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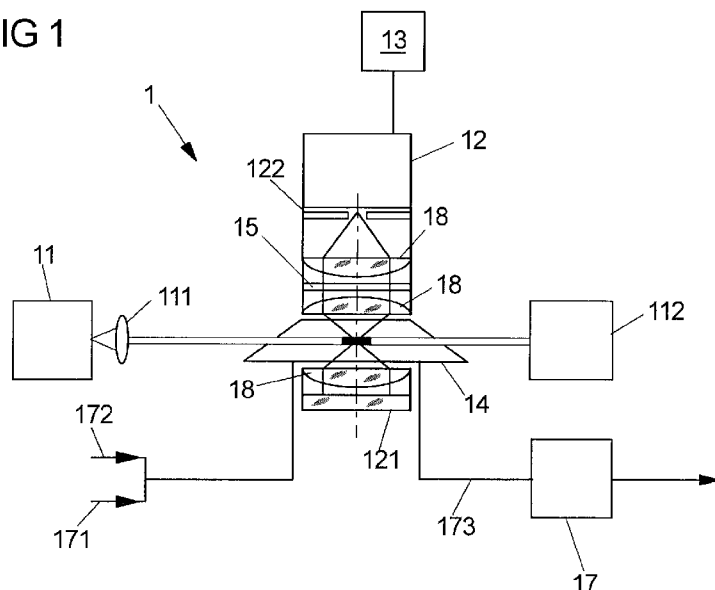
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FIG 1



(57) Abstract: The invention relates to a device (1) for measuring a concentration of at least one drug in an exhalation air of a patient comprising at least one light source (11) adapted to induce fluorescence in the at least one drug, at least one detection unit (12) adapted to detect fluorescence radiation emitted by the at least one drug and a processor (13) adapted to correlate an intensity of the fluorescence radiation with the concentration of the at least one drug in the exhalation air.

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**Method and device for measuring a concentration of at least one drug in an
exhalation air of a patient**

Description

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The invention relates to a device for measuring a concentration of at least one drug in an exhalation air of a patient according to claim 1 and to a method for measuring a concentration of at least one drug in an exhalation air of a patient according to claim 17.

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During an anesthesia or sedation procedure an anesthetic agent or sedative drug is administered to a patient over a certain period of time. During this period of time it is important that the concentration of the anesthetic agent or sedative drug in the patient's body is neither too low nor too high in order to have the desired effect. It is therefore desirable to have a possibility to monitor said concentration in the patient's body.

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Intravenously administered drugs are also present in the patient's exhalation air. It seems advantageous to monitor and analyse the exhalation air in order to determine and monitor the drug concentration in the patient's body. This allows to monitor the concentration non-invasively.

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From the state of the art it is known to use mass spectroscopy or ion mobility spectroscopy in order to determine the drug concentration in the exhalation air of a

patient These methods provide the required sensitivity and specificity to quantify drugs with concentrations in the ppb range. However, mass spectroscopy and ion mobility spectroscopy techniques are complex and expensive and cannot be used in any operating room environment under routine conditions.

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Further, from the state of the art it is known that anaesthesia gas monitoring devices use absorption spectroscopy methods to quantify the concentration of multiple molecules in the breathing air. The absorption spectroscopy methods use light sources that emit near infrared or mid infrared radiation. Filter means may be used to select multiple wavelength ranges. The light beam passes a sample gas volume with a well determined length and its intensity at the exit of the sample gas volume is detected. The light beam with a specific wavelength range is partially absorbed according the specific absorption cross sections of molecules to be detected. The intensity decrease is indicative for the concentration of the specific molecules in the sample gas. Light absorption by water molecules is critical and may disturb the concentration measurements. These absorption spectroscopy techniques are suited to detect molecules in the concentration range from ppm up to concentrations in percent.

It is an object of the present invention to provide a device and a method for measuring a concentration of at least one drug in an exhalation air of a patient in the concentration range of 0 - 100 ppb that overcome the drawbacks of the above mentioned techniques.

To solve this problem the device of claim 1 is provided. This device is adapted to measure a concentration of at least one drug in an exhalation air of a patient by means of light induced fluorescence spectroscopy. The device comprises at least one light source adapted to induce fluorescence in the at least one drug, at least one detection unit adapted to detect fluorescence radiation emitted by the at least one drug and a processor adapted to correlate an intensity of the fluorescence radiation with the concentration of the at least one drug in the exhalation air. The at least one light source is adapted to emit radiation having a wavelength adapted to induce fluorescence in the at least one drug. This wavelength is the fluorescence excitation wavelength of the at least one drug. The at least one detection unit is adapted to detect radiation having a wavelength that is within the fluorescence emission wavelength range of the at least one drug.

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Light induced fluorescence spectroscopy allows for a drug specific analysis with a high sensitivity and specificity. Depending on the detection unit the sensitivity can be in the

range of 0 to 50 ppb of the at least one drug in the patient's exhalation air. The resolution may be in the range of 1 ppb.

Preferably, the at least one light source is adapted to emit linearly polarized electromagnetic radiation. Besides drug specific fluorescence in the gas sample also Rayleigh scattering by the molecules present in the exhalation air may occur. Rayleigh scattering may perturb the fluorescence signal of the at least one drug detected by the detection unit. Rayleigh scattering cannot be neglected even if the cross section of Rayleigh scattering is orders of magnitudes smaller than the absorption cross section of the at least one drug, especially in case of short wavelengths, such as UV wavelengths. Fluorescence light (having the fluorescence emission wavelength) can be separated from the Rayleigh scattered light (having the fluorescence excitation wavelength) with a wavelength sensitive optical filter (band pass or edge filter) because the fluorescence emission wavelength is shifted to longer wavelengths with respect to the fluorescence excitation wavelength. Rayleigh scattered light has a well-defined space angle distribution and is polarized. It can therefore be suppressed by choosing a well defined detector (detection unit) orientation with respect to the polarization axis of the excitation light emitted by the light source or by using an appropriate polarization filter in the detection unit. The quantitation limit of light induced fluorescence spectroscopy is essentially better than with established absorption spectroscopy methods because the fluorescence signal is measured with respect to a low base line (which is determined by a low intensity of the scattered light) while an absorption spectroscopy signal is an intensity decrease measured with respect to a high intensity signal with a high base line (the high base line is determined by the intensity of the light beam without absorption).

According to another aspect, the light source may be adapted to emit electromagnetic radiation of a defined wavelength or wavelength range. This wavelength or wavelength range may be chosen in dependence of the at least one drug. Preferably, the at least one light source emits light in the UV wavelength range in order to allow electronic excitation of the at least one drug that is required to induce fluorescence. If the at least one drug is for instance propofol, the electromagnetic radiation may be in the wavelength range of 250 to 290 nm, preferably 270 to 280 nm. Excitation with light having a well-defined wavelength increases the sensitivity of the measurement. Water (that is present in the exhalation air) has no significant absorption cross section in this wavelength range and does not disturb the measurement of the fluorescence signal of propofol.

The at least one light source may be a laser diode. A laser diode emits electromagnetic radiation (light) of a specific wavelength with a specific polarization. The laser diode may be a continuous wave or a pulsed laser diode. As an alternative, a LED (light emitting diode) may be used, for example in combination with a filter means to select a specific wavelength (bandwidth) and/or a (further) filter means to select a specific polarization. Alternatively, any other broadband light source might be used in combination with wavelength selective filter means. The light may be collimated before passing a test cell (comprising the exhalation air) that will be described later.

The at least one detection unit may comprise a photomultiplier or a photodiode adapted to detect the fluorescence radiation emitted by the at least one drug. In case that the concentration of more than one drug shall be monitored, for each drug an individual detection unit may be provided. This is of particular relevance in case that the different drugs have overlapping fluorescence excitation wavelength ranges and emit a fluorescence radiation at different fluorescence emission wavelengths. The simultaneously emitted fluorescence radiation may be separated according to the different wavelengths by a separator and guided to the different detection units. As an alternative a single detection unit may be provided. In this case the concentration of each drug may be determined separately (for instance consecutively) by using for each drug a filter means adapted to pass light of the fluorescence emission wavelength of the selected drug. The separator or filter may be arranged such that the fluorescence radiation interacts with the separator or filter before reaching the detection unit.

The at least one detection unit may be arranged with respect to the at least one light source such that the light beam emitted by the at least one light source does not strike directly the at least one detection unit. Additionally the entire optical path (optical setup) between the at least one light source and the at least one detection unit may be designed such that the light emitted by the at least one light source is not guided towards the detection unit. Instead the at least one light source and the at least one detection unit may be arranged such that the light beam emitted by the at least one light source and the light beam detected by the at least one detection unit extend in angle with respect to each other, for instance in an angle of substantially 90°.

In case that the different drugs to be monitored have different fluorescence excitation wavelengths the required selectivity between the different drugs may be reached by providing for each drug radiation with a specific fluorescence excitation wavelength or wavelength range with a sufficiently small bandwidth. The fluorescence excitation

wavelengths or wavelength ranges should be chosen such that each drug absorbs only one of the wavelengths or in one of the wavelength ranges. For instance, for each drug at least one light source adapted to emit radiation with the drug specific fluorescence excitation wavelength or wavelength range may be provided. In case that one light source is adapted to emit radiation with a broad wavelength range comprising different fluorescence excitation wavelengths, a single light source may be used for more than one drug. A drug specific fluorescence excitation wavelength may be selected using a filter means arranged between the light source and the sample (exhalation air) comprising the drug. The filter means may select the appropriate wavelength or wavelength range with a sufficiently small bandwidth. The filter means may be tuned such as to pass one drug specific fluorescence excitation wavelength after the other. In case that the light source is adapted to emit radiation of different wavelengths in dependence of its configuration, the light source may be tuned such as to emit one drug specific fluorescence excitation wavelength after the other.

It might be the case that the different drugs to be monitored have different fluorescence excitation wavelengths and the same or a similar fluorescence emission spectrum. In this case for each drug radiation with a specific fluorescence excitation wavelength range may be provided by individual light sources. The light sources may be triggered such as to emit radiation not simultaneously but with a time delay, for instance in an alternating manner. Emission with a time delay means in this context that at each moment in time only one of the light sources emits radiation. Alternatively, a broadband light source might be used together with tuneable filter means in order to select the drug specific fluorescence excitation wavelengths. Multiple wavelength selective filter means may be mounted on a rotating modulator may in order to select a specific excitation wavelength in case that the light source is a broadband light source.

In case that the different drugs to be monitored have different fluorescence excitation wavelengths and different fluorescence emission wavelengths, for each drug an individual detection unit in combination with a separator or a single detection unit in combination with a filter means may be provided as outlined above to differentiate the fluorescence signals from each other.

It might be the case that the different drugs to be monitored and other components of the exhalation air (of no particular interest) have (partly) overlapping absorption cross section profiles. The absorption cross section profile of a molecule shows the absorption cross section of the molecule in dependence of the excitation wavelength. Besides

(partly) overlapping absorption cross section profiles these molecules may have fluorescence emission in the same or similar wavelength range. Such molecules may be distinguished spectroscopically on the basis of their different absorption cross section profiles. Although the different drugs (molecules) absorb radiation of the same fluorescence excitation wavelength, the related fluorescence intensity of these drugs (molecules) may be different. The fluorescence intensity may depend on the selected excitation wavelength in case that the bandwidth of the excitation wavelength is essentially smaller than the sum of the absorption cross section profiles. In this case the drugs may be irradiated successively with radiation of different wavelengths (with a sufficiently small bandwidth). Preferably, the number of different fluorescence excitation wavelengths is equal to or higher than the number of different drugs. The different wavelengths may be chosen such that the absorption intensities of the different drugs and other molecules present in the exhalation air change differently between the selected wavelengths. If for instance three drugs x, y and z shall be distinguished spectroscopically using light induced fluorescence spectroscopy, the drugs x, y and z may be irradiated successively with radiation of three different wavelengths λ_1 , λ_2 and λ_3 . All three drugs x, y and z may absorb the radiation of the different wavelengths λ_1 , λ_2 and λ_3 . However, their specific absorption cross sections may vary differently between the different wavelengths λ_1 , λ_2 and λ_3 . When irradiating the mixture of the three drugs successively with radiation of the wavelengths λ_1 , λ_2 and λ_3 , three different fluorescence signals $S(\lambda_1)$, $S(\lambda_2)$ and $S(\lambda_3)$ may be detected. Based on the following linear system of equations, the concentration n_x , n_y and n_z of each drug may be determined:

$$\begin{aligned} S(\lambda_1) &= k \cdot (n_x \cdot \sigma_x(\lambda_1) + n_y \cdot \sigma_y(\lambda_1) + n_z \cdot \sigma_z(\lambda_1)) \\ S(\lambda_2) &= k \cdot (n_x \cdot \sigma_x(\lambda_2) + n_y \cdot \sigma_y(\lambda_2) + n_z \cdot \sigma_z(\lambda_2)) \\ S(\lambda_3) &= k \cdot (n_x \cdot \sigma_x(\lambda_3) + n_y \cdot \sigma_y(\lambda_3) + n_z \cdot \sigma_z(\lambda_3)) \end{aligned}$$

wherein

- $S(\lambda_1)$, $S(\lambda_2)$ and $S(\lambda_3)$ are the integral fluorescence intensity signals detected after excitation at different wavelengths λ_1 , λ_2 and λ_3 , respectively,
- k is a proportionality constant,
- n_x , n_y and n_z are the concentrations of the drugs x, y and z in the exhalation air, respectively, and
- $\sigma_i(\lambda_j)$ is the absorption cross section of drug i at wavelength j, wherein i is one of x, y and z and wherein j is one of 1, 2 and 3.

The detection unit (and other optical elements used in the device) may have an optical axis that is parallel to the polarisation of the light emitted by the at least one light source. This orientation of the optical axis minimizes the probability that Rayleigh scattering is detected by the detection unit. Alternatively, the optical axis of the detection unit might
5 be perpendicular to the polarization axis of the excitation light emitted by the at least one light source. In this case an integrated polarization filter with an orientation also perpendicular to the polarization axis of the light emitted by the at least one light source may be provided in order to minimize the intensity of Rayleigh scattered light that is detected by the detection unit. Instead of a polarization filter integrated in the detection
10 unit, a polarization filter anywhere between the test cell and the detection unit may be provided.

According to a further aspect, a test cell (for instance a so-called flow through cuvette) is provided adapted to receive the exhalation air comprising the at least one drug to be
15 detected. The test cell may be arranged in the beam path of the light emitted by the at least one light source between the at least one light source and the detection unit, such that the fluorescence radiation emitted by the at least one drug present in the test cell may be detected by the detection unit. The test cell may be transparent to the electromagnetic radiation emitted by the light source and to the fluorescence radiation
20 induced in the at least one drug. The test cell may be made of quartz glass for instance.

The test cell may have various shapes. Preferably, the test cell comprises several (for instance six) plane side walls that are arranged such as to form a hollow container adapted to receive the exhalation air. For instance all side walls may be rectangular. The
25 test cell may have an orientation with respect to the polarization axis of the light beam emitted by the light source such that the light beam enters the test cell through a side wall at the so-called Brewster angle in order to minimize light reflections of the excitation light beam at the side wall which would increase the noise level. As an alternative, two of the side walls may be trapezoidal, have the same shape, size and orientation and
30 may be arranged in two planes substantially parallel to each other. In this alternative two (non-parallel) side walls may be arranged at the Brewster angle with respect to the polarization axis of the light beam emitted by the light source.

According to a further aspect, the test cell may have a volume of 1 to 5 cm³, preferably
35 of 1 to 3 cm³. Said volume has been found to be advantageous as the size of the volume allows to fractionate one breathing cycle into separate sub-volumes that are sufficiently small in order to probe (analyze) the exhalation air of one breathing cycle at

different stages (in a time-resolved manner). Also subsequent breathing cycles may be separated due to the time resolution. The precision of the concentration measurement may be increased by measuring in a time-resolved manner the profiles of each breathing cycle, especially by reliably probing exclusively the end-tidal phase of a
5 breathing cycle.

To further increase the precision of the concentration measurement, the test cell may be arranged in an optical cavity such as to enhance the fluorescence radiation emitted by the at least one drug. The optical cavity may comprise two mirrors reflecting the light
10 (light emitted from the light source and/or fluorescence radiation emitted by the at least one drug) back and forth through the test cell. The test cell may be arranged between these two mirrors.

In order to make the exhalation air substantially continuously flow through the test cell, a
15 pump may be provided that is in fluid connection with the test cell. The flow rate of the pump may be adjusted to the breathing frequency. The exhalation air may be routed to the test cell via a first line. A second line may be provided via which a gas for purging the test cell may be routed to the test cell. The pump may alternately pump the exhalation air and the purging gas through the test cell. For instance, between each
20 breathing cycle the gas may be pumped through the test cell for purging to ensure that the exhalation air of a breathing cycle is not mixed with the exhalation air of the foregoing breathing cycle. Consequently, the precision of the concentration measurement may be increased. In order to further increase the precision, light may be emitted by the light source and sensed by the detection unit also when the test cell is
25 filled with purging gas. The corresponding detection signal may be used as a reference signal in order to determine a zero base line for the fluorescence signal sensed when the test cell is filled with exhalation air for contributions from the environment.

According to a further aspect, the test cell may be heated to a temperature between 40
30 and 120°C. Heating the test cell has the advantage that condensation of components present in the exhalation air and diffraction of the light emitted from the light source (and/or fluorescence radiation emitted by the at least one drug) at the condensate on the side walls of the test cell can be avoided.

35 According to a further aspect, a filter means may be provided in an optical path of the fluorescence radiation between the test cell and the at least one detection unit. The filter means may be adapted to pass light of a defined wavelength or wavelength range.

Such a filter means is of particular relevance if the light emitted from the light source induces fluorescence in more than one compound of the exhalation air, wherein the fluorescence emission wavelengths are different for the different compounds and from the wavelength of the scattered excitation light. The filter means may in this case select the fluorescence radiation of the one drug of particular interest. Alternatively or additionally, the filter means may be adapted to pass light of a defined polarization. Such a filter means may be used to separate fluorescence from Rayleigh scattering for example.

Said filter means (adapted to pass light of a defined wavelength or wavelength range and/or adapted to pass light of a defined polarization) may be used in combination with at least one lens such that the fluorescence radiation of the at least one drug is collimated to a substantially parallel beam that propagates parallel to the optical axis of the filter means. The optical axis of the filter means is perpendicular to the surface of the filter means that may be in the shape of a plate. Optionally, a second lens is provided downstream the filter means in order to focus the fluorescence light on an aperture placed in front of the detection unit. The second lens together with the aperture define a detection volume and only fluorescence light that is present in this volume is detected by the detector. The second lens and the aperture (for instance a large numerical aperture) define a space angle for fluorescence detection and help to avoid that radiation emanating from other areas and surfaces in the optical system is detected.

According to a further aspect, the at least one drug may be propofol. Propofol is used in TIVA (total intravenous anaesthesia) procedures and for long term sedations.

According to a further aspect, the processor is adapted to determine a concentration of the at least one drug in the blood of a patient on the basis of the measured concentration of the at least one drug in the exhalation air. This correlation between measured concentration in exhaled air and the corresponding concentration in the bloodstream may be a time independent function under steady state conditions. Steady state conditions represent a stable long term status of a patient. This function might be stored in the processor memory and might be based on clinical data from a patient cohort. More advanced pharmacokinetic models may be used in case that steady state conditions cannot be assumed.

The invention also relates to a method for measuring a concentration of at least one drug in an exhalation air of a patient. According to this method light emitted from at least

one light source is shone onto the exhalation air in order to induce fluorescence in the at least one drug. The fluorescence radiation emitted by the at least one drug is detected with at least one detection unit. A processor is used to correlate an intensity of the fluorescence radiation detected by the at least one detection unit with the concentration of the at least one drug in the exhalation air. Preferably, the method uses a device according to one or more embodiments of the invention.

The method may be performed continuously or periodically at a defined repetition rate. That means that the light emitted by the light source is shone either continuously or in a pulsed manner with a predetermined pulse frequency onto the exhaled air and/or that the detection unit detects either continuously or in a pulsed manner. In case that the method is performed periodically, the repetition rate, the detection (or irradiation) duration and the moment of detection (or of irradiation) within a breathing cycle may depend on the patient's breathing rate. A time resolved measurement of singular breathing cycles is performed in case that the method is performed continuously or with a repetition rate essentially larger than the breathing rate. A mean drug concentration in the exhalation air is measured in case that the repetition rate of the method is similar or larger than the breathing rate. Repetition rate, detection (or irradiation) duration and the moment of detection (or of irradiation) within a breathing cycle have an essential influence on the precision of the concentration measurement. The repetition rate may be 0,5 to 2 Hz for instance. The method may be performed over more than one breathing cycle.

According to a further aspect, the concentration of the at least one drug in the exhalation air is determined on the basis of the air exhaled at the end of an exhalation phase (end-tidal phase). In the end-tidal phase, the air is exhaled that is present in the alveoli in which the gas exchange with the patient's blood occurs. Using only the concentration of the at least one drug in the exhalation air determined for the end-tidal phase allows to increase the precision when correlating the concentrations of the at least one drug in the patient's exhalation air and in the patient's blood and thus to increase the precision of the predicted concentration of the at least one drug in the patient's blood.

For this purpose the light source may be a continuously emitting light source or a pulsed light source. A continuously emitting light source may be used to provide a continuous irradiation of the exhalation air or in combination with an external modulator for periodically modulating the amplitude of the emitted light between 0% and 100%

according to a rectangular function in order to provide a pulsed irradiation of the exhalation air. The external modulator may be a chopper or a rotating optical element, such as a rotating mirror. In case that the pulse frequency of the pulsed light source is higher than the frequency at which light shall be shone onto the exhaled air, the external
5 modulator may be used as well. Usually a breathing cycle (comprising an inhalation phase and an exhalation phase) lasts approximately 10 seconds. Assuming that the exhalation phase lasts 5 seconds, the exhaled air of one breathing cycle may be probed 2,5 to 10 times or continuously throughout the entire exhalation phase.

10 The idea underlying the invention is shown in the figures. Herein:

Fig. 1 schematically shows a device for measuring a concentration of at least one drug in an exhalation air of a patient according to an embodiment of the invention;

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Fig. 2 schematically shows a device for measuring a concentration of at least one drug in an exhalation air of a patient according to another embodiment of the invention;

20 Fig. 3 schematically shows a device for measuring a concentration of at least one drug in an exhalation air of a patient according to another embodiment of the invention;

25 Fig. 4 shows a UV absorption spectrum of propofol (continuous line) and of acetone (dashed line), wherein the absorption spectrum of acetone has been rescaled with a scaling factor 100;

Fig. 5 shows a fluorescence emission spectrum of propofol of a static fluorescence measurement;

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Fig. 6 shows an absorption spectrum of propofol (I) and a fluorescence emission spectrum of propofol (II);

Fig. 7 shows an absorption spectrum of acetone;

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Fig. 8 shows a fluorescence emission spectrum of acetone.

Figure 1 shows one exemplary embodiment of a device 1 for measuring a concentration of at least one drug in an exhalation air of a patient. The device 1 comprises a light source 11, a detection unit 12 coupled to a processor 13 and a test cell 14.

- 5 The light source 11 is adapted to emit electromagnetic radiation for inducing fluorescence in the at least one drug. The light source 11 is a laser adapted to emit electromagnetic radiation (a laser beam) of a defined wavelength and a defined polarisation. Alternatively, the light source 11 may be a LED or any other light source adapted to emit electromagnetic radiation of a defined wavelength or wavelength range
10 (and of a defined polarisation). A lens 111 is arranged in the laser beam path in order to collimate the laser beam.

- The test cell 14 is arranged in the beam path downstream the lens 111 (seen along the direction of propagation of the laser beam). The test cell 14 is a quartz glass cuvette.
15 The quartz glass cuvette has six side walls, four of which have a rectangular shape and two of which have a trapezoidal shape. The trapezoidal side walls extend in two parallel planes and are spaced from each other by the rectangular side walls that extend in planes that are oriented substantially perpendicular with respect to the two trapezoidal side walls. The test cell 14 is arranged in the beam path such that the laser beam enters
20 the test cell (nearly) at the so-called Brewster angle (specific angle between the laser beam and the corresponding side wall) in order to avoid reflection at the surface of the entrance side wall. The laser beam leaves the test cell through the side wall opposite to the entrance side wall, also (nearly) at the Brewster angle. Alternatively, the test cell 14 may have six side walls of rectangular shape and may have an orientation with respect
25 to the laser beam axis such that the laser beam enters the test cell 14 at the Brewster angle. The test cell 14 is transparent at least to the light emitted by the light source 11 and to the fluorescence radiation emitted by the at least one drug in the exhalation air. The test cell 14 comprises an inlet opening and an outlet opening through which exhalation air enters and exits the test cell 14, respectively. A first line 171 is connected
30 to an exhalation air source on the one hand, and via the inlet opening to the test cell 14 on the other hand. A second line 172 is connected to a purging gas reservoir on the one hand, and via the inlet opening to the test cell 14 on the other hand. A third line 173 is connected to a pump 17 on the one hand, and via the outlet opening to the test cell 14 on the other hand. The pump 17 is adapted to make exhalation air flow from the
35 exhalation air source through the first line 171 and through the test cell 14. In particular the pump pumps alternately exhalation air and purging gas through the test cell 14. Valves are not shown in the figures. As the duration of a measurement by means of light

induced fluorescence spectroscopy is short allowing to measure one breathing cycle in a time-resolved manner, valves are not required to fractionate the exhalation air of one breathing cycle into sub-volumes. According to an embodiment, no valve is provided between the exhalation air source and the test cell. In order to avoid that a component of the exhalation air condenses on a surface of the test cell 14, the test cell 14 is heated to a temperature between 40 and 120°C, preferably to approximately 90°C.

A light trap (or beam dump) 112 is arranged downstream (seen along the direction of propagation of the laser beam) the test cell 14 in order to absorb excess laser light.

The test cell 14 is arranged between the detection unit 12 and a mirror 121. The mirror 121 is adapted to reflect fluorescence radiation emitted in a direction away from the detection unit 12 back through the test cell 14 towards the detection unit 12.

In order to select light with a specific wavelength (range) and/or a specific polarization to be detected by the detection unit 12, a filter means 15 is provided between the test cell 14 and the detection unit 12. A lens 18 is arranged between the filter means 15 and the test cell 14 on the one hand and between the mirror 121 and the test cell 14 on the other hand, such that the light (in particular the fluorescence radiation) propagates substantially as a parallel beam through the filter means 15 parallel to the optical axis of the filter means 15. With a parallel beam the filter means 15 can more efficiently separate Rayleigh scattering or fluorescence radiation in a different wavelength range than the one to be detected from the fluorescence radiation with the wavelength of interest. An aperture 122 is arranged in front of the detection unit 12, so that only light emanating from the test cell 14 (or a specific volume of the test cell 14) reaches the detection unit 12 and causes a detection signal. Scattered light from the environment or from the light source 11 may thus be blocked by the aperture 122 and the noise level of the detection signal may be reduced. A further lens 18 is provided between the filter means 15 and the aperture 122 in order to focus the parallel beam through the aperture 122 on the detection unit 12.

The detection unit 12 is adapted to detect fluorescence radiation emitted by the at least one drug. The detection unit 12 may comprise a photomultiplier tube, a photodiode or another suitable optical detection device. The signal detected by the detection unit is processed by a processor 13. The processor 13 is adapted to correlate the signal intensity of the fluorescence radiation with the concentration of the at least one drug in the exhalation air. The processor 13 is further adapted to correlate the concentration of

the at least one drug in the exhalation air with the concentration of the at least one drug in the blood of the patient. The processor 13 may be linked to a user interface allowing a user to enter patient specific data that are used to correlate the concentration of the at least one drug in the exhalation air with the concentration of the at least one drug in the blood of the patient.

Figure 2 shows a second embodiment of the device 1 for measuring a concentration of at least one drug in the exhalation air of a patient. The embodiment shown in Figure 2 differs from the embodiment shown in Figure 1 in that additionally an optical cavity 16 is provided. The optical cavity 16 comprises two mirrors in between which the test cell 14 is arranged. The mirrors of the optical cavity 16 and the test cell 14 are positioned on an optical axis. Said optical axis coincides with the path of the laser beam that is emitted from the light source 11. The mirrors of the optical cavity 16 reflect the laser beam emitted from the light source 11 back and forth through the test cell 14 in order to enhance the excitation light intensity inside the cavity and therefore the fluorescence radiation emitted by the at least one drug in the exhalation air in the test cell 14.

Figure 3 shows a third embodiment of the device 1 for measuring a concentration of at least one drug in the exhalation air of a patient. The embodiment shown in Figure 3 differs from the embodiment shown in Figure 2 in that three light sources 11 instead of only one light source are provided. However, the number of light sources is not limited to three, but can be chosen according to the user's needs. For instance each light source may emit radiation of a different wavelength so that three different drugs that are present simultaneously in the exhalation air and that have different fluorescence excitation wavelengths may be excited by the light emitted from the three light sources 11. The three light source 11 may in this case emit light not simultaneously, but in a time-delayed (for instance alternating) manner so that each signal of the detection unit 12 can be assigned to a specific light source and thus to a specific drug in the exhalation air. It might also be useful to probe one and the same drug that has several absorption lines with light of different wavelengths emitted from the different light sources. Also in this case, the light sources preferably emit the radiation in a time-delayed (alternating) manner. In an alternative, the different excitation wavelengths may be emitted simultaneously by one broadband light source and alternatingly selected by a rotating modulator that is placed in the light beam, wherein multiple wavelength selective filter elements are mounted on the rotating modulator.

The at least one drug is exemplarily propofol. The chemical formula of propofol is shown in Figure 4. Figure 4 also shows an absorption spectrum of propofol (continuous line). The concentration of propofol in exhaled air may vary between 0 and 50 ppb. Propofol has a strong absorption line in the UV range between 250 and 285 nm (see also Figure 6, spectrum I). Propofol may thus be probed using a fluorescence excitation wavelength at 275 nm. Also other molecules may have a fluorescence excitation wavelength between 250 and 290 nm. As exemplarily can be seen from Figure 4 (dashed line) and Figure 7, also acetone (for example) absorbs between 250 and 285 nm. As acetone is also present in the exhalation air, it may thus be excited as well when propofol is probed at 275 nm. In particular the concentration of acetone in the exhaled air is approximately 1000 times larger than the concentration of propofol, namely 0,3 to 1 ppm. This may lead to a measurement error in the concentration of propofol in air, although acetone has an absorption cross section that is approximately 100 times weaker than the absorption cross section of propofol. As can be seen from Figure 4, acetone also absorbs (dashed line) outside the absorption range of propofol (continuous line). In order to correct the fluorescence emission signal detected with an excitation wavelength of 275 nm, the exhalation air may be probed additionally at a wavelength outside the propofol excitation wavelength range, for instance at 290 nm. As an alternative use may be made of the fact that the fluorescence emission of propofol is in the range between 290 and 320 nm (Figure 5, Figure 6, spectrum II), while the fluorescence emission of acetone is in the range between 400 and 550 nm (Figure 8). Both fluorescence emission spectra are thus sufficiently separated from each other so that the fluorescence radiation emanating from acetone and from propofol may be separated. Using for example an appropriate wavelength selective filter means 15 may thus block or reflect the fluorescence emission of acetone while the fluorescence emission of propofol is transmitted to the detection unit 12. Using light induced fluorescence spectroscopy avoids cross sensitivity of propofol and acetone and thus allows to distinguish the measurement signals of propofol and acetone. Absorption spectroscopy or photo acoustic spectroscopy do not allow to differentiate between propofol and acetone. Light induced fluorescence spectroscopy has thus a high drug specific sensitivity.

Claims:

1. Device (1) for measuring a concentration of at least one drug in an exhalation air of
5 a patient comprising at least one light source (11) adapted to induce fluorescence in
the at least one drug, at least one detection unit (12) adapted to detect fluorescence
radiation emitted by the at least one drug and a processor (13) adapted to correlate
an intensity of the fluorescence radiation with the concentration of the at least one
10 drug in the exhalation air.
2. Device (1) according to claim 1, **characterized in** that the light source (11) is
adapted to emit linearly polarized electromagnetic radiation.
- 15 3. Device (1) according to claim 1 or 2, **characterized in** that the light source (11) is
adapted to emit electromagnetic radiation of a defined wavelength or wavelength
range, in particular electromagnetic radiation in the wavelength range of 260 to 280
nm.
- 20 4. Device (1) according to any of the preceding claims, **characterized in** that a test
cell (14) is provided adapted to receive the exhalation air, wherein the test cell (14)
is at least transparent to the electromagnetic radiation emitted by the light source
25 and to the fluorescence radiation induced in the at least one drug.
5. Device (1) according to claim 4, **characterized in that** the test cell (14) has a
volume of 1 to 5 cm³, preferably of 1 to 3 cm³.
- 30 6. Device (1) according to claim 4 or 5, **characterized in that** the test cell (14) is
arranged in an optical cavity (16) such as to enhance the fluorescence radiation
emitted by the at least one drug.
- 35

7. Device (1) according to any of the claims 4 to 6, **characterized in that** the test cell (14) is in fluid connection with a pump (17) that is adapted to make the exhalation air substantially continuously flow through the test cell (14).

5

8. Device (1) according to any of the claims 4 to 7, **characterized in that** the test cell (14) is heated to a temperature between 40 and 120°C.

10

9. Device (1) according to any of the claims 4 to 8, **characterized in that** a filter means (15) is provided in an optical path between the test cell (14) and the at least one detection unit (12).

15

10. Device (1) according to claim 9, **characterized in that** the filter means (15) is adapted to pass light of a defined wavelength or wavelength range and/or to pass light of a defined polarization.

20

11. Device (1) according to claim 9 or 10, **characterized in that** the filter means (15) is provided in combination with at least one lens (18) such that the fluorescence radiation of the at least one drug is a substantially parallel beam that propagates parallel to the optical axis of the filter means (15) through the filter means (15).

25

12. Device (1) according to any of the preceding claims, **characterized in that** the at least one drug is propofol.

30

13. Device (1) according to any of the preceding claims, **characterized in that** for measuring the concentration of more than one drug in the exhalation air of a patient, wherein the drugs have different fluorescence excitation wavelengths, at least one light source (11) is provided for each drug.

35

14. Device (1) according to claim 13, **characterized in** that the light sources (11) are adapted to emit electromagnetic radiation in a time-delayed manner, in case that the drugs have a similar fluorescence emission wavelength.

5

15. Device (1) according to any of the preceding claims, **characterized in** that for measuring the concentration of more than one drug in the exhalation air of a patient, wherein the drugs have different fluorescence emission wavelengths, the different fluorescence emission wavelengths are separated by a separator and
10 guided to an individual detection unit (12).

16. Device (1) according to any of the preceding claims, **characterized in** that the processor (13) is adapted to determine a concentration of the at least one drug in
15 the blood of a patient on the basis of the concentration of the at least one drug in the exhalation air.

17. Method for measuring a concentration of at least one drug in an exhalation air of a
20 patient comprising the steps of:
a) with at least one light source (11) shining light onto the exhalation air in order to induce fluorescence in the at least one drug,
b) with at least one detection unit (12) detecting fluorescence radiation emitted by the at least one drug, and
25 c) with a processor (13) correlating an intensity of the fluorescence radiation with the concentration of the at least one drug in the exhalation air,
wherein in particular the device (1) according to any of the preceding claims is used.

30 18. Method according to claim 17, **characterized in** that the method is performed continuously or periodically with a repetition rate that is smaller than a breathing rate of the patient.

19. Method according to claim 17 or 18, **characterized in** that the concentration of the at least one drug in the exhalation air is determined on the basis of the exhalation air at the end of an exhalation phase.

5

20. Method according to claim 18 or 19, **characterized in** that the concentration of the at least one drug in the exhalation air is determined periodically with a repetition rate that is smaller than the breathing rate over more than one breathing cycle.

10

FIG 1

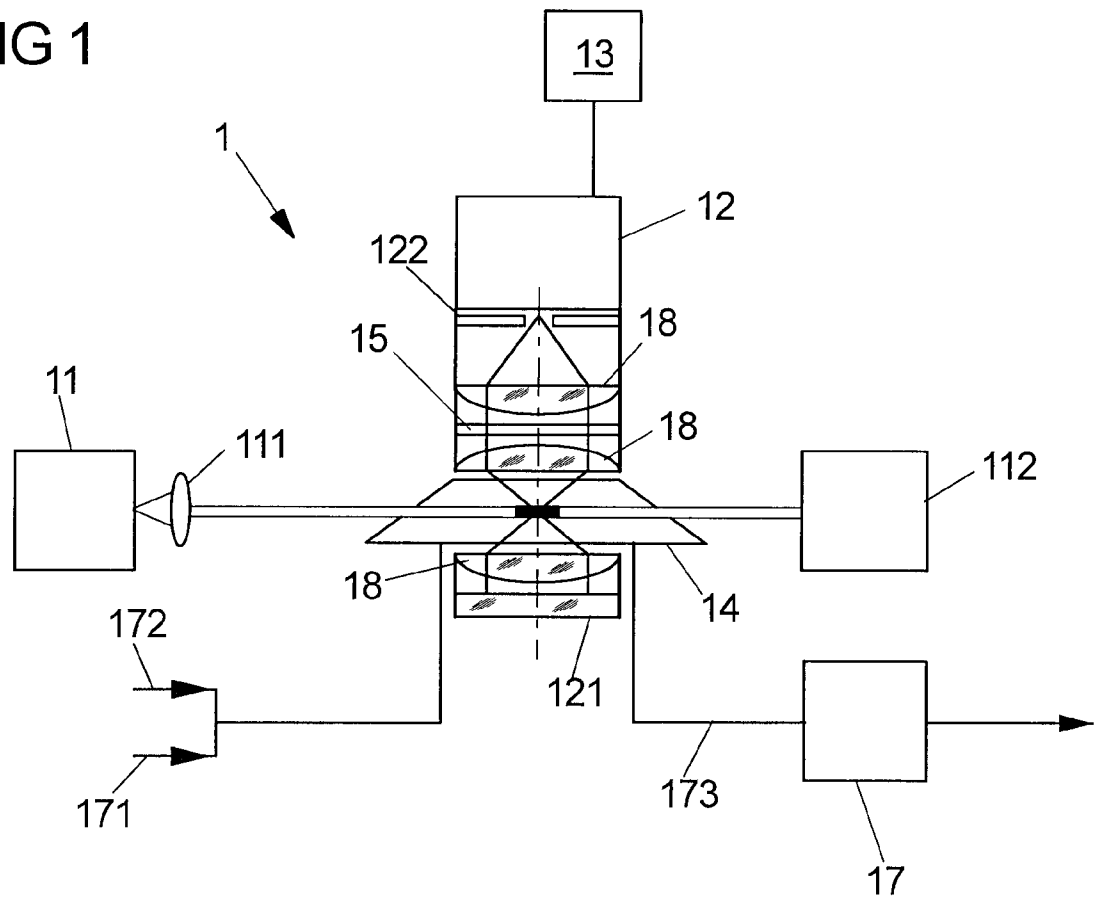


FIG 2

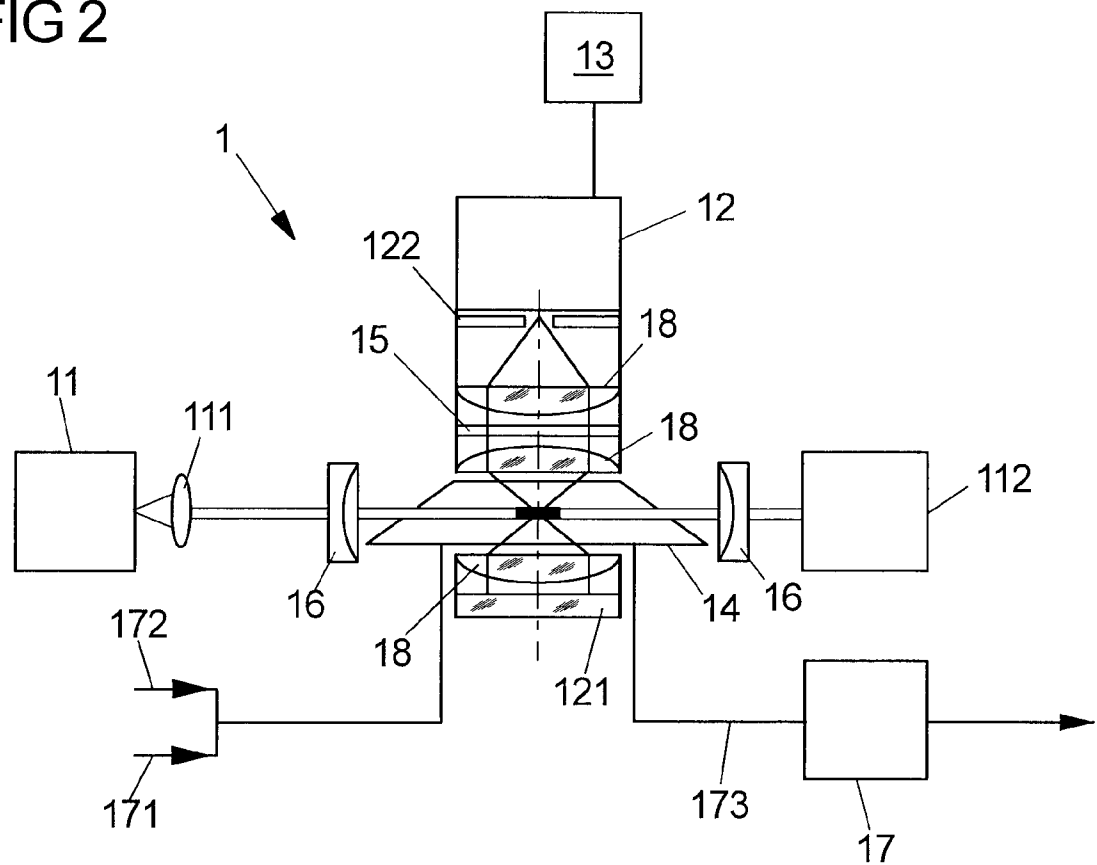


FIG 3

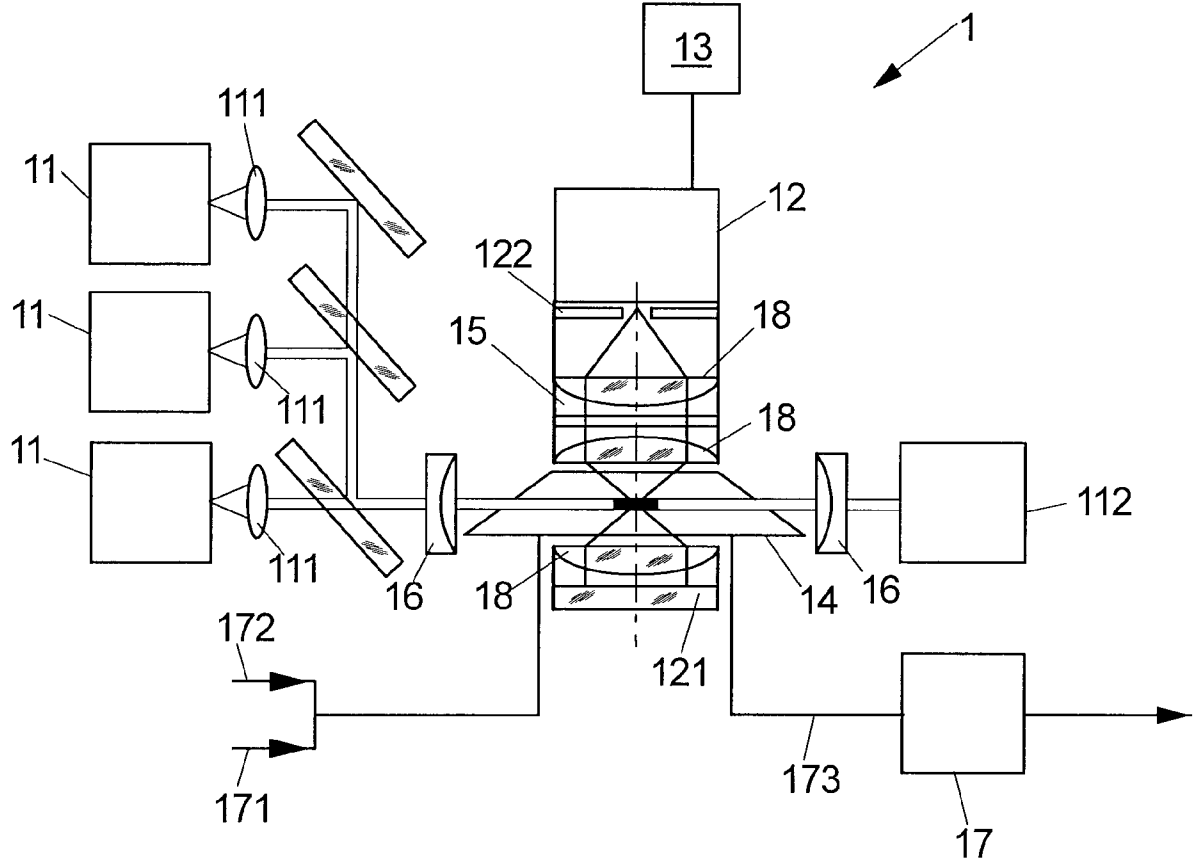


FIG 4

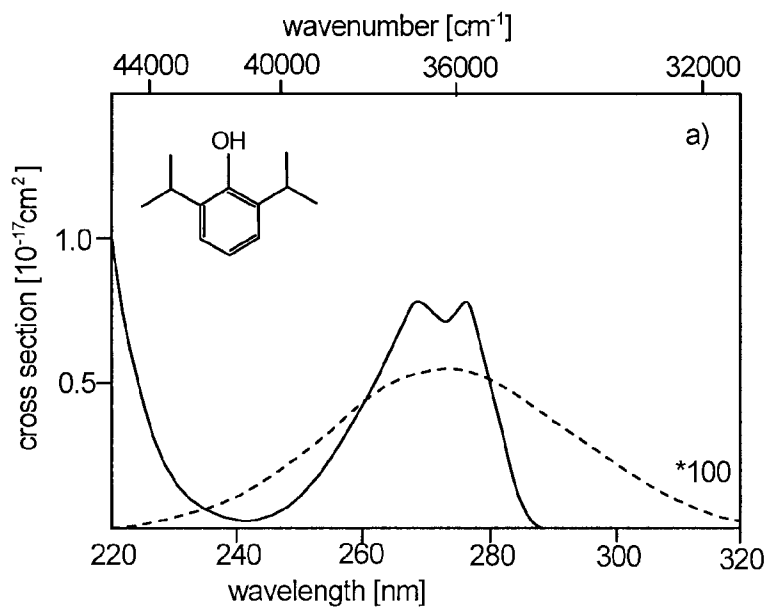


FIG 5

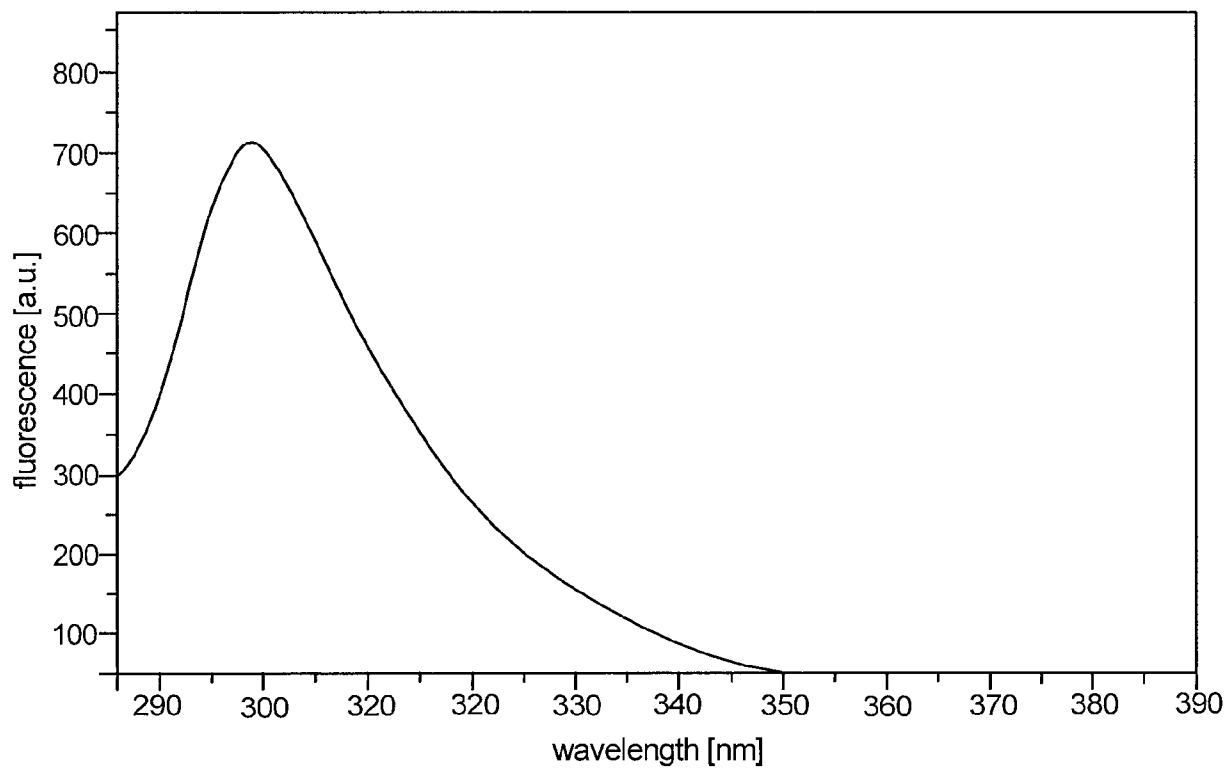


FIG 6

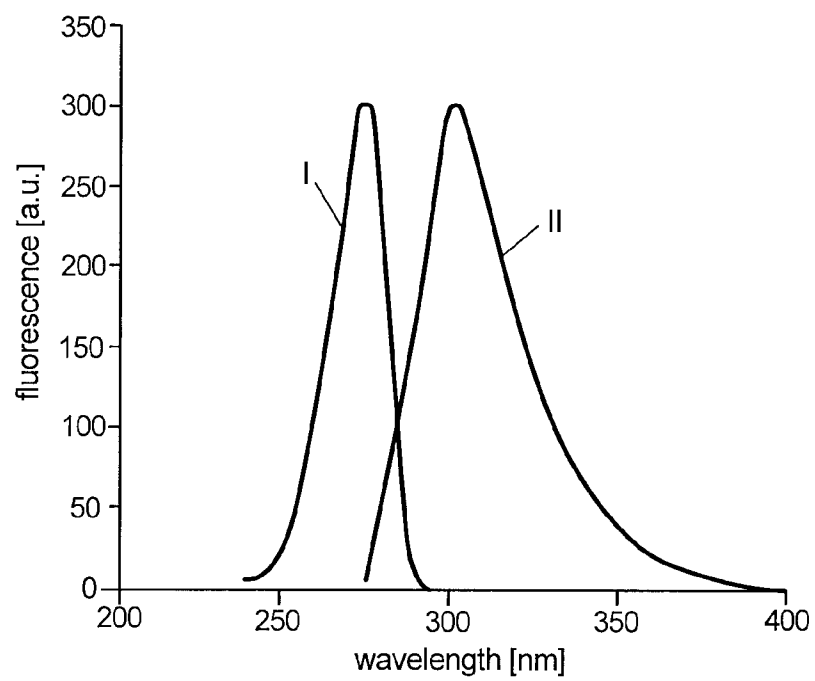


FIG 7

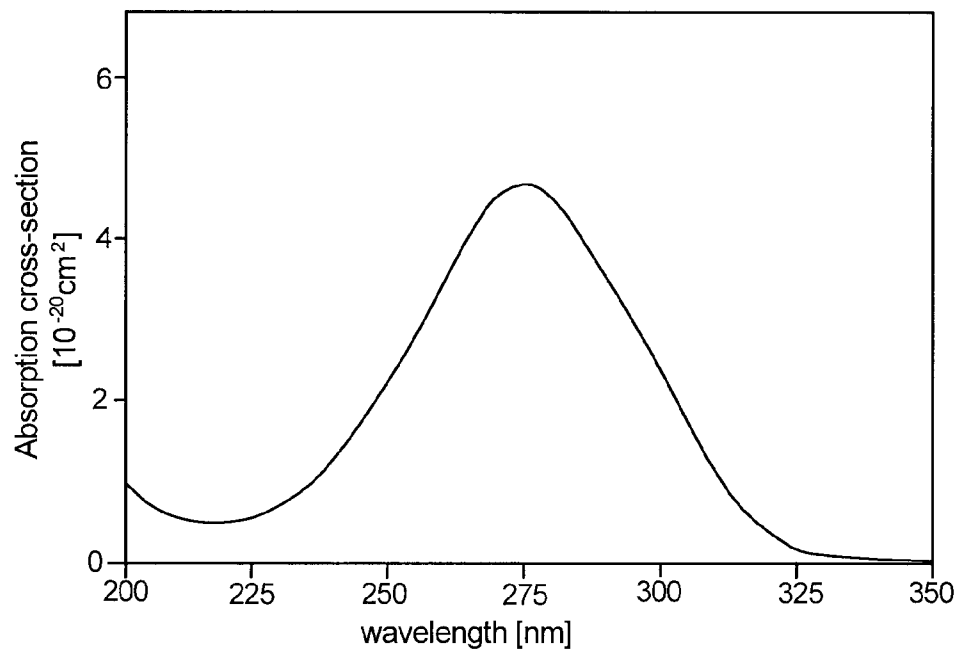
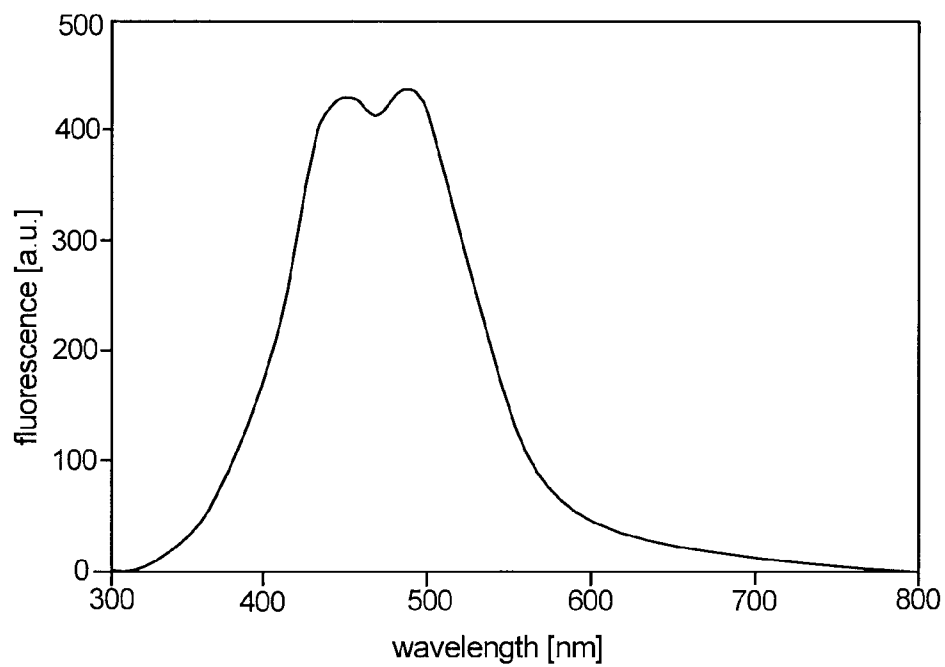


FIG 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/067978

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N21/15 G01N21/64 A61B5/08 A61B5/1455 G01N33/497
ADD. G01N21/03 G01N21/05

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)
G01N A61B

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 practicable, search terms used)

EPO-Internal, WPI Data, INSPEC, COMPENDEX

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Y	paragraphs [0002], [0016] - [0022], [0033], [0048] - [53.60], [0063], [0064], [0067], [0071], [0090] - [0101]; claim 31; example 1	2,6,8-12
Y	US 2003/208133 A1 (MAULT JAMES R [US]) 6 November 2003 (2003-11-06) paragraphs [0001], [0002], [0017], [0129], [0130], [0132]	2,6,9-11
Y	CN 102 262 082 B (UNIV XINJIANG MEDICAL) 9 July 2014 (2014-07-09)	12
A	paragraph [0015]	3
	-/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search

20 October 2016

Date of mailing of the international search report

27/10/2016

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Authorized officer

Duijs, Eric

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/067978

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	----- US 5 062 942 A (KAMBARA HIDEKI [JP] ET AL) 5 November 1991 (1991-11-05) column 11, line 29 - column 12, line 8; figure 8 -----	11

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International application No

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