Title: QUINOLINE AS CONTRAST AGENT IN LASER INDUCED FLUORESCENCE (LIF) FOR LESIONS

Abstract: The subject of this invention is to provide a compound and a contrast agent comprising a compound for a rapid, non-invasive examination process in the diagnosis of increased vascularity of lesions, especially cancerous lesions. The contrast agents comprising a compound and compounds used for diagnosis of lesions are compounds having a quinoline ring whereas the compounds may emit fluorescence in a range from 300 to 1200 nm. A method of diagnosing lesions is also subject of the present invention.
QUINOLINE AS CONTRAST AGENT IN LASER INDUCED FLUORESCENCE (LIF) FOR LESIONS

FIELD OF THE INVENTION

The subject of this invention is to provide a compound and a contrast agent comprising a compound for a rapid, non-invasive examination process in the diagnosis of increased vascularity of lesions, especially cancerous lesions. The compounds according to the present invention used for diagnosis of lesions are compounds having a quinoline ring whereas the compounds may emit fluorescence in a range from 300 to 1200 nm. A method of diagnosing lesions is also subject of the present invention.

BACKGROUND OF THE INVENTION

Laser Induced Fluorescence (LIF) has been used as a method of non-invasive diagnosis of cancerous lesions (for example, see Nishioka NS, Gastrointest. Endosc. Clin. N. Am., 1994, 4(2), pp. 313-326). Light of a certain wavelength (usually in the UV) is applied to the tissue and the emitted fluorescence is recorded. Still, the small scanning area of the LIF probe limits the practical use of this method.

Any carcinoma in the body has an increased metabolic rate due to uncontrolled cell division. In order to obtain more resources, tumours promote angiogenesis. Any metabolite that is evenly distributed within the blood should therefore accumulate in tumours by virtue of their increased blood supply. Laser induced Fluorescence (LIF) is a method of diagnosis in which excitation with a specific wavelength (in the UV region) excites fluorophores in the superficial mucosal tissue and the obtained fluorescence intensity is recorded. If a known fluorescent metabolite accumulates in tumorous tissue by virtue of its increased blood supply it results in an enhanced anatomical delineation of the screening test.

Disadvantages of the LIF according to the state of the art are the
following:

LIF according to the state of the art uses a point probe, which illuminates a small area (about 1 mm$^2$) for the differentiation between cancerous and normal tissue. Therefore, it becomes very time consuming to scan the whole of the mucosa (like oral mucosa or cervical mucosa). Glacial acetic acid has been used in the case of cervical mucosa [Schomacker et al., J. Biomed. Opt., 2006, 11(3), 034009] because acetic acid turns the tumorous area white, which can be correlated with results obtained from auto-fluorescence. Unfortunately, this may not hold true for other areas.

Secondly, diagnosis made by standard LIF does not define the cancerous areas very well. The varying thickness of the keratin layer obscures diagnosis in many cases.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide contrast agents for LIF thereby overcoming the disadvantages of the LIF according to the prior art.

The contrast agents and compounds according to the present invention circumvent problems of the prior art as they accumulate in all cancerous areas and upon UV irradiation of the mucosa, the cancerous lesions show increased fluorescence according to the present invention.

A contrast agent according to the present invention helps to delineate the tumour area properly and improves the results of the LIF scan.

In this invention, it has been surprisingly found that quinoline derivatives as e.g. chloroquine or quinine may be used as contrast agents in LIF in order to help in a more accurate diagnosis of the areas with increased vascularity of a lesion as e.g. cancerous areas. When taken orally, chloroquine accumulates in tissue and its local concentration is higher in cancerous tissues due to the increased blood supply. Thus, cancerous tissue can be differentiated from surrounding normal tissue. Thus, quinoline derivatives such as chloroquine or quinine can be used as a novel diagnostic adjunct for use together with LIF in the diagnosis of cancerous lesions. Use of the inventive contrast agent aids in localising cancerous lesions and compensate for the small scanning area of
the LIF probe.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1: Chemical structure of chloroquine with the quinoline ring
Fig 2: Chemical structure of quinine
Fig 3: Schematic diagram showing the LIF spectra of normal mucosa
Fig 4: Schematic diagram showing the LIF spectra of a malignant area
Fig 5: Schematic diagram showing the signature of chloroquine in the LIF spectra of normal mucosa. This signature would be larger in case of malignant areas due to increased chloroquine concentration in local tissue
Fig 6: Structure of the quinoline ring

DETAILED DESCRIPTION OF EMBODIMENTS

Therefore, subject of the present invention is a compound having a quinoline ring whereas the compound may emit fluorescence in a range from 300 to 1200 nm, preferred from 350 to 600 nm, even more preferred around 375 nm for diagnosing an increased vascularity of a lesion.

A compound having a quinoline ring, as it is subject of the present invention, specifies a compound having as a core structural feature a ring system as shown in fig. 6.

Thus, subject of the present invention is a contrast agent for diagnosing an increased vascularity of a lesion comprising a compound having a quinoline ring whereas the compound may emit fluorescence in a range from 300 to 1200 nm, preferred from 350 to 600 nm, even more preferred around 375 nm.

A contrast agent according to the present invention may be one of the following:

quinine, quinidine, chloroquine, amodiaquine, mefloquine, primaquine and bulaquine or derivatives thereof. Most preferred are the before-mentioned contrast
agents which are clinically used as pharmaceuticals.

In a preferred embodiment of the invention the compound is quinine or a derivative thereof.

In another preferred embodiment the compound is chloroquine or a derivative thereof.

A derivative may include a compound having a quinoline ring unsubstituted or substituted by e.g. amino groups, alkyl amino groups, alkyl groups, halo groups as chloro or fluoro groups, alkoxy groups, aminoalkyl, hydroxylamino, hydroxalkyl, alkylthio, hydroxy, carboxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, non-aromatic heterocyclic ring systems, phenyl, benzyl, aromatic ring systems, heteroaromatic ring systems, arylalkyl alkylthio, aldehyde, ketone, alkylamino, imino, alkylimino, hydroxylamino, amido, imido, urethane, carbamoyl, halogen, sulfonyl, alkylsulfonyl, arylsulfonyl, phosphoryl, carboxylic acid ester, nitro, cyano.

Preferentially, all aforementioned alkyl-group-containing groups comprise an alkyl group from C₁-C₆.

The compounds according to the present invention may be in free form or in the form of physiologically acceptable, non-toxic salts. These salts may be obtained by reacting the respective compounds with physiologically acceptable acids and bases.

Examples of such salts include but are not limited to hydrobromide, hydroiodide, hydrofluoride, nitrate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, phosphate, acid phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, isonicotinate, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, lactate, salicylate, citrate, tartrate, oxalate, malonate, suberate, sebacate, mandelate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, phenylacetate, maleate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminium, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine, N,N'-dibenzylethlenediamine,
chloroprocaine, choline, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaaine salts.

For a review on pharmaceutically acceptable salts see BERGE ET AL., 66 J. PHARM. SCI. 1-19 (1977), incorporated herein by reference.

Chloroquine derivatives may be selected from the following examples without being limited to those examples:

- 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (chloroquine);
- 7-hydroxy-4-(4-diethylamino-1-methylbutylamino)quinoline;
- chloroquine phosphate

- 7-chloro-4-(4-diethylamino-1-butylamino)quinoline (desmethylchloroquine);
- 7-hydroxy-4-(4-diethylamino-1-butylamino)quinoline;
- 7-chloro-4-(1-carboxy-4-diethylamino-1-butylamino)quinoline;
- 7-hydroxy-4-(1-carboxy-4-diethylamino-1-butylamino)quinoline;
- 7-chloro-4-(1-carboxy-4-diethylamino-1-methylbutylamino)quinoline;

- 7-hydroxy-4-(1-carboxy-4-diethylamino-1-methylbutylamino)quinoline;
- 7-chloro-4-(4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline (hydroxychloroquine);
- 7-hydroxy-4-(4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline; hydroxychloroquine phosphate;

- 7-chloro-4-(4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline (desmethylhydroxychloroquine);
- 7-hydroxy-4-(4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline;
- 7-chloro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline ;
- 7-hydroxy-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline;

- 7-chloro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline;
- 7-hydroxy-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline;
- 8-[(4-aminopentyl)amino]-6-methoxydihydrochloride quinoline;
• 1-Acetyl-1,2,3,4-tetrahydroquinoline;
• 8-[4-aminopentyl]amino]-6-methoxyquinoline dihydrochloride;
• 1-butyryl-1,2,3,4-tetrahydroquinoline;
• 7-chloro-2-(o-chlorostyryl)-4-[4-diethylamino-1-methylbutyl]aminoquinoline phosphate;
• 3-chloro-4-(4-hydroxy-α,α'-bis(2-methyl-1-pyrrolidinyl)-2,5-xylidinoquinoline;
• 4-[(4-diethylamino)-1-methylbutyl]amino]-6-methoxyquinoline;
• 3,4-dihydro-1-(2H)-quinolinecarboxyaldehyde;
• 6-methoxy-8-nitroquinoline;
• 5-aminoquinoline;
• 8-aminoquinoline;
• 4-amino-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxylic acid;
• 8-methoxy-2-(trifluoromethyl)quinolin-4-amine;
• 1-phenyl-1,4,6,7,8,8a-hexahydroisoquinolin-3(2H)-one;
• 1-phenyl-1,4,5,6,7,8-hexahydroisoquinolin-3(2H)-one;
• 1-phenyl-1,5,6,7,8,8a-hexahydroisoquinolin-3(2H)-one;
• 4,8-dimethoxy-2-(trifluoromethyl)quinoline;
• 8-methoxy-2-(trifluoromethyl)quinoline;
• 7-chloro-6-methyl-2-(trifluoromethyl)quinolin-4-ol;
• 5-chloro-6-methyl-2-(trifluoromethyl)quinolin-4-ol;
• 4-fluoro-8-methoxy-2-(trifluoromethyl)quinoline;
• 4,7-dichloro-6-methyl-2-(trifluoromethyl)quinoline;
• 4,5-dichloro-6-methyl-2-(trifluoromethyl)quinoline;
• 2-benzyl-4-fluoro-1,2,3,4-tetrahydroisoquinoline;
• 7-Chloro-4-methoxy-6-methyl-2-(trifluoromethyl)quinoline;
• 5-Chloro-4-methoxy-6-methyl-2-(trifluoromethyl)quinoline;
• 5-Fluoro-6-methyl-2-(trifluoromethyl)quinolin-4-ol;
• 7-Fluoro-6-methyl-2-(trifluoromethyl)quinolin-4-ol;
• 2-(5,6,7,8-Tetrahydroquinolin-8-yl)ethanol;
• 8-(2-Bromoethyl)-5,6,7,8-tetrahydroquinoline;
• 2-(5,6,7,8-Tetrahydroquinolin-8-yl)ethanethiol;
• 5,6,7,8-Tetrahydroquinolin-8-ylacetaldehyde;
• 8-(2,2-Diethoxyethyl)-5,6,7,8-tetrahydroquinoline and
• N-Methyl-N-[2-(5,6,7,8-tetrahydroquinolin-8-yl)ethyl]amine.

In a preferred embodiment of the invention the chloroquine derivative is
selected from the group comprising: chloroquine, (−)-(7-chloro-4-(4-diethylamino-1-
methylbutylamino) quinoline), chloroquine phosphate, (−)-(7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline phosphate, hydroxychloroquine (−)-(7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline) and enantiomers thereof.

In a more preferred embodiment of the invention either of the chloroquine
enantiomers (−)- or (+)-chloroquine (7-chloro-4-(4-diethylamino-1-
methylbutylamino)quinoline) may be used.

Compounds as quinine and chloroquine (DE 683 962) are known anti-
malarial drugs (for a review on chloroquine derivatives, see O'Neill PM, Pharmacol.
Ther., 1998, 77(1), pp. 29-58). Chloroquine (Figure 1) has been used routinely as an
antimalarial drug in high doses (10 mg base/kg body weight). It has a quinoline ring and
therefore also behaves as a fluorophore with an excitation wavelength of around 300 nm
and an emission wavelength of around 375 nm. In recent years, a large variety of
quinoline derivatives have been generated, mainly for pharmaceutical uses. For instance,
WO 03/093239 discloses the synthesis of quinoline analogs as antimalarial agents and
WO 03/106424 discloses new quinoline derivatives in the context of cell-mediated
immunity.

When taken orally, chloroquine rapidly gets absorbed into the blood. Its
471-479] and the half-life time of absorption is 0.56 h. The peak plasma concentration is
reached about 2 to 3 h after ingestion. Within the blood it is highly protein bound (46-
74%) [Adelusi et al., Gen. Pharmacol., 1982, 13(5), 433-437]. The apparent volume of
distribution of chloroquine is very high (116-285 L/kg) [Gustafsson et al., J. Clin.
Pharmacol., 1983, 15(4), 471-479]. This means that chloroquine rapidly distributes to the tissues. It also implies that the quenching by heme stops to occur or diminishes after a certain time when chloroquine flows out of the blood and binds to the tissues. The drug should be more concentrated in areas of increased blood supply.

The compound or the contrast agent according to the present invention, respectively, may be used for diagnosing cancer.

In a preferred embodiment the compound according to the present invention may be used for diagnosing epithelial cancer. Examples for epithelial cancers are oral cancer, lung cancer (through bronchoscopy), colon cancer (through colonoscopy), gastric and esophageal cancer (through endoscopy), nasopharyngeal carcinoma, cervical cancer (through colposcopy) etc. The contrast agents according to the present invention may be used preferably for diagnosing lesions that can be reached through endoscopic procedures.

Thus, subject-matter of the present invention is the application of a compound having a quinoline ring, e.g. a chloroquine or quinine analog or derivative, and pharmaceutically acceptable salts and mixtures thereof, as contrast agent for the non-invasive monitoring of cancerous tissues.

In a preferred embodiment of the invention the diagnosed tissue is mucosal tissue.

A further subject-matter of the present invention is the use of a kit comprising one or more compounds according to the present invention, having a quinoline ring, e.g. a chloroquine or quinine analog or derivative, and pharmaceutically acceptable salts and mixtures thereof in a method according to the invention.

Another subject-matter of the present invention is the use of a pharmaceutical composition comprising one or more compounds according to the present invention, having a quinoline ring, e.g. a chloroquine or quinine analog or derivative in a method according to the invention.

Subject of the present invention is a method for diagnosing an increased vascularity of a lesion comprising the steps of:

- administering to a patient a compound having a quinoline ring, whereas the compound may emit fluorescence with a wavelength in a
range from 300 to 1200 nm, preferred from 350 to 600 nm, even more preferred around 375 nm,

- exposing the area of being suspected of having a lesion with increased vascularity with light of a wavelength in a range from 200 to 1200 nm, preferred from 200 to 600 nm, even more preferred from 200 to 380 nm, most preferred around 300 nm,

- visualising the area for fluorescence.

Another subject of the present invention is a method for obtaining an image of an area of tissue comprising the steps of:

- administering to a patient a compound having a quinoline ring, whereas the compound may emit fluorescence with a wavelength in a range from 300 to 1200 nm, preferred from 350 to 600 nm, even more preferred 375 nm,

- exposing the area of the tissue with light of a wavelength in a range from 200 to 1200 nm, preferred from 200 to 600 nm, even more preferred from 200 to 380 nm, most preferred around 300 nm,

- visualising the area for fluorescence.

According to the present invention a patient may be a human being or an animal.

In a preferred embodiment of the invention the compounds according to the present invention, having a quinoline ring, e.g. a chloroquine or quinine analog or derivative is administered orally.

The method of the present invention can be used to scan a wider area of tissue, once stained with a compound according to the present invention, having a quinoline ring, e.g. a chloroquine or quinine analog or derivative, is first screened coarsely in order to quickly localise cancerous lesions. This can for instance be accomplished with the aid of a filter, which preferably only lets pass the wavelength of the emission maximum of the contrast agent according to the invention or a narrow bandwidth range around this maximum. Thereafter, identified lesions can be scanned in detail applying LIF.
Thus, subject of the present invention is a method according to the present invention whereas the area is visualized for fluorescence at the emission maximum of the compound according to the present invention with an appropriate filter. An appropriate filter can be chosen by a person skilled in the art to ideally only let pass the desired emission maximum of the contrast agent according to the present invention or a narrow bandwidth range around this maximum.

In a preferred embodiment of the invention monitoring can be accomplished utilizing light irradiation at a wavelength proper for the excitation of (-)- or (+)-chloroquine, which is about 275 to 325 nm.

The wavelength of excitation is chosen according to the excitation wavelength of the compound used. The same applies for the detection wavelength which is chosen according to the emission wavelength of the compound used.

The method of the present invention can be used in combination with LIF (Laser Induced fluorescence).

The inventive method uses the above-mentioned compounds including the preferred compounds such as e.g. quinine or chloroquine or derivatives or salts thereof as described above.

In a preferred embodiment the inventive method is used for diagnosing cancer, especially epithelial cancer as described above.

In the present invention, monitoring of the lesion can be accomplished utilizing UV light irradiation according to a preferred embodiment of the invention.

In order to decide whether a lesion is malignant one of the important measures is the loss of collagen signal in autofluorescence signal from epithelial layers. Details will be explained below.

A normal epithelial layer has an epithelial layer composed of cells containing NADH as fluorophore and a basement membrane (with dermis) containing collagen as fluorophore. In cancerous states, the thickness of epithelial layer increases and the basement membrane is broken due to metastasis. With the laser penetration being constant, the fluorescence signal of collagen as obtained in normal epithelium is lost in cancerous tissues due to the reasons stated above.

The influence of fluorescence quenching by metabolites when performing
the method using the agents according to the invention for diagnosis will be discussed below.

Two major fluorescence quenchers in the blood are halides (chloride) and the heme group in the active center of haemoglobin. Haemoglobin is present only in red blood cells and therefore, once localised to tissues, heme should not quench the fluorescence emitted by chloroquine. Among halides the quenching potential diminishes with decreasing size of the halide ion (I⁻ > Br⁻ > Cl⁻). Chloride ions quench fluorescence by dynamic means, and hence diffusion dependent. The change in intensity of fluorescence is determined by the Stern-Volmer equation:

\[ \frac{F_0}{F} = 1 + K_{sv}[Q], \]

where \( F_0 \) is the unquenched fluorescence intensity,
\( F \) is the fluorescence intensity at \([Q]\),
\([Q]\) is the concentration of quencher,
\( K_{sv} \) is the Stern-Volmer quenching constant.

Quinine (Figure 2) is one of the chemical congeners of chloroquine. It also shows fluorescence due to the quinoline ring. Therefore, the quenching effects of chloride on the fluorescence of quinine can be very well extrapolated to the effect on chloroquine.

The \( K_{sv} \) for the quenching of quinine by chlorine at 37° C is calculated to be 185 L/mol [Mayrhofer et al., http://faculty.kutztown.edu/betts/html/quench/index.htm]. The concentration of chloride in the blood is known to be 110 mmol/L. According to the Stern-Volmer equation the fluorescence intensity of quinine would be 21 times less than the intensity without chlorine. Still, even this low intensity is sufficient for the detection with sensitive sensors. Similar results can be extrapolated for chloroquine.

The advantages of the present invention will be discussed for chloroquine as an example:

Chloroquine itself already has an approval by the FDA, and is ubiquitously used as an antimalarial drug. It is inexpensive and easy to administer. It is, for instance, well
absorbed into the body when given orally. It also is non-toxic and does not visibly colour
the mucosa. That means the subject undergoing screening can very well join his/her daily
activities immediately after the test as chloroquine is visible only under UV light
irradiation.

Once the chloroquine derivative or analog accumulates in the tissue, the
drug can act as fluorophore for LIF scans. The fluorescence emitted by this contrast
agent is more intense in cancerous tissue than in the surrounding normal tissue. The
whole mucosa, once stained with a chloroquine derivative or analog, can be screened
very quickly, providing for a better anatomical localisation of the cancerous lesion,
which can thereafter be scanned in detail applying LIF.

The results obtained by LIF are enhanced by the use of chloroquine as
contrast agent. This provides for better anatomical localization of tumour lesions. The
lesions can be localised by passing the fluorescence spectra through a 375 nm filter,
thereby compensating for the small scanning area of LIF probes. The method is
independent of the localisation of the cancerous area (whether oral, cervical etc.), speeds
up and facilitates diagnosis wherever LIF can be applied.

The invention is not limited to the disclosed embodiments.

For use of chloroquine as contrast agent following steps may be taken to
obtain the diagnosis results:

Example 1
Research Method

• Chloroquine is given to the subject undergoing screening.
• After some time (usually 3 h in case of oral administration), the mucosa is
irradiated with light and visualised with a 375 nm filter. The cancerous areas are
expected to show a more intense fluorescence than the surrounding normal tissue
and a threshold is selected on the basis of experiments on known carcinoma
patients. The threshold would depend on the background fluorescence given by
the normal mucosa.

• Chloroquine has its emission maximum at around 375 nm which is
different from the emission maxima of collagen (400 nm) and NADH (440 and
460 nm) and therefore chloroquine’s signature can be very well differentiated from the spectra without chloroquine.

- After localization of the abnormal lesions the standard LIF procedure can be used for better anatomical delineation of the cancerous area.

- The dosage and route of administration of chloroquine is optimised and the time interval between the administration of chloroquine and measurement of fluorescence is standardised. Chloroquine can be given orally or parenterally. High dosages of 10 mg/kg body weight are routinely prescribed for oral treatment of malaria. Drug dosage can be optimised.

Example 2

Clinical Method:

- Chloroquine is administered to the subject undergoing screening according to the dosage and route of administration optimised in the research method.

- After the standardised time interval, the mucosa is irradiated with light and the fluorescence of the mucosa is visualised with a 375 nm filter. The areas which show fluorescence above a standardised threshold can then be individually checked with the standard LIF procedure.

- The contrast provided by chloroquine at 375 nm can help to better localise the cancerous area on standard LIF protocol.

- The application proposed herein has to be done in conjunction with the standard LIF procedure because other hyperaemic lesions like inflammations etc. may otherwise produce false positive results.
CLAIMS:

1. A compound having a quinoline ring whereas the compound may emit fluorescence with a wavelength in a range from 300 to 1200 nm for diagnosing an increased vascularity of a lesion.

2. A compound according to claim 1 whereas the compound is quinine or a derivative or a salt of quinine or a derivative thereof.

3. A compound according to claim 1 whereas the compound is chloroquine or a derivative or a salt of chloroquine or a derivative thereof.

4. A compound according to any of claims 1 to 3 for diagnosing cancer.

5. A compound according to any of claims 1 to 3 for diagnosing epithelial cancer.

6. A contrast agent for diagnosing an increased vascularity of a lesion comprising a compound having a quinoline ring whereas the compound may emit fluorescence with a wavelength in a range from 300 to 1200 nm.

7. A contrast agent according to claim 6 whereas the compound is quinine or a derivative or a salt of quinine or a derivative thereof.

8. A contrast agent according to claim 6 whereas the compound is chloroquine or a derivative or a salt of chloroquine or a derivative thereof.

9. A contrast agent according to any of claims 6 to 8 for diagnosing cancer.
10. A contrast agent according to any of claims 6 to 8 for diagnosing epithelial cancer.

11. A method for obtaining an image of an area of tissue comprising the steps of:
   • administering to a patient a compound having a quinoline ring whereas the compound may emit fluorescence with a wavelength in a range from 300 to 1200 nm,
   • exposing the area of the tissue with light of a wavelength in a range from 200 to 1200 nm,
   • visualising the area for fluorescence.
FIG. 5

FIG. 6