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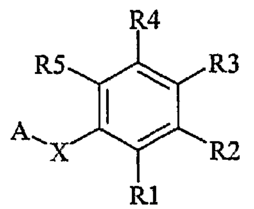
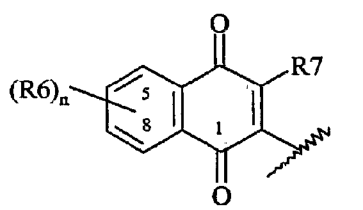
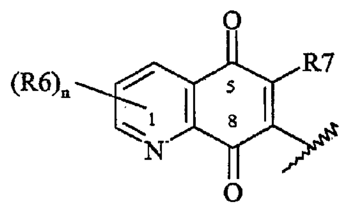
(54) Title: 1,4-NAPHTHOQUINONE DERIVATIVES AND THERAPEUTIC USE THEREOF



(I)





(57) Abstract: Derivatives of formula (I) wherein A is selected from the following rings: and their preparation and their application as antimalarial agents.

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1,4-NAPHTHOQUINONE DERIVATIVES AND THERAPEUTIC USE THEREOF

The present invention relates to derivatives of 1,4-naphthoquinones, their preparation and their application in therapeutics.

Due to spreading resistances, new drugs against malaria are continuously needed in poor countries where severe malaria kills millions of children every year. Ethical drugs must be cheap and therefore they should be easy to synthesize if they are not readily available as chemicals on the market.

Plasmodium parasites are exposed to elevated fluxes of reactive oxygen species during the life cycle in the human host and therefore high activities of intracellular antioxidant systems are needed. The most important antioxidative system consists of thiols which are regenerated by disulfide reductases; these include three validated drug targets, the glutathione reductases (GR) of the malarial parasite *Plasmodium falciparum* and of human erythrocytes as well as the thioredoxin reductase of *P. falciparum* (Schirmer et al, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 141-54; Krauth-Siegel et al, Angewandte Chemie International Edition (2005), 44(5), 690-715). One validated target against the malarial parasite *Plasmodium falciparum* is the enzyme glutathione reductase which reduces glutathione disulfide to its thiol form glutathione on the expense of NADPH. Glutathione is implicated in the development of chloroquine resistance: an elevation of the glutathione content in *P. falciparum* leads to increased resistance to chloroquine, while glutathione depletion in resistant strains restores sensitivity to chloroquine (Meierjohan et al, *Biochem. J.* **2002**, 368, 761-768). High intracellular glutathione levels depend inter alia on the efficient reduction of glutathione disulfide by GR and by reduced thioredoxin (Kanzok et al, *Science* **2001**, 291, 643-646). The contribution to the reversal of drug resistance by GR inhibitors is currently investigated for the commonly used antimalarial drug chloroquine in clinical trials (Sarma et al., *J. Mol. Biol.* **2003**, 328, 893-907). Derivatives of menadione were shown to be potent inhibitors both of human and *Plasmodium falciparum* glutathione reductases acting in the low micromolar range (Davioud-Charvet et al, *J. Med. Chem.* **2001**, 44, 4268-4276; Biot et al, *J. Med. Chem.* 47, 5972-5983; Bauer et al, *J. Am. Chem. Soc.* **2006**, 128, 10784-10794).

The malarial parasite *Plasmodium falciparum* digests a large amount of its host cell hemoglobin during its erythrocytic cycle as source of essential nutrients (Zarchin et al, *Biochem. Pharmacol.* **1986**, 35, 2435-2442). The digestion is a complex process that involves several proteases and takes place in the food vacuole of the parasite leading to the formation of iron III ferroprotoporphyrin (FPIX) (Goldberg et al, Parasitol. Today, 1992, 8, 280-283) as toxic byproduct for the parasite. Due to the toxicity of FPIX the parasites have developed a detoxification process in which FPIX (Fe3+) (hematin) is polymerized forming inert crystals of hemozoin or malaria pigment (Dorn et al, Nature 1995, 374, 269-271). FPIX (Fe2+) is an inhibitor of hematin polymerization (Monti et al, *Biochemistry* **1999**, 38, 8858-8863). Early observations indicated that free FPIX (Fe3+) is able to form complexes with aromatic compounds bearing nitrogen, e.g. pyridines, 4-aminoquinolines (Cohen et al, *Nature* **1964**, 202, 805-806; Egan et al, *J. Inorg. Biochem.* **2006**, 100, 916-926) and it is now well established that 4-aminoquinolines can form μ-oxodimers with FPIX thus preventing the formation of hemozoin. Consequently an accumulation of free heme in the food vacuole is responsible for killing the parasite (Vippagunta et al, *Biomed. Biochim. Acta* **2000**, 1475, 133-140). In the presence of reactive oxygen species iron-porphyrin complexes (e.g. free heme) are catalysts for oxidation reactions. Released in large quantities in the food vacuole of the parasite they are thought to strongly influence the activity of a drug under the specific acidic conditions of the malarial food vacuole. Drug metabolites can be more active than its precursor (pro-drug effect) or toxic (Bernadou et al, *Adv. Synth. Catal.* **2004**, 346, 171-184).

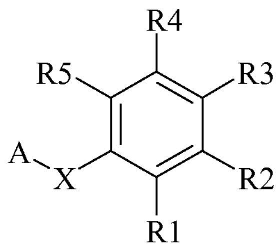
The reduction of methemoglobin(Fe^{3+}) into hemoglobin(Fe^{2+}) is of great importance in the treatment of malaria. Since the malarial parasite is much more capable of using methemoglobin as nutrient and digests methemoblobin faster than hemoglobin, the reduction of methemoglobin can be used to slow down the parasite`s methemoglobin digestion by reducing its concentration. A second reason to target the reduction of methemoglobin is that methemoglobin, the ferric form of hemoglobin, is not capable of oxygen transport. High levels of methemoglobin are found during *Plasmodium vivax* infections (Anstey et al, *Trans. R. Soc. Trop. Med. Hyg.* **1996**, 90, 147-151). A reduced oxygen carrying capacity of blood due to anaemia is even worsened by reduction in oxygen carrying capacity from even a modest concentration of methemoglobin leading to an impaired supply of oxygen for the tissue; a specific situation observed in cerebral malaria.

Since the malarial parasite *Plasmodium falciparum* multiplies in human erythrocytes, most drugs are directed against this stage of the life cycle of the parasite. Due to increasing resistance of the parasite against standard drugs such as chloroquine, newly drugs are urgently required.

There is therefore still a need for compounds having efficiency against malaria, without their usual drawbacks. Furthermore, there is a need for anti-malarial drugs which are easy to formulate in pharmaceutical compositions.

Accordingly, this invention provides novel potent anti-malarial agents and methodology of treating malaria using novel potent anti-malarial agents. The invention also provides potent anti-malarial agents that are inhibitors of *P. falciparum* glutathione reductase and active against chloroquine-sensitive and resistant malarial strains.

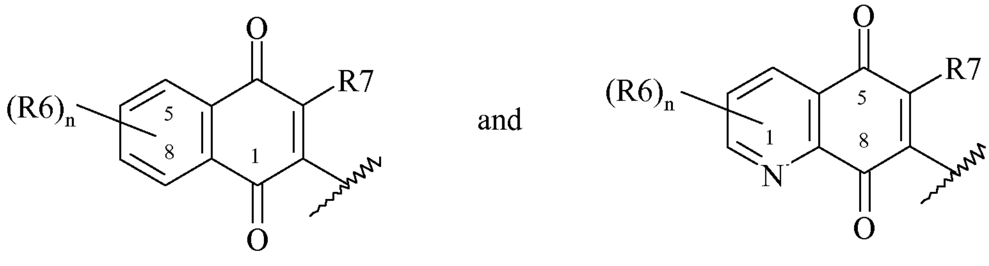
The present invention relates to compounds of formula (I)



(I)

wherein

- A is selected from the following rings:



with each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, representing independently a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4 and R7 representing a methyl group,

- X represents –C(O)– or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group,

- R1, R2, R3, R4 and R5 represent each independently of the others:

. a hydrogen atom,

. a halogen atom,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group,

. a trifluoromethyl group,

. a difluoromethyl group,

. a linear or branched (C_1-C_4)alkoxy group,

. a trifluoromethoxy group,

. a difluoromethoxy group,

. a pentafluorosulfanyl group

. -COOH,

. -COO(C_1-C_4)alkyl group,

. –CONR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group and m = 1, 2 or 3,

. –CSNR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group m = 1, 2 or 3,

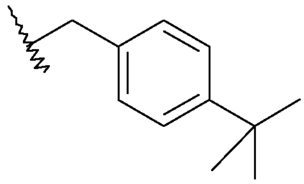
. –CONR8Het with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group, Het representing a pyridine-2-yl group optionally substituted by an amino group in -6 or by a –$CONH_2$ group in -5,

. - NO_2,

. - CN,

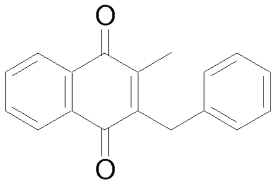
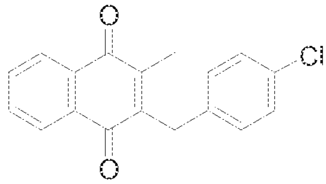
. –NR9R10 with R9 and R10 representing each independently a hydrogen atom, an amino protecting group selected from the group comprising Boc group and (C_1-C_4)alkyl group, or R9 and R10 forming with the nitrogen atom which bears them a cyclic group selected from the group comprising morpholine and piperazine groups said cyclic groups being optionally substituted,

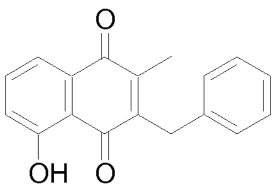
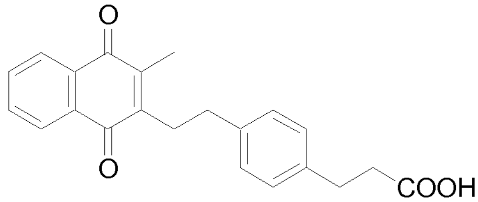
. an aryl group optionally substituted by a (C_1-C_4)alkyl group, a -NO_2 group, a –COOR11 with R11 selected from a hydrogen atom and a linear or branched (C_1-C_4)alkyl group, a -NR12R13 with R12 and R13 independently selected from the group comprising a hydrogen atom and a linear or branched (C_1-C_4)alkyl group,

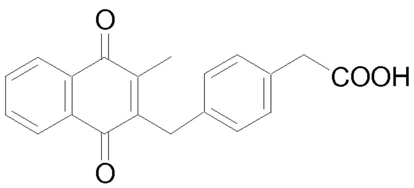
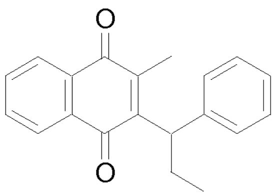
. a heterocyclic group selected from the group comprising morpholinyl group or piperazinyl group, each of said group being optionally substituted by one or several substituents selected from the group comprising a linear or branched (C_1-C_4)alkyl group, $-COOCH_2CH_3$, or a group 

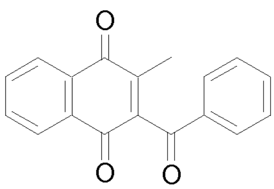
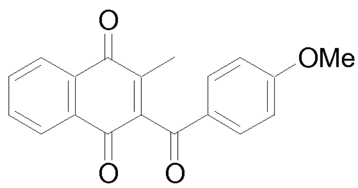
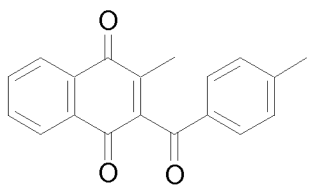
and the pharmaceutically acceptable derivatives thereof,

with the proviso that the compounds of formula (I) are not selected from the group comprising

 ,  ,

 ,  ,

 ,  ,

 ,  , 

which are disclosed in US 2417919, in *Tetrahedron Lett.* **2006**, 47, 1329-1332 by P. Waske et al, in *Chem. Pharm. Bull.*, **1997**, 45, 437-445 by Ogihara et al, in *Biochim.*

Biophys. Acta, **1965**, 105, 205-213 by Howland et al, in *J. Am. Chem. Soc.*, **2006**, 128, 10784-10794 by Bauer et al, in *J. Med. Chem.*, **2008**, 128, 10784-10794 by Friebolin et al and in *Tetrahedron* **1971**, 27(12), 2529-39 by K. Chandrasenan et al, respectively.

The term "alkyl" refers to a straight or branched chain, saturated hydrocarbon having the indicated number of carbon atoms. A (C_1-C_4) alkyl is meant to include but is not limited to methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl. An alkyl group can be unsubstituted or optionally substituted with one or more substituents.

The term "alkoxy" refers to an -O-alkyl group having the indicated number of carbon atoms. A (C_1-C_4)alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-sec-butyl, -O-tert-butyl.

The term "aryl" refers to a 6- to 18-membered monocyclic, bicyclic, tricyclic, or polycyclic aromatic hydrocarbon ring system. Examples of an aryl group include phenyl, naphthyl, pyrenyl, anthracyl, quinolyl, and isoquinolyl. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

According to the present invention, a "pharmaceutically acceptable salt" is a pharmaceutically acceptable, organic or inorganic acid or base salt of a compound of the invention. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, hydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosaliculate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts. A pharmaceutically acceptable salt can have more than one charged atom in its structure. In this instance the pharmaceutically acceptable salt can have multiple counterions. Thus, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterions.

In one embodiment, the compounds of formula (I) are those wherein

- R1, R2, R4 and R5 represent each independently of the others a hydrogen atom, a halogen atom, a di- or tri-fluoromethyl group or a (C_1-C_4)alkoxy group,

- R3 represents

. a hydrogen atom,

. a halogen atom,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group,

. a trifluoromethyl group,

. a difluoromethyl group,

. a linear or branched (C_1-C_4)alkoxy group,

. a trifluoromethoxy group,

. a difluoromethoxy group,

. a pentafluorosulfanyl group

. -COOH,

. -COO(C_1-C_4)alkyl group,

. –CONR8$(CH_2)_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group and m = 1, 2 or 3,

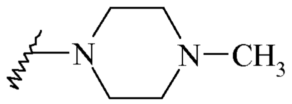
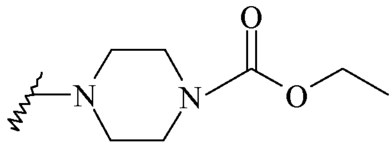
. –CSNR8$(CH_2)_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group m = 1, 2 or 3,

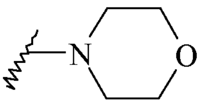
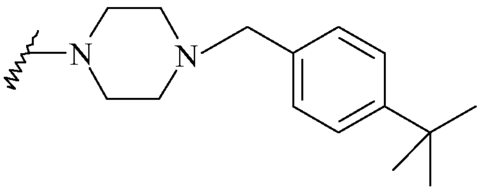
. –CONR8Het with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group, Het representing a pyridine-2-yl group optionally substituted by an amino group in -6 or a $–CONH_2$ group in -5,

. $-NO_2$,

. -CN,

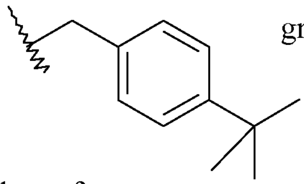
. –NR9R10 with R9 representing a hydrogen atom, or a (C_1-C_4)alkyl group and R10 representing a (C_1-C_4)alkyl group, or R9 and R10 forming with the nitrogen atom which bears them a

 , 

 or a 

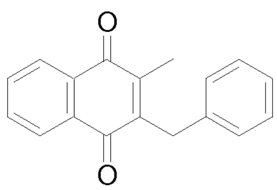
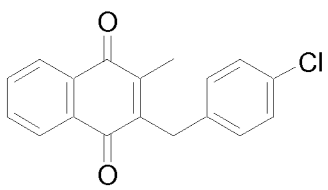
. a phenyl group optionally substituted in para by a (C_1-C_4)alkyl group, a -NO_2 group, a –COOR11 with R11 selected from a hydrogen atom and a linear or branched (C_1-C_4)alkyl group, a -NR12R13 with R12 and R13 selected from the group comprising a hydrogen atom and a linear or branched (C_1-C_4)alkyl group.

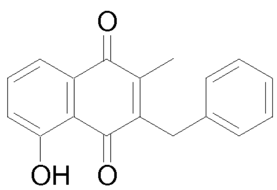
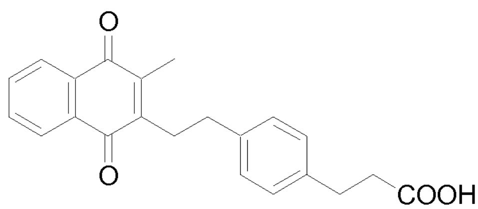
. a heterocyclic group selected from the group comprising morpholinyl group or piperazinyl group, each of said group being optionally substituted by one or several substituents selected from the group comprising a linear or branched

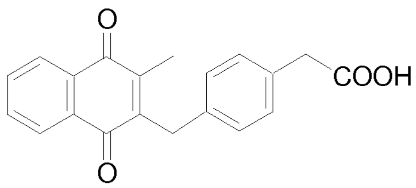
(C_1-C_4)alkyl group, -$COOCH_2CH_3$, or a  group

and the pharmaceutically acceptable derivatives thereof,

with the proviso that the compounds of formula (I) are not selected from the group comprising

 ,  ,

 ,  ,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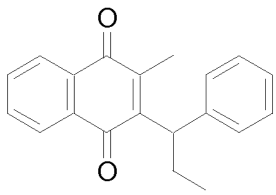
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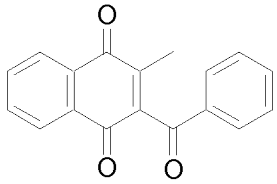
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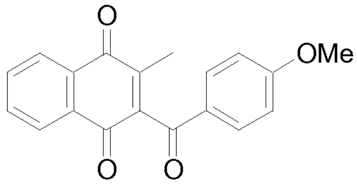
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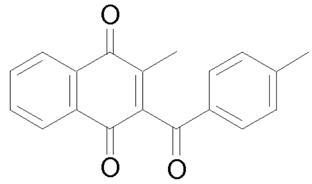
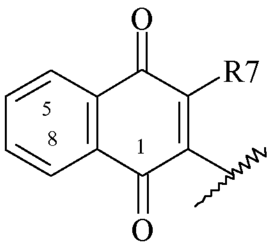
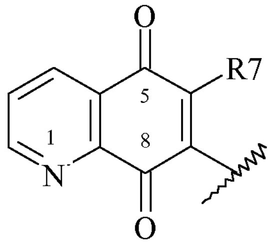


In another embodiment, A is selected from the following rings:



and



wherein R7 represents a methyl group.

In yet another embodiment X represents –C(O)- or –CH_2–.

In still another embodiment:

- R1, R2, R3, R4, R5 represent each:

. a hydrogen atom,

. a halogen atom selected from the group comprising Br, Cl and F,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group selected from the group comprising methyl and *t*-butyl,

. a di- or trifluoromethyl group,

. a methoxy group,

. a trifluoromethoxy group,

. a pentafluorosulfanyl group

. - NO_2,

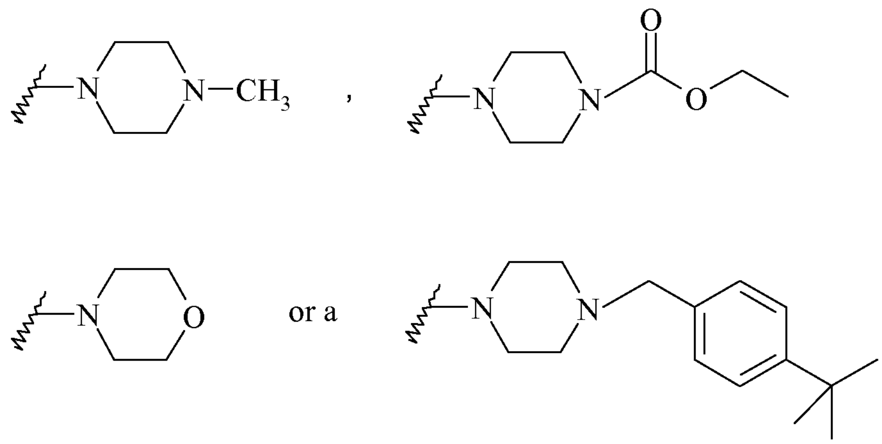
. - CN,

. –COOR14 with R14 representing hydrogen atom or methyl group,

. –CONH(CH_2)$_2$CN

. –NHBoc,

. a group selected from the group comprising



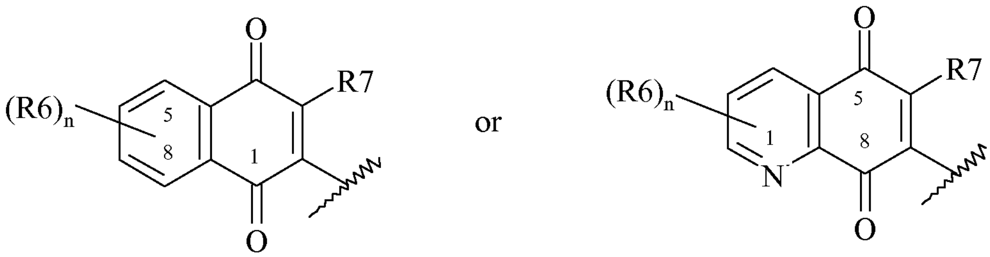
. a phenyl group substituted in para by a *t*-butyl group, -NO_2, -$N(CH_3)_2$, or -$NHC(CH_3)_3$.

In still another embodiment:

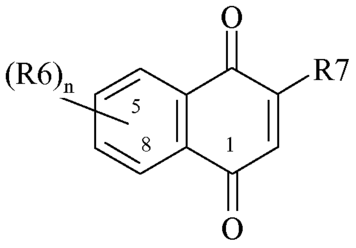
- R1, R2, R3, R4 and R5 are each independently selected from the group comprising a hydrogen atom, a hydroxy group, a methoxy group, a di- or tri-fluoromethyl group and a trifluoromethoxy group, a pentafluorosulfanyl group, or an amino group and.

In yet another embodiment R1, R2, R3, R4 and R5 represent a fluorine atom, a di- or tri-fluoromethyl group, or a trifluoromethoxy group, a pentafluorosulfanyl group.

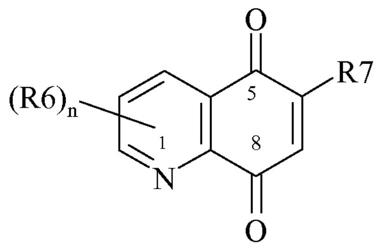
In another embodiment, the invention provides a process for preparing compounds of formula (I) wherein A represents:



comprising the reaction of a compound of formula (IIa) or (IIb)



or

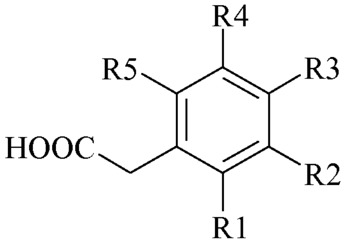


(IIa) (IIb)

wherein

- each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, represents independently a hydrogen atom, a halogen atom, an hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or trifluoromethyl group, a trifluoromethoxy group, pentafluorosulfanyl group, n being an integer comprised between 0 and 4, and
- R7 represents a methyl group,

with a phenyl acetic acid derivative of formula (III)

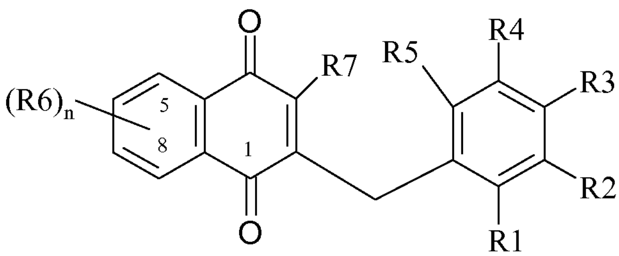


(III)

wherein

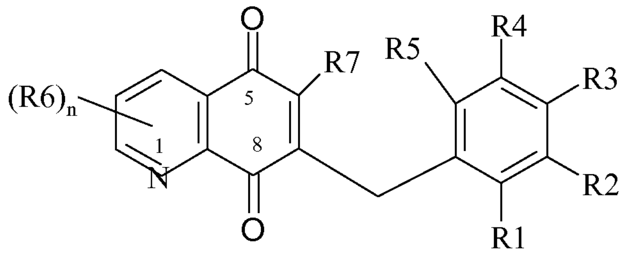
- R1, R2, R3, R4 and R5 are as defined in claim 1,

to obtain respectively a compound of formula (Ia)



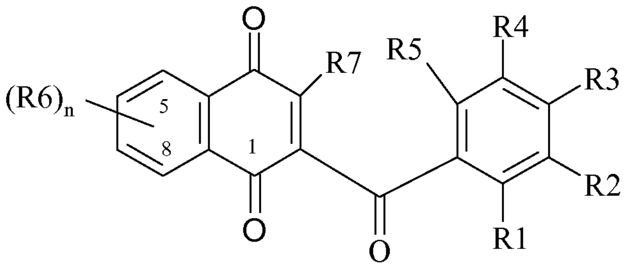
(Ia)

or of formula (Ib)



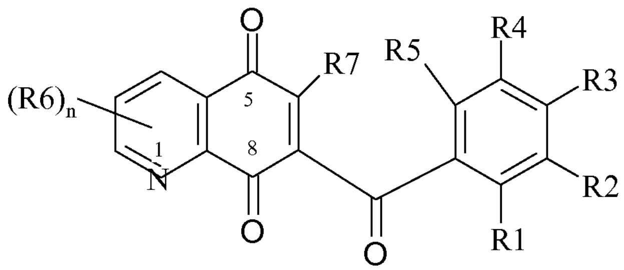
(Ib)

which may be treated in oxidative conditions to give respectively a compound of formula (Ic)



(Ic)

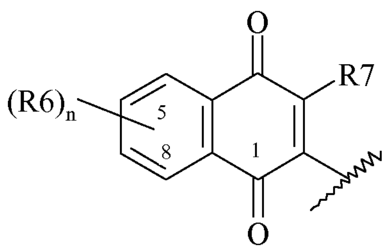
or a compound of formula (Id)



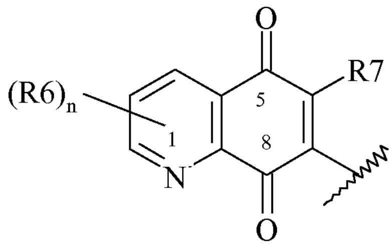
(Id)

wherein R1, R2, R3, R4, R5, R6 and n are as defined above.

The invention also provides a process for preparing compounds of formula (Ia1, Ib1, Ic1, Id1, Ie and If) corresponding to compounds of formula (I) wherein A represents



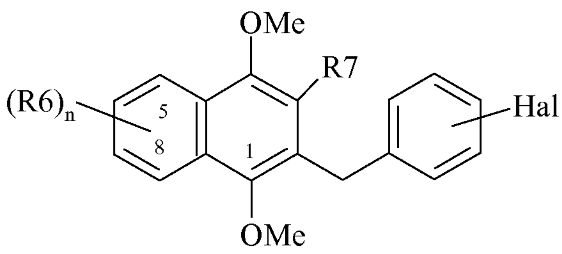
or



and X represents $-CH_2-$, or $-C(O)-$

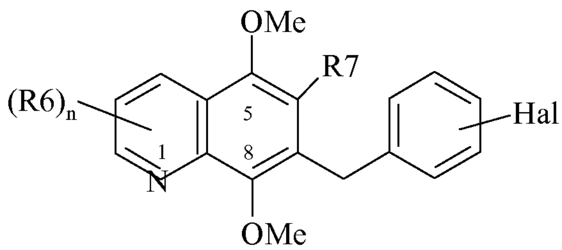
comprising

a) the preparation of a compound of formula (IIc)



(IIc)

or of formula (IId)



(IId)

wherein

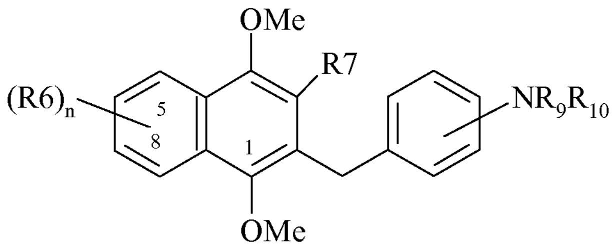
- R6 which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-dimethoxynaphthalene or in position 2, 3, or 4 of the 5,8-dimethoxyquinoline, represents a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, and n being an integer comprised between 0 and 4,
- R7 represents a methyl group and

- Hal represents a chloro, a bromo or a iodo atom,

by reduction of the corresponding quinones followed by methylation of the dihydronaphthoquinones intermediates into the corresponding dimethoxynaphthalene of formula (IIc) or dimethoxyquinoline of formula (IId),

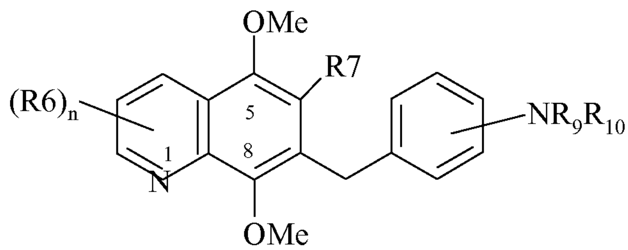
b) reaction of respectively one compound of formula (IIc) or (IId) with an amino compound of formula HNR9R10 with R9 and R10 representing each independently a hydrogen atom or a (C_1-C_4)alkyl group, with the proviso that R9 and R10 are not both a hydrogen atom, or R9 and R10 forming with the nitrogen atom which bears them a cyclic group selected from the group comprising morpholine and piperazine groups said cyclic groups being optionally substituted, in the presence of a palladium catalyst and of an appropriate palladium ligand,

to obtain a compound of formula (Ie)



(Ie)

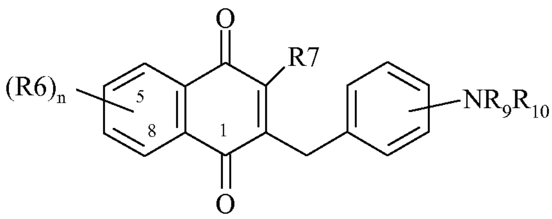
or of formula (If)



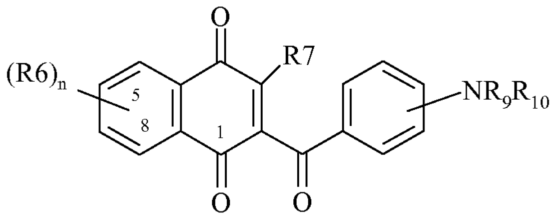
(If)

wherein R6, R7, R9 and R10 are as defined above,

c) re-oxidation of the compound of formula (Ie) or (If) to give the final compounds of formula (Ia1) or (Ic1)

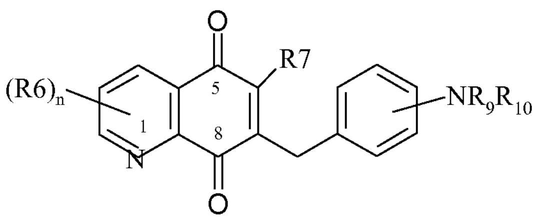


(Ia1)

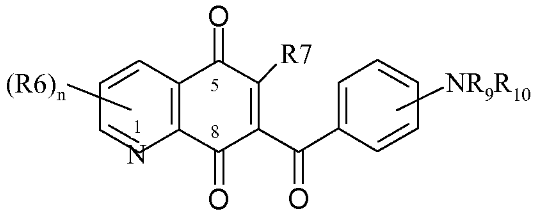


(Ic1)

or a compound of formula (Ib1) or (Id1)

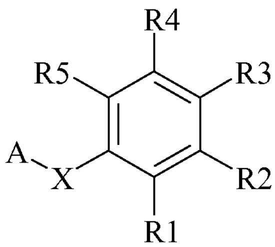


(Ib1)



(Id1)

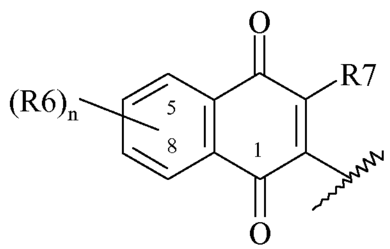
The present invention also provides a process for preparing compounds of formula (I)



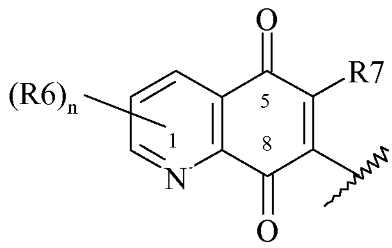
(I)

wherein

- A is selected from the following rings:



and



with each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, representing independently a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4 and R7 representing a methyl group,

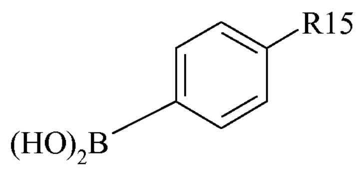
- one of R1, R2, R3, R4, R5 represents a phenyl-ring bearing in para position a *tert*butyl group, $-NO_2$, -COOR11 with R11 being hydrogen atom or a linear or branched (C_1-C_4)alkyl group, or NMe_2 group,

starting from the corresponding compound of formula (Ia) or (Ib) or (Ic) or (Id) wherein

- one of R1, R2, R3, R4 and R5 represents a halogen atom, the others being a hydrogen atom,

- X represents –C(O)– or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group and

with a boronic acid derivative of formula (IV)

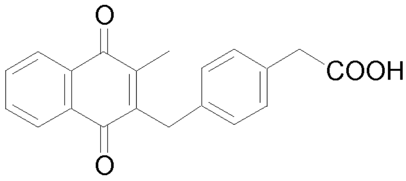


(IV)

wherein R15 represents a *tert*butyl group, $-NO_2$, -COOR11 with R11 being hydrogen atom or a linear or branched (C_1-C_4)alkyl group, or NMe_2 group in the presence of a palladium catalyst and of a base.

The present invention still provides compounds of formula (I) as a drug, especially as antimalarial agents.

In another embodiment the invention provides for the use of compounds of formula (I) in therapy or prophylaxis, with the proviso that the compounds of formula (I) are not



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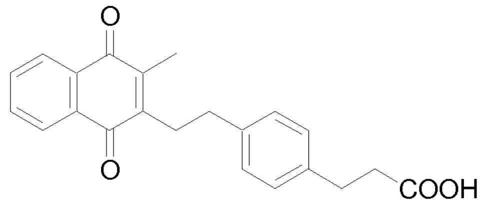


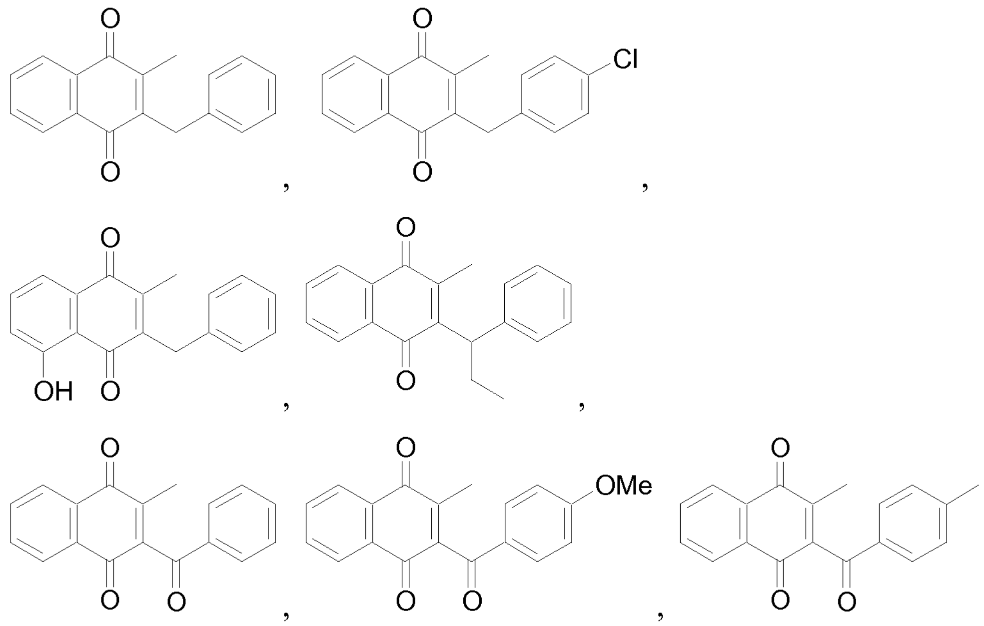
,

In accordance with this invention, the compounds of formula (I) or their pharmaceutically acceptable salts are useful in pharmaceutically acceptable compositions. The pharmaceutical compositions according to the invention comprise as active ingredient one or more of the compounds of formula (I) or its pharmaceutically acceptable salts, in combination with excipients and/or pharmaceutically acceptable diluents or carriers. Any conventional carrier material can be utilized. The carrier material can be an organic or inorganic inert carrier material, for example one that is suitable for oral administration. Suitable carriers include water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, glycerine and petroleum jelly. Furthermore, the pharmaceutical preparations may also contain other pharmaceutically active agents. Additional additives such as flavoring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding. The pharmaceutical preparations can be made up in any conventional form including a solid form for oral administration such as tablets, capsules, pills, powders, granules, and rectal suppositories. The pharmaceutical preparations may be sterilized and/or may contain adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, salts for varying the osmotic pressure and/or buffers.

The compounds of the invention can also be administered to a patient in accordance with the invention by topical (including transdermal, buccal or sublingual), or parenteral (including intraperitoneal, subcutaneous, intravenous, intradermal or intramuscular injection) routes.

The other active agents useful according to the invention may be one to three other antimalarial agents selected from the group comprising atovaquone, chloroquine, amodiaquine, mefloquine, artemisinin and the related peroxans from the pharmaceutical market like artesunate, arteether and artemether, menadione, methylene blue, proguanil, cycloguanil, chlorproguanil, pyrimethamine, primaquine, piperaquine, fosmidomycin, halofantrine, dapsone, trimethoprim, sulfamethoxazole, sulfadoxine, for a simultaneous, separated or sequential, or administration.

The invention also provides compounds of formula (I) including the compounds of formula (I) selected from the group comprising

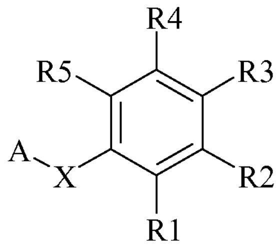


for the prevention and the treatment of malaria.

In one embodiment, the invention provides methods of inhibiting glutathione reductase in a parasite, comprising contacting said parasite with a pharmaceutical composition comprising a compound of the invention. In one embodiment, the parasite is a member of the *Plasmodium* genus. In another embodiment, the parasite is *Plasmodium falciparum*, or *Plasmodium vivax*.

In another embodiment, the invention provides methods of treating or preventing malaria, inhibiting glutathione reductase in a parasite, such as *Plasmodium falciparum* or *Plasmodium vivax*, in vitro or in vivo, or killing a *Plasmodium falciparum* or *Plasmodium vivax* parasite, wherein the pharmaceutical composition comprises a compound of formula (I).

Compounds of formula (II) corresponding to compounds of formula (I)

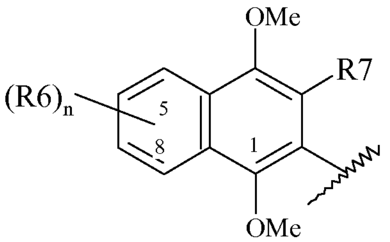


(I)

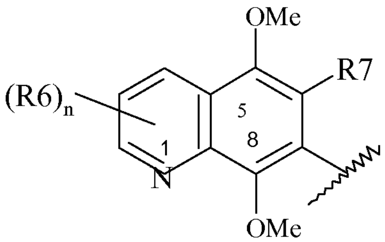
are new and are also part of the invention.

wherein

- (A) represents



or



with R6 which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-dimethoxynaphthalene or in position 2, 3, or 4 of the 5,8-dimethoxyquinoline, represents a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group and, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4 and R7 representing a methyl group and

- X = CH_2, C(O) or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group,

- R1, R2, R3, R4 and R5 represent each independently of the others:

. a hydrogen atom,

. a halogen atom,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group,

. a trifluoromethyl group,

. a difluoromethyl group,

. a linear or branched (C_1-C_4)alkoxy group,

. a trifluoromethoxy group,

. a difluoromethoxy group,

. a pentafluorosulfanyl group

. -COOH,

. -COO(C_1-C_4)alkyl group,

. –CONR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group and m = 1, 2 or 3,

. –CSNR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group m = 1, 2 or 3,

. –CONR8Het with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group, Het representing a pyridine-2-yl group optionally substituted by an amino group in -6 or by a –$CONH_2$ group in -5,

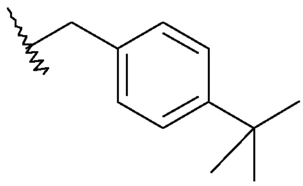
. - NO_2,

. - CN,

. –NR9R10 with R9 and R10 representing each independently a hydrogen atom, an amino protecting group selected from the group comprising Boc group and (C_1-C_4)alkyl group, or R9 and R10 forming with the nitrogen atom which bears them a cyclic group selected from the group comprising morpholine and piperazine groups said cyclic groups being optionally substituted,

. an aryl group optionally substituted by a (C_1-C_4)alkyl group, a -NO_2 group, a –COOR11 with R11 selected from a hydrogen atom and a linear or branched (C_1-C_4)alkyl group, a -NR12R13 with R12 and R13 independently selected from the group comprising a hydrogen atom and a linear or branched (C_1-C_4)alkyl group,

. a heterocyclic group selected from the group comprising morpholinyl group or piperazinyl group, each of said group being optionally substituted by one or several substituents selected from the group comprising a linear or branched (C_1-C_4)alkyl group, -$COOCH_2CH_3$, or a group



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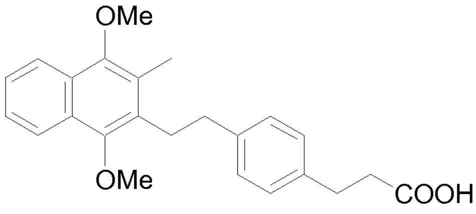
with the proviso that the compounds of formula (II) are not selected from the group comprising



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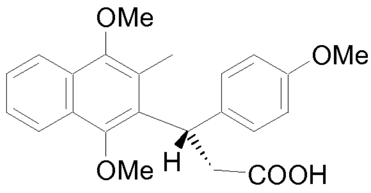


.

They may be used as intermediates for the synthesis of compounds of formula (I).

The following examples 1 to 16 are intended as illustrations of a few embodiments of the synthesis of compounds according to the invention. In these examples, melting points were determined on a Büchi melting point apparatus and were not corrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker DRX-300 spectrometer; chemical shifts were expressed in ppm relative to TMS; multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), dd (doublet of a doublet), dt (doublet of a triplet) and td (triplet of a doublet). Intensities in the IR spectra are indicated as vs (very strong), s (strong), m (medium), w (weak), b (broad). Elemental analyses were carried out at the Mikroanalytisches Laboratorium der Chemischen Fakultät der Universität Heidelberg. EI-MS and CI-MS were recorded at facilities of the Institut für Organische Chemie der Universität Heidelberg. Analytical TLC was carried out on pre-coated Sil G-25 UV_{254} plates from Macherey&Nagel. Flash chromatography was performed using silica gel G60 (230-400 mesh) from Macherey&Nagel.

The following examples 17 to 22 are intended as illustrations of the pharmacological activity of the compounds according to the invention.

Figures 1 to 8 also illustrate the invention.

Figure 1a to 1c illustrates the structure of some compounds synthesized according to the examples 1 to 16.

Figure 2 illustrates the IC_{50} values of benzyl-and benzoyl substituted derivatives of menadione according to the invention as inhibitors of *P. falciparum* and human glutathione reductase. [a] The values were determined at pH 6.9 and 25 °C in the presence of 1 mM GSSG according to example 17. [b] Data from Ref. (Bauer et al, *J. Am. Chem. Soc.* **2006**, 128, 10784-10794). [c] In the presence of 5 % DMSO. [d] Reprecipitation of the compound in the cuvette prevented IC_{50} determination. [e] In the presence of 1 % DMSO. nd: not yet determined.

Figure 3 illustrates the glutathione reductase-catalyzed naphthoquinone reductase activity as measured as disclosed in example 18. * Precipitation of the compound was observed above 10 µM; at 10 µM there is no inhibition

Figure 4 illustrates the effect of **P_TM25** on redox-cycling activity of methemoglobin(Fe^{3+}) into oxyhemoglobin(Fe^{2+}) in the presence of the NADPH/GR system measured at after 5 min (blue), 10 min (black), 20 min (green) and 30 min (red). MethHb = methemoglobin, OxyHb = Oxyhemoglobin. MB = Methylene Blue. The second plot (right) is a zoom of the spectra in the 350-450 nm area from the first plot (left).

Figure 5 illustrates IC_{50} values of menadione derivatives as cytotoxic agents against malarial parasites (Dd2, 3D7, K1, Pf-GHA) and human cells (KB, MRC-5) *in vitro*. a: CQ, Pf 3D7 IC_{50} 0.005 µM, K1 IC_{50} 0.55 µM; b: CQ, Pf K1 IC_{50} 0.01 µM; c: CQ, Pf 3D7 IC_{50} 0.0147 µM; d: CQ, Pf K1 IC_{50} 0.217 µM; e: CQ, Pf K1 IC_{50} 50.7 – 750.1 nM, Pf 3D7 IC_{50} 3.8 nM; f: CQ, Pf K1 IC_{50} 571.2 nM, Pf 3D7 IC50 11.5 – 15.3 nM; g: CQ, Pf 3D7 IC_{50} 0.02 – 0.85 µM, Pf K1 IC_{50} 0.01 - 0.02 µM; h: CQ, Pf 3D7 IC_{50} 1.9 – 5.8 nM, Pf K1 IC_{50} 57.7 – 750.1 nM; CQ = chloroquine.

Figure 6 illustrates IC_{50} and IC_{90} values against various *P. falciparum* strains as measured according to example 21. CQ = chloroquine; DHA = dihydroartemisinin; FQ = ferroquine; LMF = lumefantrine; MQ = mefloquine; MDAQ = monodesethylamodiaquine; QN, = quinine.

Figure 7 the reduction of parasitemia in *Plasmodium berghei* ANKA-infected CD1 mice as measured according to example 22. * at 1.0 mg/kg, 3.0 mg/kg and 10.0 mg/kg chloroquine displayed a reduction of the parasitemia of 2.5%, 16.6% and 94.9 %, respectively.

Figure 8 illustrates the i*n vivo* antimalarial activity in *P. berghei*-infected mice measured according to example 22.

EXAMPLE 1 General Procedure for the Silver-catalyzed Coupling Reactions of 1,4-Naphthoquinones with Carboxylic Acids

A solution of menadione or plumbagin (5.81 mmol) and a phenylacetic acid derivative (11.58 mmol) in 52.5 mL acetonitrile and 17.5 mL water was heated to 85 °C. $AgNO_3$ (90 mg, 0.58 mmol) was added. $(NH_4)_2S_2O_8$ (1.72 g, 7.54 mmol) in 15 mL acetonitrile and 5 mL water was added dropwise over a period of 45 minutes and then heated at reflux for two hours. The acetonitrile was removed *in vacuo*. The aqueous phase was extracted with dichloromethane (4 x 10 mL), dried over $MgSO_4$ and purified by flash-chromatography.

Example 1.1: 2-Methyl-3-(4-methyl-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM21)

As starting materials for the coupling reaction menadione and p-tolylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: ethylacetate = 1:1, UV), 2.82 g (10.21 mmol, 77 % yield) of **P_TM21** were isolated as yellow solid.

Melting point: 225 °C decomposition. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.05 (m, 2H), 7.64 – 7.70 (m, 2H), 7.08 (m, 4H), 3.98 (s, 2H), 2.27 (s, 3H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.42 (C_q), 184.66 (C_q), 145.53 (C_q), 144.20 (C_q), 135.97 (C_q), 134.94 (C_q), 133.42 (CH), 133.39 (CH), 132.12 (C_q), 132.06 (C_q), 129.31 (CH), 128.46 (CH), 126.44 (CH), 126.21 (CH), 31.99 (CH_2), 20.96 (CH_3), 13.23 (CH_3). – FAB MS (NBA, m/z (%)): 277.2 ($[M+H]^+$, 73), 261.1 (26), 212.1 (24). – IR (KBr): 3437 cm^{-1} (b, m), 2923 (w), 1660 (vs), 1616 (w), 1595 (m), 1512 (m), 1377 (w), 1332 (w), 1295 (vs), 809 (w), 754 (m), 705 (m). – EA: obs. C, 82.44 %; H, 5.84 %, calcd. C, 82.58 %; H, 5.84 % for $C_{19}H_{16}O_2$.

Example 1.2: 2-Methyl-3-(4-bromo-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM24)

As starting materials for the coupling reaction menadione and 4-bromophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 3.10 g (9.12 mmol, 78 % yield) of **P_TM24** were isolated as yellow solid.

Melting point: 121 – 122 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.10 (m, 2H), 7.66 – 7.71 (m, 2H), 7.36 (dt, ^3J = 8.46 Hz, ^4J = 1.95 Hz, 2H), 7.09 (d, ^3J = 8.53 Hz, 2H), 3.96 (s, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.20 (C_q), 184.54 (C_q), 144.75 (C_q), 144.57 (C_q), 137.06 (C_q), 133.58 (CH), 132.08 (C_q), 131.94 (C_q), 131.71 (CH), 130.32 (CH), 126.50 (CH), 126.35 (CH), 120.31 (C_q), 31.93 (CH_2), 13.31 (CH_3). – EI MS (70 eV, m/z (%)): 340.1 ($[M]^+$, 13), 325.0 (100), 246.1 (63), 215.1 (41), 202.1 (49), 128.1 (72), 76.0 (74). – IR (KBr): 3449 cm^{-1} (b, w), 3068 (w), 2962 (w), 1661 (vs), 1624 (m), 1618 (m), 1594 (s), 1486 (s), 1376 (m), 1332 (s), 1315 (s), 1294 (vs), 1071 (m), 1010 (s), 971 (w), 815 (m), 787 (s), 730 (m), 702 (m), 629 (w), 426 (w). – EA: obs. C, 63.02 %; H, 3.84 %, calcd. C, 63.36 %; H, 3.84 % for $C_{18}H_{13}BrO_2$.

Example 1.3: 2-Methyl-3-(4-fluoro-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM26).

As starting materials for the coupling reaction menadione and 4-fluorophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 5.34 g (19.1 mmol, 66 % yield) of **P_TM26** were isolated as yellow solid.

Melting point: 118 –119 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.08 (m, 2H), 7.65 – 7.71 (m, 2H), 7.15 – 7.20 (m, 2H), 6.93 (t, ^3J = 8.68 Hz, 2H), 3.97 (s, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.31 (C_q), 184.63 (C_q), 161.52 ($^1J_{CF}$ = 244.8 Hz, CF), 145.15 (C_q), 144.40 (C_q), 133.72 (C_q), 133.67 (C_q), 133.57 (C_q), 131.02 (CH), 130.05 ($^3J_{CF}$ = 8.0 Hz, CH), 128.95 ($^4J_{CF}$ = 3.4 Hz, C_q), 126.50 (CH), 126.34 (CH), 115.45 ($^2J_{CF}$ = 21.4 Hz, CH), 31.69 (CH_2), 13.28 (CH_3). – EI MS (70 eV, m/z (%)): 280.1 ($[M]^+$, 21), 265.1 (100), 109.0 (53), 76.0 (24). – IR (KBr): 3428 cm^{-1} (b, m), 1708 (w), 1684 (w), 1661 (vs), 1619 (w), 1597 (m), 1509 (vs), 1377 (w), 1295 (s), 1222 (m), 1158 (m), 824 (w), 705 (m). – EA: obs. C, 77.19 %; H, 4.71 %, calcd. C, 77.13 %; H, 4.67 % for $C_{18}H_{13}FO_2$.

Examlple 1.4: 2-Methyl-3-(4-trifluoro-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM29)

As starting materials for the coupling reaction menadione and 4-(Trifluoromethyl)phenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 3.09 g (9.36 mmol, 76 % yield) of **P_TM29** were isolated as yellow solid.

Melting point: 68 - 69 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.09 (m, 2H), 7.66 – 7.72 (m, 2H), 7.50 (d, ^3J = 8.21 Hz, 2H), 7.33 (d, ^3J = 8.03 Hz, 2H), 4.07 (s, 2H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.12 (C_q), 184.50 (C_q), 144.88 (C_q), 144.41 (C_q), 142.22 (C_q), 133.67 (CH), 133.66 (CH), 132.09 (C_q), 131.91 (C_q), 128.88 (CH), 128.85 ($^2J_{CF}$ = 32.4 Hz, C-CF_3), 126.53 (CH), 126.41 (CH), 125.59 ($^3J_{CF}$ = 3.8 Hz, CH), 124.19 ($^1J_{CF}$ = 278.6 Hz, CF_3), 32.37 (CH_2), 13.38 (CH_3). – EI MS (70 eV, m/z (%)): 330.0 ($[M]^+$, 30), 315.0 (100). – IR (KBr): 3400 cm^{-1} (b, m), 3047 (w), 2930 (m), 1662 (vs), 1617 (vs), 1593 (vs), 1418 (m), 1377 (s), 1329 (vs), 1295 (vs), 1259 (m), 1184 (m), 1161 (vs), 1112 (vs), 1069 (vs), 1019 (s), 977 (m), 950 (m), 823 (m), 789 (m), 758 (m), 715 (m), 691 (m). – EA: obs. C, 68.87 %; H, 3.98 %, calcd. C, 69.09 %; H, 3.97 % for $C_{19}H_{13}F_3O_2$.

Example 1.5: 2-Methyl-3-(4-chloro-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM30).

As starting materials for the coupling reaction menadione and 4-chlorophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 6.46 g (21.8 mmol, 75 % yield) of **P_TM30** were isolated as yellow solid.

Melting point: 134 – 135 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.10 (m, 2H), 7.66 – 7.72 (m, 2H), 7.22 (d, ^3J = 8.37 Hz, 2H), 7.14 (d, ^3J = 8.42 Hz, 2H), 3.98 (s, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.23 (C_q), 184.56 (C_q), 144.85 (C_q), 144.55 (C_q), 136.53 (C_q), 133.58 (CH), 132.29 (C_q), 132.10 (C_q), 131.97 (C_q), 129.93 (CH), 128.76 (CH), 126.50 (CH), 126.35 (CH), 31.87 (CH_2), 13.31 (CH_3). – EI MS (70 eV, m/z (%)): 296.1 ($[M]^+$, 25), 281.0 (100). – IR (KBr): 3439 cm^{-1} (b, m), 3076 (w), 2962 (w), 1687 (s), 1668 (vs), 1656 (vs), 1627 (m), 1595 (m), 1413 (m), 1379 (w), 1326 (vs), 1291 (vs), 1273 (m), 1235 (m), 1172 (s), 1130 (vs), 1110 (m), 1065 (s), 979 (m), 871 (m), 762 (m), 715 (w). – EA: obs. C, 72.89 %; H, 4.38 %; Cl, 11.83 %, calcd. C, 72.85 %; H, 4.42 %; Cl, 11.95 % for $C_{18}H_{13}ClO_2$.

Example 1.6: 2-Methyl-3-(4-methoxy-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM31)

As starting materials for the coupling reaction menadione and 4-methoxyphenylacetic acid were used. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 1.97 g (6.74 mmol, 45 % yield) of **P_TM31** were isolated as yellow solid.

Melting point: 112 – 113 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.09 (m, 2H), 7.64 – 7.69 (m, 2H), 7.14 (d, ^3J = 8.77 Hz, 2H), 6.78 (d, ^3J = 8.74 Hz, 2H), 3.97 (s, 2H), 3.73 (s, 3H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.45 (C_q), 184.71

(C_q), 158.14 (C_q), 145.59 (C_q), 144.02 (C_q), 133.43 (CH), 133.40 (CH), 132.10 (C_q), 132.04 (C_q), 130.02 (C_q), 129.60 (CH), 126.42 (CH), 126.21 (CH), 114.04 (CH), 55.21 (CH_3), 31.53 (CH_2), 13.19 (CH_3). – EI MS (70 eV, m/z (%)): 292.1 ($[M]^+$, 24), 277.0 (100), 250.1 (14), 219.1 (19). – IR (KBr): 3441 cm^{-1} (b, m), 2933 (w), 2841 (w), 1662 (vs), 1618 (m), 1595 (s), 1511 (vs), 1458 (w), 1375 (w), 1332 (m), 1297 (vs), 1247 (s), 1178 (m), 1035 (m), 823 (m), 793 (w), 707 (s). – EA: obs. C, 77.80 %; H, 5.51 %, calcd. C, 78.06 %; H, 5.51 % for $C_{19}H_{16}O_3$.

Example 1.7: 2-Methyl-3-(2-methoxy-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM32)

As starting materials for the coupling reaction menadione and 2-methoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 3.59 g (12.28 mmol, 82 % yield) of **P_TM32** were isolated as yellow solid.

Melting point: 117 – 118 °C. – ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 8.04 – 8.10 (m, 2H), 7.64 – 7.70 (m, 2H), 7.13 – 7.19 (m, 1H), 7.03 (d, ^3J = 6.53 Hz, 1H), 6.79 (m, 2H), 3.99 (s, 2H), 3.81 (s, 3H), 2.15 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.45 (C_q), 184.65 (C_q), 157.17 (C_q), 145.64 (C_q), 144.88 (C_q), 133.39 (CH), 133.30 (CH), 132.27 (C_q), 132.22 (C_q), 129.32 (CH), 127.54 (CH), 126.45 (CH), 126.26 (C_q), 126.22 (CH), 120.56 (CH), 110.30 (CH), 55.34 (CH_3), 26.81 (CH_2), 13.05 (CH_3). – EI MS (70 eV, m/z (%)): 292.1 ($[M]^+$, 39), 277.1 (100), 250.1 (42). – IR (KBr): 3432 cm^{-1} (b, m), 2960 (w), 2836 (w), 1695 (w), 1661 (s), 1617 (w), 1596 (m), 1493 (m), 1459 (w), 1334 (w), 1295 (s), 1259 (w), 1245 (m), 1110 (w), 1029 (m), 754 (w), 711 (w). – EA: obs. C, 77.77 %; H, 5.43 %, calcd. C, 78.06 %; H, 5.52 % for $C_{19}H_{16}O_3$.

Example 1.8: 2-Methyl-3-(4-hydroxy-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM36)

As starting materials for the coupling reaction menadione and 4-hydroxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 596 mg (2.1 mmol, 7 % yield) of **P_TM36** were isolated as yellow solid.

Melting point: 165 – 166 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.09 (m, 2H), 7.65 – 7.71 (m, 2H), 7.06 – 7.10 (m, 2H), 6.69 – 6.73 (m, 2H), 4.70 (bs, 1H), 3.93 (s, 2H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.52 (C_q), 184.80 (C_q), 154.09 (C_q), 145.60 (C_q), 144.13 (C_q), 133.50 (CH), 133.47 (C_q), 130.12 (C_q), 129.78 (CH), 129.01 (CH), 126.45 (CH), 126.26 (CH), 115.58 (CH), 115.48 (CH), 31.56 (CH_2), 13.23 (CH_3). – FAB MS (NBA): 277.9 ($[M]^+$, 49). – IR (KBr): 3480 cm^{-1} (b, s), 1659 (vs), 1616 (m), 1595 (s), 1513 (vs), 1336 (m), 1295 (vs), 1260 (m), 1217 (m), 1203 (w), 1176 (w), 708 (s). – EA: obs. C, 77.47 %; H, 5.07 %, calcd. C, 77.68 %; H, 5.07 % for $C_{18}H_{14}O_3$.

Example 1.9: 2-Methyl-3-(4-nitro-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM37)

As starting materials for the coupling reaction menadione and 4-nitrophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 7.97 g (25.9 mmol, 89 % yield) of **P_TM37** were isolated as yellow solid.

Melting point: 156 – 157 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.13 (m, 4H), 7.68 – 7.74 (m, 2H), 7.38 (d, ^3J = 8.71 Hz, 2H), 4.11 (s, 2H), 2.24 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.94 (C_q), 184.39 (C_q), 146.69 (C_q), 145.83 (C_q), 145.17 (C_q), 143.82 (C_q), 133.81 (CH), 133.76 (CH), 132.05 (C_q), 131.81 (C_q), 129.39 (CH), 126.57 (CH), 126.49 (CH), 123.91 (CH), 32.51 (CH_2), 13.45 (CH_3). – EI MS (70 eV, m/z (%)): 307.0 ($[M]^+$, 37), 292.0 (100). – IR (KBr): 3441 cm^{-1} (b, m), 3106 (w), 3076 (w), 1662 (vs), 1625 (s), 1604 (s), 1595 (vs), 1510 (vs), 1494 (m), 1381 (m), 1348 (vs), 1324 (vs), 1297 (vs), 1260 (m), 1184 (m), 982 (m), 951 (s), 847 (s), 786 (s), 742 (s), 724 (vs), 694 (s). – EA: obs. C, 70.24 %; H, 4.11 %; N, 4.65 %, calcd. C, 70.35 %; H, 4.26 %; N, 4.56 % for $C_{18}H_{13}NO_4$.

Example 1.10: 2-Methyl-3-(4-cyano-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM41)

As starting materials for the coupling reaction menadione and 4-cyanophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 565 g (1.9 mmol, 63 % yield) of **P_TM41** were isolated as yellow solid.

Melting point: 159 – 160 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.11 (m, 2H), 7.67 – 7.73 (m, 2H), 7.55 (d, ^{3}J = 8.32 Hz, 2H), 7.32 (d, ^{3}J = 8.28 Hz, 2H), 4.06 (s, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.98 (C_q), 184.42 (C_q), 145.09 (C_q), 143.91 (C_q), 143.71 (C_q), 133.78 (CH), 133.73 (CH), 132.47 (CH), 132.06 (C_q), 131.82 (C_q), 129.35 (CH), 126.56 (CH), 126.47 (CH), 118.75 (C_q), 110.49 (C_q), 32.69 (CH_2), 13.42 (CH_3). – EI MS (70 eV, m/z (%)): 287 ($[M]^+$, 8), 286.1 (33), 271.0 (100). – IR (KBr): 3430 cm^{-1} (b, m), 3087 (w), 3069 (w), 3054 (w), 2941 (w), 2227 (vs, CN), 1664 (vs), 1622 (s), 1604 (s), 1594 (s), 1505 (m), 1336 (s), 1328 (s), 1296 (vs), 1264 (w), 1178 (m), 976 (m), 952 (m), 822 (m), 749 (s), 710 (s), 691 (m), 631 (m), 567 (w). – EA: obs. C, 79.16 %; H, 4.52 %; N, 4.89 %, calcd. C, 79.43 %; H, 4.56 %; N, 4.88 % for $C_{19}H_{13}NO_2$.

Example 1.11: 2-Methyl-3-(4-*tert*-butyl-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM43)

As starting materials for the coupling reaction menadione and 4-*tert*butylphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 995 g (3.1 mmol, 67 % yield) of **P_TM43** were isolated as yellow solid.

Melting point: 60 – 61 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.09 (m, 2H), 7.64 – 7.70 (m, 2H), 7.27 (d, ^{3}J = 8.35 Hz, 2H), 7.15 (d, ^{3}J = 8.33 Hz, 2H), 3.98 (s, 2H), 2.25 (s, 3H), 1.26 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.47 (C_q), 184.70 (C_q), 149.28 (C_q), 145.52 (C_q), 144.21 (C_q), 134.90 (C_q), 133.45 (CH), 133.41 (CH), 132.15 (C_q), 132.10 (C_q), 128.28 (CH), 126.46 (CH), 126.24 (CH), 125.56 (CH), 34.36 (C_q), 31.93 (CH_2), 31.08 (CH_3), 13.30 (CH_3). – EI MS (70 eV, m/z (%)): 318.0 ($[M]^+$, 23), 303 (100), 261.0 (31), 247.0 (12). – IR (KBr): 3400 cm^{-1} (b, m), 2961 (m), 2905 (w), 2868 (w), 1659 (vs), 1619 (m), 1594 (m), 1512 (w), 1462 (w), 1369 (w), 1333 (m), 1314 (m), 1294 (vs), 1270 (w), 976 (w), 81818 (w), 717 (m), 692 (w), 571 (w), 541 (w). – EA: obs. C, 82.35 %; H, 6.80 %, calcd. C, 82.22 %; H, 7.01 % for $C_{22}H_{22}O_2 \cdot 0.1$ EtOAc.

Example 1.12: [4-(3-Methyl-1,4-dioxo-1,4,4a,8a-tetrahydro-naphthalen-2-ylmethyl)-phenyl]-carbamic acid *tert*-butyl ester (P_TM45)

As starting materials for the coupling reaction menadione and (4-*tert*-Butoxycarbonylamino-phenyl)-acetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 527 mg (1.4 mmol, 12 % yield) of **P_TM45** were isolated as yellow solid.

Melting point: 148 – 149 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.08 (m, 2H), 7.66 – 7.71 (m, 2H), 7.23 (d, ^3J = 8.26 Hz, 2H), 7.12 (d, ^3J = 8.57 Hz, 2H), 6.36 (s, 1H), 3.95 (s, 2H), 2.21 (s, 3H), 1.47 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.42 (C_q), 184.68 (C_q), 152.73 (C_q), 145.38 (C_q), 144.21 (C_q), 136.70 (C_q), 133.47 (CH), 133.44 (CH), 132.61 (C_q), 132.10 (C_q), 132.03 (C_q), 129.14 (CH), 126.45 (CH), 126.25 (CH), 118.88 (CH), 80.49 (C_q), 31.74 (CH_2), 28.30 (CH_3), 13.22 (CH_3). – EI MS (70 eV, m/z (%)): 377.2 ($[M]^+$, 18), 321.1 (66), 305.9 (100), 261.1 (59), 201.3 (14), 160.1 (18), 121.1 (21). – IR (KBr): 3439 (b, vs), 1704 (w), 1685 (w), 1660 (s), 1618 (m), 1596 (m), 1521 (m), 1370 (w), 1315 (m), 1296 (m), 1236 (w), 1162 (s), 709 (w). – EA: obs. C, 72.94 %; H, 6.16 %; N, 3.74 %, calcd. C, 73.19 %; H, 6.14 %, N, 3.71 % for $C_{23}H_{23}NO_4$.

Example 1.13: 4-(3-Methyl-1,4-dioxo-1,4,4a,8a-tetrahydro-naphthalen-2-ylmethyl)-benzoic acid (P_TM50)

As starting materials for the coupling reaction menadione and 4-carboxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 102 mg (0.33 mmol, 12 % yield) of **P_TM50** were isolated as yellow solid.

Melting point: 206 – 208 °C. – ^{1}H-NMR (300 MHz, DMSO): δ = 7.99 – 8.04 (m, 2H), 7.79 – 7.89 (m, 4H), 7.35 (d, ^3J = 8.15 Hz, 2H), 4.06 (s, 2H), 2.15 (s, 3H). – ^{13}C-NMR (75 MHz, DMSO): δ = 184.57 (C_q), 184.03 (C_q), 167.26 (C_q), 144.76 (C_q), 143.79 (C_q), 143.33 (C_q), 133.95 (CH), 133.90 (CH), 131.71 (C_q), 131.43 (C_q), 129.51 (CH), 128.40 (CH), 125.98 (CH), 125.88 (CH), 31.78 (CH_2), 13.05 (CH_3). – EI MS (70 eV, m/z (%)): 305.9 ($[M]^+$, 22), 290.9 (100), 260.9 (21). – IR (KBr): 3455 cm^{-1} (b, vs), 3071 (m), 2932 (m), 1701 (vs), 1659 (vs), 1610 (s), 1594 (s), 1423 (m), 1376 (m), 1319 (m), 1295 (vs), 1234 (m), 1181 (m), 1114 (w), 949 (w), 778 (m), 757 (m), 719 (m), 695 (m), 631 (w). – EA: obs. C, 73.28 %; H, 4.84 %, calcd. C, 73.42 %; H, 4.70 % for $C_{19}H_{14}O_4 \cdot 0.25\ H_2O$.

Example 1.14: 2-(3,4-Dimethoxy-benzyl)-3-methyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM54)

As starting materials for the coupling reaction menadione and 3,4-dimethoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 4.25 g (13.2 mmol, 65 % yield) of **P_TM54** were isolated as orange solid.

Melting point: 102 – 103 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 – 8.08 (m, 2H), 7.67 – 7.69 (m, 2H), 6.79 (s, 1H), 6.71 – 6.74 (m, 2H), 3.95 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.25 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.43 (C_q), 184.78 (C_q), 149.01 (C_q), 147.67 (C_q), 145.41 (C_q), 144.13 (C_q), 133.48 (CH), 133.46 (CH), 132.11 (C_q), 132.04 (C_q), 130.47 (C_q), 126.45 (CH), 126.26 (CH), 120.46 (CH), 112.19 (CH), 111.27 (CH), 55.88 (CH_3), 31.99 (CH_2), 13.26 (CH_3). – EI MS (70 eV, m/z (%)): 322.2 ($[M]^+$, 28), 307.1 (100). – IR (KBr): 3400 cm^{-1} (b, s), 3002 (w), 2954 (w), 2935 (w), 2834 (w), 1660 (vs), 1618 (m), 1594 (m), 1514 (vs), 1461 (m), 1444 (m), 1419 (w), 1376 (w), 1334 (m), 1295 (vs), 1262 (vs), 1238 (s), 1184 (w), 1143 (s), 1027 (m), 976 (w), 748 (m), 701 (m). – EA: obs. C, 74.28 %; H, 5.64, calcd. C, 74.52 %; H, 5.63 % for $C_{20}H_{18}O_4$.

Example 1.15: 2-(2,4-Dimethoxy-benzyl)-3-methyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM56)

As starting materials for the coupling reaction menadione and 2,4-dimethoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 922 mg (2.86 mmol, 37 % yield) of **P_TM56** were isolated as orange solid.

Melting point: 103 – 105 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$,): δ = 8.03 – 8.09 (m, 2H), 7.64 – 7.70 (m, 2H), 6.95 (d, ^3J = 8.33 Hz, 1H), 6.41 (d, ^4J = 2.40 Hz, 1H), 6.35 (dd, ^3J = 8.34 Hz, ^4J = 2.44 Hz, 1H), 3.91 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 2.16 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.95 (C_q), 185.18 (C_q), 159.87 (C_q), 158.47 (C_q), 146.21 (C_q), 145.03 (C_q), 133.76 (CH), 133.67 (CH), 132.69 (C_q), 132.62 (C_q), 130.21 (CH), 126.82 (CH), 126.59 (CH), 118.98 (C_q), 104.46 (CH), 98.90 (CH), 55.74 (CH_3), 26.67 (CH_2), 13.39 (CH_3). – EI MS (70 eV, m/z (%)): 322.2 ($[M]^+$, 23), 307.2 (89), 138.1 (25). – IR (KBr): 3445 cm^{-1} (b, m), 2994 (w), 2937 (w), 2836 (w), 1660 (vs), 1614 (s), 1591 (s), 1506 (s), 1462 (m), 1421 (w), 1376 (w), 1331 (m), 1295 (vs), 1262 (s), 1209 (m), 1183 (m), 1157 (m), 1119 (m), 1037 (m), 828 (w), 707 (m). – EA: obs. C, 74.33%, H, 5.75 %, calcd. C, 74.52 %; H, 5.63 % for $C_{20}H_{18}O_4$.

Example 1.16: 2-Methyl-3-pentafluorophenylmethyl-4a,8a-dihydro[1,4]naphtha-quinone (P_TM57)

As starting materials for the coupling reaction menadione and 2,3,4,5,6-pentafluorophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 306 mg (0.87 mmol, 44 % yield) of **P_TM57** were isolated as yellow solid.

Melting point: 103 – 104 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.00 – 8.07 (m, 2H), 7.67 – 7.70 (m, 2H), 4.02 (s, 2H), 2.24 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.70 (C_q), 183.67 (C_q), 146.93 (CF), 145.43 (C_q), 143.66 (CF), 141.85 (C_q), 139.15 (CF), 138.36 (CF), 135.77 (CF), 133.73 (CH), 133.71 (CH), 131.97 (C_q), 131.73 (C_q), 126.48 (CH), 126.47 (CH), 111.95 (C_q), 20.90 (CH_2), 12.98 (CH_3). – EI MS (70 eV, m/z (%)): 352.1 ($[M]^+$, 100), 332.1 (9), 303.1 (25). – IR (KBr): 3438 cm^{-1} (b, m), 1667 (vs), 1621 (m), 1594 (s), 1523 (vs), 1501 (vs), 1459 (w), 1375 (s), 1331 (vs), 1294 (vs), 1258 (m), 1119 (s), 1066 (m), 1027 (w), 1002 (s), 972 (s), 952 (vs), 729 (m), 713 (m). – EA: obs. C, 61.18 %; H, 2.68 %, calcd. C, 61.37 %; H, 2.58 % for $C_{18}H_9F_5O_2$.

Example 1.17: 2-(3,5-Dimethoxy-benzyl)-3-methyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM58)

As starting materials for the coupling reaction menadione and 3,5-dimethoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 555 mg (1.72 mmol, 75 % yield) of **P_TM58** were isolated as yellow solid.

Melting point: 127 – 128 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 – 8.06 (m, 2H), 7.63 – 7.69 (m, 2H), 6.35 (d, ^4J = 2.17 Hz, 2H), 6.26 (t, ^4J = 2.20 Hz, 1H), 3.94 (s, 2H), 3.72 (s, 6H), 2.21 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$,): δ = 185.21 (C_q), 184.49

(C_q), 160.84 (C_q), 144.87 (C_q), 144.55 (C_q), 140.22 (C_q), 133.39 (CH), 133.37 (CH), 132.05 (C_q), 131.95 (C_q), 126.40 (CH), 126.18 (CH), 106.78 (CH), 97.94 (CH), 55.18 (CH_3), 32.43 (CH_2), 13.20 (CH_3). – EI MS (70 eV, m/z (%)): 322.1 ($[M]^+$, 20), 307.1 (30), 292.1 (10). – IR (KBr): 3438 cm^{-1} (b, m), 2958 (w), 2941 (w), 2837 (w), 1661 (vs), 1600 (vs), 1471 (s), 1426 (m), 1376 (m), 1332 (s), 1292 (vs), 1262 (w), 1208 (s), 1157 (vs), 1071 (m), 1055 (m), 975 (w), 822 (m), 737 (vs), 691 (m). – EA: obs. C, 74.24 %; H, 5.61 %, calcd. C, 74.52 %; H, 5.63 % for $C_{20}H_{18}O_4$.

Example 1.18 : 2-Methyl-3-(3,4,5-trimethoxy-benzyl)-4a,8a-dihydro-[1,4]naphthaquinone (P_TM59)

As starting materials for the coupling reaction menadione and 3,4,5-trimethoxyphenylacetic acid were used. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 1.98 g (5.62 mmol, 85 % yield) of **P_TM59** were isolated as yellow solid.

Melting point: 147 – 149 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 – 8.07 (m, 2H), 7.63 – 7.69 (m, 2H), 6.42 (s, 2H), 3.92 (s, 2H), 3.77 (s, 6H), 3.75 (s, 3H), 2.24 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.23 (C_q), 184.63 (C_q), 153.18 (C_q), 144.97 (C_q), 144.23 (C_q), 136.59 (C_q), 133.54 (C_q), 133.44 (CH), 131.98 (C_q), 131.89 (C_q), 126.37 (CH), 126.20 (CH), 106.61 (CH), 105.75 (CH), 60.73 (CH_3), 56.06 (CH_3), 32.57 (CH_2), 13.28 (CH_3). – EI MS (70 eV, m/z (%)): 352.1 ($[M]^+$, 54), 337.1 (100). – IR (KBr): 3481 cm^{-1} (b, s), 2942 (w), 2836 (w), 1658 (vs), 1592 (s), 1507 (m), 1458 (m), 1330 (m), 1296 (s), 1127 (vs), 731 (m). – EA: obs. C, 71.25 %; H, 5.75 %, calcd. C, 71.58 %, H, 5.72 % for $C_{21}H_{20}O_5$.

Example 1.19: 2-(2,5-Dimethoxy-benzyl)-3-methyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM60)

As starting materials for the coupling reaction menadione and 2,5-dimethoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 1.96 g (6.08 mmol, 80 % yield) of **P_TM60** were isolated as yellow solid.

Melting point: 140 – 142 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.08 (m, 2H), 7.64 – 7.69 (m, 2H), 6.76 (d, ^3J = 8.80 Hz, 1H), 6.66 (dd, ^3J = 8.81 Hz, ^4J = 2.96 Hz, 1H), 6.59 (d, ^4J = 2.92 Hz, 1H), 3.98 (s, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 2.15 (s, 3H).

– ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.35 (C_q), 184.55 (C_q), 153.52 (C_q), 151.50 (C_q), 145.40 (C_q), 144.94 (C_q), 133.36 (CH), 133.28 (CH), 132.22 (C_q), 132.21 (C_q), 127.62 (C_q), 126.43 (CH), 126.20 (CH), 116.20 (CH), 111.14 (CH), 110.91 (CH), 55.93 (CH_3), 55.61 (CH_3), 26.68 (CH_2), 12.99 (CH_3). – EI MS (70 eV, m/z (%)): 322.1 ($[M]^+$, 100), 307.1 (67), 291.1 (38), 277.0 (20). – IR (KBr): 3450 cm^{-1} (b, m), 3006 (w), 2955 (w), 2833 (w), 1660 (vs), 1612 (s), 1590 (s), 1499 (vs), 1465 (m), 1372 (m), 1325 (m), 1295 (vs), 1280 (s), 1261 (s), 1235 (vs), 1163 (m), 1051 (s), 1022 (m), 793 (m), 708 (s). – EA: obs. C, 73.16 %; H, 5.51 %, calcd. C, 72.97 %; H, 5.54 % for $C_{20}H_{18}O_4 \cdot 0.1\ CH_2Cl_2$.

Example 1.20: 2-Methyl-3-(2,3,4-trimethoxy-benzyl)-4a,8a-dihydro-[1,4]naphtha-quinone (P_TM61)

As starting materials for the coupling reaction menadione and 2,3,4-trimethoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:9, UV), 544 mg (1.540 mmol, 76 % yield) of **P_TM61** were isolated as yellow solid.

Melting point: 102 – 103 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.08 (m, 2H), 7.64 – 7.69 (m, 2H), 6.70 (d, ^3J = 8.69 Hz, 1H), 6.52 (d, ^3J = 8.60 Hz, 1H), 3.94 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.15 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.40 (C_q), 184.59 (C_q), 152.40 (C_q), 151.68 (C_q), 145.70 (C_q), 144.53 (C_q), 142.28 (C_q), 133.38 (CH), 133.31 (CH), 132.18 (C_q), 132.16 (C_q), 126.40 (CH), 126.21 (CH), 123.98 (C_q), 123.36 (CH), 107.18 (CH), 60.75 (CH_3), 60.69 (CH_3), 55.94 (CH_3), 26.52 (CH_2), 12.99 (CH_3). – EI MS (70 eV, m/z (%)): m/z = 352.2 ($[M]^+$, 61), 337.2 (100), 191.1 (28). – IR (KBr): 3440 cm^{-1} (b, m), 2974 (w), 2941 (w), 2927 (w), 1663 (vs), 1616 (m), 1594 (s), 1493 (s), 1465 (s), 1416 (m), 1332 (m), 1296 (vs), 1260 (m), 1202 (w), 1101 (vs), 1044 (s), 973 (w), 786 (w), 713 (w), 696 (w). – EA: obs. C, 71.49 %, H, 5.76 %, calcd. C, 71.58 %; H, 5.72 % for $C_{21}H_{20}O_5$.

Example 1.21: 2-Methyl-3-benzyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM62)

As starting materials for the coupling reaction menadione and phenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 2.50 g (9.53 mmol, 86 % yield) of **P_TM62** were isolated as yellow hygroscopic solid.

Melting point: 103 – 104 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.09 (m, 2H), 7.63 – 7.68 (m, 2H), 7.16 – 7.33 (m, 5H), 4.02 (s, 2H), 2.24 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.16 (C_q), 184.45 (C_q), 145.17 (C_q), 144.26 (C_q), 137.95 (C_q), 133.33 (CH), 133.30 (CH), 131.97 (C_q), 131.89 (C_q), 128.53 (CH), 128.50 (CH), 126.31 (CH), 126.11 (CH), 32.29 (CH_2), 13.14 (CH_3). – EI MS (70 eV, m/z (%)): 262.2 ($[M]^+$, 30), 247.1 (100). – IR (KBr): 3454 cm^{-1} (b, m), 3061 (w), 3028 (w), 2937 (w), 1662 (vs), 1654 (vs), 1620 (m), 1593 (m), 1333 (m), 1293 (vs), 718 (s), 698 (m). – EA: obs. C, 82.39 %; H, 5.47 %, calcd. C, 82.42 %; H, 5.38 % for $C_{18}H_{14}O_2$.

Example 1.22: 3-(4-Bromo-benzyl)-5-hydroxy-2-methyl-4a,8a-dihydro-[1,4]naphthoquinone (P_TM42)

As starting materials for the coupling reaction plumbagin and 4-bromophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (cyclohexane : ethyl acetate = 3:1, UV), 1.35 g (3.8 mmol, 71 % yield) of **P_TM42** were isolated as red solid.

Melting point: 163 – 164 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.07 (s, 1H), 7.54 – 7.63 (m, 2H), 7.38 (d, ^{3}J = 8.38 Hz, 2H), 7.22 (dd, ^{3}J = 7.94 Hz, ^{4}J = 1.53 Hz, 1H), 7.09 (d, ^{3}J = 8.33 Hz, 2H), 3.94 (s, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 189.68 (C_q), 184.42 (C_q), 161.33 (C_q), 146.01 (C_q), 144.54 (C_q), 136.72 (C_q), 136.17 (CH), 132.07 (C_q), 131.81 (CH), 130.21 (CH), 124.07 (CH), 120.47 (C_q), 119.09 (CH), 114.86 (C_q), 31.32 (CH_2), 13.44 (CH_3). – EI MS (70 eV, m/z (%)): 356.0 ($[M]^+$, 26), 341 (100), 261.1 (25), 107 (40), 77.0 (80). – IR (KBr): 3440 cm^{-1} (b, m), 3047 (w), 1658 (s), 1635 (vs), 1610 (s), 1486 (s), 1456 (s), 1376 (w), 1359 (w), 1315 (w), 1294 (vs), 1266 (vs), 1198 (m), 1163 (w), 1070 (w), 1011 (m), 831 (w), 752 (m), 742 (w). – EA: obs. C, 60.54 %; H, 3.75 %; Br, 22.52 %, calcd. C, 60.52 %; H, 3.67 %; Br, 22.37 % for $C_{18}H_{13}BrO_3$.

Example 1.23: 3-(4-*tert*-Butyl-benzyl)-5-hydroxy-2-methyl-[1,4]naphthoquinone (P_TM81)

As starting materials for the coupling reaction plumbagin and 4-*tert*butylphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 1.25 g (3.73 mmol, 70 % yield) of **P_TM81** were isolated as red solid.

Melting point: 112 – 113 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.15 (s, 1H), 7.51 – 7.61 (m, 2H), 7.29 (d, ^3J = 8.34 Hz, 2H), 7.14 – 7.21 (m, 3H), 3.97 (s, 2H), 2.25 (s, 3H), 1.28 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 189.82 (C_q), 184.55 (C_q), 161.16 (C_q), 149.39 (C_q), 145.57 (C_q), 145.18 (C_q), 135.91 (CH), 134.48 (C_q), 132.05 (C_q), 128.11 (CH), 125.57 (CH), 123.83 (CH), 118.84 (CH), 114.88 (C_q), 34.32 (C_q), 31.27 (CH_2), 31.26 (CH_3), 13.36 (CH_3). – EI MS (70 eV, m/z (%)): 334.14 ($[M]^+$, 31), 319.11 (100), 277.07 (38), 263.06 (5), 173.05 (8), 152.03 (9). – IR (KBr): 3443 cm^{-1} (b, w), 2964 (m), 1660 (s), 1634 (vs), 1612 (vs), 1514 (m), 1456 (vs), 1384 (w), 1360 (s), 1323 (m), 1305 (vs), 1294 (vs), 1270 (vs), 1199 (m), 1163 (m), 1058 (w), 831 (m), 761 (s), 748 (s), 710 (m). – EA: obs. C, 78.61 %; H, 6.60 %, calcd. C, 79.02 %; H, 6.63 % for $C_{22}H_{22}O_3$.

Example 1.24: 2-(3-Methoxy-benzyl)-3-methyl-[1,4]naphthoquinone (P_TM96)

As starting materials for the coupling reaction menadione and 3-methoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 1.64 g (5.61 mmol, 75 % yield) of **P_TM96** were isolated as yellow solid.

Melting point: 87 – 88 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.08 (m, 2H), 7.66 – 7.69 (m, 2H), 7.16 (t, ^3J = 7.87 Hz, 1H), 6.69 – 6.81 (m, 3H), 3.99 (s, 2H), 3.74 (s, 3H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.36 (C_q), 184.62 (C_q), 159.78 (C_q), 145.14 (C_q), 144.53 (C_q), 139.58 (C_q), 133.49 (CH), 133.46 (CH), 132.13 (C_q), 132.04 (C_q), 129.59 (CH), 126.49 (CH), 126.27 (CH), 120.97 (CH), 114.68 (CH), 111.42 (CH), 55.16 (CH_3), 32.37 (CH_2), 13.29 (CH_3). – EI MS (70 eV, m/z (%)): 292.19 ($[M]^+$, 39), 277.16 (100), 172.10 (12). – IR (KBr): 3066 cm^{-1} (w), 2978 (w), 2945 (w), 2838 (w), 1659 (vs), 1617 (s), 1599 (vs), 1490 (vs), 1470 (s), 1434 (m), 1383 (s), 1327 (vs), 1294 (vs), 1264 (vs), 1256 (vs), 1163 (s), 1040 (vs), 976 (m), 849 (m), 799 (s), 788 (m), 745 (vs), 710 (m), 697 (s). – EA: obs. C, 78.31 %; H, 5.53 %, calcd. C, 78.06 %; H, 5.52 % for $C_{19}H_{16}O_3$.

Example 1.25: 2-Methyl-3-(4-trifluoromethoxy-benzyl)-[1,4]naphthoquinone (P_TM97)

As starting materials for the coupling reaction menadione and 4-(trifluoromethoxy)phenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 494 mg (1.43 mmol, 78 % yield) of **P_TM97** were isolated as yellow solid. Melting point: 64 – 65 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 – 8.10 (m, 2H), 7.65 – 7.71 (m, 2H), 7.34 (d, ^3J = 8.74 Hz, 2H), 7.09 (d, ^3J = 8.08 Hz, 2H), 4.01 (s, 2H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.17 (C_q), 184.52 (C_q), 147.42 (C_q), 144.72 (C_q), 144.57 (C_q), 136.76 (C_q), 133.57 (CH), 132.07 (C_q), 131.92 (C_q), 129.87 (CH), 126.47 (CH), 126.33 (CH), 121.15 (CH), 120.44 (q, $^1J_{CF}$ = 256.91 Hz), 31.78 (CH_2), 13.27 (CH_3). – EI MS (70 eV, m/z (%)): 346.0 ($[M]^+$, 32), 331.1 (100), 261.1 (8), 175.1 (71), 76.0 (10), 28.0 (49). – IR (KBr): 3077 cm^{-1} (w), 3047 (w), 3021 (w), 3003 (w), 2963 (w), 2948 (w), 2853 (w), 2143 (w), 2004 (w), 1975 (w), 1901 (w), 1876 (w), 1664 (vs), 1620 (m), 1596 (s), 1508 (s), 1446 (w), 1435 (w), 1378 (m), 1333 (s), 1297 (vs), 1271 (vs), 1217 (vs), 1188 (vs), 1166 (vs), 1111 (m), 1019 (w), 976 (m), 793 (w), 770 (w), 708 (s), 692 (w). – EA: obs. C, 65.78 %; H, 3.98 %, calcd. C, 65.90 %; H, 3.78 % for $C_{19}H_{13}F_3O_3$.

Example 1.26: 2-Methyl-3-(2-bromo-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM98)

As starting materials for the coupling reaction menadione and 2-bromophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 1.75 g (5.14 mmol, 88 % yield) of **P_TM98** were isolated as yellow solid.

Melting point: 94 – 95 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 – 8.11 (m, 2H), 7.66 -7.72 (m, 2H), 7.56 (dd, ^3J = 7.87 Hz, ^4J = 1.32 Hz, 1H), 7.13 (dt, ^3J = 7.47 Hz, ^4J = 1.35 Hz, 1H), 7.04 (dt, ^3J = 7.69 Hz, ^4J = 1.75 Hz, 1H), 6.89 (dd, ^3J = 7.61 Hz, ^4J = 1.56 Hz, 1H), 4.11 (s, 2H), 2.10 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.98 (C_q), 184.30 (C_q), 145.85 (C_q), 144.53 (C_q), 137.31 (C_q), 133.55 (CH), 133.53 (CH), 132.87 (CH), 132.13 (C_q), 131.96 (C_q), 128.59 (CH), 127.93 (CH), 127.55 (CH), 126.53 (CH), 126.33 (CH), 124.67 (C_q), 32.65 (CH_2), 13.26 (CH_3). – EI MS (70 eV, m/z (%)): 261.1 ($[M\text{-}Br]^+$, 100), 231.1 (11), 202.1 (11), 130.1 (8), 76.0 (10). – IR (KBr): 3441 cm^{-1} (b, s), 3068 (w), 3017 (w), 2923 (w), 1660 (vs), 1621 (s), 1594 (s), 1467 (m), 1439 (m), 1376 (w), 1318 (m), 1296 (vs), 1263 (m), 1223 (w), 1184 (w), 1025 (m), 976 (m), 787 (w), 749 (s), 729 (m), 695 (w), 663 (w). – EA: obs. C, 63.12 %; H, 3.91 %; Br, 23.31 %, calcd. C, 63.36 %; H, 3.84 %; Br, 23.42 % for $C_{18}H_{13}BrO_2$.

Example 1.27: 2-Methyl-3-(3-bromo-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM99)

As starting materials for the coupling reaction menadione and 3-bromophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 328 mg (0.96 mmol, 52 % yield) of **P_TM99** were isolated as yellow solid.

Melting point: 108 – 109 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.98 – 8.02 (m, 2H), 7.59 – 7.65 (m, 2H), 7.28 (s, 1H), 7.24 (td, ^3J = 6.78 Hz, ^4J = 1.97 Hz, 1H), 7.02 – 7.09 (m, 2H), 3.92 (s, 2H), 2.16 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.16 (C_q), 184.45 (C_q), 144.78 (C_q), 144.50 (C_q), 140.35 (C_q), 133.59 (CH), 132.10 (C_q), 131.94 (C_q), 131.52 (CH), 130.16 (CH), 129.65 (CH), 127.26 (CH), 126.54 (CH), 126.36 (CH), 122.72 (C_q), 32.09 (CH_2), 13.35 (CH_3). – EI MS (70 eV, m/z (%)): 340.0 ([M]$^+$, 28), 325.06 (100), 246.13 (18), 215.14 (7), 202.12 (8), 184.99 (12), 76.0 (10). – IR (KBr): 3430 cm^{-1} (b, w), 1658 (vs), 1620 (vs), 1595 (vs), 1568 (s), 1474 (s), 1431 (m), 1381 (s), 1334 (vs), 1290 (vs), 1261 (s), 1180 (s), 1074 (m), 974 (s), 955 (s), 793 (s), 780 (vs), 728 (vs), 692 (s), 687 (s), 422 (m). – EA: obs. C, 63.55 %; H, 3.94 %; Br, 23.69 %, calcd. C, 63.36 %; H, 3.84 %; Br, 23.42 % for $C_{18}H_{13}BrO_2$.

Example 1.28: 2-Methyl-3-(4-isopropyl-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM100)

As starting materials for the coupling reaction menadione and 4-isopropylphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 395 mg (1.30 mmol, 58 % yield) of **P_TM100** were isolated as yellow solid.

Melting point: 64 – 65 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.09 (m, 2H), 7.65 – 7.69 (m, 2H), 7.14 (d, ^3J = 8.24 Hz, 2H), 7.11 (d, ^3J = 8.24 Hz, 2H), 3.99 (s, 2H), 2.83 (sep, ^3J = 6.90 Hz, 1H), 2.25 (s, 3H), 1.19 (d, ^3J = 6.94 Hz, 6H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.45 (C_q), 184.68 (C_q), 146.99 (C_q), 145.52 (C_q), 144.20 (C_q), 135.26 (C_q), 133.44 (CH), 133.40 (CH), 132.13 (C_q), 132.07 (C_q), 128.53 (CH), 126.68

(CH), 126.45 (CH), 126.23 (CH), 33.66 (CH), 32.02 (CH_2), 23.97 (CH_3), 13.29 (CH_3). – EI MS (70 eV, m/z (%)): 304.1 ($[M]^+$, 31), 289.2 (100), 261.2 (31). – IR (KBr): 3447 cm^{-1} (b, m), 2960 (m), 2928 (w), 2870 (w), 1660 (vs), 1618 (m), 1594 (s), 1511 (m), 1460 (w), 1419 (w), 1377 (w), 1333 (m), 1294 (vs), 1259 (w), 1181 (w), 975 (w), 818 (w), 788 (w), 718 (m), 694 (m). – EA: obs. C, 82.94 %; H, 6.54 %, calcd. C, 82.86 %; H, 6.62 % for $C_{21}H_{20}O_2$.

Example 1. 29: 2-(4-Bromo-benzyl)-3-difluoromethyl-[1,4]naphthoquinone (P_TM101)

As starting materials for the coupling reaction difluoromenadione and 4-bromophenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 132 mg (0.35 mmol, 73 % yield) of **P_TM101** were isolated as yellow solid.

Melting point: 103 – 104 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 – 8.13 (m, 1H), 7.99 – 8.05 (m, 1H), 7.70 – 7.79 (m, 2H), 7.36 (d, ^3J = 8.46 Hz, 2H), 7.24 (t, ^1J = 53.87 Hz, 1H, CHF_2), 7.18 (d, ^3J = 8.42 Hz, 2H), 4.19 (s, 2H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.38 (C_q), 182.79 (C_q), 149.21 (C_q), 136.03 (C_q), 134.41 (CH), 131.76 (C_q), 131.63 (CH), 130.89 (CH), 126.87 (CH), 126.54 (CH), 120.67 (C_q), 110.45 (CHF_2, ^1J = 239.85 Hz), 31.66 (CH_2). – EI MS (70 eV, m/z (%)): 377.1 ($[M]^+$, 21), 325.1 (11), 257.1 (10), 169.0 (100), 90.1 (18). – IR (KBr): 3436 cm^{-1} (b, w), 3100 (w), 3076 (w), 3049 (w), 3018 (w), 2936 (w), 1672 (vs), 1657 (vs), 1625 (s), 1594 (s), 1487 (vs), 1406 (m), 1329 (s), 1297 (vs), 1181 (m), 1123 (s), 1082 (s), 1071 (m), 1035 (vs), 1013 (s), 876 (m), 831 (s), 788 (s), 733 (s), 713 (m), 535 (m). – EA: obs. C, 57.01 %; H, 3.12 %, calcd. C, 57.32 %; H, 2.94 % for $C_{18}H_{11}BrF_2O_2$.

Example 1.30: 2-(2-Bromo-4-methoxy-benzyl)-3-methyl-[1,4]naphthoquinone (P_TM102)

As starting materials for the coupling reaction menadione and 2-bromo-4-methoxyphenylacetic acid were used. Synthesis is realized according to the general procedure described in general procedure of example 1. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV), 857 mg (2.31 mmol, 57 % yield) of **P_TM102** were isolated as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 – 8.08 (m, 2H), 7.63 – 7.69 (m, 2H), 7.09 (d, ^{4}J = 2.63 Hz, 1H), 6.79 (d, ^{3}J = 8.57 Hz, 1H), 6.66 (dd, ^{3}J = 8.61 Hz, ^{4}J = 2.63 Hz, 1H), 3.99 (s, 2H), 3.70 (s, 3H), 2.08 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.06 (C_q), 184.40 (C_q), 158.55 (C_q), 145.64 (C_q), 144.90 (C_q), 133.54 (CH), 133.51 (CH), 132.14 (C_q), 132.01 (C_q), 129.22 (C_q), 129.08 (CH), 126.52 (CH), 126.31 (CH), 124.71 (C_q), 118.13 (CH), 113.67 (CH), 55.48 (CH_3), 31.76 (CH_2), 13.27 (CH_3). – EI MS (70 eV, m/z (%)): 370.11 ($[M]^+$, 2), 355.08 (8), 291.17 (100), 276.14 (8), 248.14 (5), 202.12 (3). – IR (film): 3295 cm^{-1} (w), 3069 (w), 3004 (w), 2940 (w), 2987 (w), 1685 (m), 1660 (vs), 1596 (vs), 1566 (m), 1491 (vs), 1439 (m), 1331 (m), 1295 (vs), 1239 (vs), 1186 (m), 1029 (s), 861 (m), 712 (s), 696 (s). – EA: obs. C, 61.64 %; H, 4.35 %, calcd. C, 61.47 %; H, 4.07 % for $C_{19}H_{15}BrO_3$.

EXAMPLE 2 2-(3,6-Dioxo-cyclohexa-1,4-dienylmethyl)-3-methyl-4a,8a-dihydro-[1,4] naphthoquinone (P_TM63)

P_TM60 (200 mg, 0.62 mmol) obtained according to example 1.19 was dissolved in a mixture of 40 mL CH_3CN and 10 mL H_2O by gently warming to give a yellow solution. Cerium(IV) ammonium nitrate (CAN) (918 mg, 1.67 mmol) in 10 mL CH_3CN/H_2O (v/v = 1:1) was added to the previous mixture at room temperature to give an orange-red solution which was stirred for 1.5 hours. CH_3CN was removed *in vacuo*, the product was extracted with CH_2Cl_2 (5 x 20 mL), dried over $MgSO_4$ and purified by flash-chromatography. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 74 mg (0.25 mmol, 41 % yield) of **P_TM63** were isolated as yellow solid. Melting point: 142 – 144 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$)*:* δ = 8.10 (dd, ^{3}J = 6.62 Hz, ^{4}J = 2.27 Hz, 1H), 8.05 (dd, ^{3}J = 6.86 Hz, ^{4}J = 1.99 Hz, 1H), 7.69 – 7.74 (m, 2H), 6.81 (d, ^{3}J = 10.10 Hz, 1H), 6.71 (dd, ^{3}J = 10.10 Hz, ^{4}J = 2.49 Hz, 1H), 6.35 (d, ^{4}J = 1.85 Hz, 1H), 3.79 (s, 2H), 2.17 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 187.14 (C_q), 186.48 (C_q), 184.49 (C_q), 183.90 (C_q), 146.28 (s, C_q), 145.70 (C_q), 142.11 (C_q), 136.69 (CH) , 136.43 (CH), 133.85 (CH), 133.76 (CH), 132.61 (CH), 132.06 (C_q), 131.79 (C_q), 126.56 (CH), 126.54 (CH), 26.32 (CH_2), 13.32 (CH_3). – EI MS (70 eV, m/z (%)): 292.1 (M^+, 100), 264.1 (15), 235.1 (19), 221.1 (13). – IR (KBr): 3423 cm^{-1} (b, m), 3027 (w), 2937 (w), 1659 (vs), 1624 (m), 1596 (m), 1379 (w), 1334 (m), 1295 (vs), 731 (m), 694 (m). – EA: obs. C, 72.83 %, H, 4.26 %, calcd. C, 73.07 %; H, 4.22 % for $C_{12}H_{14}O_4 \cdot 0.2\ H_2O$.

EXAMPLE 3 2-Methyl-3-(4-amino-benzyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM103)

To a solution of **P_TM45** (100 mg, 0.265 mmol) obtained according to example 1.12 in 7 mL dry CH_2Cl_2, trifluoroacetic acid (157 µL, 2.04 mmol) was added at 0 °C. The solution was stirred for 16 h at room temperature. The mixture was quenched by addition of 20 mL sat. Na_2CO_3-solution, the product was extracted with CH_2Cl_2 (4 x 10 mL), dried over $MgSO_4$ and purified by flash-chromatography on silica gel (CH_2Cl_2 : MeOH = 9:1, UV) to give 62 mg (0.22 mmol) of analytically pure **P_TM103** as red solid in yield of 84 %.

Melting point: 152 – 153 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 – 8.06 (m, 2H), 7.65 – 7.68 (m, 2H), 7.00 (d, ^3J = 8.32 Hz, 2H), 6.57 (d, ^3J = 8.36 Hz, 2H), 3.89 (s, 2H), 2.23 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.54 (C_q), 184.78 (C_q), 145.83 (C_q), 144.77 (C_q), 144.71 (C_q), 143.83 (C_q), 133.38 (CH), 133.34 (CH), 132.11 (C_q), 129.51 (CH), 126.39 (CH), 126.17 (CH), 115.39 (C_q), 115.36 (CH), 31.53 (CH_2), 13.17 (CH_3). – EI MS (70 eV, m/z (%)): 277.1 ($[M]^+$, 52), 262.2 (100), 106.1 (12). – IR (KBr): 3439 cm^{-1} (b, s), 3380 (m), 1659 (vs), 1619 (s), 1594 (m), 1515 (s), 1334 (w), 1295 (vs), 1261 (w), 819 (w), 786 (w), 771 (w), 708 (m), 693 (w), 630 (w), 605 (w), 572 (w), 512 (w), 458 (w), 423 (w). – EA: obs. C, 76.46 %; H, 5.41 %; N, 4.85 %, calcd. C, 76.46 %; H, 5.69 %; N, 4.88 % for $C_{18}H_{15}NO_2 \cdot 0.3\ CH_3OH$.

EXAMPLE 4 General Procedure for the Oxidation of Benzyl Derivatives to the corresponding Benzoyl-Derivatives

H_5IO_6 (1.40 g, 6.16 mmol) was dissolved in 25 mL acetonitrile by vigorous stirring and then CrO_3 (17.6 mg, 0.18 mmol) was dissolved into the mixture to give an orange solution. The benzyl-derivative (0.88 mmol) was added to the above solution with stirring. The solution turned to an orange suspension within a few seconds that turned yellow after a few minutes. The solution was stirred at room temperature until all starting material was consumed (TLC control). The solvent was removed *in vacuo* and the residue was purified by flash-chromatography to give the corresponding benzoyl-derivative.

Example 4.1: 4-(3-Methyl-1,4-dioxo-1,4,4a,8a-tetrahydro-naphthalene-2-carbonyl)-benzoic acid (P_TM22)

As starting material **P_TM21** synthetized according to example 1.1 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (CH_2Cl_2 : MeOH : CH_3COOH = 19:1:0.1, UV), 389 mg (1.22 mmol, 67 % yield) of **P_TM22** were isolated as yellow solid.

Melting point: 201 °C decomposition. – ^{1}H-NMR (300 MHz, DMSO): δ = 13.38 (s, 1H), 7.87 – 8.19 (m, 8H), 1.95 (s, 3H). – ^{13}C-NMR (75 MHz, DMSO): δ = 193.64 (C_q), 184.07 (C_q), 183.37 (C_q), 166.40 (C_q), 144.34 (C_q), 142.58 (C_q), 138.23 (C_q), 135.79 (C_q), 134.51 (CH), 134.16 (CH), 131.96 (C_q), 131.17 (C_q), 129.94 (CH), 129.31 (CH), 126.19 (CH), 125.70 (CH), 13.47 (CH_3). – HR-EI MS m/z (%): obs. 320.0699, calcd. 320.0685 for $C_{19}H_{12}O_5$. – IR (KBr): 3437 cm^{-1} (b, m), 3070 (w), 1774 (w), 1685 (vs), 1669 (vs), 1594 (m), 1502 (w), 1407 (w), 1292 (vs), 1226 (m), 1110 (w), 979 (w), 763 (m), 730 (w), 714 (w), 691 (w), 652 (w). – EA: obs. 71.07 %; H, 4.00 %, calcd. C, 71.25 %; H, 3.78 % for $C_{19}H_{12}O_5$.

Example 4.2: 2-Methyl-3-(4-bromo-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM25)

As starting material **P_TM24** prepared according to example 1.2 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 133 mg (0.38 mmol, 43 % yield) of **P_TM25** were isolated as yellow solid.

Melting point: 170 – 171°C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.14 – 8.17 (m, 1H), 8.03 – 8.06 (m, 1H), 7.73 – 7.81 (m, 4H), 7.64 (t, ^3J = 2.08 Hz, 1H), 7.61 (t, ^3J = 1.95 Hz, 1H), 2.05 (s, CH_3). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.72 (C_q), 184.63 (C_q), 183.32 (C_q), 144.30 (C_q), 143.85 (C_q), 134.49 (C_q), 134.30 (CH), 134.19 (CH), 132.48 (CH), 131.87 (C_q), 131.49 (C_q), 130.52 (CH), 130.01 (C_q), 126.78 (CH), 126.44 (CH), 13.60 (CH_3). – EI MS (70 eV, m/z (%)): 353.9 ([M]$^+$, 41), 275.0 (100), 182.9 (71), 115.0 (50), 76.0 (41). – IR (KBr): 3442 cm^{-1} (b, m), 1669 (vs), 1653 (vs), 1627 (vs), 1586 (m), 1568 (m), 1398 (m), 1378 (m), 1329 (s), 1291 (vs), 1272 (s), 1241 (m), 1176 (m), 1069 (m), 1011 (m), 978 (s), 864 (m), 784 (s), 722 (m), 692 (m). – EA: obs. C, 60.96 %; H, 3.24 %; Br, 22.60 %, calcd. C, 60.87 %; H, 3.12 %; Br, 22.50 % for $C_{18}H_{11}BrO_3$.

Example 4.3: 2-Methyl-3-(fluoro-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM27)

As starting material **P_TM26** prepared according to example 1.3 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 110 mg (0.37 mmol, 35 % yield) of **P_TM27** were isolated as yellow solid.

Melting point: 157 – 158 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 – 8.16 (m, 1H), 8.03 – 8.06 (m, 1H), 7.90 – 7.95 (m, 2H), 7.75 – 7.78 (m, 2H), 7.12 – 7.18 (m, 2H), 2.05 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.02 (C_q), 184.69 (C_q), 183.33 (C_q), 166.58 ($^1J_{CF}$ = 257.5 Hz, CF), 144.13 (C_q), 144.07 (C_q), 134.23 ($^3J_{CF}$ = 7.1 Hz, CH), 132.30 ($^4J_{CF}$ = 2.8 Hz, C_q), 132.01 (CH), 131.88 (CH), 131.54 (C_q), 126.77 (CH), 126.45 (CH), 116.41 ($^2J_{CF}$ = 22.2 Hz, CH), 13.56 (CH_3). – HR-EI MS (m/z): obs. 294.0674, calcd. 294.0692 for $C_{18}H_{11}FO_3$. – IR (KBr): 3436 cm^{-1} (b, m), 1674 (vs), 1655 (vs), 1623 (m), 1597 (vs), 1507 (w), 1412 (w), 1332 (m), 1293 (vs), 1274 (m), 1240 (s), 1156 (m), 979 (w), 866 (w), 841 (w), 768 (w), 712 (w), 618 (m). – EA: obs. C, 73.21 %; H, 3.97 %, calcd. C, 73.47 %; H, 3.77 % for $C_{18}H_{11}FO_3$.

Example 4.4: 2-Methyl-3-(4-trifluoromethyl-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM33)

As starting material **P_TM29** prepared according to example 1.4 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 174 mg (0.51 mmol, 36 % yield) of **P_TM33** were isolated as yellow solid.

Melting point: 155 – 156 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 – 8.16 (m, 1H), 7.99 – 8.04 (m, 3H), 7.72 – 7.81 (m, 4H), 2.05 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.87 (C_q), 184.46 (C_q), 183.32 (C_q), 144.65 (C_q), 143.57 (C_q), 138.28 (C_q), 135.51 ($^2J_{CF}$ = 32.8 Hz, $\underline{C}$-CF_3), 134.36 (CH), 134.23 (CH), 131.83 (C_q), 131.39 (C_q), 129.38 (CH), 126.80 (CH), 126.39 (CH), 126.15 ($^3J_{CF}$ = 3.68 Hz, CH), 123.36 ($^1J_{CF}$ = 273.1 Hz, CF_3), 13.54 (CH_3). – EI MS (70 eV, m/z (%)): 344.0 ($[M]^+$, 100), 315 (14), 275 (51), 173.0 (98), 145.0 (47). – IR (KBr): 3433 cm^{-1} (b, m), 3071 (w), 3032 (w), 2972 (w), 1659 (vs), 1617 (m), 1594 (m), 1490 (m), 1407 (w), 1377 (w), 1333 (m), 1296 (vs), 1103 (w), 1091 (w), 1013 (w), 970 (w), 813 (w), 786 (w), 734 (m), 703 (m), 691 (m), 651 (m). – EA: obs. C, 66.03 %; H, 3.33 %, calcd. C, 66.28 %; H, 3.22 % for $C_{19}H_{11}F_3O_3$.

Example 1.5 2-Methyl-3-(4-chloro-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM38)

As starting material **P_TM30** prepared according to example 1.5 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:10, UV), 560 mg (1.80 mmol, 48 % yield) of **P_TM38** were isolated as yellow solid.

Melting point: 136 – 137 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 – 8.16 (m, 1H), 8.02 – 8.05 (m, 1H), 7.83 (d, ^3J = 8.60 Hz, 2H), 7.75 – 7.78 (m, 2H), 7.45 (d, ^3J = 8.59 Hz, 2H), 2.04 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.50 (C_q), 184.65 (C_q), 183.34 (C_q), 144.27 (s, C_q), 143.89 (s, C_q), 141.16 (s, C_q), 134.30 (CH), 134.20 (CH), 134.10 (C_q), 131.87 (C_q), 131.49 (C_q), 130.49 (CH), 129.49 (CH), 126.77 (CH), 126.44 (CH), 13.59 (CH_3). – EI MS (70 eV, m/z (%)): 310.9 ($[M]^+$, 100), 284.9 (41). – IR (KBr): 3453 cm^{-1} (b, m), 1668 (vs), 1628 (m), 1587 (vs), 1571 (m), 1401 (m), 1380 (w), 1329 (m), 1292 (vs), 1274 (s), 1236 (m), 1091 (s), 978 (m), 829 (w), 784 (m), 730 (w), 704 (w), 691 (w), 531 (w). – EA: obs. C, 69.28 %; H, 3.63%; Cl, 11.18 %, calcd. C, 69.58 %; H, 3.57 %; Cl, 11.41 % for $C_{18}H_{11}ClO_3$.

Example 4.6: 2-Methyl-3-(4-methoxy-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM34)

As starting material **P_TM31** prepared according to example 1.6 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:10, UV), 541 mg (1.77 mmol, 64 % yield) of **P_TM34** were isolated as yellow solid.

Melting point: 150 – 151 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.11 – 8.14 (m, 1H), 8.02 – 8.05 (m, 1H), 7.86 (d, ^3J = 8.92 Hz, 2H), 7.71 – 7.78 (m, 2H), 6.93 (d, ^3J = 8.93 Hz, 2H), 3.85 (s, 3H), 2.03 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 191.88 (C_q), 184.92 (C_q), 183.36 (C_q), 164.65 (C_q), 144.55 (C_q), 143.59 (C_q), 134.05 (CH), 134.01 (CH), 131.86 (C_q), 131.62 (CH), 128.88 (C_q), 126.59 (CH), 126.36 (CH), 114.32 (CH), 55.58 (CH_3), 13.54 (CH_3). – EI MS (70 eV, m/z (%)): 306.0 ($[M]^+$, 85), 275 (14), 134.9 (100). – IR (KBr): 3400 (b, m), 3076 (w), 3006 (w), 2937 (w), 2843 (w), 1668 (vs), 1653 (vs), 1624 (m), 1598 (s), 1573 (s), 1511 (s), 1423 (s), 1379 (m), 1344 (m), 1329 (s), 1291 (vs), 1265 (vs), 1246 (vs), 1171 (vs), 1026 (m), 978 (m), 834 (m), 765 (s), 715 (m), 618 (m). – EA: obs. C, 74.15 %; H, 4.60 %, calcd. C, 74.50 %; H, 4.61 % for $C_{19}H_{14}O_4$.

Example 4.7: 2-Methyl-3-(2-methoxy-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM35)

As starting material **P_TM32** prepared according to example 1.7 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (CH_2Cl_2: ethyl acetate = 1:1, UV), 279 mg (0.91 mmol, 33 % yield) of **P_TM35** were isolated as yellow solid.

Melting point: 146 - 147 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.12 – 8.18 (m, 1H), 8.02 – 8.11 (m, 2H), 7.69 – 7.74 (m, 2H), 7.51 – 7.61 (m, 1H), 7.10 (t, ^3J = 2.93 Hz, 1H), 6.85 (d, ^3J = 3.26 Hz, 1H), 3.54 (s, 3H), 2.02 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 191.70 (C_q), 185.74 (C_q), 183.33 (C_q), 159.90 (C_q), 147.88 (C_q), 139.86 (C_q), 135.93 (CH), 133.85 (CH), 131.99 (C_q), 131.77 (C_q), 130.86 (CH), 126.55 (CH), 126.01 (CH), 125.68 (C_q), 121.31 (CH), 112.30 (CH), 55.91 (CH_3), 12.91 (CH_3). – EI MS (70 eV, m/z (%)): 306.0 ($[M]^+$, 100), 274.0 (32), 135.0 (100). – IR (KBr): 3400 cm^{-1} (b, m), 3100 (w), 3068 (w), 2997 (w), 2943 (w), 2837 (w), 1661 (vs), 1652 (vs), 1626 (m), 1595 (vs), 1484 (s), 1466 (m), 1435 (m), 1385 (m), 1330 (s), 1295 (vs), 1265 (m), 1247 (m), 1224 (m), 1185 (m), 1161 (m), 1018 (m), 981 (s), 770 (vs), 755 (vs), 723 (m). – EA: obs. C, 73.90 %; H, 4.65 %, calcd. C, 73.74 %; H, 4.68 % for $C_{19}H_{14}O_4 \cdot 0.2\ H_2O$.

Example 4.8: 2-Methyl-3-(4-nitro-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM40)

As starting material **P_TM37** prepared according to example 1.9 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:10, UV), 506 mg (1.57 mmol, 48 % yield) of **P_TM40** were isolated as yellow solid.

Melting point: 170 - 171 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 – 8.33 (d, ^3J = 8.81 Hz, 2H), 8.14 – 8.17 (m, 1H), 8.01 – 8.06 (m, 3H), 7.74 – 7.82 (m, 2H), 2.07 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.47 (C_q), 184.34 (C_q), 183.34 (C_q), 150.98 (C_q), 145.12 (C_q), 143.19 (C_q), 140.00 (C_q), 134.54 (CH), 134.36 (CH), 131.83 (C_q), 131.33 (C_q), 130.05 (CH), 126.93 (CH), 126.46 (CH), 124.30 (CH), 13.63 (CH_3). – EI MS (70 eV, m/z (%)): 321 ($[M]^+$, 51), 272.9 (100), 245.1 (52), 153.0 (42), 115.1 (46). – IR (KBr): 3433 cm^{-1} (b, s), 1689 (s), 1668 (vs), 1654 (vs), 1627 (w), 1596 (m), 1527 (vs), 1378 (w), 1345 (s), 1322 (m), 1292 (vs), 1272 (m), 1228 (m), 979 (m), 856 (w), 781 (m), 724 (m), 697 (w). – EA: obs. C, 66.39 %; H, 3.64 %; N, 4.19 %, calcd. C, 66.55 %; H, 3.54 %; N, 4.31 % for $C_{18}H_{11}NO_5 \cdot 0.2\ H_2O$.

Example 4.9: 2-Methyl-3-(4-cyano-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM46)

As starting material **P_TM41** prepared according to example 1.10 was used. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:3, UV), 148 mg (0.49 mmol, 47 % yield) of **P_TM46** were isolated as yellow solid.

Melting point: 185 – 186 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 – 8.18 (m, 1H), 8.02 – 8.05 (m, 1H), 7.98 (d, ^3J = 8.46 Hz, 2H), 7.77 – 7.79 (m, 4H), 2.06 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.63 (C_q), 184.36 (C_q), 183.35 (C_q), 145.03 (C_q), 143.26 (C_q), 138.58 (C_q), 134.51 (CH), 134.34 (CH), 132.91 (CH), 131.84 (C_q), 131.36 (C_q), 129.37 (CH), 126.92 (CH), 126.46 (CH), 117.64 (C_q), 117.58 (C_q), 13.70 (CH_3). – EI MS (70 eV, m/z (%)): 300.8 ($[M]^+$, 60), 270.9 (14), 130.0 (41), 102.0 (45). – IR (KBr): 3444 cm^{-1} (b, m), 2233 (w), 1685 (vs), 1658 (vs), 1626 (m), 1594 (m), 1407 (w), 1377 (w), 1330 (m), 1292 (vs), 1271 (m), 1234 (m), 1184 (m), 978 (m), 870 (w), 834 (w), 792 (w), 752 (m), 711 (m), 545 (w). – EA: obs. C, 75.47 %; H, 3.96 %; N, 4.50 %, calcd. C, 75.74 %; H, 3.68 %; N, 4.65 % for $C_{19}H_{11}NO_3$.

Example 4.10: 2-Methyl-3-(4-*tert*butyl-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM48)

As starting material **P_TM43** prepared according to example 1.11 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:10, UV), 103 mg (0.31 mmol, 33 % yield) of **P_TM48** were isolated as yellow solid.

Melting point: 64 – 65 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$,): δ = 8.11 – 8.14 (m, 1H), 8.02 – 8.05 (m, 1H), 7.82 (d, ^3J = 8.56 Hz, 2H), 7.72 – 7.76 (m, 2H), 7.47 (d, ^3J = 8.58 Hz, 2H), 2.04 (s, 3H), 1.31 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$,): δ = 193.17 (C_q), 184.84 (C_q), 183.38 (C_q), 158.48 (C_q), 144.53 (C_q), 143.71 (C_q), 134.06 (CH), 134.01 (CH), 133.10 (C_q), 131.85 (C_q), 131.54 (C_q), 129.13 (CH), 126.60 (CH), 126.32 (CH), 126.02 (CH), 35.27 (C_q), 30.95 (CH_3), 13.53 (CH_3). – EI MS (70 eV, m/z (%)): 332 ($[M]^+$, 4), 317.1 (18), 275 (100), 161.1 (41). – IR (KBr): 3447 cm^{-1} (b, m), 2965 (w), 1668 (s), 1657 (s), 1632 (s), 1604 (s), 1328 (w), 1291 (s), 729 (w), 701 (w), 691 (w), 668 (w), 652 (w), 547 (w), 505 (w). – EA: obs. C, 78.38 %; H, 6.12 %, calcd. C, 78.64 %; H, 6.12 % for $C_{22}H_{20}O_3 \cdot 0.2\ H_2O$.

Example 4.11: 3-(4-bromo-benzoyl)-5-hydroxy-2-methyl 4a,8a-dihydro-[1,4]naphthoquinone (P_TM47)

As starting material **P_TM42** prepared according to example 1.22 was used. Synthesis is realized according to the general procedure described in general procedure of example 4. After chromatography on silica gel (petroleum ether: ethyl acetate = 3:1, UV), 216 mg (0.58 mmol, 52 % yield) of **P_TM47** were isolated as orange solid. Melting point: 161 – 162 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 11.59 (s, 1H), 7.77 (d, ^3J = 8.63 Hz, 2H), 7.62 – 7.71 (m, 4H), 7.28 (dd, ^3J = 7.84 Hz, ^4J = 1.70 Hz, 1H), 2.03 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.12 (C_q), 188.28 (C_q), 183.83 (C_q), 161.50 (C_q), 145.73 (C_q), 143.78 (C_q), 136.85 (CH), 134.36 (C_q), 132.59 (CH), 131.66 (C_q), 130.47 (CH), 130.28 (C_q), 124.80 (CH), 119.75 (CH), 114.44 (C_q), 13.70 (CH_3). – EI MS (70 eV, m/z (%)): 370 ($[M]^+$, 41), 290.2 (100), 183.0 (81). – IR (KBr): 3450 cm^{-1} (b, m), 1677 (vs), 1636 (vs), 1615 (s), 1585 (vs), 1570 (m), 1456 (s), 1399 (m), 1382 (m), 1367 (m), 1296 (s), 1273 (vs), 1238 (s), 1068 (m), 1009 (m), 972 (m), 766 (m), 743 (m). – EA: obs. C, 58.21 %; H, 3.13 %, calcd. C, 58.24 %; H, 2.99 % for $C_{18}H_{11}BrO_4$.

Example 5: 4-(3-Methyl-1,4-dioxo-1,4-dihydro-naphthalene-2-carbonyl)-benzoic acid methyl ester (P_TM28)

P_TM22 (500 mg, 1.56 mmol) prepared according to example 4.1 was suspended in 4 mL $SOCl_2$ and refluxed for three hours. The $SOCl_2$ was removed in vacuo and 5 mL methanol was added. The reaction mixture was stirred for three hours at room temperature to give a yellow suspension. The methanol was removed *in vacuo* and the residue was purified by chromatography.

After chromatography on silica gel (petroleum ether: ethyl acetate = 1:1, UV), 351 mg (1.05 mmol, 67 % yield) of **P_TM28** were isolated as yellow solid.

Melting point: 162 – 162 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 – 8.18 (m, 1H), 8.13 (d, ^3J = 8.52 Hz, 2H), 8.04 – 8.06 (m, 1H), 7.95 (d, ^3J = 8.21 Hz, 2H), 7.77 – 7.81 (m, 2H), 3.93 (s, 3H), 2.06 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 193.33 (C_q), 184.62 (C_q), 183.36 (C_q), 165.93 (C_q), 144.44 (C_q), 143.89 (C_q), 138.75 (C_q), 135.06 (C_q), 134.35 (CH), 134.24 (CH), 131.89 (C_q), 131.49 (C_q), 130.26 (CH), 129.00 (CH), 126.83 (CH), 126.47 (CH), 52.62 (CH_3), 13.63 (CH_3). – EI MS (70 eV, m/z (%)): 334.1

($[M]^+$, 69), 275.1 (86), 163.0 (100). – IR (KBr): 3425 cm^{-1} (b, w), 1725 (s), 1670 (s), 1655 (s), 1595 (w), 1436 (w), 1407 (w), 1328 (m), 1291 (vs), 1231 (w), 1110 (m), 978 (w), 777 (w), 733 (w), 720 (w), 697 (w), 692 (w). – EA: obs. C, 71.46 %; H, 4.30 %, calcd. C, 71.85 %; H, 4.22 % for $C_{20}H_{14}O_5$.

Example 6: 2-Methyl-3-(4-hydroxy-benzoyl)-4a,8a-dihydro-[1,4]naphthoquinone (P_TM39)

P_TM34 (100 mg, 0.33 mmol) prepared according to example 4.6 was dissolved in 5 mL dry dichloromethane and cooled to – 78 °C. 1.0 mL BBr_3 (1M in CH_2Cl_2) was added dropwise within 20 minutes to give a red solution. The mixture was allowed to warm to room temperature and stirred overnight. 1 mL H_2O was added, stirred for 5 minutes, 2 mL H_2O was added and the mixture was stirred for further ten minutes. The product was extracted with CH_2Cl_2 (5 x 5 mL), dried over $MgSO_4$ and purified by chromatography.

After chromatography on silica gel (cyclohexane : ethyl acetate = 1:2, UV), 75 mg (0.25 mmol, 78 % yield) of **P_TM39** were isolated as yellow solid.

Melting point: 184 – 185 °C. – ^1H-NMR (300 MHz, $CDCl_3$): δ = 8.13 – 8.16 (m, 1H), 8.03 – 8.06 (m, 1H), 7.72 – 7.81 (m, 4H), 6.84 (d, ^3J = 8.77 Hz, 2H), 6.24 (bs, 1H), 2.04 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): = 192.01 (C_q), 184.92 (C_q), 183.67 (C_q), 161.58 (C_q), 144.48 (C_q), 143.88 (C_q), 134.25 (CH), 134.13 (CH), 132.01 (CH), 131.90 (C_q), 131.58 (C_q), 128.84 (C_q), 126.72 (CH), 126.46 (CH), 116.00 (CH), 13.64 (CH_3). – EI MS (70 eV, m/z (%)): 292.0 ($[M]^+$, 63), 275 (6), 121.0 (100). – IR (KBr): 3443 cm^{-1} (b, vs), 1667 (vs), 1599 (vs), 1517 (w), 1442 (w), 1331 (w), 1292 (vs), 1245 (m), 1167 (m), 773 (w). – EA: obs. C, 72.76 %; H, 4.21 %, calcd. C, 72.62; H, 4.27 % for $C_{18}H_{12}O_4 \cdot 0.3\ H_2O$.

Example 7: (4-Bromo-phenyl)-(1,4-dimethoxy-3-methyl-naphthalen-2-yl)-methanol (P_TM7)

A solution of 7.0 mL *n*BuLi (1.6 M in hexane) in 20 mL absolute THF was added at - 78 °C dropwise to a solution of 2-bromo-3-methyl-1,4-dimethoxynaphthalene (3.0 g, 10.67 mmol) in 30 mL absolute THF under an atmosphere of nitrogen. The yellow solution was stirred for 30 minutes at – 78 °C. Then a solution of 4-bromobenzaldehyde (1.97 g, 10.67 mmol) in 15 mL absolute THF was added at – 78 °C via transfer canula. The resulting mixture was stirred for 30 minutes at – 78 °C and was then allowed to warm to room temperature. The colour turned from yellow to orange to yellow. After stirring for two hours at room temperature the reaction was quenched by addition of 15 mL saturated NH_4Cl-solution. 20 mL diethylether was added and the phases were separated. The aqueous phase was extracted twice with 10 mL diethylether. The organic phases were pooled and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give a pale-yellow raw product which was purified by chromatography. After chromatography on silica gel (CH_2Cl_2 : petroleum ether = 1:2, then 4:1, then pure ethyl acetate, UV), 3.5 g (9.06 mmol, 85 % yield) of **P_TM7** were isolated as pale-yellow solid.

Melting point: 67 – 68 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 – 8.05 (m, 1H), 7.89 – 7.93 (m, 1H), 7.37 – 7.49 (m, 4H), 7.14 – 7.18 (m, 2H), 6.19 (s, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 2.28 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.76 (C_q), 150.59 (C_q), 143.52 (C_q), 131.96 (CH), 131.54 (C_q) 131.32 (C_q), 127.58 (CH), 127.19 (C_q), 126.53 (C_q), 126.05 (CH), 125.59 (CH), 122.37 (CH), 122.29 (CH), 120.83 (C_q), 70.42 (CH), 62.69 (CH_3), 61.52 (CH_3), 12.66 (CH_3). – EI MS (70 eV, m/z (%)): 386.1 ($[M]^+$, 53), 260.1 (14), 184.9 (34), 61.1 (100). – IR (KBr): 3427 cm^{-1} (bs), 3068 (w), 2935 (w), 2839 (m), 1624 (w), 1590 (m), 1486 (m), 1456 (m), 1378 (w), 1351 (vs), 1268 (w), 1193 (w), 1172 (w), 1098 (m), 1068 (vs), 1030 (m), 1009 (s), 961 (m), 774 (m), 727 (w). – EA: obs. C, 61.92 %; H, 5.00 %, calcd. C, 62.03%, H, 4.95 % for $C_{20}H_{19}BrO_3$.

Example 8: 2-[(4-Bromo-phenyl)-hydroxy-methyl]-3-methyl-[1,4]naphthoquinone (P_TM23)

P_TM7 (500 mg, 1.29 mmol) prepared according to example 7 was dissolved in 40 mL CH_3CN/H_2O (v/v = 3:1). Cesium (IV) ammonium nitrate (2.13 g, 3.89 mmol) was added at room temperature to form an orange solution which was stirred overnight at room temperature. The CH_3CN was removed *in vacuo*, the product was extracted with CH_2Cl_2 (4 x 15 mL), dried over $MgSO_4$ and purified by flash-chromatography. After chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:10, UV), 395 mg (1.11 mmol, 86 % yield) of **P_TM23** were isolated as yellow solid.

Melting point: 61 – 62 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 – 8.11 (m, 1H), 7.97 – 8.01 (m, 1H), 7.67 – 7.76 (m, 2H), 7.45 (d, ^3J = 8.36 Hz, 2H), 7.26 (d, ^3J = 8.95 Hz, 2H), 5.92 (d, ^3J = 9.84 Hz, 1H), 4.33 (d, ^3J = 10.78 Hz, 1H), 2.21 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.87 (C_q), 186.43 (C_q), 144.80 (C_q), 143.77 (C_q), 140.63 (C_q), 134.11 (CH), 133.84 (CH), 131.83 (C_q), 131.68 (CH), 127.05 (CH), 126.53 (CH), 126.40 (CH), 121.51 (C_q), 71.06 (CH), 12.54 (CH_3). – EI MS (70 eV, m/z (%)): 356.0 ($[M]^+$, 8), 340.9 (100), 275.1 (25), 202.1 (39), 184.9 (42), 115.1 (80), 77.0 (41). – IR (KBr): 3443 cm^{-1} (bs), 1657 (s), 1619 (m), 1592 (m), 1485 (w), 1329 (w), 1292 (s), 1187 (w), 1072 (w), 1010 (w), 785 (w), 718 (w), 536 (w). – EA: obs. C, 60.25 %; H, 3.73 %, calcd. C, 60.52 %; H, 3.67 % for $C_{18}H_{13}BrO_3$.

Example 9: *N*-(2-Cyano-ethyl)-4-(3-methyl-1,4-dioxo-1,4,4a,8a-tetrahydronaphthalen-2-ylmethyl)-benzamide (P_TM53)

P_TM50 (90 mg, 0.29 mmol) prepared according to example 1.13 was dissolved in 3 mL $SOCl_2$ and heated at reflux for two hours to give an orange solution. The $SOCl_2$ was removed *in vacuo* and the residue was redissolved in 4 mL dry CH_2Cl_2. Then 3-aminopropionitrile (22 µL, 0.29 mmol) was added and stirred for 1 hour at room temperature. The reaction was quenched with 10 mL H_2O and the product was extracted with CH_2Cl_2 (5 x 10 mL), dried over $MgSO_4$ and purified by flash-chromatography (cyclohexane : acetone = 1:1, SiO_2, UV) to give 19 mg **P_TM53** as yellow solid in a yield of 18 %.

Melting point: 131 – 132 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$,): δ = 8.06 – 8.09 (m, 2H), 7.66 – 7.71 (m, 4H), 7.29 (d, ^3J = 8.10 Hz, 2H), 6.49 (s, 1H), 4.07 (s, 2H), 3.68 (q, ^3J = 6.10 Hz, 2H), 2.71 (t, ^3J = 6.16 Hz, 2H), 2.22 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.17 (C_q), 184.53 (C_q), 67.57 (Cq), 144.85 (C_q), 144.51 (C_q), 142.63 (C_q), 133.64 (CH), 132.10 (C_q), 131.93 (C_q), 131.71 (sC_q), 128.94 (CH), 127.38 (CH), 126.53 (CH), 126.39 (CH), 118.17 (C_q), 36.20 (CH_2), 32.43 (CH_2), 18.56 (CH_2), 13.37 (CH_3). – EI MS (70 eV, m/z (%)): 358.2 ($[M]^+$, 28), 343.2 (29), 291.1 (40), 40.0 (100). – IR (KBr): 2920 cm^{-1} (m), 2252 (w), 1695 (w), 1660 (vs), 1613 (s), 1594 (s), 1548 (m), 1295 (vs), 1261 (w), 723 (w), 698 (w). – HPLC analysis: R_t = 18.08 min.

Example 10: *N*-(2-Cyano-ethyl)-4-(3-methyl-1,4-dioxo-1,4,4a,8a-tetrahydronaphthalene-2-carbonyl)-benzamide (P_TM51)

P_TM51 was prepared according to the synthesis of **P_TM53** in example 9. The starting material was **P_TM22** prepared according to example 4.1. The compound was obtained as orange solid in a yield of 18 %. Melting point: 172 – 173 °C. – ^{1}H-NMR (300 MHz, DMSO): δ = 9.07 (t, ^3J = 5.53 Hz, 1H), 8.16 (d, ^3J = 8.40 Hz, 2H), 8.09 – 8.11 (m, 1H), 7.88 – 7.98 (m, 5H), 3.51 (q, ^3J = 6.30 Hz, 2H), 2.78 (t, ^3J = 6.46 Hz, 2H), 1.92 (s, 3H). – ^{13}C-NMR (75 MHz, DMSO,): δ = 193.59 (C_q), 184.15 (C_q), 183.41 (C_q), 165.64 (C_q), 144.22 (C_q), 142.66 (C_q), 139.03 (C_q), 137.26 (C_q), 134.51 (CH), 134.18 (CH), 132.01 (C_q), 131.22 (C_q), 129.31 (CH), 128.01 (CH), 126.20 (CH), 125.71 (CH), 119.21 (C_q), 35.51 (CH_2), 17.44 (CH_2), 13.50 (CH_3). – EI MS (70 eV, m/z (%)): 372.2 ($[M]^+$, 100), 303.1 (30), 276.1 (29), 201.1 (61). – IR (KBr): 3419 cm^{-1} (b, s), 3071 (w), 2926 (w), 2252 (w), 1666 (vs), 1595 (m), 1540 (s), 1502 (w), 1440 (w), 1419 (w), 1406 (w), 1379 (w), 1328 (m), 1293 (vs), 1235 (m), 1185 (m), 978 (m), 778 (m), 719 (m), 691 (m), 651 (m). – HPLC analysis: R_t = 17.59 min.

Example 11: General Procedure for the Suzuki Coupling Reaction for the Synthesis of P_TM66, P_TM67 and P_TM69

A Schlenk-tube was flushed with argon and successively filled with 1 equivalent **P_TM24** (100 mg, 0.29 mmol) prepared according to example 1.2, 1.1 equivalent boronic acid derivative (0.32 mmol), 3.0 equivalent K_2CO_3 (122 mg, 0.88 mmol) and finally dissolved in dioxane/water (12 mL / 3 mL). The solution was degassed by bubbling argon through the mixture for 20 minutes. Then 4 mol% $PdCl_2$(dppf) (10 mg, 0.012 mmol) was added, the Schlenk-tube was sealed and heated overnight at 80 °C. The reaction was quenched by adding 10 mL H_2O. All volatiles were removed *in vacuo*, the product was extracted with CH_2Cl_2, dried over $MgSO_4$ and purified by flash-chromatography.

Example 11.1: 2-(4'-*tert*-Butyl-biphenyl-4-ylmethyl)-3-methyl-[1,4]naphthoquinone (P_TM66)

As boronic acid *tert*butylphenylboronic acid was used as coupling partner for **P_TM24** prepared according to example 1.2. After chromatography on silica gel (CH_2Cl_2 : petroleum ether = 3:1, UV), 113 mg (0.286 mmol, 97 % yield) of **P_TM66** were isolated as yellow solid.

Melting point: 112 – 114 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.06 – 8.13 (m, 2H), 7.66 – 7.71 (m, 2H), 7.41 – 7.50 (m, 6H), 7.24 – 7.30 (m, 2H), 4.06 (s, 2H), 2.28 (s, 3H), 1.35 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.34 (C_q), 184.63 (C_q), 150.13 (C_q), 145.25 (C_q), 144.40 (C_q), 139.24 (C_q), 137.85 (C_q), 136.75 (C_q), 133.45 (CH), 132.12 (C_q), 132.03 (C_q), 128.93 (CH), 127.21 (CH), 126.59 (CH), 126.46 (CH), 126.25 (CH), 125.64 (CH), 34.47 (C_q), 32.08 (CH_2), 31.32 (CH_3), 13.30 (CH_3). – EI MS (70 eV, m/z (%)): 394.3 ($[M]^+$, 42), 379.2 (100). – IR (KBr): 3439 cm^{-1} (b, m), 2962 (w), 1659 (vs), 1620 (m), 1595 (m), 1498 (w), 1462 (w), 1377 (w), 1334 (w), 1295 (s), 1182 (w), 1114 (w), 976 (w), 815 (m), 790 (w), 713 (w), 568 (w). – EA: obs. C, 85.16 %; H, 6.66 %, calcd. C, 85.25 %; H, 6.64 % for $C_{28}H_{26}O_2$.

Example 11.2: 2-(4'-nitro-Butyl-biphenyl-4-ylmethyl)-3-methyl-[1,4]naphthoquinone (P_TM67)

As boronic acid 4-nitrophenylboronic acid was used as coupling partner for **P_TM24** prepared according to example 1.2. After chromatography on silica gel (CH_2Cl_2 : petroleum ether = 3:1, UV), 67 mg (0.175 mmol, 59 % yield) of **P_TM67** were isolated as yellow solid.

Melting point: 197 – 199 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.23 – 8.26 (m, 2H), 8.05 – 8.11 (m, 2H), 7.65 – 7.73 (m, 4H), 7.51 (d, ^3J = 8.27 Hz, 2H), 7.34 (d, ^3J = 8.22 Hz, 2H), 4.08 (s, 2H), 2.27 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.27 (C_q), 184.65 (C_q), 147.18 (C_q), 147.00 (C_q), 144.86 (C_q), 144.68 (C_q), 139.16 (C_q), 136.95 (C_q), 133.63 (CH), 132.12 (C_q), 131.98 (C_q), 129.40 (CH), 127.65 (CH), 127.59 (CH), 126.52 (CH), 126.38 (CH), 124.12 (CH), 32.22 (CH_2), 13.40 (CH_3). – EI MS (70 eV, m/z (%)): 383.3 ([M]$^+$, 41), 368.2 (100). – IR (KBr): 3436 cm^{-1} (b, m), 3073 (w), 2934 (w), 1661 (vs), 1620 (m), 1596 (vs), 1513 (vs), 1485 (m), 1375 (w), 1344 (vs), 1295 (vs), 1261 (w), 1182 (w), 1111 (m), 974 (w), 852 (m), 821 (m), 787 (w), 745 (m), 711 (m), 693 (m), 555 (w). – EA: obs. C, 72.95 %; H, 4.47 %; N, 3.56 %, calcd. C, 72.79 %; H, 4.68 %; N, 3.54 % for $C_{24}H_{17}NO_4 \cdot 0.7\ H_2O$.

Example 11.3: 2-(4'-Dimethylamino-biphenyl-4-ylmethyl)-3-methyl-[1,4]naphthoquinone (P_TM69)

As boronic acid 4-dimethylaminophenylboronic acid was used as coupling partner for **P_TM24** prepared according to example 1.2. After chromatography on silica gel (CH_2Cl_2 : petroleum ether = 3:1, UV), 96 mg (0.25 mmol, 86 % yield) of **P_TM69** were isolated as black solid.

Melting point: 170 – 171 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.11 (m, 2H), 7.65 – 7.71 (m, 2H), 7.43 (d, ^3J = 8.39 Hz, 4H), 7.24 (d, ^3J = 8.17 Hz, 2H), 6.76 (d, ^3J = 8.09 Hz, 2H), 4.03 (s, 2H), 2.96 (s, 6H), 2.27 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.47 (C_q), 184.74 (C_q), 145.43 (C_q), 144.34 (C_q), 139.43 (C_q), 135.69 (C_q), 133.49 (CH), 133.46 (CH), 132.15 (C_q), 132.09 (C_q), 128.94 (CH), 127.58 (CH), 126.53 (CH), 126.52 (CH), 126.28 (CH), 112.75 (CH), 40.60 (CH_3), 32.08 (CH_2), 13.37

(CH_3). – EI MS (70 eV, m/z (%)): 381.2 ($[M]^+$, 100), 366.1 (19). – IR (KBr): 3432 cm^{-1} (b, m), 3028 (w), 2922 (w), 2855 (w), 2803 (w), 1660 (vs), 1612 (vs), 1595 (s), 1534 (w), 1504 (vs), 1444 (w), 1375 (w), 1357 (m), 1333 (m), 1294 (vs), 1226 (w), 1168 (w), 946 (w), 810 (s), 790 (s), 766 (w), 722 (w), 711 (w), 692 (w). – EA: obs. C, 81.58 %; H, 619 %; N, 3.60 %, calcd. C, 81.86 %; H, 6.08 %; N, 3.67 % for $C_{26}H_{23}NO_2$.

Example 12: 2-(4-Chloro-benzyl)-1,4-dimethoxy-3-methyl-naphthalene (P_TM75)

P_TM30 (2g, 6.74 mmol) prepared according to example 1.5 was suspended in 20 mL EtOH. $SnCl_2$ (3.83g, 20.22 mmol) was dissolved in 4.5 mL 36% HCl and added dropwise to the previous solution at room temperature and stirred for 40 minutes. The solvent was removed *in vacuo* to give a white precipitate which separated and dried *in vacuo*. The white solid was dissolved in 34 mL acetone and dimethylsulfate (3.2 mL, 33.70 mmol) was added. KOH (3.78 g, 67.4 mmol) was dissolved in 15 mL MeOH and added dropwise to the previous solution at 60 °C. The solution turned black and a white precipitate was formed. The mixture was heated at 60 °C for 4 hours. The reaction was quenched by adding 30 mL 20 % KOH-solution. The product was ectracted with CH_2Cl_2 (6 x 30 mL), dried over $MgSO_4$ and purified by chromatography on silica gel (CH_2Cl_2 : petroleum ether = 1:1, UV), to give 1.49 g (4.569 mmol, 68 % yield) of **P_TM75** as white solid.

Melting point: 101 – 102 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 – 8.17 (m, 2H), 7.50 – 7.56 (m, 2H), 7.22 (d, ^3J = 8.42 Hz, 2H), 7.08 (d, ^3J = 8.39 Hz, 2H), 4.26 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.49 (C_q), 150.40 (C_q), 138.90 (C_q), 131.46 (C_q), 129.38 (CH), 128.56 (C_q), 128.40 (CH), 128.00 (C_q), 127.13 (C_q), 126.76 (C_q), 125.81 (CH), 125.48 (CH), 122.42 (CH), 122.19 (CH), 62.21 (CH_3), 61.31 (CH_3), 32.07 (CH_2), 12.58 (CH_3). – EI MS (70 eV, m/z (%)): 326.12 ($[M]^+$, 100), 311.10 (43), 296.08 (8), 279.07 (10), 261.11 (5), 244.10 (10), 215.10 (8). – IR (KBr): 3443 cm^{-1} (b, m), 2990 (w), 2933 (m), 2838 (w), 1592 (m), 1490 (s), 1456 (m), 1377 (m), 1353 (vs), 1273 (m), 1193 (w), 1096 (s), 1063 (vs), 1028 (m), 1014 (vs), 963 (m), 804 (w), 784 (m), 770 (s), 694 (w). – EA: obs. C, 73.30 %; H, 5.90 %; Cl, 10.84 %, calcd. C, 73.50 %; H, 5.86 %, Cl, 10.85 % for $C_{20}H_{19}ClO_2$.

Example 13: General Procedure for the Buchwald-Hartwig Coupling Reaction between P_TM75 and different amines

A Schlenk-tube was flushed with argon and successively filled with 1 equivalent **P_TM75** (100 mg, 0.306 mmol) prepared according to example 12, 2.0 equivalent NaO^{t}Bu (59 mg, 0.612 mmol), 5 mol% 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (7 mg, 0.015 mmol), 5 mol% Pd(dba)$_2$ (8 mg, 0.015 mmol), 4.0 equivalent amine (1.224 mmol) and 3 mL dry DME. The Schlenk-tube was sealed and heated at 80 °C for 4 to 24 h. The solvent was removed *in vacuo* and the residue was purified by flash-chromatography.

Example 13.1: 1-(4-*tert*-Butyl-benzyl)-4-[4-(1,4-dimethoxy-3-methyl-naphthalen-2-ylmethyl)-phenyl]-piperazine (P_TM78)

As amine 1-(4-tert-butylbenzyl)piperazine was used. After chromatography on silica gel (CH_2Cl_2 : MeOH = 40:1, UV), 390 mg (0.746 mmol, 81 % yield) of **P_TM78** were isolated as grey solid.

Melting point: 63 – 65 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 – 8.11 (m, 2H), 7.46 – 7.52 (m, 2H), 7.35 (d, ^3J = 8.35 Hz, 2H), 7.27 (d, ^3J = 8.31 Hz, 2H), 7.00 (d, ^3J = 8.62 Hz, 2H), 6.80 (d, ^3J = 8.68 Hz), 4.20 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.54 (s, 2H), 3.14 (t, ^3J = 4.74 Hz, 4H), 2.59 (t, ^3J = 4.95 Hz, 4H), 2.27 (s, 3H), 1.33 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.41 (C_q), 150.25 (C_q), 149.97 (C_q), 149.46 (C_q), 134.74 (C_q), 131.38 (C_q), 129.63 (C_q), 128.90 (CH), 128.66 (CH), 127.82 (C_q), 127.21 (C_q), 125.55 (CH), 125.28 (CH), 125.09 (CH), 122.45 (CH), 122.15 (CH), 116.14 (CH), 62.67 (CH_2), 62.26 (CH_3), 61.32 (CH_3), 53.09 (CH_2), 49.34 (CH_2), 34.45 (C_q), 31.83 (CH_2), 31.39 (CH_3), 12.63 (CH_3). MALDI MS (Dith., m/z): 522.1 (M^+). – IR (KBr): 3436 cm^{-1} (s), 2958 (s), 2904 (m), 2879 (m), 2817 (m), 1612 (m), 1592 (m), 1514 (s), 1454 (s), 1375 (m), 1353 (vs), 1268 (m), 1242 (m), 1229 (m), 1147 (m), 1108 (m), 1097 (m), 1066 (s), 1014 (m), 771 (m). EA: obs. C, 80.19 %; H, 8.01 %; N, 5.35 %, calcd. C, 80.42 %; H, 8.10 %, N, 5.36 % for $C_{35}H_{42}N_2O_2$.

Example 14: 2-[4-(4-Ethyl-piperazin-1-yl)-benzyl]-3-methyl-[1,4]naphthoquinone (P_TM87)

59 mg (0.0957 mmol) **P_TM78** prepared according to example 13.1 was dissolved in 2 mL dry CH_2Cl_2 and cooled to - 78 °C. 0.5 mL (0.478 mmol, 1M in CH_2Cl_2) BBr_3 was added, the mixture was allowed to warm to room temperature and the red suspension was stirred overnight. The mixture was quenched by addition of 2 mL H_2O, extracted with CH_2Cl_2 (5 x 10 mL), dried over $MgSO_4$ and purified by chromatography

to give analytically pure **P_TM87**. After chromatography on silica gel (CH_2Cl_2 : MeOH = 40:1, UV), 37 mg (0.075 mmol, 78 % yield) of **P_TM87** were isolated as red solid. Melting point: 81 – 82 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.05 – 8.08 (m, 2H), 7.65 – 7.68 (m, 2H), 7.33 (d, ^3J = 8.23 Hz, 2H), 7.24 (d, ^3J = 8.16 Hz, 2H), 7.11 (d, ^3J = 8.50 Hz, 2H), 6.80 (d, ^3J = 8.58 Hz, 2H), 3.93 (s, 2H), 3.51 (s, 2H), 3.13 (t, ^3J = 4.76 Hz, 4H), 2.58 (t, ^3J = 4.99 Hz, 4H), 2.24 (s, 3H), 1.30 (s, 9H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.48 (C_q), 184.72 (C_q), 149.99 (C_q), 149.90 (C_q), 145.67 (C_q), 143.86 (C_q), 134.71 (C_q), 133.36 (CH), 133.33 (CH), 132.09 (C_q), 132.05 (C_q), 129.28 (CH), 128.91 (CH), 128.77 (C_q), 126.38 (CH), 126.16 (CH), 125.10 (CH), 116.19 (CH), 62.65 (CH_2), 53.01 (CH_2), 49.11 (CH_2), 34.43 (C_q), 31.48 (CH_2), 31.36 (CH_3), 13.18 (CH_3). – FAB MS (NBA, m/z (%)): 492.2 ($[M]^+$, 100). – IR (KBr): 3448 cm^{-1} (b, vs), 2961 (m), 2819 (w), 1660 (vs), 1616 (s), 1595 (m), 1514 (s), 1333 (w), 1295 (vs), 1261 (w), 1243 (w), 1230 (w), 815 (w), 803 (w), 707 (w), 581 (w), 555 (w), 537 (w), 528 (w). – EA: obs. C, 77.34 %; H, 7.43 %; N, 5.32 %, calcd. C, 77.19 %; H, 7.12 %; N, 5.41 % for $C_{33}H_{36}N_2O_2 \cdot 0.3 CH_2Cl_2$.

Example 15: 2-Difluoromethyl -1,4-dimethoxy-naphthalene (HB39)

The reaction was conducted in a Teflon® bottle under N_2-atmosphere. To a solution of 750 mg (3.47 mmol) 1,4-dimethoxy-naphthalene-2-carbaldehyde prepared according to Uno et al, (*J. Org. Chem.* **1986**, 51(3), 350-8) in 10 mL dry CH_2Cl_2 was added 775 µl (950 mg, 5.90 mmol) diethylaminosulfur trifluoride (DAST) or the equal amount of Deoxo-Fluor® and 10 µL (0.17 mmol) ethanol at 0 °C. The reaction mixture was stirred for 1 h at this temperature and then heated overnight to 40 °C. To run the reaction to completion another 140 µL DAST was added followed by incubation at 40 °C for additional 5 h. 10 mL of saturated $NaHCO_3$-solution was added in small portions to quench the reaction. The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 20mL), dried over $MgSO_4$ and purified by flash-chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV) to give 723 mg **HB39** (3.03 mmol, 88 %) of an almost colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.25 - 8.30 (m, 1H), 8.06 - 8.11 (m, 1H), 7.53 - 7.62 (m, 2H), 7.16 (t, ^1J = 55.8 Hz, 1H, CHF_2), 6.90 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 152.3 (C_q), 148.5 (C_q), 127.9 (C_q), 126.9 (CH), 126.7 (CH), 122.6 (C_q), 122.5 (CH), 122.2 (C_q), 122.0 (CH), 111.7 (t, ^1J = 235 Hz, CHF_2), 98.6 (CH), 63.8 (CH_3), 55.5 (CH_3). – ^{19}F-NMR ($CDCl_3$): δ = - 112.37 (d, ^1J =

55.8 Hz); MS (EI, *m/z*) 238.07 calc. 238.08. – EA: obs. C, 65.39 %; H, 5.20 %, calcd. C, 65.54 %; H, 5.08 % for $C_{13}H_{12}F_2O_2$.

Example 16: 2-Difluoromethyl-1,4-naphthoquinone (HB49)

500 mg (2.10 mmol) 2-difluoromethyl-1,4-dimethoxy-naphthalene (**HB39**) prepared according to example 15 was dissolved in 10 mL CH_3CN and a solution of 3.45 g (6.30 mmol) CAN in 8 mL H_2O was added. The reaction mixture was stirred for 15 min at room temperature, the acetonitrile was removed *in vacuo*, the product was extracted with CH_2Cl_2 (5 x 10 mL), dried over $MgSO_4$ and purified by flash-chromatography on silica gel (petroleum ether: CH_2Cl_2 = 1:1, UV) to give 405 mg **HB49** as yellow solid (1.95 mmol, 93%).

Melting point: 74 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 - 8.15 (m, 2H), 7.76 - 7.83 (m, 2H), 7.19 (m, 1H), 6.83 (t, ^1J = 53.9 Hz, C*H*F_2, 1H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ 183.9 (C_q), 182.4 (C_q), 140.4 (t, ^2J = 21.2 Hz, C_q), 135.1 (CH), 134.9 (CH), 134.3 (CH), 134.2 (CH), 131.6 (C_q), 131.3 (C_q), 126.4 (CH), 109.2 (t, ^1J = 240.4 Hz, CHF_2). – ^{19}F-NMR ($CDCl_3$) δ = -123.85 (d, ^1J = 53.9 Hz). - MS (EI, *m/z*) 208.02 calc. 208.03. – EA: obs. C, 63.58 %; H, 3.02 %, calcd. C, 63.47 %; H, 2.91 % for $C_{11}H_6F_2O_2$.

Example 17: Inhibition of *P. falciparum* and Human Glutathione Reductase Under Steady-State-Conditions.

17.1. Materials and methods

The standard assay was conducted at 25 °C in a 1 mL-cuvette. The assay mixture contained 100 µM NADPH and 1 mM GSSG in GR buffer (100 mM potassium phosphate buffer, 200 mM KCl, 1 mM EDTA, pH 6.9). IC_{50} values were evaluated in duplicate in the presence of seven inhibitor concentrations ranging from 0 to 100 µM. Inhibitor stock solutions were prepared in 100 % DMSO. 1 % DMSO concentration was kept constant in the assay cuvette. The reaction was started by adding enzyme (8 mU human GR, 6.5 mU P. falciparum GR) and initial rates of NADPH oxidation were monitored at 340 nm ($\varepsilon_{340\,nm}$ = 6.22 mM^{-1} cm^{-1}).

17.2 Results

They are shown in Figure 2.

The IC_{50} values were determined for the benzyl- (**P_TM24**, **P_TM26**, **P_TM29**, **P_TM30**, **P_TM31**, **P_TM36**, **P_TM63**) and benzoyl-substituted derivatives

(**P_TM22**, **P_TM25**, **P_TM27**, **P_TM28**, **P_TM33**, **P_TM34**, **P_TM40**, and **P_TM47**), under steady-state conditions and were compared with menadione as reference.

In the assay 1 mM glutathione disulfide (GSSG) concentration was used in order to select the most potent Gluthatione reductase inhibitors. This high GSSG concentration used is not a cell-physiological condition but rather a cell-pathological condition at which the GSSG concentration starts to be toxic for the parasite.

Menadione displayed an IC_{50} value of 42.0 μM for *Pf*GR and 27.5 μM for *h*GR (Bauer et al, *J. Am. Chem. Soc.* **2006**, 128, 10784-10794). In general, all benzyl- and benzoyl- substituted derivatives displayed IC_{50} values ranging from 0.8 μM to 8.2 μM for *Pf*GR and 0.3 μM to 8.6 μM for *h*GR. In particular in the *Pf*GR assay, the benzyl-series showed only moderate inhibition properties with **P_TM26** being the best *Pf*GR inhibitor in this series with an IC_{50} value of 7.8 μM. The complete benzyl-series had higher inhibitory capabilities towards the human GR in accordance with **P_TM29** being the best hGR inhibitor in this series with an IC_{50} value of 1.6 μM. Compared to their corresponding benzyl-analogues the benzoyl-series displayed lower IC_{50} values: for *Pf*GR with values ranging from 0.8 μM to 6.3 μM and for *h*GR from 0.3 μM to 2.0 μM attesting a better recognition of a keto group next to the redox-cycling naphthoquinone-moiety towards the human enzyme resulting in an improved inhibition. The "benzhydrol" **P_TM23** also behaved as a potent best GR inhibitor in both enzyme assays with IC_{50} values of 4.5 (*Pf*GR) and 1.3 μM (hGR).

Example 18 1,4-Naphthoquinone Reductase Activity of *P. falciparum* Glutathione Reductase.

18.1. Materials and methods

The reduction assay mixture consisted of 100 mM potassium phosphate buffer pH 6.9, 200 mM KCl, 1 mM EDTA and 100 μM NADPH in a total volume of 1 mL. 1,4-naphthoquinone reductase activity was determined by recording the initial velocities in the presence of increasing naphthoquinone concentrations (0 – 300 μM). The 1,4-naphthoquinone was first dissolved in DMSO, and a final 1 % DMSO concentration was kept constant in the 1,4-naphthoquinone reductase assay. For the determination of K_M and V_{max} values, the steady-state rates were fitted by using nonlinear regression analysis software (Kaleidagraph) to the Michaelis-Menten equation. From these values, the turnover number k_{cat} and the catalytic efficiency k_{cat}/K_M were calculated.

18.2 Results

They are given in Figure 3.

The catalytic parameters of menadione against *Plasmodium falciparum* GR were shown in Biot et al, 2004 J. Med. Chem. 47, 5972-5983) to be 82.2 μM and 9.6 min^{-1} for K_M and k_{cat}, respectively, leading to a catalytic efficiency k_{cat}/K_M of 1.99 mM^{-1} s^{-1}

Compared with menadione as reference, the tested compounds **P_TM26**, **P_TM36**, **P_TM27**, **P_TM25**, **P_TM34** and **P_TM33** bearing a various set of substituents showed low K_M values ranging from 6.1 μM (**P_TM25**) to 56.1 μM (**P_TM27**) indicating a tighter binding to the enzyme *Pf*GR when compared to menadione. Only **P_TM36** with a K_M value of 87 μM showed similar affinity to the enzyme compared to menadione. From the catalytic efficiencies, expressed as k_{cat}/K_M values, **P_TM27**, **P_TM25**, **P_TM34**, **P_TM23**, **P_TM39**, **P_TM40**, **P_TM47**, and **P_TM63** behaved as very effective substrates of *Pf*GR with respect to menadione. Compounds with two redox active moieties like **P_TM63** (with a second quinone) and **P_TM40** (with a nitrophenyl group) showed 17.2-fold and 3.9-fold increased catalytic efficiencies with respect to menadione. Also an increased oxidant character, expressed with the plumbagin derivative **P_TM47**, led to 6.3-fold higher substrate efficiency when compared to menadione.

Example 19 Redox-cycling Activity of Methemoglobin(Fe^{3+}) into Oxyhemoglobin(Fe^{2+})

19. 1 Material and methods

Since FPIX(Fe^{2+}) is an inhibitor of hematin polymerization, compounds displaying the ability to reduce FPIX(Fe^{3+}) into FPIX(Fe^{2+}) might synergistically contribute with GR inhibition to increased oxidative stress in infected-red blood cells. To evaluate the redox-cycling activity of FPIX(Fe^{3+}) into FPIX(Fe^{2+}) we set up an assay using the naphthoquinone, the glutathione reductase/NADPH-based system to regenerate the dihydronaphthoquinone continuously and methemoglobin(Fe^{3+}) (MetHb). The UV-spectrum of MetHb between 300 nm and 700 nm is characterized by a maximal absorbance at 405 nm and a broad band centered at around 630 nm. After reduction the spectrum of oxyhemoglobin(Fe^{2+}) (OxyHb) shows a shift of the maximal absorbance from 405 nm to 410 nm and two weak bands at 536 and 576 nm. We used 20 μM methylene blue as positive control of this redox-cycling activity.

In an Eppendorf tube containing 6.4 mg MetHb dissolved in 885 µL GR buffer (47 mM potassium phosphate buffer pH 6.9, 200 mM KCl, 100mM EDTA), 10 µL 20 mM **P_TM25** dissolved in DMSO and 100 µL NADPH dissolved in GR buffer were added. The reaction was started by the addition of 5 µL human GR and then incubated at 37 °C. In a 1 mL cuvette 20 µL of the reaction mixture was diluted with 980 µL GR buffer and a UV-spectra between 300 nm and 700 nm was done after 5 min, 10 min, 20 min and 30 min incubation time. The final concentrations in the reaction mixture were 100 µM MetHb, 200 µM **P_TM25**, 400 µM NADPH and 1.06 µmol hGR, final DMSO concentration 1 %.

Spectra were measured after 5 min (blue), 10 min (black), 20 min (green) and 30 min (red).

19.2 Results

They are shown in Figure 4.

P_TM25 can undergo redox-cycling of methemoglobin in the presence of GR under physiological conditions, supporting – albeit shown only for **P_TM25** – that the compounds of the 2-benzyl- and 2-benzoyl-series have several targets making a fast development of resistance in the parasite unlikely, i.e. (i) uncompetitive inhibition of human and *Plasmodium falciparum* glutathione reductases in the low micromolar range with the benzoyl series displaying more potent inhibition properties compared to their benzyl analogs; (ii) redox-cycling of both enzymes (subversive substrates) catalyzing the antioxidant glutathione reductase into a prooxidant enzyme in the presence of the compounds, especially the 2-benzoyl derivatives, (iii) in addition to the redox-cycling of methemoglobin in the presence of the NADPH/GR system and the 2-benzoyl menadione representative **P_TM25**.

Figure 4 shows the redox-cycling effect of 100 µM MetHb in the presence of 200 µM **P_TM25**, 400 µM NADPH and 1 µmol human GR, but the shift of the maximal absorbance from 405 nn to 410 nm is already visible from 50 µM **P_TM25** as in the case of menadione (data not shown). The reaction of **P_TM 25** with MetHb in the presence of NADPH and human GR causes a shift in the λ_{max} of MetHb (from 405 to 410 nm). For **P_TM25** the shift starts being visible at a **P_TM** concentration of 50 µM as in the case of menadione. Under the same conditions a clear shift of λ_{max} of MetHb was observed in the presence of 20 µM Methylene Blue (MB).

Example 20: The Antimalarial and Cytotoxic Effects *in Vitro*

20. 1 Material and methods

Inhibition of the growth of *P. falciparum* by the naphthoquinones was evaluated by determining the inhibitor concentration required to kill 50 % of the parasite (IC_{50} values) using different parasite strains and different assays.

The IC_{50} values against the multidrug-resistant strain Dd2 were determined using the ^{3}H-hypoxanthine assay (Desjardins et al, 1979) as well as for the determination of the IC_{50} values against the chloroquine sensitive strains 3D7 and the chloroquine resistant strain K1. The IC_{50} values against Pf-GHA and MRC-5 were determined by using the less sensitive colorimetric NBT-based lactate dehydrogenase assay (Makler et al, *Am. J. Trop. Med. Hyg.* **1993**, 48(6), 739-741) based on redox-reactions.

20.1.1 Determination of IC_{50} values of Dd2 growth inhibition.

The IC_{50} was tested by standard *in vitro* antiproliferation assays (Desjardins et al, 1979 *Antimicrob. Agents Chemother* **1979**, 16, 710-718). Infected erythrocytes in ring stage (0.5 % parasitemia, 2.5 % hematocrit) in 96-well plates were exposed to the compounds for 48 h and then to radioactive hypoxanthine for 24 h. The amount of radioactivity in precipitable material served as an index of cell proliferation.

20.1.2 Determination of IC_{50} values of 3D7, K1 and Cytotoxicities with human KB cells.

Parasite Cultures. The CQ-sensitive 3D7 clone of the NF54 isolate (Ponnurai et al, 1981 *Trop. Geogr. Med.*, 33, 50-54) and the chloroquine-, pyrimethamine-, and cycloguanil-resistant K1 strain (Thailand) of *Plasmodium falciparum* were acquired from MR4 (Malaria Research and Reference Reagent Resource Center, Manassas, VA). *P. falciparum in vitro* culture was carried out using standard protocols (Trager et al, 1976 *Science*, 193, 673-675) with modifications. Briefly, parasites were maintained in tissue culture flasks in human A Rh+ erythrocytes at 5 % hematocrit in RPMI 1640 supplemented with 25 mM HEPES, 24 mM $NaHCO_3$, 0.2 % (w/v) glucose, 0.03 % L-glutamine, 150 μM hypoxanthine, and 0.5 % Albumax II® (Invitrogen) in a 5 % CO_2/air mixture at 37 °C, and the medium was changed daily.

***In Vitro* Antiparasitic Bioassays.** Drug susceptibility of *P. falciparum* was studied using a modified method (Cameron et al, 2004 *J. Biol. Chem.* 279, 31429 – 31439) of the protocol described previously (Desjardins et al, 1979). All assays included CQ diphosphate (Sigma, UK) as a standard and control wells with untreated infected and uninfected erythrocytes. IC_{50} values were derived by sigmoidal regression analysis (Microsoft *xl*fit™).

Evaluation of the Cytotoxicity. Cytotoxicity on human KB cells (human oral pharyngeal carcinoma) was evaluated using the Alamar Blue assay as described. The positive control drug was podophyllotoxin (Sigma). IC_{50} values were calculated compared to blanks and untreated controls.

20.1.3 Determination of IC_{50} values of Pf-GHA and Cytotoxicities against MRC-5 cells.

***In Vitro* Antiparasitic Bioassays.** The strain is maintained in RPMI-1640 medium supplemented with 0.37 mM hypoxanthine, 25 mM HEPES, 25 mM $NaHCO_3$, and 10 % O^+ human serum together with 2-4 % washed human O^+ erythrocytes. All cultures and assays are conducted under an atmosphere of 4 % CO_2, 3 % O_2 and 93 % N_2. Assays are performed in 96-well microtiter plates, each well containing 10 μL of the watery compound dilutions together with 190 μL of the malaria parasite inoculum (1 % parasitaemia, 2 % HCT). After 72 h incubation, plates are frozen and stored at – 20 °C. After thawing, 20 μL of each well is transferred into another plate together with 100 μL Malstat reagent and 20 μL of 1/1 mixture of PES (phenazine ethosulfate, 0.1 mg/mL) and NBT (Nitro Blue Tetrazolium Grade III, 2 mg/mL). Change in colour is measured spectrophotometrically at 655 nm. The results are expressed as % reduction in parasitaemia compared to control wells. Compounds are treated at 5 concentrations (64 – 16 – 4 – 1 and 0.25 μM or μg/mL). Artesunate (IC_{50} = 0.005 + 0.004 μM) and chloroquine (IC_{50} 0.05 + 0.08 μM) are included as reference drugs.

Evaluation of the Cytotoxicity. Human MRC-5_{SV2} cells are cultured in Earl`s MEM + 5 % FCSi. Assays are performed in 96-well microtiter plates, each well containing about 10^4 cell/well. After 3 days incubation, cell viability is assessed fluorimetrically after addition of resazurin and fluorescence is measured (λ_{ex} 550 nm, λ_{em} 590 nm). The results are expressed as % reduction in cell growth/viability compared to untreated control wells and CC_{50} is determined. Compounds are tested at 5 concentrations (64 – 14 – 4 – 1 and 0.25 μM or mg/mL). When the CC_{50} is lower than 4 μg/mL or μM, the compound is classified as toxic.

20.2. Results

They are given in Figure 5.

The assay against Dd2 parasites revealed 16 compounds with IC_{50} values below 100 nM. As references standard drugs like atovaquone and chloroquine were also tested displaying IC_{50} values < 0.1 nM and 291 nM respectively. These 16 compounds belong to the benzyl series bearing halide- (**P_TM24**, **P_TM26**, **P_TM30**, **P_TM57**), (several) methoxy- (**P_TM31**, **P_TM32**, **P_TM58**, **P_TM59**, **P_TM60**, **P_TM61**), -hydroxy- (**P_TM36**), cyano- (**P_TM41**), nitro- (**P_TM37**) and alkyl-substituents (**P_TM29**, **P_TM43**). The unsubstituted derivative **P_TM62** was less active. Compared to the benzyl series the corresponding benzoyl-series displayed lower antimalarial activities with IC_{50} values being superior to 1 μM except in the case of the nitro derivative **P_TM40**. With a nitro-substituent in para position to the benzyl chain the compound displayed an IC_{50} value of 103 nM which is three-fold higher than in the case of its benzyl analogue **P_TM37** with an IC_{50} value of 46 nM.

When testing the compounds against 3D7 and K1 *P. falciparum* strains the results confirmed the high antimalarial activities previously found against Dd2. The most active compounds belong to the benzyl series with IC_{50} values below 1 μM. As control chloroquine was used displaying IC_{50} values around 1 μM against K1 and around 20 nM against 3D7. In contrast with the Dd2 assays only **P_TM21** showed a high activity (0.27 μM against 3D7 and 0.10 μM against K1) which was not detected in the previous test displaying an activity against Dd2 of 791 nM.

The third assay – based on the colorimetric detection of the formazan dye as an indicator of the antimalarial activity - only revealed a few compounds active against the parasite strains Pf-GHA. As reference atovaquone was used displaying an IC_{50} value of 0.31 μM. **P_TM21**, **P_TM24**, **P_TM26**, **P_TM29**, **P_TM30**, **P_TM33**, **P_TM36**, **P_TM38**, **P_TM39**, **P_TM41**, **P_TM42**, **P_TM46**, **P_TM57**, **P_TM58**, **P_TM59**, **P_TM66**, **P_TM67**, **P_TM69**, **P_TM72**, **P_TM79**, and **P_TM81**, displayed an antimalarial activity with IC_{50} values below 5 μM, confirming the antimalarial effects but none of the compounds was as active as atovaquone.

Example 21 The Antimalarial Activity against *P. falciparum* Strains *in Vitro* Exhibiting Different Degrees of Resistance to Chloroquine and Various Known Antimalarial Drugs

21.1. Material and methods

***Plasmodium falciparum* cultures.** Twelve parasite strains or isolates from a wide panel of countries (Africa (3D7), Brazil (Bre), Cambodia (K2 and K14), Cameroon (FCM29), Djibouti (Voll), the Gambia (FCR3), Indochina (W2), Niger (L1), Senegal (8425), Sierra Leone (D6), and Uganda (PA)) were maintained in culture in RPMI 1640 (Invitrogen, Paisley, United Kingdom), supplemented with 10 % human serum (Abcys S.A. Paris, France) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Parasites were grown in A-positive human blood under controlled atmospheric conditions that consists of 10 % O_2, 5 % CO_2 and 85 % N_2 at 37 °C with a humidity of 95 %.

Drugs. Ferroquine base (SR97193) (FQ) was obtained from Sanofi-Aventis (France). Chloroquine diphosphate (CQ), quinine hydrochloride (QN) and dihydroartemisinin (DHA) were purchased from Sigma (Saint Louis, MO). Monodesethylamodiaquine (MDAQ) was obtained from the World Health Organization (Geneva, Switzerland), mefloquine (MQ) from Hoffman-LaRoche (Bale, Switzerland) and lumefantrine (LMF) from Novartis Pharma (Basel, Switzerland).

FQ and synthetic compounds were resuspended and then diluted in RPMI-DMSO (99v/1v) to obtain final concentration ranged from 0.125 to 500 nM.

CQ was resuspended in water in concentrations ranging between 5 to 3200 nM. QN, MDAQ, MQ, and DHA which were dissolved first in methanol and then diluted in water to obtain final concentration ranged from 5 to 3200 nM for QN, from 1.56 to 1000 nM for MDAQ, 3.2 to 400 nM for MQ and from 0.1 to 100 nM for DHA. Stock solutions were prepared in ethanol for LMF and then diluted in ethanol to obtain concentrations ranged from 0.5 to 310 nM.

***In vitro* assays.** For *in vitro* isotopic microtests, 25 µL/well of antimalarial drug and 200 µL/well of the parasitized red blood cell suspension (final parasitemia, 0.5 %; final hematocrit, 1.5 %) were distributed into 96 well plates. Parasite growth was assessed by adding 1 µCi of tritiated hypoxanthine with a specific activity of 14.1 Ci/mmol (Perkin-Elmer, Courtaboeuf, France) to each well at time zero. The plates were then incubated for 48 h in a controlled atmospheric condition. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on standard filter microplates (Unifilter GF/B; Perkin-Elmer) and washed using a cell harvester (Filter-Mate Cell Harvester; Perkin-Elmer). Filter microplates were dried, and 25 µL of scintillation cocktail (Microscint O; Perkin-Elmer) was placed in each well. Radioactivity incorporated by the parasites was measured with a scintillation counter (Top Count; Perkin-Elmer).

The IC_{50}, the drug concentration able to inhibit 50 % of parasite growth, was assessed by identifying the drug concentration corresponding to 50 % of the uptake of tritiated hypoxanthine by the parasite in the drug-free control wells. The IC_{50} value was determined by non-linear regression analysis of log-based dose-response curves (Riasmart™, Packard, Meriden, USA).

The cut-off values, defined statistically (> 2SD above the mean with or without correlation with clinical failures), for *in vitro* resistance or reduced susceptibility to chloroquine, quinine, mefloquine, monodesethylamodiaquine, lumefantrine and dihydroartemisinin were 100 nM, 800 nM, 30 nM, 60 nM, 150 nM and 10.5 nM, respectively.

21.2. Results

P_TM24, **P_TM29**, **P_TM37**, **P_TM41**, **P_TM45 P_TM57**, **P_TM58**, and **P_TM60** in *P. falciparum* strains *in vitro* exhibiting different degrees of resistance to chloroquine (CQ) and various known antimalarial drugs are given in Figure 6.

From the most sensitive to the most resistant to chloroquine, the strains are: 3D7, D6, 8425, Voll, L1, PA, Bres, FCR3, W2, K2, K14, and FCM29 and displayed various suceptibilities to known antimalarial agents used as references (Figure 6). With respect to chloroquine (CQ) the strains showed IC_{50} values from 21.3 (3D7) to 879.0 (FCM29) and IC_{90} from 40.4 nM (3D7) to 1241.7 nM (FCM29). The other known antimalarial drugs are compounds used in human medicine or in clinical studies: quinine (QN), monodesethylamodiaquine (MDAQ), lumefantrine (LMF), mefloquine (MQ), dihydroartemisinin (DHA) and ferroquine (FQ).

Example 22 : *In Vivo* Antimalarial Activity Against *P. berghei* in Mice

22.1. Material and methods

The *in vivo* tests in the mouse model were done according to a standard protocol (Peters et al *Handbook of Animal Models of Infection*; Academic Press, London, 1999; pp. 756-771). Compounds were tested in the *P. berghei* model by using the 4-day suppressive test, as indicated by Peters, and using chloroquine as a positive control. Briefly, naive 18–20-g ANKA BALB/c mice were infected intravenously with 2 x 10^6 parasitized red cells on day +0. For administration, compounds were freshly prepared in 10 % DMSO in sterile phosphate-buffered saline the day of use. Two hours post-infection mice received the first treatment by the intraperitoneal route. Mice were further treated on days +1–3. Blood films from tail blood were prepared on day +4, and parasitaemia was determined by microscopic examination of Giemsa-stained blood films. Compounds were tested with a daily dose of 50 or 30 mg/kg by the intraperitoneal or oral route. Chloroquine treatment p.o. at 10 mg/kg/day was included as a positive control and resulted in complete inhibition (data not shown). Intraperitoneous administrations of CQ have shown similar activity (98.9 % inhibition at 10mg/kg i.p). Mice were treated and levels of parasitemia determined as described.

22.2. Results

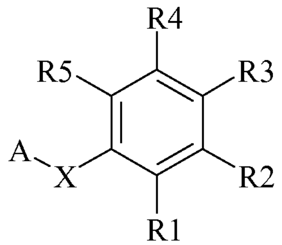
They are given in Figures 7 and 8

Six of the most active compounds (**P_TM24 = HB67, P_TM29, P_TM31, P_TM36, P_TM37, P_TM43**) were tested in *P. berghei*-infected mice by intraperitoneal administration. Results of *in vivo* screens for the six compounds conducted against chloroquine-sensitive *P. berghei* ANKA BALB/c mice according to the Peters's four-day test are given in Figure 7. For comparative purposes, data acquired in the same screens for CQ and the six derivatives are included. Compounds **P_TM37**, **P_TM43**, **P_TM36**, **P_TM29** and **P_TM24** showed significant activity on 4-day treatment. The two most active drugs **P_TM43** (**BJ321**) and **P_TM37** (**BJ323**) caused a 43.4 % reduction and 42.4 % reduction respectively in parasitaemia using a daily dose of 30 mg/kg. At this dose level **P_TM31**, **P_TM36** and **P_TM29** could only cause a 20.7 – 28.4 % inhibition of parasitaemia which might result from a poor bioavailability. The compound **P_TM24** (**HB67**) showed only a decrease of 35.6 % in parasitaemia at a daily dose of 50 mg/kg ip.

Additional data showing the antimalarial effects of compounds **P_TM41**, **P_TM45**, and **P_TM57** in *P. berghei*-infected mice by intraperitoneal administration are given in Figure 8.

CLAIMS

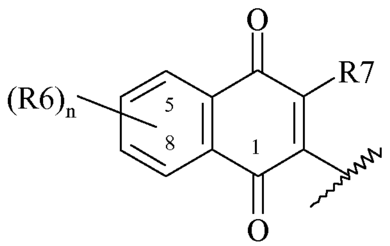
1. Compounds of formula (I)



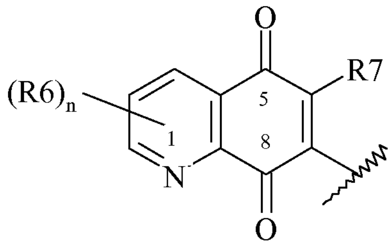
(I)

wherein

- A is selected from the following rings:



and



with each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, representing independently a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4 and R7 representing a methyl group,

- X represents –C(O)– or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group,

- R1, R2, R3, R4 and R5 represent each independently of the others:

. a hydrogen atom,

. a halogen atom,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group,

. a trifluoromethyl group,

. a difluoromethyl group,

. a linear or branched (C_1-C_4)alkoxy group,

. a trifluoromethoxy group,

. a difluoromethoxy group,

. a pentafluorosulfanyl group,

. -COOH,

. -COO(C_1-C_4)alkyl group,

. –CONR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group and m = 1, 2 or 3,

. –CSNR8(CH_2)$_m$CN, with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group m = 1, 2 or 3,

. –CONR8Het with R8 being a hydrogen atom or a linear or branched (C_1-C_4)alkyl group, Het representing a pyridine-2-yl group or the said group substituted by an amino group in -6 or by a –$CONH_2$ group in -5,

. - NO_2,

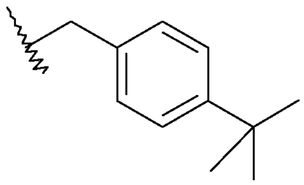
. - CN,

. –NR9R10 with R9 and R10 representing each independently a hydrogen atom, an amino protecting group selected from the group comprising Boc group and (C_1-C_4)alkyl group, or R9 and R10 forming with the nitrogen atom which bears them a cyclic group selected from the group comprising morpholine and piperazine groups **or** said cyclic groups being substituted,

. an aryl group or an aryl group substituted by one or several substituents selected from the group comprising a (C_1-C_4)alkyl group, a -NO_2 group, a –COOR11 with R11 selected from a hydrogen atom and a linear or branched (C_1-C_4)alkyl group, a -NR12R13 with R12 and R13 independently selected from the group comprising a hydrogen atom and a linear or branched (C_1-C_4)alkyl group,

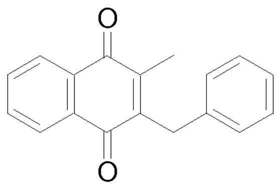
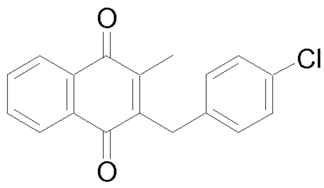
. a heterocyclic group selected from the group comprising morpholinyl group or piperazinyl group, or each of said group being substituted by one or several substituents selected from the group comprising a linear or branched

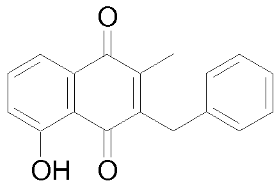
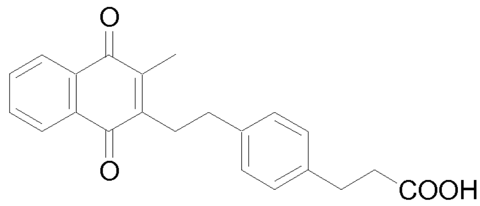
(C_1-C_4)alkyl group, $-COOCH_2CH_3$, or a group

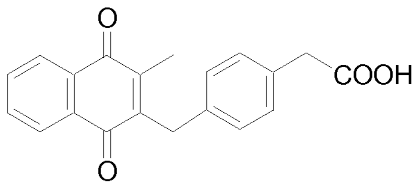
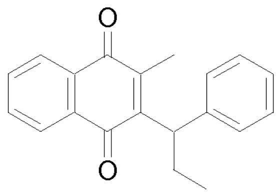


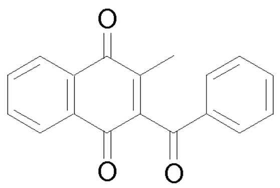
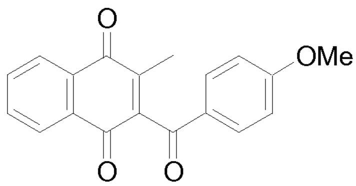
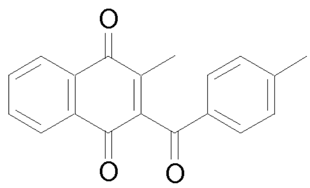
and the pharmaceutically acceptable salt thereof,

with the proviso that the compounds of formula (I) are not selected from the group comprising

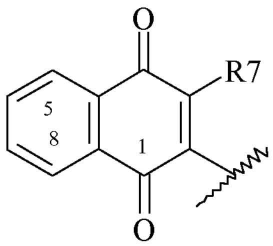
,
,

,
,

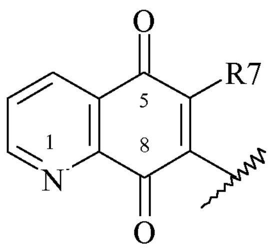
,
,

,
,


2. Compounds according to claim 1 wherein A is selected from the following rings:



and



wherein R7 represents a methyl.

3. Compounds according to anyone of claims 1 or 2 wherein X represents –C(O)- or $–CH_2–$.

4. Compounds according to anyone of claims 1 to 3 wherein:

- R1, R2, R3, R4, R5 represent each independently of the others:

. a hydrogen atom,

. a halogen atom selected from the group comprising Br, Cl and F,

. a hydroxy group,

. a linear or branched (C_1-C_4)alkyl group selected from the group comprising methyl and *t*-butyl,

. a di- or trifluoromethyl group,

. a methoxy group,

. a trifluoromethoxy group,

. a pentafluorosulfanyl group

. - NO_2,

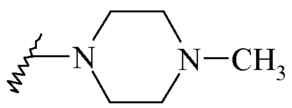
. - CN,

. –COOR14 with R14 representing hydrogen atom or methyl group,

. $–CONH(CH_2)_2CN$

. –NHBoc,

. a group selected from the group comprising



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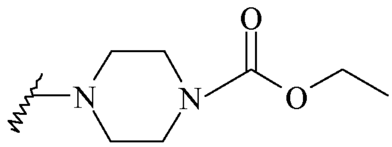
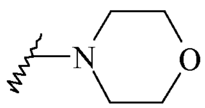
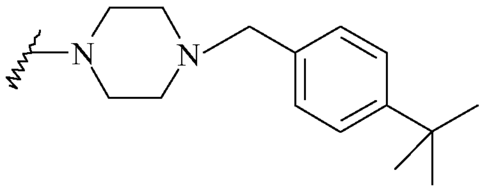




or a



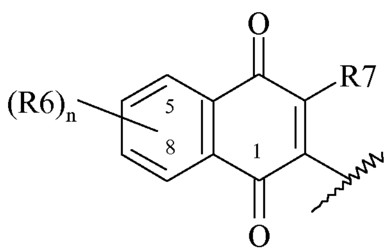
. a phenyl group substituted in *para* by a *t*-butyl group, $-NO_2$, $-N(CH_3)_2$, or $-NHC(CH_3)_3$.

5. Compounds according to anyone of claims 1 to 4 wherein:

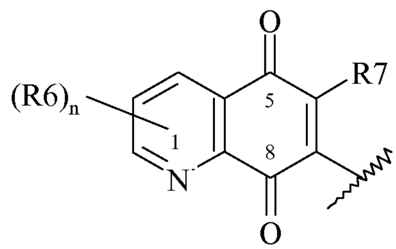
- R1, R2, R3, R4 and R5 are each independently selected from the group comprising a hydrogen atom, a hydroxy group, a methoxy group, a di- or tri-fluoromethyl group and a trifluoromethoxy group, a pentafluorosulfanyl group, or an amino group.

6. Compounds according to anyone of claims 1 to 2 wherein R1, R2, R3, R4 and R5 represent a fluorine atom, a di- or tri-fluoromethyl group, or a trifluoromethoxy group, a pentafluorosulfanyl group.

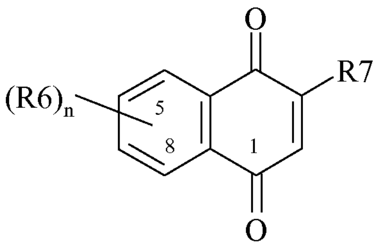
7. A process for preparing compounds of formula (I) according to claim 1 wherein A represents



or

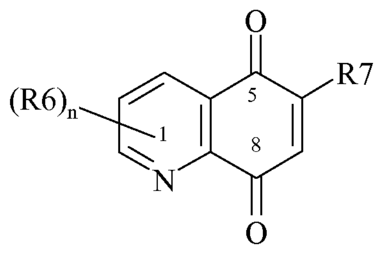


comprising the reaction of a compound of formula (IIa) or (IIb)



(IIa)

or



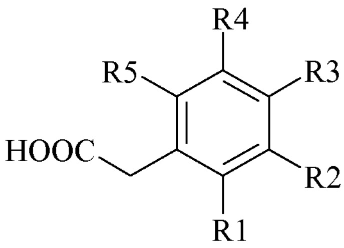
(IIb)

wherein

- each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, represents independently a hydrogen atom, a halogen atom, an hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4, and

- R7 represents a methyl group,

with a phenyl acetic acid derivative of formula (III)

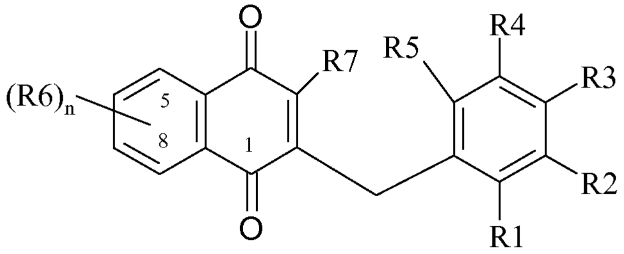


(III)

wherein

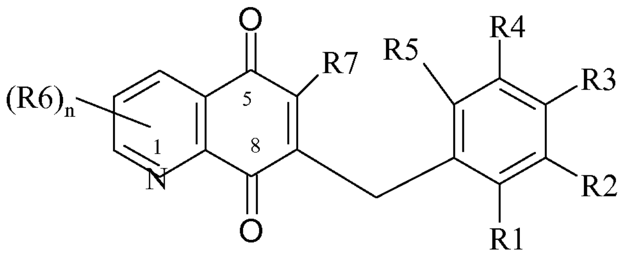
- R1, R2, R3, R4 and R5 are as defined in claim 1,

to obtain respectively a compound of formula (Ia)



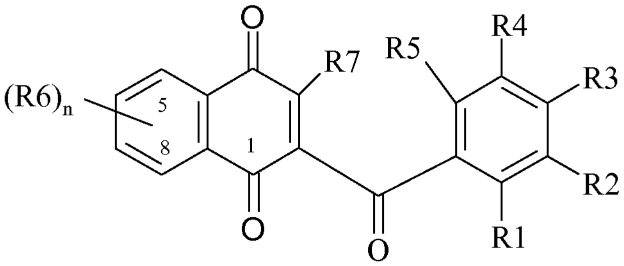
(Ia)

or of formula (Ib)



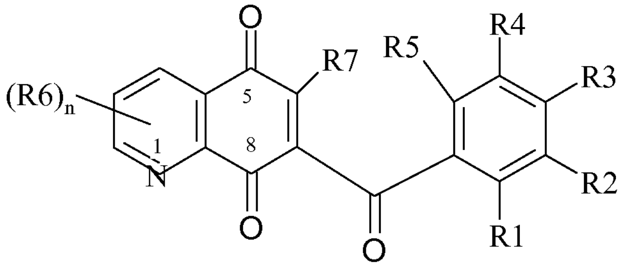
(Ib)

which is treated in oxidative conditions to give respectively a compound of formula (Ic)



(Ic)

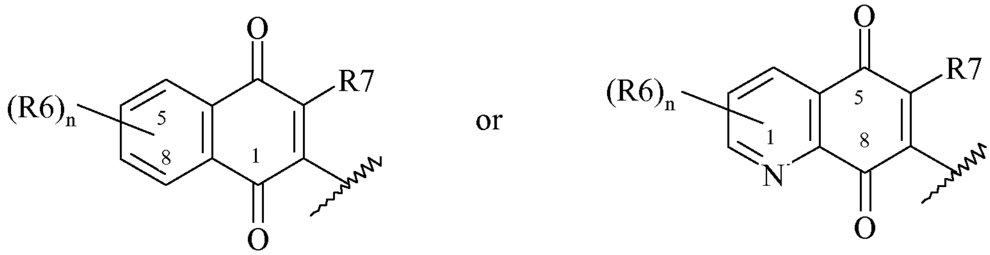
or a compound of formula (Id)



(Id)

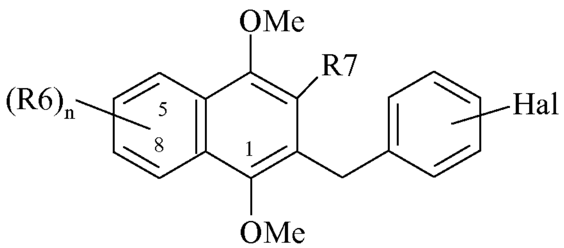
wherein R1, R2, R3, R4, R5, R6 and n are as defined above.

8. A process for preparing compounds of formula (Ia1, Ib1, Ic1, Id1, Ie and If) corresponding to compounds of formula (I) according to claim 1 wherein A represents



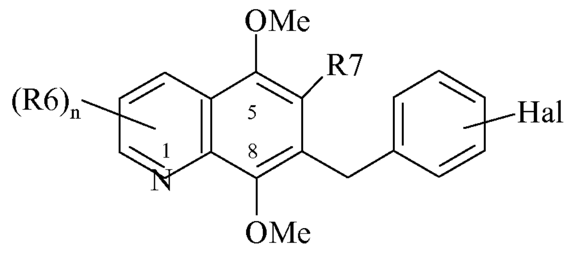
and X represents $-CH_2$- or –C(O)-
comprising

a) the preparation of a compound of formula (IIc)



(IIc)

or of formula (IId)



(IId)

wherein

- R6 which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-dimethoxynaphthalene or in position 2, 3, or 4 of the 5,8-dimethoxyquinoline, represents a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, and n being an integer comprised between 0 and 4,

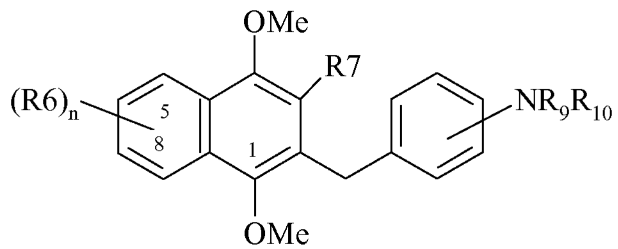
- R7 represents a methyl and

- Hal represents a chloro, a bromo or a iodo atom,

by reduction of the corresponding quinones followed by methylation of the dihydronaphthoquinones intermediates into the corresponding dimethoxynaphthalene of formula (IIc) or dimethoxyquinoline of formula (IId),

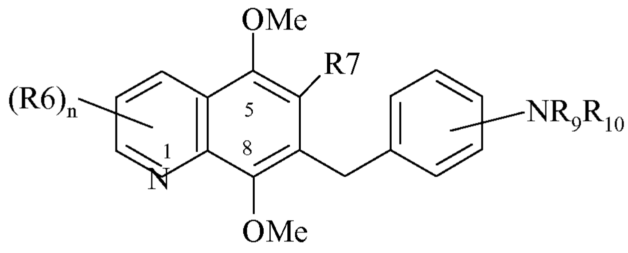
b) reaction of respectively one compound of formula (IIc) or (IId) with an amino compound of formula HNR9R10 with R9 and R10 representing each independently a hydrogen atom or a (C_1-C_4)alkyl group, with the proviso that R9 and R10 are not both a hydrogen atom, or R9 and R10 forming with the nitrogen atom which bears them a cyclic group selected from the group comprising morpholine and piperazine groups**, or** said cyclic groups being substituted, in the presence of a palladium catalyst and of an appropriate palladium ligand,

to obtain a compound of formula (Ie)



(Ie)

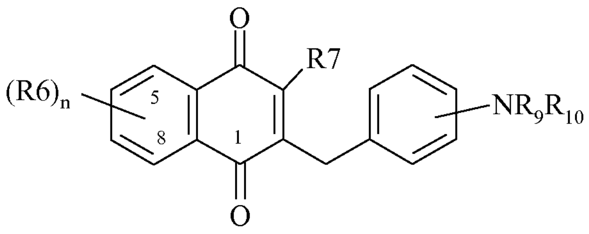
or of formula (If)



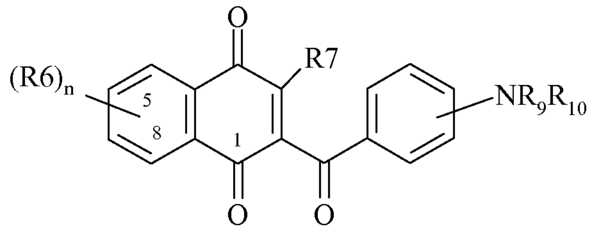
(If)

wherein R6, R7, R9 and R10 are as defined above,

c) re-oxidation of the compound of formula (Ie) or (If) to give the final compounds of formula (Ia1) or (Ic1)

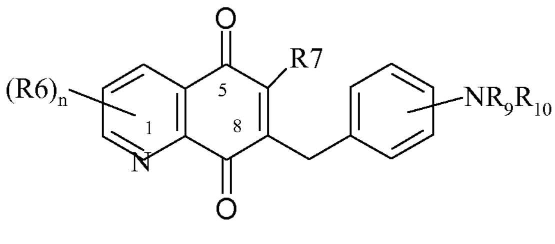


(Ia1)

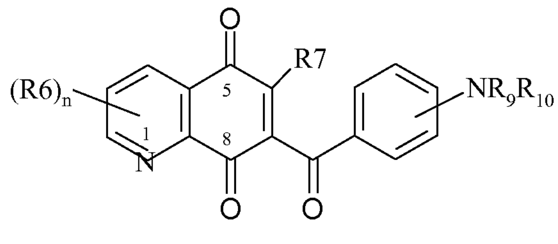


(Ic1)

or a compound of formula (Ib1) or (Id1)

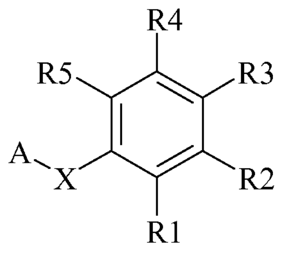


(Ib1)



(Id1)

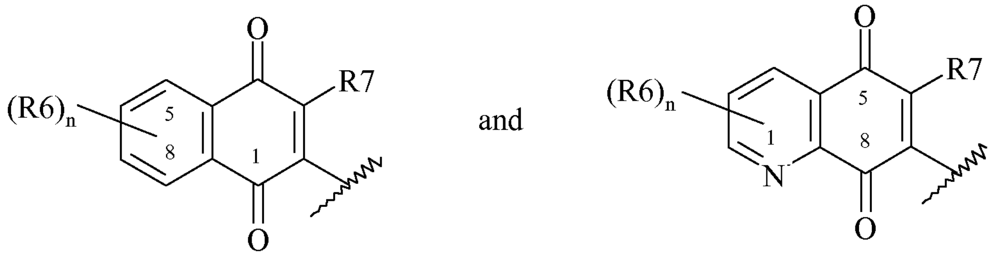
9. Process for preparing compounds of formula I



(I)

wherein

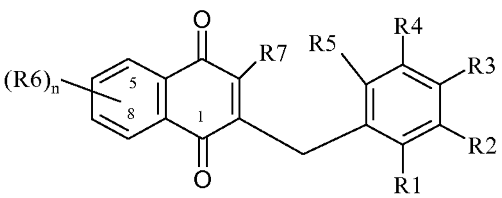
- A is selected from the following rings:



with each of R6, which may be in position 5, 6, 7, or 8 of the phenyl ring of the naphthoquinone or in position 2, 3, or 4 of the quinoline-5,8-dione, representing independently a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, n being an integer comprised between 0 and 4 and R7 representing a methyl group,

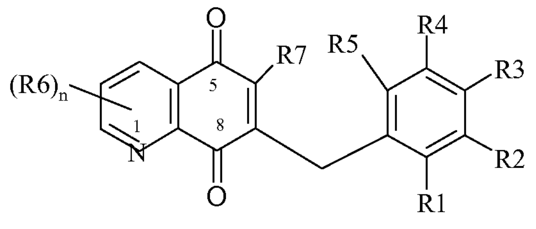
- one of R1, R2, R3, R4, R5 represents a phenyl-ring bearing in para position a *tert*butyl group, $-NO_2$, -COOR11 with R11 being hydrogen atom or a linear or branched (C_1-C_4)alkyl group, or NMe_2 group,

starting from the corresponding compound of formula (Ia)



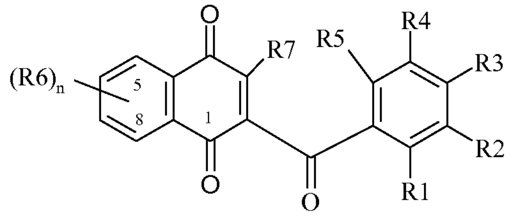
(Ia)

or (Ib)



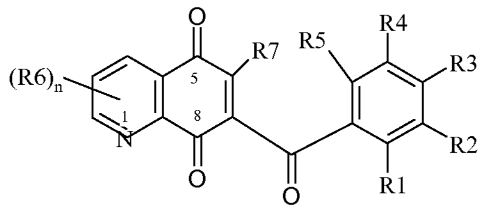
(Ib)

or (Ic)



(Ic)

or (Id)



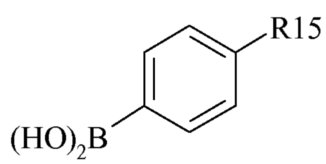
(Id)

wherein

- one of R1, R2, R3, R4 and R5 represents a halogen atom, the others being a hydrogen atom,

- X represents –C(O)– or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group and

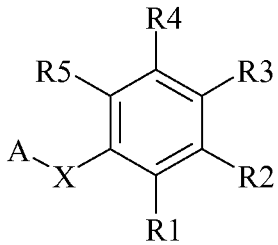
with a boronic acid derivative of formula (IV)



(IV)

wherein R15 represents a *tert*butyl group, $-NO_2$, -COOR11 with R11 being hydrogen atom or a linear or branched (C_1-C_4)alkyl group, or NMe_2 group in the presence of a palladium catalyst and of a base.

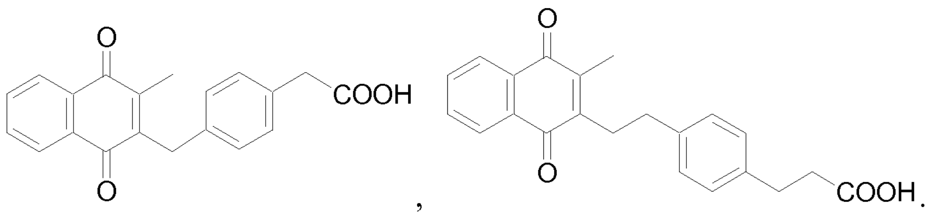
10. Compounds of formula (I)



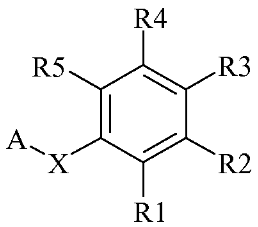
(I)

wherein A, X, R1, R2, R3, R4, R5 are as defined in claim 1 as drug

with the proviso that the compounds of formula (I) are not



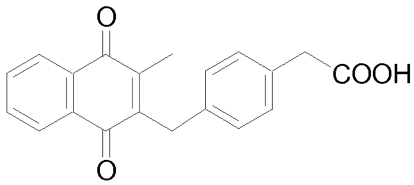
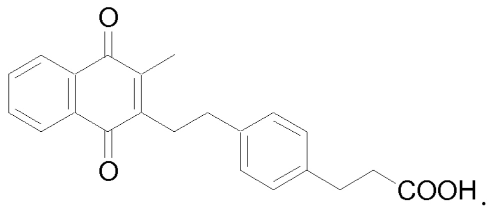
11. Compounds of formula (I),



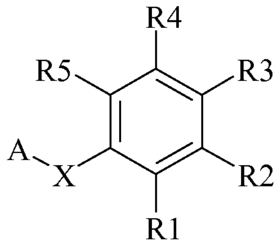
(I)

wherein A, X, R1, R2, R3, R4, R5 are as defined in claim 1**,** for its use in therapy or prophylaxis

with the proviso that the compounds of formula (I) are not

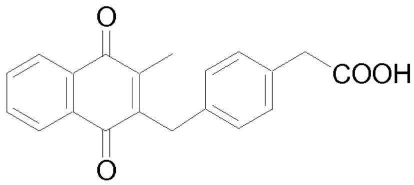
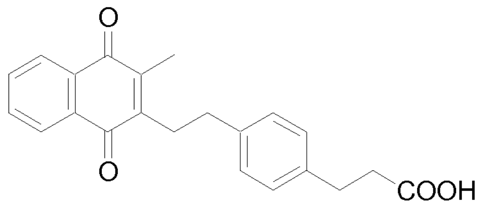
 , 

12. Compounds of formula (I),

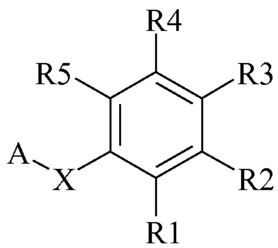


(I)

wherein A, X, R1, R2, R3, R4, R5 are as defined in claim 1**,** as antimalarial agent with the proviso that the compounds of formula (I) are not

 , 

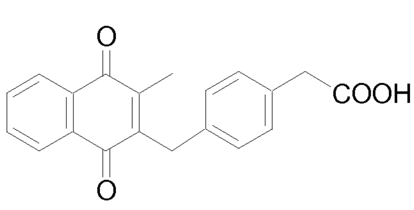
13. Pharmaceutical compositions comprising as active ingredient one or more of the compounds compound of formula (I),



(I)

wherein A, X, R1, R2, R3, R4, R5 are as defined in claim 1**,** in combination with excipients and/or pharmaceutically acceptable diluents or carriers,

with the proviso that the compounds of formula (I) are not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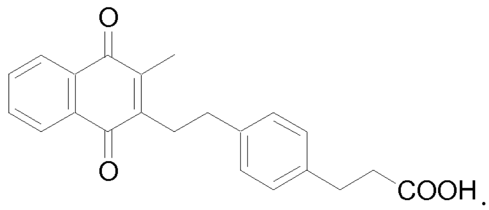
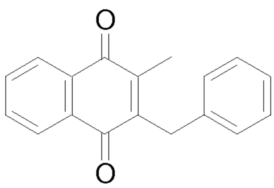


14. Pharmaceutical compositions according to claim 13 further comprising as active ingredient one to three other antimalarial agents selected from the group comprising atovaquone, chloroquine, amodiaquine, mefloquine, artemisinin and the related peroxans from the pharmaceutical market like artesunate, arteether and artemether, menadione, methylene blue, proguanil, cycloguanil, chlorproguanil, pyrimethamine, primaquine, piperaquine, fosmidomycin, halofantrine, dapsone, trimethoprim, sulfamethoxazole, sulfadoxine, for a simultaneous, separated or sequential administration.

15. Compounds of formula (I) including the compounds of formula (I) selected from the group comprising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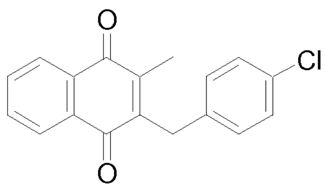
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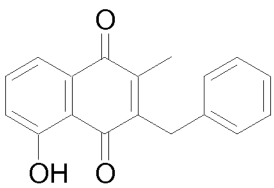
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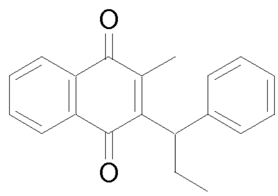
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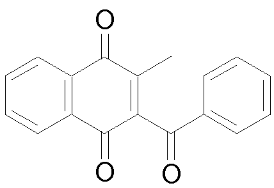
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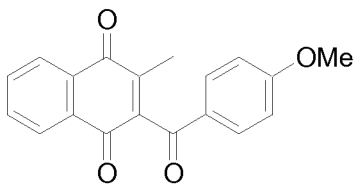
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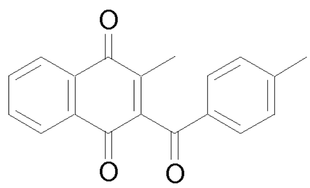
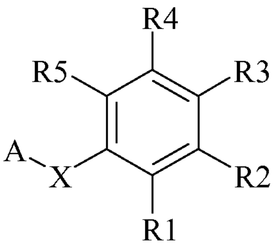


for use in a method of prevention and or of treatment of malaria.

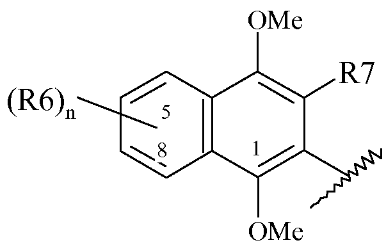
16. Compounds of formula (II), corresponding to compounds of formula (I)



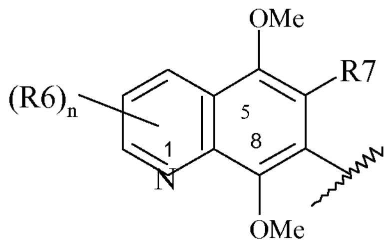
(I)

wherein

- (A) represents



or

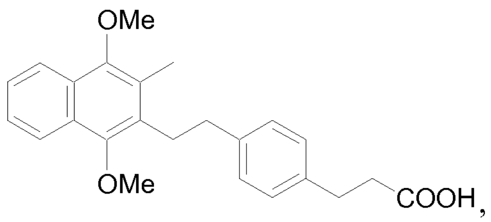


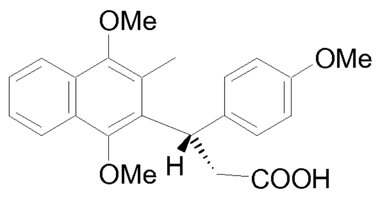
with R6 which may be in position 5, 6, 7, or 8 of the phenyl ring of the 1,4-dimethoxynaphthalene or in position 2, 3, or 4 of the 5,8-dimethoxyquinoline, represents a hydrogen atom, a halogen atom, a hydroxy group, a linear or branched (C_1-C_4)alkyl group, a di- or tri-fluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, and n being an integer comprised between 0 and 4 and R7 representing a methyl group and

- X = CH_2, C(O) or –CHY– with Y selected from the group comprising hydrogen atom, hydroxy group, a linear or branched (C_1-C_4)alkyl group and (C_3-C_6)cycloalkyl group,

- R1, R2, R3, R4 and R5 are as defined in Claim 1,

with the proviso that the compounds of formula (II) are not selected from the group comprising

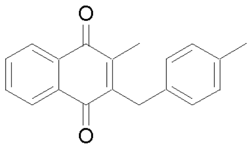




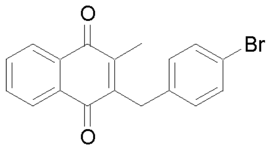
17. Compounds according to claim 16 as intermediates for the synthesis of compounds of formula (I).

FIGURE 1a

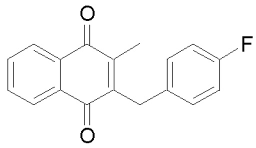
Structures of the benzyl series (1)



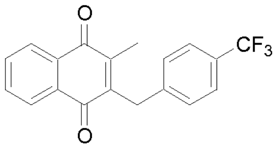
P_TM21



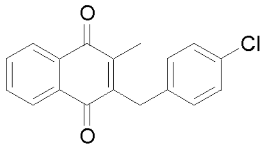
P_TM24 = HB67



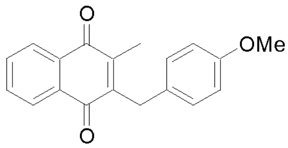
P_TM26



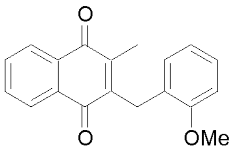
P_TM29



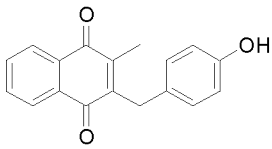
P_TM30



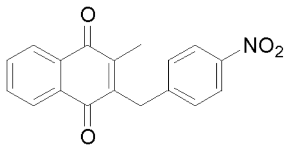
P_TM31



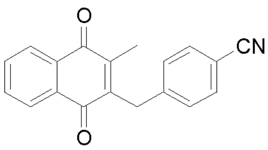
P_TM32



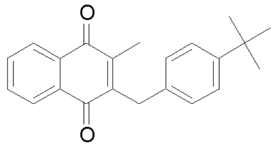
P_TM36



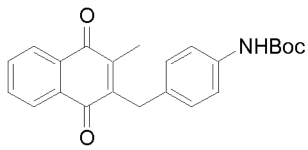
P_TM37



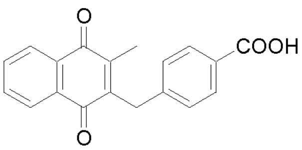
P_TM41



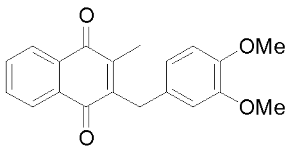
P_TM43



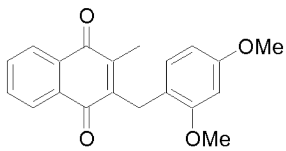
P_TM45



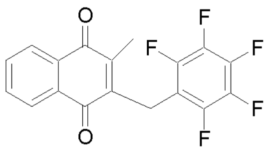
P_TM50



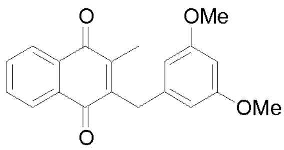
P_TM54



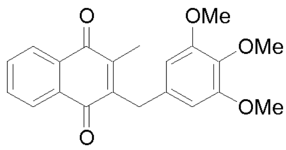
P_TM56



P_TM57



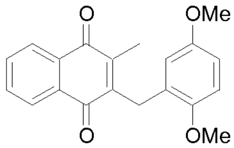
P_TM58



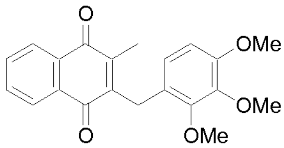
P_TM59

FIGURE 1b

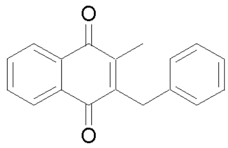
Structures of the benzyl-series (2)



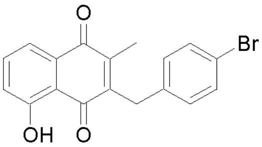
P_TM60



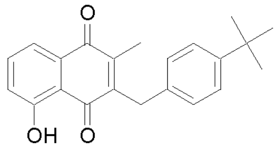
P_TM61



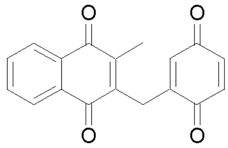
P_TM62



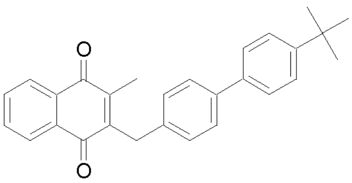
P_TM42



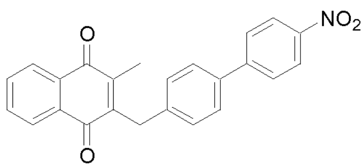
P_TM81



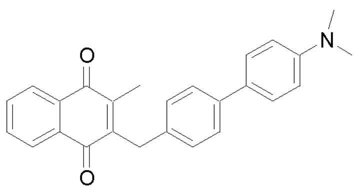
P_TM63



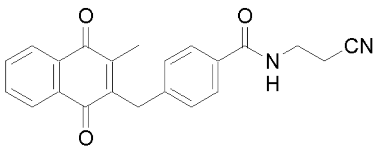
P_TM66



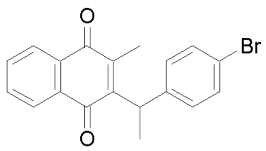
P_TM67



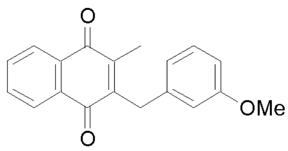
P_TM69



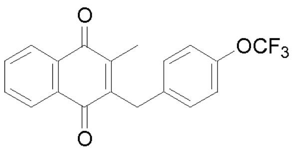
P_TM53



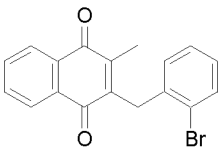
P_TM91



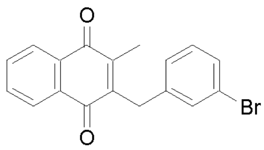
P_TM96



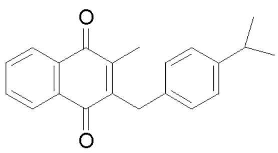
P_TM97



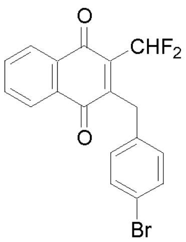
P_TM98



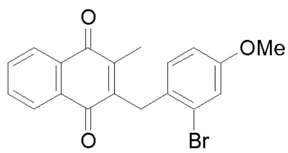
P_TM99



P_TM100

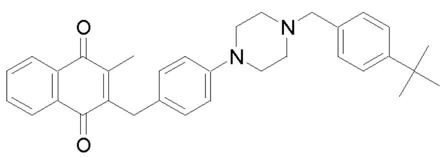


P_TM101

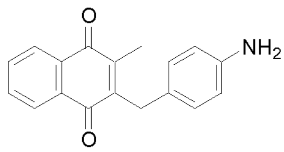


P_TM102

FIGURE 1c
Structures of the benzyl-series (3)

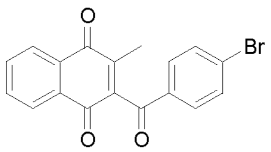


P_TM87

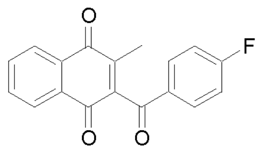


P_TM103

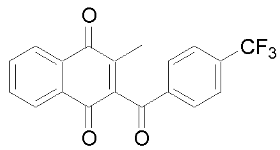
Figure 1d
Structures of the Benzoyl series



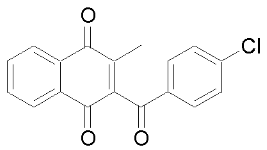
P_TM25



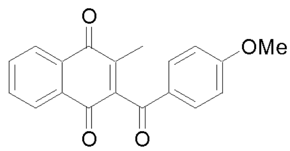
P_TM27



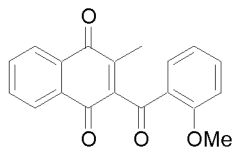
P_TM33



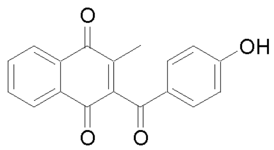
P_TM38



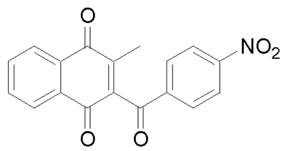
P_TM34



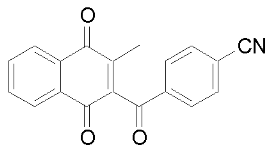
P_TM35



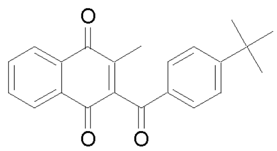
P_TM39



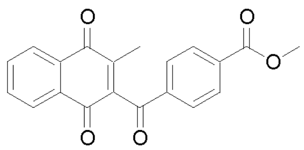
P_TM40



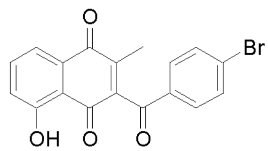
P_TM46



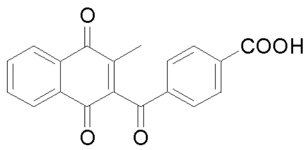
P_TM48



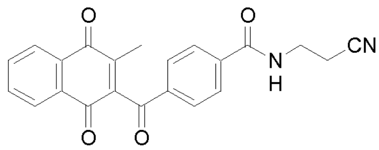
P_TM28



P_TM47

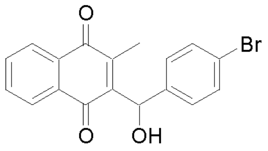


P_TM22

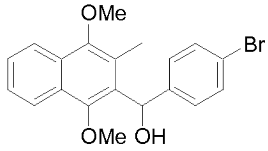


P_TM51

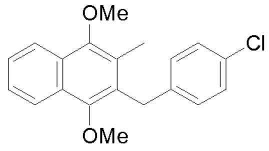
Figure 1(e)
Structures of precursors and biometabolites



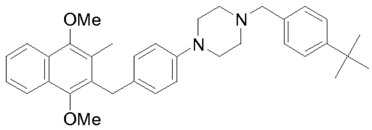
P_TM23



P_TM7



P_TM75



P_TM78

FIGURE 2

IC_{50} Values of Benzyl- and Benzoyl-Substituted Derivatives of Menadione as Inhibitors of *P. falciparum* and Human Glutathione Reductases.

	Compound	IC_{50} (µM)	
		in P. falciparum GR assay[a]	in human GR assay[a]
Benzyl-series	**P_TM24 = HB67**	> 10[c,d] (nd)[e]	1.0[c] (2.3)[e]
	P_TM26	7.8	3.3
	P_TM30	25	1.5
	P_TM31	17	4.5
	P_TM29	> 50	1.6
	P_TM63	9	12
	P_TM36	8.2	8.6
Benzoyl-series	**P_TM22**	1.1	0.7
	P_TM27	1.5	1.2
	P_TM25	1.2	0.3
	P_TM34	1.9	1.5
	P_TM33	6.3	0.7
	P_TM28	n.d.	2.0
	P_TM40	0.8	0.4
	P_TM47	2.5	0.75
Other cpnds	**menadione**[b]	42.0	27.5
	P_TM23	4.5	1.3

FIGURE 3

Glutathione Reductase-Catalyzed Naphthoquinone Reductase Activity

	Compound	**Naphthoquinone Reductase Activity of *Pf*GR**		
		K_M (µM)	**k_{cat} (min^{-1})**	**k_{cat} / K_M (mM^{-1} s^{-1})**
Benzyl-series	**P_TM26**	26	2.53	1.62
	P_TM36	87	4.09	0.78
	P_TM63	96.5	198	34.2
	P_TM24 = HB67	n.a.*	n.a.*	n.a.*
Benzoyl-series	**P_TM27**	56.1	16.7	4.96
	P_TM25	6.1	2.31	6.31
	P_TM39	84.2	26.6	5.26
	P_TM40	18	8.38	7.76
	P_TM47	3.07	2.3	12.5
	P_TM34	38.4	6.6	2.86
	P_TM33	42.4	3.36	1.32
Other cpnds	**Menadione**	82.2	9.6	1.99
	P_TM23	8.5	2.17	4.25

FIGURE 4

Methemoglobin Redox-cycling activity in the presence of the benzoyl derivative **P_TM25**

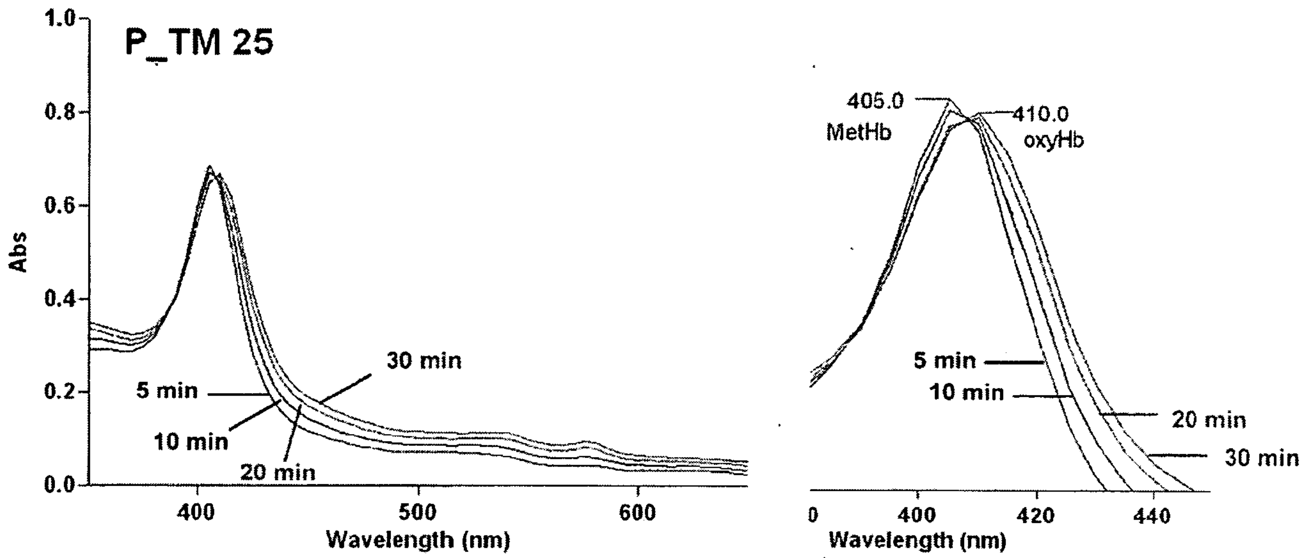


Figure 5

IC_{50} Values of Menadione Derivatives as Cytotoxic Agents Against Malarial Parasites (Dd2, 3D7, K1, Pf-GHA) and Human Cells (KB, MRC-5) *in vitro*.

	Dd2		3D7	K1	Tox	Pf-GHA	Tox
Compound	**IC_{50} (nM)**	**IC_{50} (nM)**	**IC_{50} (µM)**	**IC_{50} (µM)**	**IC_{50} (µM)**	**IC_{50} (µM)**	**MRC-5 (µM)**
P_TM21	791		0.27[g]	0.10[g]	45.5[g]	3.00	> 32.00
P_TM22	>1µM		> 30[g]	13.28[g]	183.41[g]	7.00	> 32.00
P_TM23	634						
P_TM24	54	54	n.d.	0.04[a]	189.5[a]	4.00	> 32.00
= HB67			0.026[h]	0.029[h]	156.65[h]		
P_TM25	>1µM		1.02[g]	2.96[g]	206.49[g]	> 32.00	> 32.00
P_TM26	65	66	0.2[g]	0.1[g]	62[g]	3.00	12.00
P_TM27	>1µM		2.49[a]	8.45[a]	255.21[a]	> 32.00	> 32.00
P_TM28	>1µM		0.44[a]	10.97[a]	211.51[a]	> 32.00	> 32.00
P_TM29	30	28	0.002[a]	0.16[a]	80.26[a]	1.00	> 32.00
P_TM30	65	34	0.003[a]	0.11[a]	8.68[a]	1.00	> 32.00
P_TM31	95	85	0.041[a]	0.46[a]	113.66[a]	16.00	> 32.00
P_TM32	88	110	0.35[a]	1.12[a]	186.48[a]	11.00	> 32.00
P_TM33	>1µM		1.90[a]	1.70[a]	123.81[a]	3.00	> 32.00
P_TM34	>1µM		1.67[a]	3.86[a]	32.42[a]	> 32.00	> 32.00
P_TM35	>1µM		2.78[c]	5.50[a]	58.69[a]	> 32.00	> 32.00
P_TM36	58	64	0.36[a]	0.40[a]	224.9[a]	4.00	> 32.00
P_TM37	46	54	0.12[a]	0.19[a]	58.6[a]	> 37.00	> 32.00
P_TM38	>1µM		1.14[a]	3.17[a]	138.07[a]	4.00	> 32.00
P_TM39	>1µM		> 30[c]			5.00	> 32.00
P_TM40	103		1.03[c]			15.00	> 32.00
P_TM41	48	46	n.d.	7.79	222.74	0.87	> 32.00
P_TM42	190		0.006[a]	0.35[a]	7.92[a]	0.89	> 32.00
P_TM43	80	74	0.0005[a]	0.005[a]	45.71[a]	11.00	10.00
P_TM45	42	43				12.00	> 32.00
P_TM46	>1µM					4.00	> 32.00
P_TM47	>1µM					> 32.00	> 32.00
P_TM48	>1µM					12.00	> 32.00
P_TM50	>1µM		2.3[f]	5.9[f]	254.8[f]	> 32.00	> 32.00
P_TM51	>1µM					> 32.00	> 32.00
P_TM53	552					> 32.00	> 32.00
P_TM54	274					8.00	> 64.00
P_TM56	111					9.00	> 64.00
P_TM57	55	42				< 0.25	> 64.00
P_TM58	21	51				2.00	> 64.00
P_TM59	49	168				2.00	> 64.00
P_TM60	29	58				> 64.00	> 64.00
P_TM61	70	230				> 64.00	> 64.00
P_TM62	>1µM					9.00	> 64.00
P_TM63	>1µM					8.00	> 64.00
P_TM64	262					6.35	33.01
P_TM65	417					7.81	> 64.00

Figure 6 : IC_{50} and IC_{90} values against various *P. falciparum* strains

Inhibitory concentration 50% (IC50) and inhibitory concentration 90% (IC90) in nM and confidence interval 95% (CI95%) of Plasmodium falciparum strains

Compounds	3D7		W2		K2		K14		Bres		FCM29		8425		D6		L1		FCR3		PA		Voll	
	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]	IC_{50} [CI95%]	IC_{90} [CI95%]
CQ	21.3 [17.9-25.3]	40.4 [33.2-49.0]	485.3 [377-625]	693.4 [598-805]	493.2 [388-626]	912.0 [659-1262]	648.6 [529-795]	1129.8 [1042-1225]	442.6 [392-500]	613.8 [561-672]	879.0 [771-1002]	1241.7 [1129-1365]	25.5 [19.6-33.1]	59.2 [45.5-76.9]	23.0 [18.8-28.0]	44.4 [37.2-52.9]	273.5 [235-319]	417.8 [355-492]	477.5 [376-607]	685.5 [555-848]	330.4 [275-398]	483.1 [377-619]	262.4 [236-292]	316.2 [241-415]
QN	103.8 [73-148]	597.0 [512-696]	683.9 [576-812]	1247.4 [1109-1403]	619.4 [558-687]	1510.1 [1278-1785]	495.5 [421-583]	1636.8 [1404-1908]	688.7 [392-500]	613.8 [572-827]	543.3 [416-709]	1199.5 [1024-1405]	130.3 [87-195]	389.9 [272-560]	61.8 [44.5-85.9]	464.5 [337-640]	530.9 [441-639]	995.4 [809-1225]	665.3 [546-811]	1111.7 [928-1332]	626.6 [505-778]	1106.6 [871-1406]	421.7 [377-472]	843.3 [753-944]
MDAQ	19.5 [14.1-26.9]	31.4 [23.4-42.1]	146.2 [113-189]	201.8 [170-240]	91.2 [81-103]	143.6 [102-202]	160.3 [134-192]	220.3 [180-270]	100.2 [85-119]	143.2 [116-176]	317.7 [278-369]	407.4 [349-475]	26.4 [20.9-33.2]	41.4 [29.9-57.3]	17.5 [11.2-27.3]	37.0 [24.3-56.3]	86.1 [72-103]	125.0 [96-162]	79.1 [66.3-94.3]	129.7 [110-153]	72.8 [56.5-93.7]	106.4 [82-138]	77.5 [71.1-84.4]	11[illegible] [102-[illegible]
LMF	23.6 [18.7-29.7]	47.3 [37.1-60.4]	36.1 [26.7-48.8]	61.9 [48.6-79.0]	25.8 [21.6-30.7]	50.0 [39.7-62.9]	29.5 [25.7-33.9]	48.8 [39.8-59.7]	26.5 [21.2-33.0]	41.1 [31.9-52.9]	16.8 [11.9-23.6]	29.4 [26.4-32.8]	29.1 [25.7-33.0]	49.9 [41.8-59.5]	35.4 [31.2-40.2]	65.3 [59.1-72.1]	21.4 [17.5-26.3]	35.7 [30.0-42.3]	22.8 [19.5-26.7]	36.6 [30.3-44.2]	20.9 [15.7-27.8]	41.2 [34.6-49.1]	24.6 [20.2-30.0]	41[illegible] [31.9-[illegible]
MQ	52.1 [47.0-57.8]	119.4 [103-138]	32.0 [27.4-37.3]	49.2 [41.5-58.4]	33.3 [28.2-39.3]	97.3 [82-116]	30.7 [26.6-35.5]	94.2 [83-107]	30.2 [23.4-39.1]	51.5 [40.0-65.1]	27.5 [21.1-36.0]	49.1 [32.9-73.4]	44.1 [38.7-50.2]	85.3 [74.2-98.1]	62.1 [52.5-73.4]	111.9 [97-129]	38.0 [32.3-44.7]	78.5 [68.0-90.7]	35.9 [28.5-45.2]	59.2 [47.0-74.5]	36.9 [31.5-43.2]	63.2 [53.3-75.1]	32.5 [25.8-40.9]	53[illegible] [42.3-[illegible]
DHA	1.9 [1.4-2.7]	3.5 [2.7-4.6]	2.5 [1.9-3.3]	4.2 [3.1-5.6]	1.4 [0.9-2.2]	2.9 [1.7-4.9]	1.8 [1.0-3.1]	2.9 [1.6-5.5]	1.2 [0.6-2.2]	2.0 [1.3-3.0]	1.1 [0.7-1.6]	2.3 [1.8-2.9]	1.6 [0.9-2.6]	3.1 [2.1-4.7]	1.4 [1.0-1.8]	2.4 [2.1-2.8]	1.1 [0.8-1.6]	2.1 [1.7-2.5]	0.9 [0.5-1.6]	1.8 [1.2-2.7]	1.4 [0.9-2.1]	2.2 [1.5-3.2]	1.0 [0.5-1.9]	1.[illegible] [1.0-[illegible]
FQ	3.5 [3.0-4.0]	6.5 [5.8-7.3]	7.1 [6.7-7.4]	12.6 [11.4-13.9]	9.0 [7.2-11.9]	16.3 [12.7-20.7]	12.6 [11.0-14.4]	25.6 [16.9-39.0]	1.2 [0.8-1.8]	13.7 [10.1-18.4]	10.0 [9.8-10.3]	19.3 [17.5-21.3]	6.5 [6.4-6.7]	9.4 [8.2-10.8]	5.6 [5.1-6.1]	8.0 [7.7-8.3]	8.0 [6.3-10.2]	13.8 [10.4-18.3]	11.5 [9.7-13.5]	16.9 [16.6-17.1]	7.0 [6.8-7.2]	13.0 [10.5-16.1]	11.0 [8.8-13.6]	18[illegible] [14.0-[illegible]
PTM24	143.2 [115-179]	303.4 [277-332]	216.3 [178-263]	350.0 [311-394]	120.0 [87-165]	271.6 [234-315]	117.5 [86-160]	277.3 [241-319]	195.0 [162-235]	342.8 [318-370]	24.4 [13.0-46.0]	76.7 [38-155]	117.2 [76-180]	242.7 [155-379]	174.2 [145-210]	323.6 [298-351]	130.3 [96-176]	261.2 [204-335]	116.1 [101-133]	279.9 [266-294]	108.6 [85-139]	270.4 [245-299]	113.2 [95-134]	27[illegible] [258-[illegible]
PTM29	94.2 [80-111]	246.6 [216-281]	215.3 [198-235]	368.1 [349-389]	163.3 [134-199]	310.5 [272-354]	57.2 [41.5-78.7]	92.3 [82-104]	191.4 [177-207]	328.1 [297-362]	41.0 [36.2-46.6]	107.4 [85-135]	54.3 [46.2-63.9]	135.8 [135-137]	138.0 [101-189]	248.3 [172-358]	104.0 [82-133]	201.4 [124-328]	73.5 [48-112]	160.7 [91-284]	70.8 [59.1-84.8]	195.0 [162-235]	68.6 [44-107]	14[illegible] [75-[illegible]
PTM37	149.6 [133-169]	308.3 [293-324]	170.2 [148-196]	311.9 [272-357]	140.9 [133-149]	301.3 [295-308]	192.8 [178-209]	335.0 [313-358]	173.4 [156-192]	327.3 [314-341]	18.0 [12.8-25.4]	72.4 [51-102]	105.9 [75-149]	247.2 [185-330]	175.8 [165-187]	327.3 [316-339]	113.2 [97-132]	236.6 [173-325]	124.5 [118-131]	285.1 [276-294]	124.2 [92-167]	282.5 [239-334]	172.4 [110-148]	289.7 [273-307]
PTM41	141.3 [123-162]	305.5 [291-321]	163.7 [122-221]	319.9 [285-360]	104.5 [96-113]	266.7 [257-277]	130.0 [122-139]	291.7 [284-300]	145.9 [116-184]	305.5 [279-334]	25.5 [20.3-32.1]	101.2 [76-135]	68.2 [40-117]	222.3 [198-250]	157.8 [147-170]	316.2 [308-325]	113.2 [97-132]	111.4 [81-154]	114.0 [92-141]	230.7 [160-333]	73.8 [69.9-77.9]	163.3 [156-171]	102.8 [100-106]	261.8 [251-273]
PTM45	221.3 [208-236]	356.5 [339-375]	209.4 [159-276]	353.2 [316-395]	134.9 [114-160]	299.2 [280-320]	166.7 [148-188]	322.1 [307-339]	227.5 [206-251]	353.2 [320-390]	108.1 [92-128]	270.4 [250-292]	150.3 [110-205]	309.0 [274-349]	224.9 [196-258]	363.9 [345-384]	117.8 [96-144]	278.0 [257-300]	159.2 [148-172]	314.1 [300-329]	171.4 [161-183]	323.6 [312-336]	141.3 [107-186]	301.3 [270-356]
PTM57	171.0 [159-184]	325.8 [317-335]	220.3 [194-250]	360.6 [343-379]	148.9 [108-206]	290.4 [247-342]	103.5 [80-134]	251.2 [218-289]	153.8 [134-177]	313.3 [297-331]	49.7 [35.9-68.7]	166.0 [123-224]	77.2 [42-141]	229.6 [174-302]	183.2 [146-230]	342.0 [300-390]	140.3 [99-200]	301.3 [262-346]	200.9 [184-220]	342.8 [337-349]	105.7 [89-126]	269.8 [250-291]	128.5 [108-153]	291.7 [373-412]
PTM58	156.3 [134-183]	314.1 [295-335]	260.6 [199-342]	384.6 [348-425]	165.2 [153-178]	322.1 [314-331]	178.2 [147-216]	331.1 [307-358]	185.8 [167-207]	336.5 [323-351]	91.4 [65-128]	213.8 [160-285]	170.2 [165-176]	327.3 [322-333]	187.1 [178-197]	334.2 [322-347]	172.6 [149-200]	329.6 [311-350]	129.4 [122-138]	291.7 [284-300]	167.9 [143-197]	322.9 [303-344]	171.0 [152-192]	325.8 [312-341]
PTM60	162.9 [159-167]	319.2 [316-322]	150.0 [119-190]	304.8 [271-343]	140.6 [126-157]	301.3 [289-314]	166.0 [146-188]	321.4 [306-338]	179.9 [179-181]	331.9 [330-333]	82.2 [66-102]	221.3 [199-247]	144.2 [117-178]	304.1 [279-331]	155.6 [131-185]	261.2 [179-382]	139.3 [135-144]	295.8 [284-308]	113.5 [94-137]	276.1 [256-298]	138.7 [122-158]	299.2 [284-316]	109.4 [96-125]	273.5 [259-288]

	Dd2		3D7	K1	Tox	Pf-GHA	Tox
Compound	**IC50 (nM)**	**IC50 (nM)**	**IC50 (µM)**	**IC50 (µM)**	**IC50 (µM)**	**IC50 (µM)**	**MRC-5 (µM)**
P_TM66	485					1.49	> 64.00
P_TM67	474					1.85	> 64.00
P_TM69	223					2.31	> 64.00
P_TM72	218					1.95	57.20
P_TM76	>1µM					53.98	43.85
P_TM77	>1µM					> 64.00	> 64.00
P_TM78	>1µM					> 64.00	> 64.00
P_TM79	>1µM					2.31	> 64.00
P_TM80	>1µM					-	-
P_TM81	>1µM					< 0.25	17.80
P_TM82	>1µM					-	-
P_TM87	369					< 0.25	38.05
Atovaquone	< 0.1					0.31	> 64.00
Chloroquine	291					< 0.25	51.54

Figure 7 : Reduction of Parasitemia in *Plasmodium berghei* ANKA-Infected CD1 Mice.

Compound	Dose	% reduction i.p.	% reduction p.o.
Untreated control	-	0	0
Chloroquine	10 mg/kg. x4	94.9	98.8
P_TM24(HB67)	30 mg/kg x4	n.d.	0
P_TM24(HB67)	50 mg/kg x4	35.6*	0.8
P_TM37(BJ323)	30 mg/kg x4	42.4	10.4
P_TM43 (BJ321)	30 mg/kg x4	43.4	34.9
P_TM31	30 mg/kg x4	24.4	n.d.
P_TM36 (BJ319)	30 mg/kg x4	28.4	n.d.
P_TM29	30 mg/kg x4	20.7	n.d.

Figure 8: *In vivo* Antimalarial Activity in *P. berghei*-Infected Mice

Compound	Treatment	Animals	% Parasitaemia (dpi)				% Suppression (dpi)				Health status
			4	7	11	14	4	7	11	14	
Untreated control	-	5	38.28	42.2	67.7	61.9	0	0	0	0	From d4 p.i. onwards:poor appearance, tremor, body weight loss, rough hair, 4 animals died before d7 p.i.
CQ	10 mg/kg	5	5.24	9.8	32.1	56.2	86.30	76.84	52.66	9.23	From d9 p.i. onwards: poor appearance, tremor, body weight loss, rough hair One animal dies before d14 p.i.
P_TM41	50 mg/kg	4	nd	nd	nd	nd	nd	nd	nd	nd	From d7 p.i. onwards: poor appearance, all animals died before d11 p.i.
P_TM45	50 mg/kg	4	9.37	7.7	41.9	69.3	75.52	81.79	38.12	- 11.97	From d7 p.i. onwards: poor appearance (intermittent), one animal died before d14 p.i.
P_TM57	50 mg/kg	4	9.19	17.3	38.8	63.1	75.99	58.90	42.69	- 1.87	From d8 p.i. onwards: poor appearance (intermittent), 3 animals died before d14 p.i.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/053483

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C50/14 C07C50/24 C07C50/32 C07C50/38 C07D295/116
C07D295/096 A61K31/04 A61K31/122 A61K31/495 A61P33/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOWLAND JOHN L: "Inhibition of mitochondrial succinate oxidation by alkyl hydroxy naphthoquinones" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, vol. 105, no. 2, 1 January 1965 (1965-01-01), pages 205-213, XP008093702 ISSN: 0006-3002 cited in the application page 205 page 207; table 1, entry 8 page 208, lines 1,2 -----	15

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[X] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2009	02/07/2009

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAUER, HOLGER ET AL: "A Fluoro Analogue of the Menadione Derivative 6-[2'-(3'-Methyl)-1',4'-naphthoquinolyl]hexanoic Acid Is a Suicide Substrate of Glutathione Reductase. Crystal Structure of the Alkylated Human Enzyme" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 128(33), 10784-10794 CODEN: JACSAT; ISSN: 0002-7863, 2006, XP002486600 cited in the application abstract page 10787; compound 7 * p. 10792, column 1 paragraph on antiparasitic and cytotoxic activities in vitro* * p. 10794, column 1, paragraph on antiparasitic and cytotoxic activities in vitro* -----	1-17
A	FRIEBOLIN WOLFGANG ET AL: "Antimalarial dual drugs based on potent inhibitors of glutathione reductase from Plasmodium falciparum." JOURNAL OF MEDICINAL CHEMISTRY 13 MAR 2008, vol. 51, no. 5, 9 February 2008 (2008-02-09), pages 1260-1277, XP002486601 ISSN: 0022-2623 cited in the application *page 1267; par. on Drug combination assays with clinically used antimalarials* *page 1273; par. on synth. of compd 36, l. 1 from GP4 on* *page 1274; par. on synth. of compd 41, l. 1 from GP5 on* * p. 1267; col. 1; paragraph on Drug combination assays with clinically used antimalarials * -----	1-17

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