dacarbazine and temozolomide are to date the only triazenes remaining in clinical use of the treatment of glioblastomas, even though they are associated with considerable side effects such as bone marrow depression, neurotoxicity and liver toxicity, emesis, hair loss and exanthems.

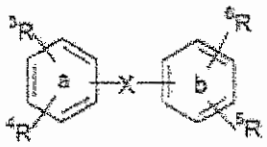
A first attempt to overcome the tolerability problems of selected triazenes with a view to selective use in the case of breast cancer is described in DE 17 93 115 A1 and DE 21 47 781 A1.

A second attempt to overcome severe side effects of selected triazenes is described in WO 2004/106358 A1. Some severe side effects of the known triazenes are said to be reduced by introduction of oxycarboxylic acid groups. However, owing to undesirable side effects on the kidney they are not suitable for long-term use.

It is an object of the present invention to provide oncocidal active compounds which are suitable for long-term therapy virtually without toxic side effects and with at the same time improved effectiveness.

Summary

In one aspect, the present invention refers to a diphenyl derivative having the formula



(1)

where

X is a direct C-C bond between the rings a and b, CH_2, CHOH, CO, S, SO, SO_2, -N=N-, $-CR^7=CR^8-$ or a divalent -C(O)-C*=CH-O- radical which together with the two adjacent carbon atoms of the ring a on which it is located forms a pyranone ring, with the ring b being located on the C* atom of this radical,

R^3, R^6 are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-S-, C_1-C_4-alkyl-SO-, C_1-C_4-alkyl-SO_2-, halogen, nitro, cyano or an $-OSO_2Y$ group,

R^4, R^5 are each, independently of one another, an $-N=N-N(R^2)_2$ group or an $-OSO_2Y$ group,

R^7 is hydrogen, methyl, ethyl or a phenyl radical which is substituted by the radicals R^9, R^{10} and is bound directly to the R^7-bearing carbon atom,

R^8 is hydrogen, ethyl, CN, NO_2, $-CH_2CH_2$-halogen or CH_2CH_2OH,

R^9, R^{10} are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, nitro, cyano, an $-N=N-N(R^2)_2$ group or an $-OSO_2Y$ group,

Y is OH or $N(R^1)_2$,

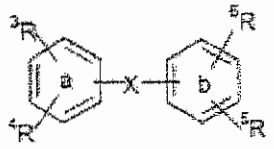
R^1 is hydrogen, methyl or ethyl and

R^2 is methyl or ethyl,

with the proviso that, per total molecule (1), one or two $-N=N-N(R^2)_2$ groups and one or two $-OSO_2Y$ groups are located on any ring carbons of aromatic rings,

and also its salts, free acids, solvates and the solvates of these salts and the solvates of these free acids.

In another aspect, the present invention refers to a process for preparing diphenyl derivatives as defined herein, wherein aminophenyl derivatives of the formula



(2)

where

X is a direct C-C bond, CH_2, CHOH, CO, S, SO, SO_2, -N=N-, $-CR^7=CR^8-$ or a divalent $-C(O)-C^*=CH-O-$ radical which together with the two adjacent carbon atoms of the ring a on which it is located forms a pyranone ring, with the ring b being located on the C* atom of this radical,

R^3, R^6 are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-S-, C_1-C_4-alkyl-SO-, C_1-C_4-alkyl-SO_2-, halogen, nitro, cyano or an $-OSO_2Y$ group,

R^4, R^5 are each, independently of one another, an $-NH_2$ group or an $-OSO_2Y$ group,

R^7 is hydrogen, methyl, ethyl or a phenyl radical which is substituted by the radicals R^9, R^{10} and is bound directly to the R^7-bearing carbon atom,

R^8 is hydrogen, ethyl, CN, NO_2, $-CH_2CH_2$-halogen or CH_2CH_2OH,

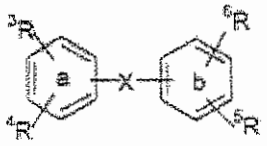
R^9, R^{10} are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, nitro, cyano, an $-NH_2$ group or an $-OSO_2Y$ group,

Y is OH or $N(R^1)_2$, and

R^1 is hydrogen, methyl or ethyl,

with the proviso that, per total molecule (2), one or two NH_2 groups and one or two $-OSO_2Y$ groups are located on any ring carbons of aromatic rings,

are diazotized by means of a diazotizing agent in the presence of strong acid at low temperature in aqueous-acidic solution to form diazonium salts of the formula



(3)

where

X is a direct C-C bond, CH_2, CHOH, CO, S, SO, SO_2, -N=N-, $-CR^7=CR^8-$ or a divalent $-C(O)-C^*=CH-O-$ radical which together with the two adjacent carbon atoms of the ring a on which it is located forms a pyranone ring, with the ring b being located on the C* atom of this radical,

R^3, R^6 are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-S-, C_1-C_4-alkyl-SO-, C_1-C_4-alkyl-SO_2-, halogen, nitro, cyano or an $-OSO_2Y$ group,

R^4, R^5 are each, independently of one another, an $-N_2^+An^-$ group or an $-OSO_2Y$ group,

R^7 is hydrogen, methyl, ethyl or a phenyl radical which is substituted by the radicals R^9, R^{10} and is bound directly to the R^7-bearing carbon atom,

R^8 is hydrogen, ethyl, CN, NO_2, $-CH_2CH_2$-halogen or CH_2CH_2OH,

R^9, R^{10} are each, independently of one another, hydrogen, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, nitro, cyano, an $-N_2^+$ An^- group or an $-OSO_2Y$ group,

An^- is a halogen anion or ½ sulfate (SO_4^{2-}) anion,

Y is OH or $N(R^1)_2$, and

R^1 is hydrogen, methyl or ethyl,

with the proviso that, per total molecule (3), one or two diazonium groups and one or two $-OSO_2Y$ groups are located on any ring carbons of aromatic rings,

and the diazonium salts (3) obtained are then reacted with dialkylamines of the formula

$H\ N(R^2)_2$ (4)

where R^2 is methyl or ethyl,
in the presence of acid binding agents,
optionally followed by preparation of the salts from the compounds obtained and optionally followed by setting-free of the hydroxyl and/or acid groups from these salts.

In yet another aspect, the present invention refers to a medicament containing at least one diphenyl derivatives as defined herein or its salts, solvates, and solvates of these salts, optionally together with one or more pharmacologically acceptable auxiliaries or supports.

In a further aspect, the present invention refers to the use of at least one diphenyl derivative as defined herein or its salts, solvates and solvates of these salts in the manufacture of a medicament for treating any one of the following tumors of the skin, breast, prostate and testicle or the target organs dependent on sex hormones in human beings and animals.

Detailed description

We have found new diphenyl derivatives containing (i) at least one dialkyltriazenyl group and (ii) at least one sulfooxy group and/or at least one sulfamoyloxy group per molecule, and their salts, solvates and solvates of these salts.

The novel diphenyl derivatives of the invention surprisingly have a greatly improved antitumor effect in the case of tumors of important target organs (e.g. colon, lung, liver, pancreas, kidney), in particular as selective oncocides against tumors of the skin, breast, prostate and testicle and also of the target organs dependent on sex hormones compared to similar known active compounds (WO 2004/106358 A1, DE 17 93 115 A1