light at the red end of the visible spectrum, and take up in cancerous tissue are retained. Such further substituted compounds, when derivatised as discussed below, are regarded as forms of the compounds of the innovation and included in the scope of the claims herein.

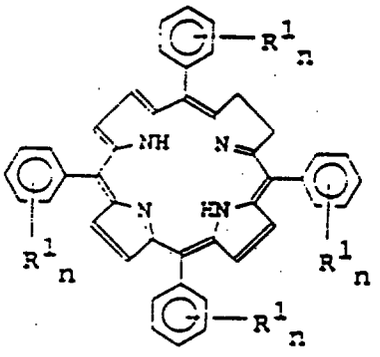
Any of the compounds may be in the form of their salts at acidic or basic centres, or their metal complexes (e.g. Zn, Ga), or their hydrates or other solvates particularly with lower, e.g. C_1 - C_4, aliphatic alcohols.

Various specific compounds within the above formulae (each phenyl group carrying an **R** group) are given in Table 1 below:-

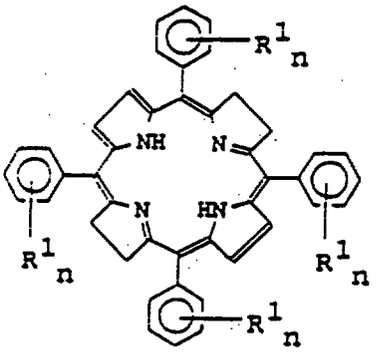
TABLE 1

No.	n	R
1a	1	meta OH
1b	1	para OH
1c	1	ortho OH
2a	1	meta OH

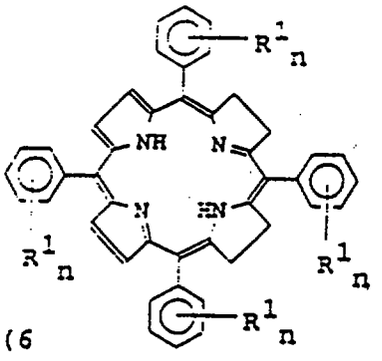
The present invention concerns the derivatisation or partial derivatisation of the phenolic hydroxyl groups of compounds of formulae (1), (2) and (3) with polyethylene glycols with or without a linking group, the terminal hydroxyl being etherified or esterified with C_1-C_{12} alkyl or acyl groups, the methyl group being the most preferred. This results in compounds of types (4), (5) and (6) as shown below:



(4)



(5)



(6

Wherein **R'** may be **R** but in at least two instances is a chain of formula **(- O - X_p - $[CH_2CH_2O]_m$ - Y)q** wherein **q = 1 to 3, m = 5 to 250** and **p = 0 to 1.** The group **Y** may be a **C_1 - C_{12}** alkyl or acyl group but preferably a methyl group. The linking group **X** may be present or absent, but if present may be of the following alternative forms:-

R^2 = - (C = O) - $(CH_2)_r$ - O - where r = 1 to 5

R^3 = CH_2 - CH(OH) - $(CH_2)_s$ - O - where s = 1 to 4

R^4 = - (C = O) - $(CH_2)_t$ - (C = O) - O - where t = 1 to 4.

Desirably the chain length of the terminally substituted polyethylene glycol chains is such as to provide compounds of types (4), (5) and (6) of overall molecular weight of

no less than 5,000 D and no more than 20,000 D which is the exclusion limit of the kidneys.

In any of the above compounds, any free hydroxyl groups may be otherwise derivatised and salts with mineral acids (ie. hydrochlorides, sulphates, etc), metal complexes (ie. with Zn, Ga, etc), hydrates and solvates with lower (C_1 - C_4) alcohols may be formed. All such forms are included in the claims therein.

Compounds of types (4), (5) and (6) were R^1 is herein before defined and $p = 0$ may be formed by reaction of compounds of types (1), (2) and (3) where R is herein before defined with compounds of type (7) where R^1 and n are herein before defined and $p = 0$ in the presence of an alkali metal bicarbonate in a mixture of water and a suitable water soluble non-hydroxylic solvent, ie. 1,4-dioxan at a temperature between 0 and 30°C.

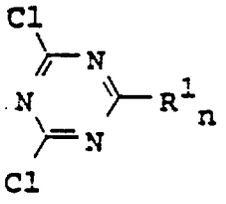
Compounds of types (4), (5) and (6) were R^1 is herein before defined, $p = 1$ and $X = R^2$ may be formed by reaction of compounds of types (1), (2) and (3) where R is herein before defined with compounds of type (8) where R^1 and n are herein before defined, $p = 1$, $X = R^2$ and Z = Cl or Br in the presence of a tertiary organic base, ie. pyridine and in a suitable solvent, ie. acetonitrile at a temperature between 0 and 100°C.

Compounds of types (4), (5) and (6) were R^1 is herein before defined, $p = 1$ and $X = R^4$ may be formed by reaction of compounds of types (1), (2) and (3) where R is herein before defined with compounds of type (8) where R^1 and n are herein before defined, $p = 1$, $X = R^4$ and Z = Cl or Br in the presence of a tertiary organic base, ie. pyridine and in a suitable solvent, ie. acetonitrile at a temperature between 0 and 100°C.

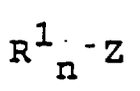
Compounds of types (4), (5) and (6) were R^1 is herein before defined, $p = 1$ and $X = R^3$ may be formed by reaction of compounds of types (1), (2) and (3) where R is herein before defined with compounds of type (9) where R^1, n and s are herein before defined and $p = 0$, in the presence of a catalytic amount of an organic tertiary base, ie.

triethylamine or an inorganic base, ie. sodium hydroxide at a temperature between 0 and 120°C.

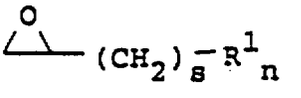
Compounds of types (7), (8) and (9) may be obtained commercially or synthesised by known methods by those skilled in the art.



(7)



(8)



(9)

The derivatised dihydro and tetrahydro porphyrin compounds (4), (5) and (6) have the following properties:

1. Increased aqueous solubility.
2. Longer circulation time in body.
3. Increased binding to plasma proteins.
4. Increased tumour accumulation rates when compared to parent compound.
5. Decreased skin photosensitisation.

Polyethylene glycol derivatised tetra-(3-hydroxy phenyl) chlorins (4) have been shown in various animal tumour models to have enhanced tumour concentration properties when compared with the parent drug, to an extent that is surprising when compared with that in derivatised porphyrins such as are disclosed *inter alia* in WO91/18630 (DKZ).

Routes of Administration

By parenteral or any other suitable route.

Pharmaceutical Presentations

Any suitable presentation for example:-

1. Injectible solution in an ampoule.
2. Freeze dried powder for injection.
3. Infusion solution for addition to saline or other vehicle.

Dosages are such as to give the desired chlorin/bacteriochlorin concentration in the tumour and are between 0.01 mg/kg up to 100 mg/kg depending on the drug.

EXAMPLE 1

To a solution of 2,3-dihydro-5,10,15,20-tetra-(3'-hydroxyphenyl) porphyrin (**1a**) and compound (**7a, [R^1 has p = 0, m = 110-120, Y = CH_3]**, 2.0g) in dioxan (50 ml) was added an aqueous solution of sodium bicarbonate (715 mg in 50 ml water). The mixture was stirred at room temperature under nitrogen and then allowed to stand for 15 hours. After freeze drying, the resulting brown powder was reconstituted in water (50 ml) and passed through a 0.2 mm filter and then through a molecular filter (Cut off : 10,000 D). The resulting concentrated residue was diluted to 50 ml with water and passed through the molecular filter again. Dilution and molecular filtration were repeated four times. The residue was diluted once more and subjected to freeze drying to give compound mixture (**4a, 0 to 2 R^1 = R + 4 to 2 R^1 [p = 0, m = 110-120, Y = CH_3]**, 702 mg) as a brown semi-crystalline powder.

In a similar manner but replacing 2,3-dihydro-5,10,15,20-tetra-(3'-hydroxyphenyl) porphyrin (**1a**) with the appropriate amount of 2,3,12,13-tetrahydro-5,10,15,20-tetra-(3'-hydroxyphenyl) porphyrin (**2a**), there was prepared compound mixture (**5a, 1 to 2 R^1 = R + 4 to 2 R^1 [p = 0, m = 110-120, Y = CH_3]**) as a brown semi-crystalline power.

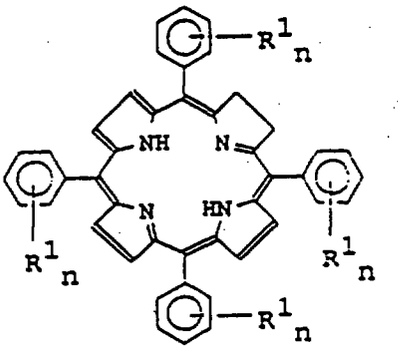
In a similar manner but replacing compound (**7a**) with the appropriate amount of compound (**7b, R^1 has p = 0 and m = 40-50**) and using a molecular filter (Cut off :

5,000 D), there was prepared compound mixture (**4b**, **0 to 2 R^1 = R + 4 to 2 R^1 [p = 0, m = 40-50, Y = CH_3]**).

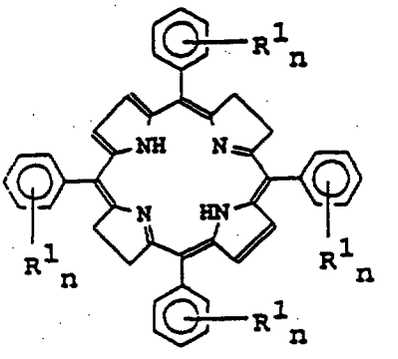
* C L M S *

CLAIMS

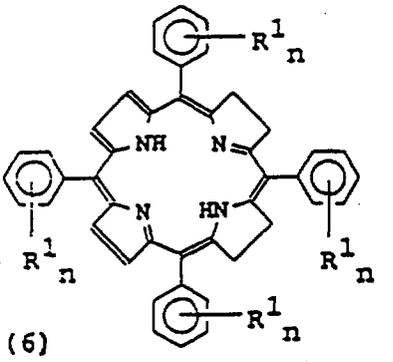
1. Compounds being polyethylene glycol derivatised, pharmacologically acceptable, tumour locating dihydro or tetra-hydro porphyrins of the formulae (4), (5) and (6)



(4)



(5)



(6)

wherein R^1_n may be -OH but in at least two instances is a chain of formula $(-O-X_p-[CH_2CH_2O]_m-Y)_n$ wherein $n = 1$ to 3, $m = 5$ to 250 and $p = 0$ to 1; the group Y may be a C_1 - C_{12} alkyl or acyl group but preferably a methyl group; the linking group X may be present or absent, but if present may be of the following alternative forms:-

$R^2 = -(C = O) - (CH_2)_q - O$ - where $q = 1$ to 5

$R^3 = -CH_2 - CH(OH) - (CH_2)_s - O$ - where $s = 1$ to 4

$R^4 = -(C = O) - (CH_2)_t - (C = O) - O$ - where $t = 1$ to 4.

2. Compounds of claim 1 as derivatives wherein one or more hydroxyl group is otherwise derivatised; or as hydrochlorides, sulphates or other salts with mineral acids;

or as metal complexes with Zn, Ga or other metals; or as hydrates or solvates with lower (C_1-C_4) alcohols.

3. Methods of using compounds of formulae (4), (5) and (6) to make medicaments for therapy of tumours susceptible to necrosis when such a compound is administered to locate in the tumour followed by irradiation of the tumour with visible light of a wavelength absorbed by the compound, the said methods making use of the compounds by associating them with a pharmaceutical diluent or carrier.

4. The subject matter of claims 1 and 2 or 3, wherein the molecular weight of the compounds (4), (5) or (6) is 5,000 D to 20,000 D.