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(71) Applicant: **ANATOLIA TANI VE BIYOTEKNOLOJI URUNLERI ARASTIRMA GELISTIRME SANAYI VE TICARET ANONIM SIRKETI** [TR/TR]; Egitim Mah. Kasap Ismail Sk. Istanbul, Plaza No:11/23 Kat 3 Kadıköy, 34722 Istanbul (TR).

(72) Inventors: **AKYUZ, Elif**; Eğitim Mah. Kasap Ismail Sk., Istanbul Plaza No:11/23 Kat 3 Kadikoy, 34722 Istanbul (TR). **AKYUZ, Alper**; Eğitim Mah. Kasap Ismail Sk., Istanbul Plaza No:11/23 Kat 3 Kadikoy, 34722 Istanbul (TR).

(74) Agent: **DESTEK PATENT, INC.**; Konak Mah. Lefkose Cad. NM Ofis Park B, Blok No: 36 / 5 Besevler Nilufer, 16110 Bursa (TR).

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(54) Title: LABORATORY AUTOMATION SYSTEM

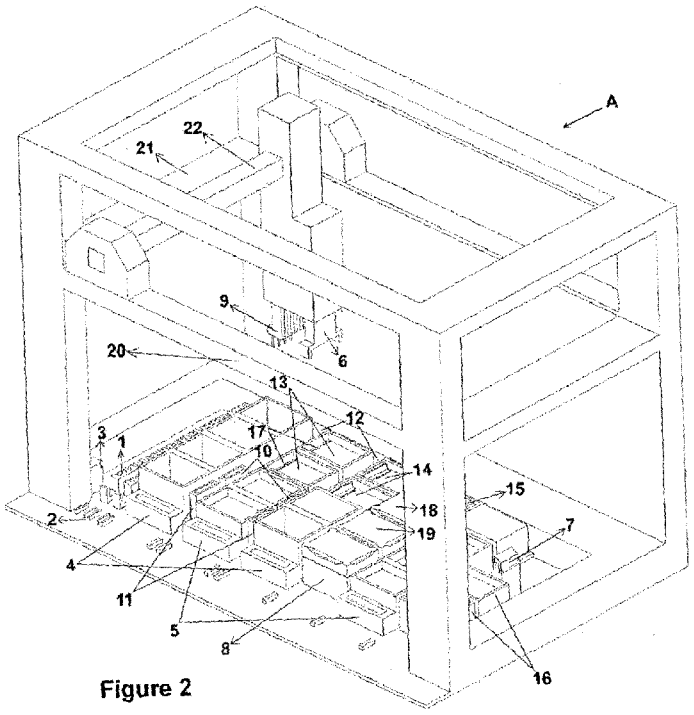

Figure 2

[Continued on next page]

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(57) Abstract: The invention is related to a laboratory automation system that enables automated extraction and preparation of nucleic acids from biological samples, to be used readily in downstream molecular genetic analyses.

DESCRIPTION

LABORATORY AUTOMATION SYSTEM

TECHNICAL FIELD

The invention is related to a laboratory automation system that enables automated extraction and preparation of nucleic acids from biological samples, to be used readily in downstream molecular genetic analyses.

BACKGROUND OF THE INVENTION

Most of the few present laboratory automation systems in the market (the number is not more than 10 all over the world) are prone to nucleic acids spread to negative controls and target DNA/RNA negative samples which is called as contamination and these systems are amenable to false positive results. Hence, especially their usage in diagnostics and high sensitivity-viral quantitation processes is objectionable. A few laboratory automation systems in the market which provide reliable results has generally high price and high consumption cost. Therefore these systems has high operating costs and the operation procedure takes too long.

In the patent investigation performed, it was determined that there is no similar exposed patent or utility model application for the laboratory automation system which is the object of invention and some of the patents carried out in the similar technical field are indicated below.

Assortment class C12N15/00 number 2012/00187 entitled as "In vitro DNA detection method and storage unit" patent application is related to a DNA separation method and the unit which is used for storage of the separated DNA. Deoxyribonucleic acid or briefly DNA is a nucleic acid which carries the required genetic instructions for the vital processes and biological development of all organisms and some viruses. It aims to separate the person to separate his/her own DNA from other cell components and make it observable out of laboratory environment. Besides, development of the environment and the container to enable the storage of this DNA for long term is another purpose of this application.

Assortment class C12Q1/68 press number EP2162549B1 entitled as "Process for nucleic acids diagnosis" patent application; reveals a process for diagnosis of nucleic acids including the steps indicated below. Through the hybridization of at least one oligonucleotide to at least one part of the target nucleic acid, the procurement of at least one nanoparticle functionalized for the target nucleic acid, the functionalized nanoparticle contact with the

sample containing the target nucleic acid and the measurement of a characteristic to supply information about the hybridization level of at least one oligonucleotide with the target nucleic acid, in addition, the process includes the step of excitation of the nanoparticles to generate heat; via photothermal effect. This invention is especially suitable for highly efficient DNA analysis.

OBJECT OF THE INVENTION

The main purpose of the invention; is to develop a laboratory automatization system which enables the automatic extraction of nucleic acids from biologic samples and preparation for the molecular genetic analyses.

The system that is the subject of the invention, includes the advantageous properties indicated below and these properties does not exist in the present systems:

- Including specific structural and procedural precautions intended to prevent contamination,
- Instead of discard, the storage of the remaining unused part of extracted DNA/RNA samples in the PCR setup step, for further usage in barcode-defined plastic reservoir in the refrigerator region,
- The feature of being an open system,
- Flexible work order (processability of two different parameter at the same time, processing and placement of the biological samples with different volumes and in different tubes),
- Cheaper and easier manufacturing compared to present systems,
- Acquiring the results faster than the present systems.

It takes longer time to extract DNA/RNA with the present systems which comprises more complicated and more exprensive production, requires special consumables because of being closed system, there are some points prone to contamination in these techniques.

The system that is the subject of invention is an open system, therefore the protocol can be achieved by using serially produced standard plastic consumables. This feature, enables the users to use their own solutions, consumables and protocols if required.

The specific features developed against contamination are; the safe route of the pipettes, special gaps left between the modules, the prefilled buffers in ready to use plastic reservoirs with a specific design from the outside-in direction order, piercing of the foil covering the plastic reservoir by the pipette tips with a specific 4-side move, discard of the pipette tips after washing with a solution, specially designed magnetic modules/stations, the storage of all critical liquids (PCR kit solutions, the extracted DNA/RNA samples) in the refrigerator

regions closed by special lids carried by the transfer arm until the step of their usage in order to prevent the contamination from air.

The system that is the subject of invention produces faster results compared to present systems that contain similar pipette number.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1, is the isometric drawing of the laboratory automation system related to the invention.

Figure 2, is the isometric drawing of the laboratory automation system related to the invention, from a different angle.

Figure 3, is the isometric drawing of the laboratory automation system related to the invention, from a different angle.

Figure 4, is the step by step algorithm of the workflow of the automation system.

Reference Numbers Related to the Invention

A. Laboratory automation system
1. Sample tube carrier modules
2. Module guiding rails
3. Barcode reader 1
4. Pipette tip carrier modules
5. Deep well plate carrier modules
6. Transfer arm
7. Barcode reader 2
8. PCR kit reagent cooler
9. Pipettes
10. Pipette tip discard modules
11. Pipette tip washing modules
12. Pipette travel spaces
13. Magnetic modules/stations
14. Heater shaker units
15. Heaters
16. Deep well plastic plate storage stations
17. Magnets with adjustable height

18. DNA/RNA sample cooler

19. PCR master mix cooler

20. UV lamp 1

21. UV lamp 2

22. UV lamp 3

DETAILED EXPLANATION OF THE INVENTION

The invention is related to a laboratory automation system (A) that enables automated extraction and preparation of nucleic acids from biological samples, to be used readily in downstream molecular genetic analyses.

Isometric drawings from different angles of the laboratory automation system involved in the invention, are displayed in Figure 1, 2 and 3. The laboratory automation system (A) involved in the invention is composed of the elements which are described in detail below:

The sample tube carrier modules (1) of the laboratory automation system (A) can be easily placed in and removed from the system via a rail system. The sample tube carrier modules (1), which enable loading of biological samples with varying volumes in various tubes, obviates the neccessity for an extra step for the end user's transfering the biological samples in different tubes with varying volumes to standard tubes in specific volumes.

Module guiding rails (2) that have been placed in various positions of the system; enable the correct, accurate and easy placement and removal of the sample tube carrier modules (1), the pipette tip carrier modules (4) and the deep well plate carrier modules (5) into and out of the system.

Barcode reader 1 (3) that reads the barcodes on the sample tubes, enables classification and treatment of samples conveniently all throughout the procedure. Barcode reader 2 (7) reads both barcodes on the pipette tip boxes and the barcodes on the reagent reservoirs and enables the control of the pipette tip loading and monitoring of the chemicals.

Pipette tip carrier modules (4), are modules in which 96 well plates full of disposable plastic pipette tips are placed. These modules (4) can be easily placed in and easily removed from the device via module guiding rails (2).

Deep well plate carrier modules (5), enables ready-to-use sealed deep well plats prefilled with DNA/RNA extraction chemical reagents/buffers, which are neccessary for sample treatment, to be placed in and easily removed from the device via module guiding rails (2).

Transfer arm (6); has been designed to lift and carry the deep well plate plastic reservoirs and extracted DNA samples from one station to another, via its transferring arm integrated to the pipette head.

The system also contains a Peltier system cooled PCR kit reagent cooler (8) which is a special compartment covered by special lids that can be carried by the transfer arm (6). PCR kit reagent cooler (8), enables storage of fragile PCR reagents between 2-8 degrees conveniently without activity loss and preventing exposure to light, all throughout the protocol.

Pipettes (9) with liquid level detection sensors and adjustable distance, are used in the laboratory automation system (A) that is related to the invention. The pipettes in the pipette head, which is composed of 2, 4 or 8 independent pipettes, sense the level/amount of the liquid to be aspirated and the parameters related to the pipetting are determined according to this liquid level. As this information is processed, error messages are received at neccessary steps. Liquid level detection allows pipette tip to begin pipetting just at the specified liquid level, thus pipette tip does not immerse completely into the fluid, preventing the contamination of its whole outer surface. The loaded samples and reagents in different types of tubes and having varying volume and levels can be processed with high sensitivity. As the distance between the pipettes (9) can be adjusted between 9-22 mm, the system can accomplish liquid transfer between; different sample tubes, deep well plate plastic reservoirs, tubes of different size and shapes.

Pipette tip discard modules (10) has been designed so that the pipettes (9) can discard used pipette tips after use, and they are tip waste containers/wells made of metal plates with U shape. Pipette tip washing modules (11) are next to the tip discard modules (10) and have been designed in order to wash the pipette tips with the cleaning solution inside just before discard at certain stages of the protocol, thus to prevent contamination.

The laboratory automation system (A) related to the invention; contains special pipette travel spaces (12) left between modules. This feature enables the pipettes (9) to travel in a safe route; so that the operating disposable pipette tip will not pass over any samples other than the one it pipettes or over any reagents, thus contamination is prevented. The pipette travel spaces (12) left between modules, also confers functionality to the module guiding rails (2).

Magnetic modules/stations (13) are modules that contain moving or fixed magnets, and have been designed in order to collect the paramagnetic beads inside the wells lined along the edges of the deep well plate plastic reservoirs at the side walls of the wells. This enables

DNA and RNA that bind to the paramagnetic beads inside the wells located at the edges, to be purified after being treated with various chemicals/solutions.

Heater shaker units (14) enables heating and mixing of the chemicals/solutions and the samples inside the deep well plastic plates. These heater shaker units that have L shaped special heating ends, allow the chemical solutions inside the wells at the edges of the deep well plastic plates to heat more. A separate heater (15) is used in order to heat the chemical reagents in the deep well plastic plates.

The deep well plastic plate storage stations (16), that have been designed to allow the plate(s) that are not being treated, to be stored during their incubation period while the samples in the multiple deep well plastic plates are being processed, enable the workflow to proceed without any flaw and all the samples in all the plates to be processed equally/similarly.

Magnets with adjustable height (17) are employed to allow effective separation of the magnetic beads within different volume solutions at the various steps of the DNA/RNA extraction procedure.

Peltier system cooled DNA/RNA sample cooler (18), which has been covered by special lids that can carried by the transfer arm (6), allows the barcoded plastic reservoirs to be stored between 2-8 degrees conveniently, in order to enable future reuse of the portions of the isolated DNA/RNA samples that will not be used in the PCR setup stage, instead of disposal.

PCR master mix cooler (19) that is cooled by a Peltier system; is a special compartment covered by special lids that can be carried by the transfer arm (6), and enables storage of the prepared PCR master mixes between 2-8 degrees conveniently.

The laboratory automation system (A) related to the invention also utilizes UV lamp 1 (20), UV lamp 2 (21) and the UV lamp 3 (22). Thanks to the stationary and mobile three UV lamps (20, 21, 22) after the protocol is completed, potential DNA/RNA spread to all the work place is eliminated, thus contamination is prevented.

The sequence of processes that is performed by the laboratory automation system (A) relevant to the invention are given below.

A. Örneklerin ve çözelti içeren plastik haznelerin üzerlerindeki Reading of the barcode numbers on the samples and plastic reservoirs prefilled with the solutions by the barcode readers 1 and 2 (3, 7), treatment of the biological samples in different tubes with differing volumes.
B. Transfer of various fluids from one reservoir or tube to another is accomplished by the pipettes (9) with adjustable distance and liquid level detection sensors. During this

process, pipettes (9) move downwards and leaves special air gaps while aspirating the fluids (this prevents the dripping of the sample's or fluid's aspirated in the pipette while traveling, and avoids contamination of the fluids below), and they are allowed to travel following a special route utilizing the special pipette travel spaces (12) left between the modules. This special route design enables the operating disposable pipette tips never pass over a sample or reagent other than it's treating, thus avoiding contamination.

C. Pipettes (9) take pipette tips and after the pipetting operation discard the used tips directly into the pipette tip discard modules (10) which are tip waste containers, or discards the tips after immersing into the solution in the pipette tip washing modules (11) at some certain steps. This allows the decontamination of the wastes from DNA/RNA and to avoid a contamination that could be caused by the waste container.

D. The pipettes (9) mix the biological samples by pipetting into the ready to use plastic reservoirs and the transfer arm (6) carries these reservoirs to specially designed magnetic modules/stations (13), to heater shaker units (14) with L shaped special heating ends, to heaters (15), to special deep well plastic plate storage stations (16), and DNA/RNA is obtained from the biological samples via the magnetic beads that interact with the magnets with adjustable height (17).

E. The pipettes (9) with liquid level detection sensors and adjustable distance, prepares the PCR master mixes by pipetting the PCR kit components and performs the PCR setup by mixing the DNA/RNA extracted from biological samples with the PCR kit reagents.

F. All the neccessary extraction and PCR kit reagents, extracted DNA/RNA samples, prepared PCR master mixes are kept cool, via the PCR kit reagent cooler (8), the DNA/RNA sample cooler (18) and the PCR master mix cooler (19).

G. At neccessary steps, the fluids in the deep well plastic plates are either mixed and/or heated with heater shaker units (14) with L shaped special heating ends, or only heated via heaters (15).

H. The portions of the extracted DNA/RNA samples in barcoded plastic reservoirs left after the PCR setup stage can be stored, for future use instead of being disposed, in the cooling compartment; DNA/RNA sample cooler (18).

İ. The device is cleaned via the UV lamp 1, 2 and 3 (20, 21, 22).

J. Pipettes (9) pierce the aluminum foil sealing the plastic reservoir with the pipette tips in order to aspirate the chemicals/solutions in the deep well plate plastic reservoirs and expands the diameter of the hole in the foil by a special movement in four directions performed by the pipette tips while piercing the aluminum foil covering the deep well plate plastic reservoir. This prevents the contact of the chemicals/solutions

with air until use and avoids their evaporation. Due to the piercing fuction of the pipettes there is no need to use a separate piercing apparatus.

K. Pipettes (9) move starting from top to bottom while aspirating the liquids.

Pipettes (9) avoid the overflow of the liquid and prevent contamination by ensuring that the pipette tip's whole outer surface is not immersed in the fluid, by first contacting just the upper level as they dip the pipette tips into the liquid and then gradually moving down to lower levels as liquid level drops while aspirating the liquid . They also allow use of the reservoirs that contain solutions with maximum efficiency, and avoids long term damage to the instrument.

L. Thanks to the ready-to-use sealed deep well plastic reservoirs prefilled with buffers in a specially designed order of DNA/RNA chemical reagents/buffers required to process 16 samples, having a processing sequence from outer wells to inner wells; time is saved by minimizing number and duration of pipetting during extraction. The practicality of the system is enhanced due to this ready-to-use plastic reservoir and need to supply extra plastic disposables and packaging material along with the system is eliminated. This specially designed sequence of chemical reagents ensures that disposable pipette tips do not pass over any sample or buffer other than the one they process, thus eliminating contamination.

Just as other various molecular laboratory techniques, PCR technique also requires the purification of DNA or RNA by isolation from different biological samples, to be used as the starting material. Mixing the purified nucleic acid with specified quantities of kit ingredients deliberately and placing in the Real Time PCR instrument enables this device to detect, genotype or quantitate the genomic material.

DNA/RNA extraction generally includes; the lysis of cell membrane and cell wall, inactivation of the nuclease activity,cleansing the solution from proteins by washing, concentrating the nucleic acids and the proper storage of the extracted DNA/RNA steps.

The separation process which the magnetic beads are used as solid-phase, is faster, more simple, applicable to automated systems and more effective method compared to other techniques and it enables to perform large-scaled isolations easily. Magnetic extraction is based on serparation of magnetic beads by means of a magnet

In recent years, it has been started preferring full-automated systems for DNA/RNA supply (isolation) from biological samples and preparation for molecular genetic analysis via Real-Time PCR (PCR setup) processes for the purpose of diagnosis or research in the molecular test laboratories around the world.

Through the automation systems, the errors which can be caused during the manual processing of laboratory technicians and the false-positive test results which may be resulted by false applications can be prevented. Besides, full-automatic systems enable technicians to perform other works during the automatic analysis period eliminating the laboratory work load.

The working principle of the system that is the subject of the invention, has been summarized in the order of the operation steps:

Sample tubes that are placed into the sample tube carrier modules (1), are loaded in the device via module guiding rails (2), at this point the barcodes of the tubes are read by barcode reader 1 (3) automatically. System allows biological samples of varying volumes in different tubes to be processed.

Disposable pipette tips that are placed in the pipette tip carrier modules (4) are loaded in the device via module guiding rails (2).

Plastic reservoirs filled with solutions, are placed into the deep well plate carrier modules (5) which are loaded in the device via module guiding rails (2). They are carried by the transfer arm (6) and their barcodes are read automatically by the barcode reader 2 (7).

Chemical solutions that must be kept cool, are placed in a special cooler compartment cooled by a Peltier system and covered by special lids that can be carried by the transfer arm (6); namely the PCR kit reagent cooler (8), after their barcodes are read by the by the barcode reader 2 (7).

The step by step algorithm of the workflow of the automation system is given in Figure 4. In order to complete the steps described in Figure 4, pipettes (9) with liquid level detection sensors and adjustable distances, take the pipette tips, aspirate the fluids, moves to the relevant location and dispenses them from one reservoir or tube to another. Pipette tips pierce the aluminum foil sealing the plastic reservoir with the pipette tips in order to aspirate the chemicals/solutions in the deep well plate plastic reservoirs and expands the diameter of the hole in the foil by a special movement in four directions performed by the pipette tips while piercing the aluminum foil covering the deep well plate plastic reservoir.

After the pipetting operation, used pipette tips are either discarded directly into the pipette tip discard modules (10) or discarded after immersing into the solution in the pipette tip washing modules (11) at some certain steps. During pipetting, the pipettes (9) move downwards and leaves special air gaps while aspirating the fluids, and they travel following a special route utilizing the special pipette travel spaces (12) left between the modules.

The steps described in Figure 4 are executed according to the recorded in the instrument's software, in the specified order; the fluids in the ready-to-use plastic reservoirs are pipetted and mixed with biological samples; carried by the transfer arm (6) to specially designed magnetic modules/stations (13), to heater shaker units that have L shaped special heating ends (14), to the heaters (15), to special deep well plastic plate storage stations (16); after they are mixed, heated and incubated for certain periods, and elution of DNA/RNA of biological samples via magnetic beads as a result of the interactions with the magnets (17) with adjustable height; PCR master mixes are prepared by pipetting the PCR kit components and the PCR setup is achieved by mixing the DNA/RNA extracted from biological samples with the PCR kit reagents.

All the neccessary liquids are kept without losing their activities in relevant cooling sections; extraction and PCR kit reagents are stored in the PCR kit reagent cooler (8), prepared PCR master mixes are stored in the the PCR master mix cooler (19), and portions of the extracted DNA/RNA samples left after PCR setup are kept in the DNA/RNA sample cooler (18) in barcoded plastic reservoirs to enable future use.

System is cleaned via stationary and mobile UV lamps (20, 21 ve 22).

CLAIMS

1. A laboratory automation system (A) which allows automated extraction of nucleic acids from biological samples and enables their preparation to be used in molecular genetic analyses; it contains sample tube carrier modules (1) that allow biological samples with varying volumes in different tubes to be placed in the device and to be processed, module guiding rails (2) that enables the sample tube carrier modules (1), the pipette tip carrier modules (4) filled with disposable plastic pipette tips, the deep well plate carrier modules (5) to be correctly and accurately placed into and easily removed out of the instrument, barcode reader 1 (3) that reads the barcodes on the sample tubes, a transfer arm (6) which is used to hold the deep well plastic reservoirs and the extracted DNA samples firmly from sides and carry them from one station to another, barcode reader 2 (7) which reads the barcodes both on the pipette tip boxes and on the reservoirs filled with reagents, PCR kit reagent cooler (8) that enables storage of fragile PCR reagents between 2-8 ^{0}C conveniently without activity loss and light exposure, pipettes (9) with liquid level detection and adjustable distance, heater (15) that allows heating of the chemicals in the deep well plastic reservoir, special deep well plastic plate storage stations (16) that have been designed to allow the plate(s) that are not being treated, to be stored during their incubation period while the samples in the multiple deep well plastic plates are being processed, Peltier system cooled PCR master mix cooler (19); a special compartment covered by special lids that can be carried by the transfer arm (6), which enables storage of the prepared PCR master mixes between 2-8 degrees conveniently, UV lamp 1 (20), UV lamp 2 (21) and UV lamp 3 (22) with stationary and mobile features employed to clean the system,

   And it is characterized to contain the following;

   - Pipette tip discard modules (10), used to enable the pipettes (9) to discard the used pipette tips as the pipetting is over,
   - Pipette tip washing modules (11) which are next to the tip discard modules (10) and have been designed in order to wash the pipette tips with the cleaning solution inside just before discard at certain stages of the protocol, thus to prevent contamination.
   - Special pipette travel spaces (12) left between modules, that enable the pipettes (9) to travel in a safe route; so that the operating disposable pipette tip will not pass over any samples or any reagents other than the one it pipettes.
   - Magnetic modules/stations (13) which have been designed in order to collect the paramagnetic beads inside the wells lined along the edges of the deep well plate plastic reservoirs at the side walls of the wells.
   - Heater shaker units (14) that enables heating and mixing of the chemicals/solutions and the samples inside the deep well plastic plates.

- Magnets with adjustable height (17) which allow effective separation of the magnetic beads within different volume solutions at the various steps of the DNA/RNA extraction procedure.

- Peltier system cooled DNA/RNA sample cooler (18), which has been covered by special lids that can carried by the transfer arm (6), allowing the barcoded plastic reservoirs to be stored between 2-8 ^{0}C conveniently, in order to enable future reuse of the portions of the isolated DNA/RNA samples that will not be used in the PCR setup stage, instead of disposal

2. The method of claim 1, is a laboratory automation system (A) that is characterized by the pipette tip discard modules (10) that comprise U shaped metal plates.

3. The method of claim 1, is a laboratory automation system (A) that is characterized by magnetic modules/stations (13) that comprise magnets that are capable of moving up and down or fixed magnets.

4. The method of claim 1 is a laboratory automation system (A) that is characterized by; heater shaker units (14) that comprise special L shaped heating ends.

5. A method caried out by a laboratory automation system (A) that involves the following steps:

- Barcode reading of the barcode numbers on the plastic reservoirs filled with samples and buffers by the barcode reader 1 and barcode reader 2 (3, 7) and processing of samples with carying volumes in different tubes,
- PCR master mix preparation via mixing the PCR kit components by pipettes (9) with liquid level detection sensor and adjustable distance, and PCR setup where DNA/RNA eluted from biological samples are mixed by PCR kit components,
- Keeping all the neccessary extraction and PCR kit reagents, extracted DNA/RNA samples, prepared PCR master mixes cool,
- Shaking, mixing and/or only heating of the liquids in the deep well plastic plates at neccessary steps,
- System's cleaning by UV light,
- Pipettes' (9) moving starting from top to bottom while aspirating the liquids

And characterized to contain the following steps:

- Transfer of various liquids from one reservoir or tube to another by the pipettes (9) with liquid level detection sensor and adjustable distance, during this operation pipettes'(9) moving starting from top to bottom while aspirating the liquids and leaving special air gaps in the pipette tips (preventing dripping of the samples or liquids while moving and avoiding contamination of other samples and liquids), traveling of the pipettes (9) following a special route employing the special travel spaces(12) left between the modules, eliminating the operating disposable pipette tips to pass over any sample or buffer other than the one it processes thanks to this special route design,
- Ability of the pipettes' (9) to take the pipette tips and discard the used pipette tips after pipetting directly into the pipette tip discard modules (10) or to discard the used pipette tips after immersing into the solution in the pipette tip washing modules (11) at some certain steps,
- Pipetting and mixing of the fluids in the ready-to-use plastic reservoirs with biological samples by the pipettes (9); transfer by the transfer arm (6) to specially designed magnetic modules/stations (13), to heater shaker units that have L shaped special heating ends (14), to the heaters (15), to special deep well plastic plate storage stations (16); and elution of DNA/RNA of biological samples via magnetic beads as a result of the interactions with the magnets (17) with adjustable height,
- Storage of the portions of the extracted DNA/RNA samples in barcoded plastic reservoirs left after the PCR setup stage, for future use instead of being disposed, in the cooling compartment; DNA/RNA sample cooler (18),
- Piercing of the aluminum foil sealing the plastic reservoir by the pipettes (9) with the pipette tips in order to aspirate the chemicals/solutions in the deep well plate plastic reservoirs and expanding of the diameter of the hole in the foil by a special movement in four directions performed by the pipette tips while piercing the aluminum foil covering the deep well plate plastic reservoir.

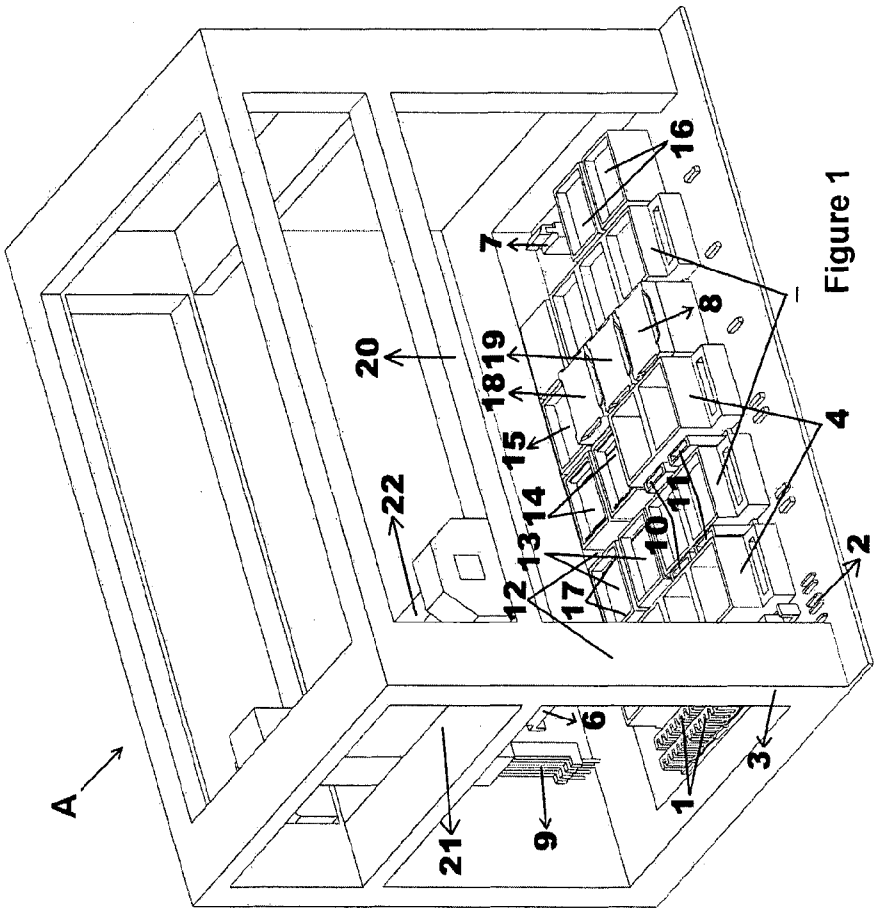

Figure 1

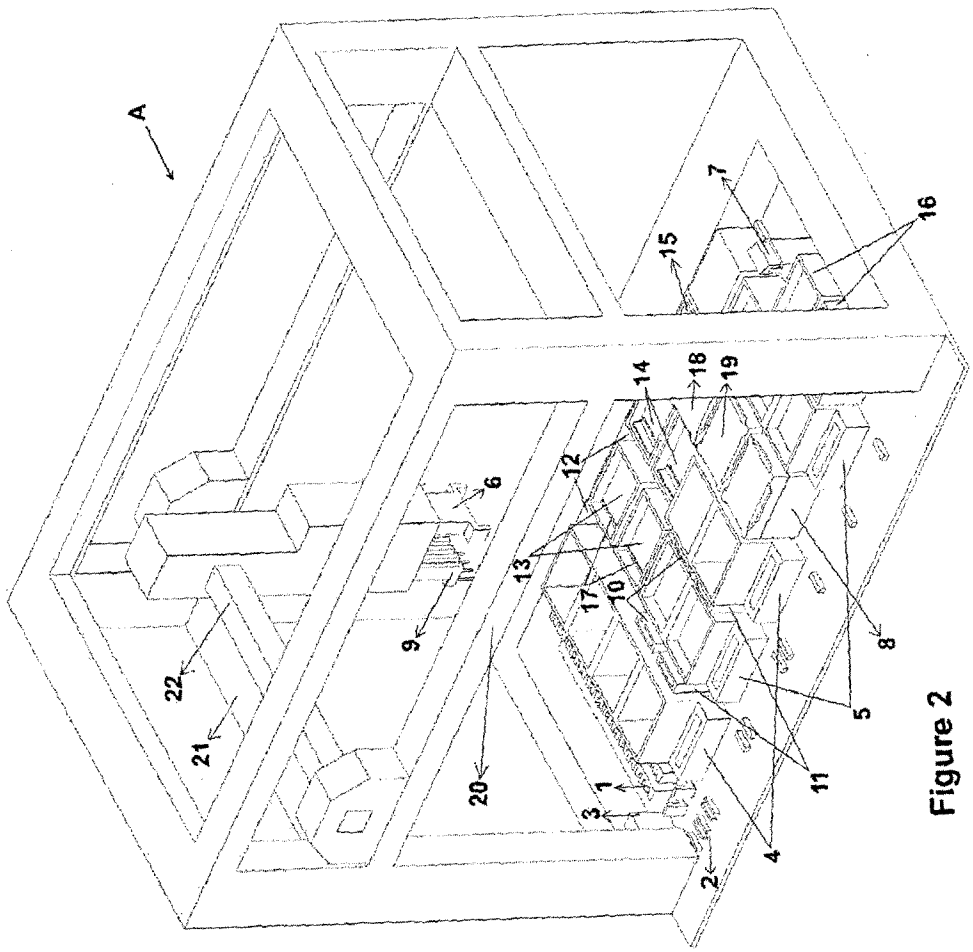

Figure 2

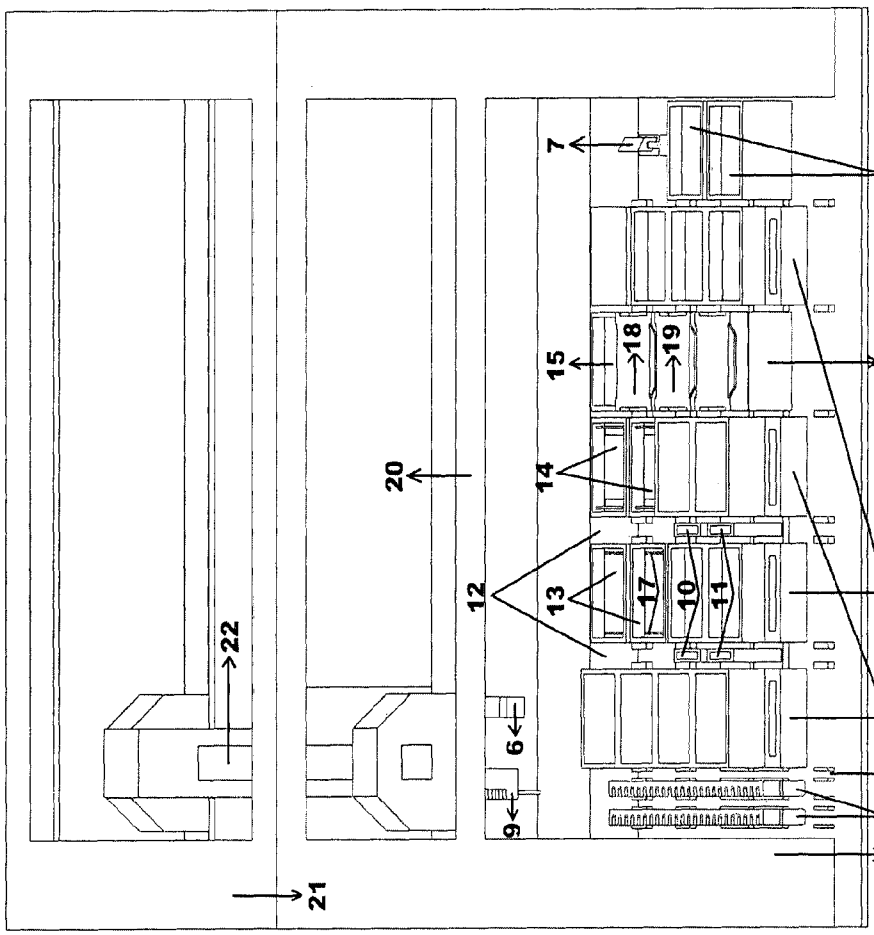

Figure 3

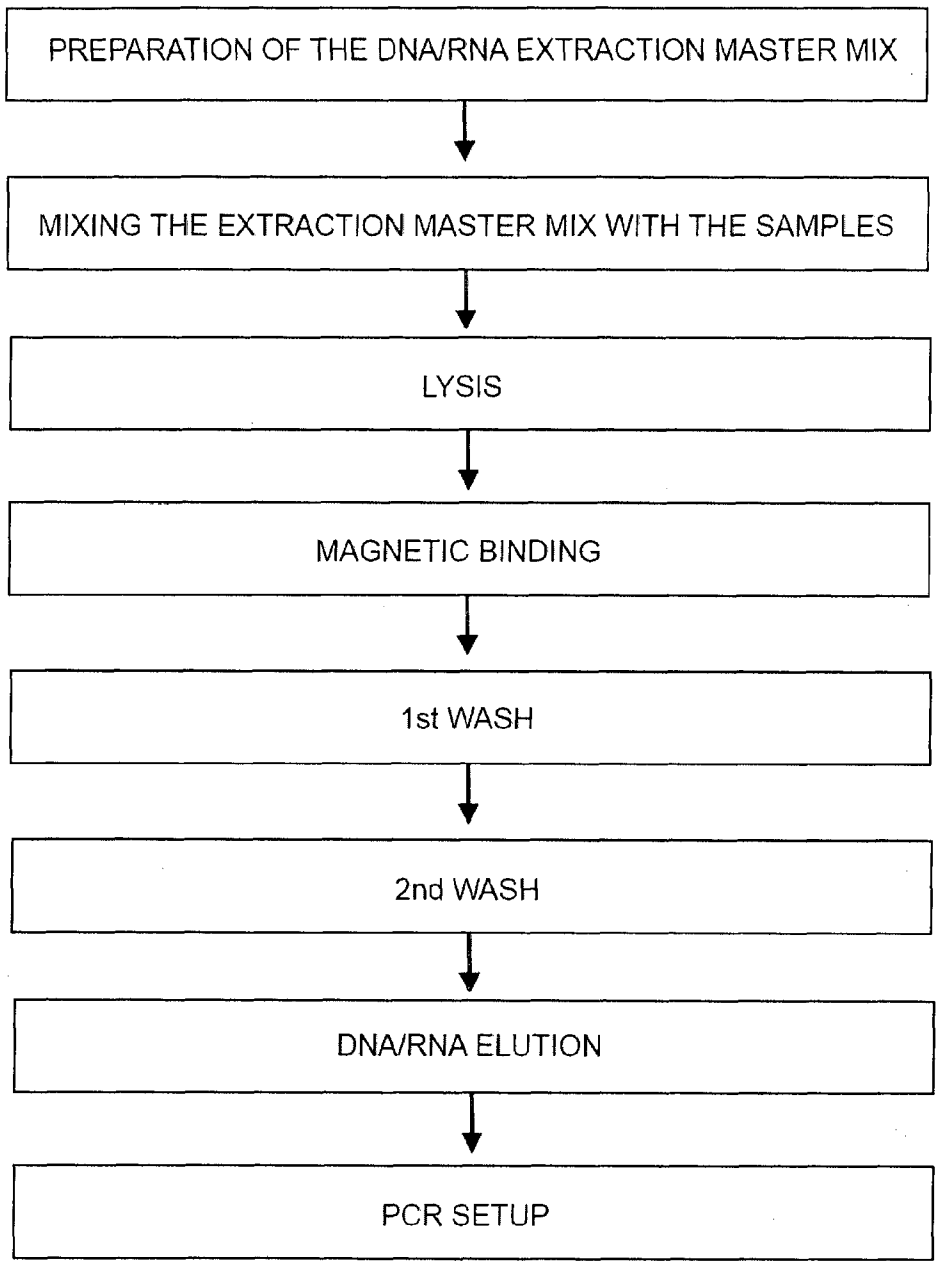
PREPARATION OF THE DNA/RNA EXTRACTION MASTER MIX
MIXING THE EXTRACTION MASTER MIX WITH THE SAMPLES
LYSIS
MAGNETIC BINDING
1st WASH
2nd WASH
DNA/RNA ELUTION
PCR SETUP

Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2014/000362

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L7/00 C12Q1/68 G01N35/00
ADD.

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 C12Q C12N B01L

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 623 764 A2 (GEN PROBE INC [US]) 8 February 2006 (2006-02-08) column 6, par. 20; column 13 and 14, par. 44; column 17, par. 62; column 18, par. 66; column 27, par. 118; column 28, par. 121; column 33, par. 145; column 35 and 36, par. 152 and 155; column 37 and 38, par. 164; column 39 par. 168; column 43, par. 183; column 52, par. 223; column 53, par. 231; column 54, par. 234; column 58, par. 253; column 60, par. 263; column 75, par. 325; claim 1; figure 14	1-5
A	US 2013/137110 A1 (KRAIHANZEL CHARLES S [US]) 30 May 2013 (2013-05-30) paragraphs [0243], [0295]	1-5

☐ 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
3 March 2015	10/03/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lokajova, Jana

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