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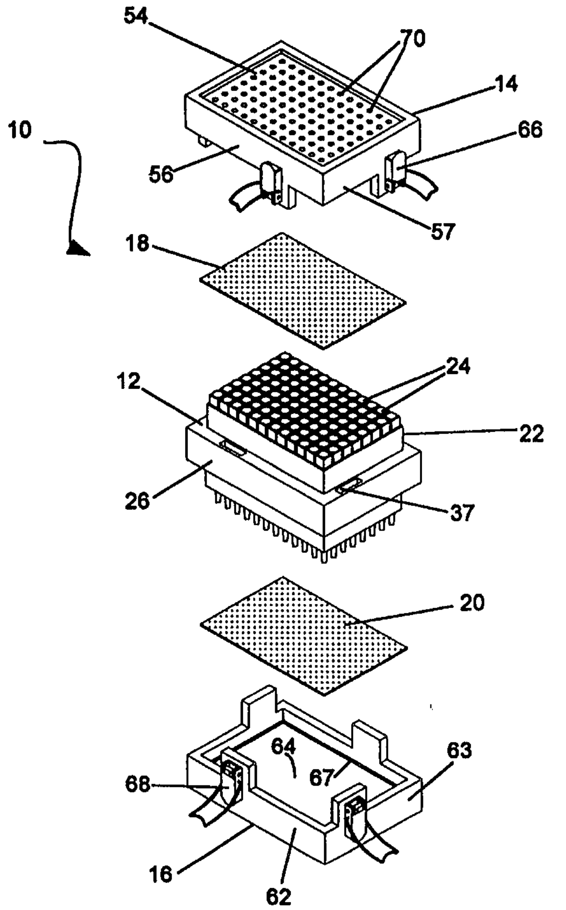
(54) Title: APPARATUS FOR MULTI-WELL MICROSCALE SYNTHESIS

(57) Abstract

A multi-well synthesis and filtration apparatus (10) for performing multiple, simultaneous chemical reactions, workups and purifications on a micro scale. The apparatus (10) includes a deep-well synthesis block (12) having a plurality of wells (24) fitted with filter disks (48), an upper cover (14), a lower cover (16) and a pair of sheet gaskets (18 and 20). The sheet gaskets (18 and 20) are interposed between the upper and lower covers (14 and 16) to seal inlet portions (38) and outlet spouts (40) of the wells (24). Apertures (70) in the upper cover (14) provide that the sheet gasket (18) may be punctured for introduction of materials and/or maintenance of an inert atmosphere. The design is such that either the synthesis block (12) alone, or the block (12) as covered, is dimensionally of a size that provides for a footprint that is the same as a standard microplate.



APPARATUS FOR MULTI-WELL MICROSCALE SYNTHESIS

This application claims priority from U.S. Provisional Applications Serial Nos. 60/031,024, filed 18 November 1996, and 60/043,211, filed 9 April 1997, which have the same inventors as the present application.

TECHNICAL FIELD

The present invention relates generally to apparatus for synthesizing and culturing chemical and biological compounds, to chemical and biological filtration apparatus, and to multi-well apparatus, and more particularly to such apparatus used for performing multiple simultaneous syntheses and filtrations on a micro scale.

BACKGROUND ART

As the scale on which chemical compounds and biological materials are capable of being analyzed, tested, purified and otherwise manipulated for research and clinical purposes continues to decrease, there is a call for increasingly more efficient methods of synthesizing and culturing such compounds and materials. Numerous benefits, in particular, are offered by the extremely small or "micro" scale preparation of chemical and biochemical molecules. Among such benefits are that costs with respect to the reagents, solvents and other materials employed for reaction, workup and purification - many of which can be quite expensive - are greatly reduced. Further, the amounts of by-products and other waste materials generated are also greatly reduced, thereby lowering disposal costs and also reducing the potential for environmental damage by hazardous materials. Moreover, the speed with which large numbers of chemical compounds can be synthesized for biological screening purposes can be greatly increased, since a large number of such microscale reactions can potentially be run and processed simultaneously in a single piece of apparatus using batch equipment.

Given that only a very minute percentage of chemical entities that are investigated will exhibit the desired characteristics for which they have been targeted and synthesized, and given that relatively small changes in chemical structure can produce profoundly different biological properties, the ability to rapidly synthesize large numbers of new compounds and analogs for evaluation is of especially great commercial importance, indeed, it is often a matter of economic survival to pharmaceutical and biotechnological companies involved in the development of new therapeutic agents.

It has been the case for a number of years in the peptide field that use has been made of mechanized, computer-aided equipment capable of simultaneously synthesizing a number of different peptides by the sequential coupling of amino acids to functionalized solid supports. Such mechanized equipment may be employed because the conditions necessary for most such coupling reactions are uniformly simple and straightforward.

In the case of the synthesis of organic compounds generally, however, there is a great variance in the conditions and techniques which must be employed, which precludes or makes impractical the use of fully automated instruments. For example, magnetic stirring, shaking, or some other form of agitation may be needed, and heating or cooling to great temperature extremes may be required. With respect to reactions requiring heating, provision for the reflux of volatile solvent may also be necessary. Further, many chemical reactions are air sensitive and so may require an inert atmosphere for their performance. Reagents and substrates may be air sensitive (e.g., hygroscopic or pyrophoric) or corrosive and require special handling techniques, such as transfer via a syringe or canula, or even handling in a glove box. Many organic synthetic procedures require the addition of materials in both solid and liquid form or employ an addition sequence that is complex. Additionally, some delicate reactions must be closely monitored through intermittent sampling in order to bring the reaction to a successful fruition. Where an instrument(s) is capable of performing any of the above, it is still the case that throughput is limited, further, such instruments are extremely expensive.

One prior art attempt at providing an apparatus for the simultaneous, multiple synthesis of organic compounds is found in U.S. Pat. No. 5,324,483 issued June 28, 1994 to Cody et al. In Cody, which is directed toward solid phase synthesis, the lower ends of a plurality of reaction tubes (in the nature of conventional gas dispersion tubes) are each received by a plurality of reaction wells. The reaction tubes are held vertically in place by a holder block, while the reactions wells are contained by a reservoir block. A seal is provided between the holder block and the reservoir block. A manifold covers the reaction tubes, with a seal being provided between the manifold and the holder block. Means are provided for detachably fastening together the reservoir block to the holder block and the holder block to the manifold. The dispersion tubes provide a glass frit type of filtering capability so that a solid support may be retained and rinsed as necessary after performance of a coupling reaction or cleavage of product from the support.

The invention of Cody offers the advantage that multiple reactions may be carried out simultaneously - even at reflux at atmospheric pressure conditions and while under an inert atmosphere, if necessary. However, the apparatus appears to be rather complex, bulky, awkward to use, fragile, and difficult to clean. The apparatus also is not very amenable to use with standard liquid handling systems and other batch-processing type equipment. Additionally, the apparatus is not well-suited for true microscale synthesis because the surface area of the components, particularly the gas dispersion tubes, is such that undesirable "hold-up" of liquid material is prone to occur.

Shown in an article by Meyers et al. entitled "Multiple simultaneous synthesis of phenolic libraries," Molecular Diversity, 1 (1995), pp. 13-20, is an apparatus for multiple, simultaneous (solid phase) synthesis that is considerably better suited to use with batch processing techniques. As described at p. 16 of the article (Fig. 4), Meyers uses a conventional "deep-well" multi-well plate in the standardized 96-well, 8 x 12 rectangular array format. Each well is modified by drilling a small hole in the well bottoms and then installing a filter frit in each well bottom. The deepwell plate is made to be liquid tight by sandwiching it between a clamping arrangement that utilizes a solid base element fitted with four threaded steel posts and a (open) frame element that sits on top of the plate and which is secured by knurl nuts. A planar rubber gasket, which rests on top of the base element, seals the openings at the bottoms of the wells, while the tops of the wells are sealed with 8-well strip caps (a total of twelve such strips would be required for sealing all of the wells). The invention provides that reactions may be carried out within the wells, with the solid support upon which the chemistry is conducted able to then be filtered and washed within the same wells by virtue of the fritted nature of the wells and the removable sealing means at the bottom.

As noted in Meyers, the 96-well format is ubiquitous and used in numerous applications. Meyers' invention is therefore theoretically able to be used in conjunction with automated high-throughput screens and many other types of equipment (e.g., multi-channel pipettors) that are based on that (standard) 96-well format. However, Meyers is limited in several respects. Perhaps most importantly, the sealing arrangement that is used for the bottom of the wells, i.e., the provision of a clamping frame about the periphery of a multi-well plate having a standard footprint, causes the apparatus to lose that footprint because the frame is naturally dimensionally larger than the multi-well plate. Thus, the multi-well plate with the bottom openings sealed (i.e., with the frame attached) cannot be fitted within the holders of such instruments as automated dispensing equipment that are designed to hold an object that is no larger than the size of the multi-well plate itself.

Another problem is that the outlets at the bottom of the wells are simply holes. There is no provision for a directing nozzle or other structure to be present at the bottom of each well that would enable effluent to properly drain into a collection multi-well plate. Cross-contamination and difficulty with collection into small diameter collecting vessels are highly likely with the Meyer's invention, especially during forced elution with a vacuum manifold.

Yet another problem is that there appears to be no provision made for heating of the contents of the wells. Since a "frame clamp" is used on top of the multi-well plate - "frame" indicating an open structure that rests about the perimeter of the top surface of the plate, there is nothing holding the strip-caps in place in the tops of the wells other than a friction fit. Accordingly, any significant expansion of solvent within the wells due to heating would force the caps off. Indeed, the only syntheses described in the article are carried out at 25 degrees C (i.e., room temperature).

Still another problem lies in the use of caps themselves. Although Meyers describes the use of caps that are in the form of "eight-well strip caps" (p. 15), this still necessitates the use of twelve such strips, the caps of each of which must be individually pressed into each well to secure a tight seal. In total, 96 caps must be manipulated and dealt with during performance of a reaction sequence involving all of the wells. Not only is this awkward generally, but cross-contamination may occur if material that is splashed onto the caps inadvertently drips into other wells, or when the caps, after temporary removal, are placed back on their respective wells. Further such caps do not function as a self-sealing gasket to allow the syringed introduction of liquid materials under an inert atmosphere.

Because of the limitations associated with presently available apparatus for multiple, simultaneous synthesis, a great need still exists for such apparatus which can be used on a micro scale, which is suitable for both solid phase synthesis and for organic synthesis generally, which may be used in conjunction with batch processing type equipment, and which is simple and convenient to use.

DISCLOSURE OF THE INVENTION

Accordingly, it is an object of the present invention to provide an apparatus for multiple simultaneous chemical and biological synthesis, chromatography, separation, extraction, analysis and cell culturing on a micro scale which is simple to use, and which is more efficient and inherently capable of a greater range of operations than has heretofore been possible.

It is another object of the invention to provide such an apparatus which is suitable for general organic synthesis, including provision for heating, agitation, addition by syringe, and the like.

It is a further object to provide such an apparatus which has a standard microplate dimension and which is compatible with standard liquid handling and other batch processing equipment.

It is another object to provide such an apparatus which has independently removable upper and lower covers for sealing of the tops and bottom of a multi-well container.

It is a further object to provide such an apparatus with independently removable covers capable of sealing the tops and/or bottoms of all of the wells of a multi-well container simultaneously.

It is yet another object to provide such an apparatus which has an expedient and integral filtration capability.

It is yet a further object to provide such an apparatus that is conveniently used with a vacuum manifold for assisted elution.

It is still another object of the present invention to provide a carrier apparatus that is capable of heating and agitating multiple ones of the synthesis apparatuses simultaneously.

Briefly, the preferred embodiment of the present invention is a multi-well synthesis and filtration apparatus for performing multiple, simultaneous chemical reactions on a micro scale. The synthesis apparatus is generally comprised of a deep-well synthesis block having a plurality of nozzle-equipped wells fitted with filter disks and dimensionally arrayed in a standard multi-well format, an upper cover, a lower cover, and a pair of first and second sheet gaskets. The synthesis block includes a skirt which protrudes about the periphery of the block at mid-level, the lateral extent of the protrusion being dimensionally approximately the same as a standard microplate footprint. The skirt provides a site for the independent attachment of the upper and the lower covers to the block via a plurality of clips which are present on the covers. The width and length of the covers are also dimensionally approximately the same as a standard microplate footprint. The first and second sheet gaskets are interposed between the upper and lower covers, respectively, whereupon the attachment of the covers provides for a tight clamping action to seal inlet portions and outlet spouts of the wells for various reaction and manipulative purposes. Apertures in the upper cover provide that the first gasket may be punctured for introduction of materials and/or maintenance of an inert atmosphere via syringe needle.

There is also provided an alternative embodiment of the synthesis block having wells that are double in volume compared to the first embodiment but which is able to use a multi-well collection plate of the same dimensional array. In this embodiment, there are half the number of wells as compared to the original embodiment, with the wells of a rectangular shape having double the width or diameter of the original wells, but with outlet spouts that depend from the block in an off-center fashion relative to the wells. The outlet spouts are situated so as to drain effluent into every other column of wells of the collection plate. A 180 degree turn of the recycled same block or a second block of the same design provides that the remaining columns of wells of the collection plate may be utilized. An inclined bottom surface portion provides that all liquid properly drains to the outlet spouts.

There is also provided an alternative synthesis apparatus which additionally includes a reinforcement assembly to improve the clamping action of the covers upon the synthesis block. The reinforcement assembly includes an upper collar, a lower collar, and a pair of finger screws. The collars fit about the synthesis block to opposably sandwich the skirt therebetween. The collars are held together by the finger screws and mating nuts which are present on the collars. The reinforcement assembly provides that the covers may be attached to the collars, rather than to the skirt directly, in order to spread the clamping force that is exerted.

Once a synthesis reaction has been carried out, a vacuum manifold apparatus is provided to forcibly elute liquid material from the wells as necessary for workup and washing. The manifold apparatus includes a base, a removable lid, a first gasket, a second gasket. The base has an open chamber sized to receive a collection plate and an outlet for applying a reduced pressure to the chamber. The lid has an open area bounded by a shelf. The first and second gaskets have a generally rectangular band shape such that the first gasket is interposable between the base top surface and the lid, and the second gasket is interposable between the shelf and the lower surface perimeter of the synthesis block. With the block located upon the shelf, thereby covering the open area of the lid, a vacuum can be created within the chamber to draw material from the wells and into the collection plate.

For actual performance of a synthesis reaction, a carrier apparatus and a modified incubator oven assembly are provided to enable agitation and heating of multiple ones of the synthesis blocks simultaneously. The carrier apparatus is generally comprised of a platform, a plurality of containment arm assemblies, and a rotation assembly. The platform is open and compartmentalized, and further has a dual-sided nature. The rotation assembly includes a shaft which extends from each end of the platform, one end of the shaft having an engagement head. An oven drive mechanism, which includes a slotted bearing cup to receive the engagement head, rotates the shaft. The synthesis apparatuses are held in cage-like fashion upon one or both sides of the platform during rotation by the containment arm assemblies. In the preferred embodiment, heating and agitation of as many as four of the synthesis apparatuses are permitted simultaneously.

An advantage of the present invention is that the upper and lower covers may be independently attached to and removed from the synthesis block as needed. Thus, for example, reagents and materials may be conveniently added to the wells by removal of a single (upper) cover. On the other hand, during such removal, leakage of material from the outlet spouts is prevented by the attached lower cover. A securely attached upper cover causes liquid material to be retained (by a partial vacuum effect) when the lower cover is removed for transfer of the synthesis block to a vacuum manifold for filtration, among many other examples of benefits provided by such an independent cover system.

Another advantage of the invention is that the provision of securely clampable upper and lower covers allows for heating of the wells (or vigorous agitation) without loss of solvent.

A further advantage is that the design of the synthesis block and cover arrangement provides for a footprint of the same size as a standard multi-well plate -- with respect to either the block alone, or the block when fully covered, thereby permitting use of standard liquid handling and other batch processing equipment.

Yet another advantage is that the sheet gasket arrangement and an upper cover which has apertures allows for introduction of materials via syringe and also for a gas inlet (via needle-equipped tubing) for provision of an inert atmosphere.

Yet a further advantage is that the synthesis block is integrally moldable, inexpensive, and disposable.

Still another advantage is that the use of individual filter frits, as compared to some prior art multi-well filtering arrangements which use a sandwiched filter sheet, prevents wicking and cross-contamination between wells.

These and other objects and advantages of the present invention will become clear to those skilled in the art in view of the description of the best presently known mode of carrying out the invention as described herein and as illustrated in the several figures of the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an exploded perspective view of the synthesis apparatus of one embodiment of the present invention;

Fig. 2 is a partially cutaway, side elevational view of the synthesis apparatus of Fig. 1;

Fig. 3 is a partially cutaway, side elevational view of the synthesis block of the present invention;

Fig. 3a is a cross-sectional view of an alternative tube bore;

Fig. 4 is a top plan view of the synthesis block of Fig. 3;

Fig. 5 is a bottom plan view of the synthesis block of Fig. 3;

Fig. 6 is a top plan view of an alternative synthesis block;

Fig. 7 is a partially cutaway, side elevational view of the alternative synthesis block of Fig. 6;

Fig. 8 is an exploded side elevational view of an alternative synthesis apparatus (now preferred);

Fig. 9 is a side elevational view of the alternative synthesis apparatus of Fig. 8;

Fig. 10 is a top view of the upper collar of the alternative synthesis apparatus of Fig. 8;

Fig. 11 is effectively a bottom view of the lower collar of the alternative synthesis apparatus of Fig. 8;

Fig. 12 is an exploded perspective view of the manifold apparatus and synthesis block of the present invention;

Fig. 13 is a partially transparent side elevational view of the manifold apparatus and synthesis block of Fig. 12;

Fig. 14 is a perspective view of the carrier apparatus of the present invention;

Fig. 15 is an end view of the loaded carrier apparatus of Fig. 14; and

Fig. 16 is a perspective view of the oven assembly of the present invention.

DESCRIPTION AND BEST MODE OF THE INVENTION

The preferred embodiment of the present invention is a combination multi-well synthesis and filtration apparatus for performing multiple, simultaneous chemical reactions and workups on a micro scale. The synthesis apparatus of the preferred embodiment is directed toward solid phase organic synthesis and is set forth in Figs. 1 and 2, where it is designated therein by the general reference character **10**.

Referring initially to the exploded perspective view of Fig. 1 and also to the side elevational view depicted in Fig. 2 of the drawings, the synthesis apparatus **10** is shown to be generally comprised of elements of three major types. Thus, present are a deep-well synthesis block **12**, an upper cover **14**, a lower cover **16**, and a pair of first and second sheet gaskets **18** and **20**, respectively, which are disposed between the covers (**14** and **16**) and the synthesis block **12** as indicated. By a tight clamping action of the upper and lower covers (**14** and **16**) upon the synthesis block **12** (see Fig. 2), these primary elements together effectively provide a multiplicity of micro-vessels for "one-pot" chemical reactions and workup procedures, as will be explained in greater detail below.

Continuing to refer to Fig. 1, with reference now also to the side elevational view of Fig. 3 of the drawings, the synthesis block **12** is shown to incorporate a block body **22**, a plurality of reaction wells **24**, and a laterally protruding skirt **26**. Each of the foregoing named elements are integrally fashioned together as a molded plastic piece. As the designated name suggests, the synthesis block **12** has a generally rectangular block shape.

As shown in Fig. 3, the skirt **26** is disposed midway about the portion of the periphery of the block body **22** that is vertically extending (i.e., the sides). For reference purposes only, the skirt **26** may be considered to "divide" the block body **22** into an upper block portion **30** and a lower block portion **32.** The upper block portion **30** includes what is denoted herein as a block body upper surface **34**, while the lower block portion **32** includes a block body lower surface **36.**

As also shown in the top and bottom elevational views of Figs. 4 and 5, respectively, the skirt **26** includes a number of vertically extending indented grooves or cutouts **37**. As will be described below, the skirt **26** and cutouts **37** provide the sites of attachment upon the synthesis block **12** for both the upper and the lower covers (**14** and **16**).

The reaction wells **24** are tubular structures which are vertically disposed within the block body **22** and, in the illustrated preferred embodiment, are arrayed in a rectangular, 8 x 12 format. Such a 96-well array, with specific (i.e., 9 mm) center-to-center spacing, has become a standard in the industry for various of the multi-well plates that are now generally available. The overall dimensional area of the synthesis block **12**, including the lateral extension of the skirt **26**, also provides for a footprint of the same size as these standard 96-well plates, thereby permitting interchangeable use of the synthesis block **12** with standard equipment holders, automated well washers and the like. It should be apparent, however, that the present invention might employ any of a variety of arrays other than an 8 x 12 format, and the array format need not even be rectangular. One such alternative array, which affords an additional unique capability, is described later below.

Referring to Fig. 3, each of the wells **24** includes as a primary element an inlet portion **38**, an outlet spout **40**, and a tube bore **42**, the length or height of the latter being determined from a well bottom **44** up and through the inlet portion **38** and to a well rim **46**. The inlet portion **38** extends upward from the block body upper surface **34**, while the outlet spout **40** depends from the block body lower surface **36**. Again, each of the inlet portion **38**, the outlet spout **40**, and the tube bore **42** are structures that are integrally fashioned together with the block body **22** during the molding or fabrication process.

Although in the primary drawing figures, the tube bores **42** are shown as having a cylindrical shape (i.e., a circular cross-section), it is expected that a tube bore **42** having a rounded square cross-sectional geometry will be employed and, indeed, may be favored (see Fig. 3a). Such a square container shape allows for a greater well volume as compared to a circular one. Rounding the corners of such a square container shape decreases undesirable wicking which would otherwise be prone to occur with internal corners that are acutely fashioned.

Continuing to refer to Fig. 3, each well bottom **44** is in flow-through communication with a respective discharge or outlet spout **40** and simultaneously provides a seat for a filter disk **48**. The filter disks **48** are circular frits made of glass or plastic which are press-fitted into each well bottom **44**. The filter disks **48** enable the wells **24** to have a resin-retaining ability during solid phase reaction synthesis and a filtration capability as necessary to elute solution and solvent from the resin support during subsequent work-up procedures.

Now also referring to Fig. 5, the outlet spouts **40** each include an orifice **50** and incorporate the well-known, slightly tapered "Luer-tip" shape that is suitable for attachment of standard laboratory syringe needle hubs. Such a needle attachment might be used, for example, where a smaller effluent orifice is desired for elution of a very small amount of solution from within the wells **24**, or where a cannulated type transfer of sensitive product-containing solution under an inert atmosphere is desired. Further, this nozzle shape provides a directed stream and prevents wicking and cross-contamination of eluted material.

In the illustrated embodiment of Figs. 1 and 4, the inlet portions **38** are seen to be delineated into square block-shaped structures and are separated from one another by a series of orthogonally intersecting rifts **52**. The rifts **52** are narrow voids that extend vertically from the block body upper surface **34** to the tops of the inlet portions **38**. These rifts **52** fulfill the important function of preventing liquid migration of solutions between the wells **24** in the event of spillage or jostling of the synthesis block **12** when the first sheet gasket **18** and upper cover **14** are not in place.

As shown in Fig. 3, the well rims **46** are presented at the top of the inlet portions **38** and comprise a distinct element. The well rims **46** have the appearance of a cylindrical tube shape of small height. This round, thin-walled shape tends to provide a better seal when the first sheet gasket **18** is pressed down upon the well rims **46** by the action of the upper cover **14**, as compared to a wider, planar surface which would be presented by the square block shape that comprises most of the inlet portion **38** were these well rims **46** not present.

It should be apparent that the entirety of the inlet portions **38** might in fact be round (or some other shape) and thin-walled such that a specially delineated well rim such as **46** would not be present, although there may be some loss of sturdiness.

Referring now to Figs. 6 and 7 of the drawings, there is provided an alternative synthesis block **412** which is fundamentally similar to the previously described synthesis block **12** but which provides for reaction wells **424** that are double in size compared to reaction wells **24**. However, the wells **424** are configured such that the block **412** not only retains the same footprint size as the block **12**, but is also able to use the same standard 96-well plate that is used with the block **12** for collection purposes (see more on the preferred collection technique later below). (In Figs. 6 and 7, to the extent those elements of the alternative synthesis block **412** are identical or substantially similar to those appearing in the first embodiment block **12**, those elements will be referred to by a reference number which incorporates the original reference number prefaced with the digit "4.")

The reaction wells **424**, are arrayed in a rectangular, 8 row x 6 column format, and, accordingly, total 48 in number. The wells **424** have inlet portions **438**, tube bores **442**, and well rims **446** which are all of a rectangular cross-sectional shape with a length that is approximately double the width (diameter) of the corresponding elements found in the wells **24**. (It would be apparent that the reaction wells **424** might have an oval tubular shape, as opposed to a rectangular one; this would decrease the well **424** volume obtainable for a given size of synthesis block **412**, however.)

Importantly, outlet spouts **440** depend from block body lower surface **436** in an off-center fashion relative to the tube bores **442**. In fact, the outlet spouts **440** are situated such that the spouts **440** of each column of wells **424** are capable of alignment with every other column of wells present in a standard 96-well plate. This means that during collection of the liquid material contained within the wells **424**, one synthesis block **412**, oriented with the outlet spouts **440** at the "left" side of the tube bores **442**, as shown in the drawings, can be caused to empty the contents of those wells **424** into the odd numbered columns of the wells of the multi-well plate used for collection. Subsequently, if desired, the contents of the wells **424** of an identical second synthesis block **412** (or the wells **424** of the first block **412** where the block has simply been reused) can be eluted into the even numbered columns of the wells of the same collection plate by simply turning the second block **412** 180 degrees (such that the outlet spouts **440** would now have the appearance of being situated at the "right" side of the tube bores **442**). The total eluted contents can then be conveniently manipulated and processed as necessary in the single collection plate. Thus, a mechanism has been provided by which reaction and analysis procedures can be carried out on a larger scale in the 48-well block **412** while employing the same collection equipment - including the same standard 96 multi-well plate - that is used with the 96-well block **12** (again, collection is detailed later below).

Referring now to the cross-sectional view of Fig. 7, so that the entire contents of each larger volume well **424** can be obtained upon elution, and more particularly in view of the off-set nature of the outlet spouts **440**, an angled or inclined bottom surface portion **53** is present to cause all of the liquid material present within the tube bores **442** to drain to well bottoms **444** and out of the outlet spouts **440** (a filter disk which would correspond to filter disk **48** is omitted from the drawing).

The synthesis block **12** (and including block **412**) of the embodiment **10** is integrally formed by conventional injection molding, with the preferred injection material being polypropylene plastic. It would be apparent that other molding processes, and machining, etc., are also viable production processes. It would also be apparent to one with ordinary skill in the art that the synthesis block **12** might be formed from other thermoplastics, e.g., Teflon®, and from other sufficiently inert materials such as glasses, metals, and other types of resins as well. The block **12** might also be made from a combination of materials permanently or removably joined or fitted together, e.g., glass for the wells **24** and plastic for the remainder of the block body **22**.

Referring again to Fig. 2, when it is desired that the wells **24** retain solution, i.e., that liquid not be permitted to flow out of the outlet spouts **40**, which will naturally be the case when the wells **24** are filled with solution and reagents for synthesis, the second sheet gasket **20**, in conjunction with the lower cover **16**, is used to simultaneously seal the orifices **48** of each of the outlet spouts **40**. (In this and the following descriptions, it is understood that synthesis block **412** might be interchangeably employed with block **12**.)

Likewise, and as also shown in Fig. 2, during syntheses in which the synthesis block **12** is subjected to agitation or rotation, as will virtually always be employed to achieve an efficient reaction process, and during heating of volatile solvents, the first sheet gasket **18**, in conjunction with the upper cover **14**, is used to simultaneously seal down upon the well rims **46** and thus prevent loss of liquid material from the tops of the wells **24**.

Referring to Fig. 1 in addition to Fig. 2 now, the upper cover **14** is shown to include a recessed top surface **54**, pairs of opposing vertical outer side surfaces **56** and outer end surfaces **57**, and a planar inner surface **58** (see Fig. 2). Correspondingly, the lower cover **16** includes a bottom surface **60**, pairs of opposing vertical outer side surfaces **62** and outer end surfaces **63**, and a planar inner surface **64**.

The inner surfaces (**58** and **64**) of the upper and lower covers (**14** and **16**) each extend into shallow recesses **65** and **67**, respectively. The recesses (**65** and **67**) provide that the first and second sheet gaskets (**18** and **20**) may be inserted therein in order to hold the sheet gaskets (**18** and **20**) in proper position with respect to the wells **24** for the aforementioned sealing purposes. The recesses (**65** and **67**) permit an easier manipulation of the covers (**14** and **16**) and sheet gaskets (**18** and **20**) upon the synthesis block **12** in general. It would be apparent that laterally projecting nubbles or other similarly intermittently overhanging structures might be used to retain the sheet gaskets (**18** and **20**) rather than the continuously fashioned recesses (**65** and **67**).

Still referring to Figs. 1 and 2, present upon each of the pairs of outer side and end surfaces (**56** and **57**, and **62** and **63**) of the upper and lower covers (**14** and **16**) are lockable latches or clips **66** and **68**, respectively. When the covers (**14** and **16**) are positioned on the synthesis block **12**, these clips (**66** and **68**) are situated so as to be in vertical alignment with the cutouts **37** that are present within the protruding skirt **26**. Thus, insertion of the clips **66** and **68** into the cutouts **37** (Fig. 2) ensures that the covers (**14** and **16**) are properly aligned when attached to the synthesis block **12**. As shown, the clips (**66** and **68**) (and cutouts **37**) are located in an offset fashion such that the clips **66** of the upper cover **14** do not interfere with the clips **68** of the lower cover **16** when both are latched onto the skirt **26**.

It would be apparent that, rather than employing cutouts **37**, tab-type structures located on the skirt **26** could be employed onto which a suitable type of clip could be latched. It would also be apparent that an arrangement other than a continuous skirt **26** might be used for attachment of the clips (**66** and **68**). Individual, distinct structures protruding about the periphery of the synthesis block **12** might simply be used ("periphery" meaning at least either the sides of the synthesis block **12**, upon which the skirt **26** is presently located, and/or the perimeters of the block body upper and lower surfaces (**34** and **36**)). Further, an offset clip arrangement can be avoided by incorporating two levels of such skirts or protruding structures, or by locating cutouts for a slightly modified type of clip in the sides of a single skirt such as skirt **26**, etc.

When the clips (**66** and **68**) are latched upon the skirt **26**, a secure attachment of the upper and lower covers (**14** and **16**) upon the synthesis block **12** is achieved. This attachment provides a liquid tight seal because of the tight sandwiching of the first and second sheet gaskets (**18** and **20**) between the upper and lower covers (**14** and **16**) and the well rims **46** and outlet spouts **40**, respectively. The seal is sufficient to allow for agitation or inversion of the synthesis apparatus **10** and moderate heating of volatile solvents without loss of liquid material.

Importantly, the employment of the skirt **26** as an attachment site provides that the two covers (**14** and **16**) may be independently removed from the synthesis block **12** as necessary for reaction purposes and workup, as opposed, for example, to a threaded rod-type clamping arrangement of such covers (**14** and **16**) in which the same clamping means would be used to hold the two covers (**14** and **16**) simultaneously onto such a container as the block **12** and whereby the versatility of the apparatus **10** afforded by independently removable covers (**14** and **16**) might otherwise be limited. Again, other attachment structures for a clip or related fastening device could serve to provide for the novel ability of the present invention to allow for such independent cover removal.

Additionally, the design also provides that the two covers (**14** and **16**) may each have a footprint that is dimensionally the same as a standard multi-well microplate and with no interfering structures to prevent placement of the synthesis block **12** with the covers (**14** and **16**) attached into the holders of automated equipment designed for standard microplates.

With continued reference to Figs. 1 and 2, it will be noted that the upper cover **14** includes, in addition, an array of uniformly spaced perforations or holes **70** which extend completely through the cover **14** and open onto both of the top and inner surfaces (**54** and **58**). The holes **70** are arrayed so as to permit axial alignment with the wells **24**. As shown in the cut-away aspect of Fig. 2, the holes **70** are tapered top to bottom.

The holes **70** allow for the introduction (and/or removal) via syringe of reagents and liquid materials as necessary to perform the particular synthesis or procedure. The needle of a syringe simply enters the upper cover **14** through a hole **70** and penetrates the first sheet gasket **18** whereupon the syringe needle is located within a well **24** and liquid material can then be dispensed (or decanted). The tapered design of the holes **70** helps insure that the syringe needle does not stray and miss entry into the desired well **24**. The holes **70** also allow for the provision of introduction and/or maintenance of an inert atmosphere via needle-fitted tubing drawing from a nitrogen gas or argon gas source.

The covers (**14** and **16**) are made of high strength, anodized aluminum alloy, but other sturdy, non-corrosive materials suitable for laboratory environs, such as stainless steel, may be employed as well. The first and second sheet gaskets (**18** and **20**) are made of the chemical resistant rubber materials as are well known to be used for forming septa for sealing the round-bottomed and Erlenmeyer flasks and other containers commonly used by researchers, e.g., Viton® and Santoprene®. The nature of this rubber material provides that upon puncturing and withdraw of a syringe needle, a sufficiently good seal for most reaction purposes is still maintained despite the puncturing. Such rubber materials may also be in the form of laminates as well.

Referring now to Figs. 8, 9, 10 and 11 of the drawings, there is provided an alternative synthesis apparatus **300** which is now actually most preferred. The alternative synthesis apparatus **300** is very similar to the previously described synthesis apparatus **10**, but additionally includes a reinforcement assembly **372** to improve the clamping action of the covers (**314** and **316**) upon the synthesis block **312** in order to better prevent leakage or escape of solvent.

(In Figs. 8-11, to the extent those elements of the alternative synthesis apparatus **300** are identical or substantially similar to those appearing in the original embodiment **10**, those elements will be referred to by a reference number which incorporates the original reference number prefaced with the digit "3.")

With reference to the exploded side elevational view of Fig. 8 and also the side elevational view of Fig. 9, the reinforcement assembly **372** includes an upper collar **374**, a lower collar **376**, and a pair of finger screws **378**. The upper and lower collars (**374** and **376**) are identical, except that the lower collar **376** further includes a pair of stationary nuts **380** for tightenably receiving the finger screws **378**. The interaction of the finger screws **378** and nuts **380** is described below. (As shown in the views of Figs. 10 and 11, each collar (**374** and **376**) also includes a cutout **381**, which is used for alignment purposes to make more obvious the assembly of the components of the apparatus **310**. Thus, in this respect, the collars (**374** and **376**) bear a mirror image relation to one another as opposed to an identical one.)

Each collar (**374** and **376**) includes a collar body **382** in the form of a flat, substantially rectangular portion having a large central open area sized to closely receive and fit about the upper and lower block portions (**330** and **332**) of the synthesis block **312**. Each collar body **382** includes a pair of opposing sides **384** and ends **386**. In use, the collar bodies **382** flushly contact either an upper or lower skirt surface (**339** or **341**), as the case may be, and have a footprint (i.e., perimeter and inner edge outlines) to match those surfaces (**339** and **341**).

Located at the perimeter edges of each collar body **382**, and integrally formed therewith, are six catch support members **388** which are formed to extend in a unidirectional orthogonal orientation relative to the plane defined by the collar body **382**. Two pairs of catch support members **388** are located at the sides **384** while one pair is located at the ends **386**. As between the two sides **384** or the two ends **386**, the catch support members **388** bear a facing, offset relation. As between each upper and lower collar (**374** and **376**), the catch support members **388** are also located in an offset fashion so as not to interfere with one another when both collars (**374** and **376**) are attached to the skirt **326** and to the covers (**314** and **316**) as will be described. (Note: In Fig. 8, the catch support members **388** and corresponding cover portions located on the far side of the drawing are omitted for clarity.)

Located at the inner edge of each collar body **382**, and also integrally formed therewith, are four flanges **390** which are similarly formed to extend in a unidirectional orthogonal orientation relative to the plane of the collar body **382**, but on an opposite side of the plane from the catch support members **388**. Each flange **390** spans most of the length of the associated side **384** or end **386** and provides resistance to bending and deformation and generally makes the collars (**374** and **376**) more rigid.

Extending orthogonally from each end **386**, but this time co-planar with the collar body **382**, is additionally present an integral extension formation **392**. Each extension formation **392** includes a centrally located aperture **394**. It is upon the extension formations **392** of the lower collar **376**, and in alignment with those **394** apertures, then, that are present the aforementioned nuts **380**. In the preferred embodiment **310**, the nuts **380** are attached to the extension formations **392** by electrical induction welding. It would be apparent that an integral nut-like structure might also be provided where the extension formations **392** were made to be thicker (i.e., the extension formations **392** themselves might be tapped to provide a threaded nut structure).

When the collars (**374** and **376**) are placed about the upper and lower block portions (**330** and **332**) of the synthesis block **312** as shown, the apertures **394** of the upper collar **374** are caused to be in axial alignment with the apertures **394** of the lower collar **376**. Thus, a threaded end **396** of each finger screw **378** is able to be inserted simultaneously through those aligned apertures **394** and screwed into the stationary nuts **380**. A knurled head **398** of the finger screw **378** is too large to pass through the apertures **394** and so is retained atop the extension formations **392** of the upper collar **374**. In this manner, the collars (**374** and **376**) can be tightened together upon the upper and lower surfaces (**339** and **341**) of the skirt **326**. The attachment of the reinforcement assembly **372** to the synthesis block **312** provides that the collars (**374** and **376**)

- especially the lower collar **376** - will remain conveniently in place during latching and removal of the covers (**314** and **316**), as will be further described.

It would be apparent that a number of other attachment designs could be used to hold the collars (**374** and **376**) in place upon the synthesis block **312**. For example, a latching arrangement, similar to that as will be further described for attachment of the covers (**314** and **316**) to the reinforcement assembly **372** itself, might also be used. Thus it is not intended that the attachment manner be limited to a screw and nut arrangement.

Moreover, and analogous to what was previously described with respect to alternative sites for attachment of the covers (**14** and **16**) in the unreinforced embodiment **10**, the reinforcement assembly **372** might not be attached to the side periphery of the synthesis block **312** (e.g., to the skirt **326**), but rather to the periphery constituted by the perimeters of the block body upper and lower surfaces (**334** and **336**). That is to say, similar collars to **374** and **376** would rest upon those upper and lower surfaces (**334** and **336**). This would require longer screws or threaded rods (of the finger type, such as **378**, or otherwise) to extend between such collars in order to hold them onto the block **312**. Alternatively, an independent manner of affixing such collars could be used. For example, screws for each such collar could be screwed directly into the block body **322** as opposed to their extending between those collars. In any event, the covers (**314** and **316**) would then be attached in an independent fashion to collars (similar to **374** and **376**, or otherwise) which are themselves independently held in place.

As the designated name would imply, each catch support member **388** provides a situs for attachment of a catch element **396**. These catch elements **396** take the place of the previously mentioned cutouts **37** present in the skirt **26** of the earlier described synthesis block **12**. In the preferred embodiment, the catch elements **396** are attached to the catch support members **388** using rivets **398**. It should be noted at this point that the skirt **326** of the synthesis block **312** of the alternative embodiment **310** does not include the cutouts **37**, which are made unnecessary by embodiment **310**, but rather has a solid form.

When assembled as indicated in Figs. 8 and 9, the catch elements **396** of the upper collar **374** are in vertical alignment with the fastening clips **368** of the lower cover **316**. Conversely, the catch elements **396** of the lower collar **376** are in vertical alignment with the fastening clips **366** of the upper cover **314**. (In the alternative embodiment **310**, it will be noted that there have been provided two additional pairs of clips (**366** and **368**) and catch elements **396** to further enhance the sealing capability of the invention.) Thus, for sealing purposes, the clips (**366** and **368**) are latched onto the catch support members **388** as opposed to a direct attachment upon the skirt **326**.

In the case of the earlier described embodiment **10**, it was observed that the portion of the skirt **26** in close proximity to the plastic cutouts **37**, and into which the clips (**66** and **68**) of the covers (**14** and **16**) are inserted for latching, would sometimes deform sufficiently during certain operations (e.g., heating at elevated temperatures) to prevent a tight seal of the sheet gaskets (**18** and **20**) and covers (**14** and **16**) upon the well rims **46** and outlet spouts **40** (please refer to the earlier drawing figures). In the alternative embodiment **310**, no deformation of the skirt **326** occurs because the attachment of the covers (**314** and **316**) to the skirt **326** occurs indirectly via the collar bodies **382**. The force of the clamping is distributed evenly and in a neutralizing fashion upon substantially the entirety of the upper and lower surfaces (**339** and **341**) of the skirt **326**.

Importantly, the reinforcement assembly **372** still maintains what is assertedly a novel aspect of significant importance to the present invention, namely, the capability to independently remove the upper and lower covers (**314** and **316**) to maintain a seal upon either or both of the well rims **346** and outlet spouts **340** for reagent addition, solvent removal, etc., as needed.

It would be apparent that a skirt **326** might be provided which is of itself made of metal, or otherwise reinforced with metal such that deformation of a plastic portion would not occur. The design of the reinforcement assembly **372** as provided, however, offers the advantage that the synthesis block **312**, which is intended to be disposable (or at least not infinitely reusable), may be discarded without also discarding an expensive metal component.

In the alternative embodiment **310**, the components similar to those previously described are constructed from the same materials, with the collars (**374** and **376**) being fashioned from heavy gauge stainless steel sheet metal using conventional stamping and forming techniques.

Once a synthesis reaction or step has been carried out and it is desired that solvent be eluted from the wells or that some other filtration operation carried out, a vacuum manifold apparatus **100** is further provided for complimentary use with the synthesis apparatus **10** (understood also to include the alternative embodiment **310** from this point on).

Referring now to the exploded perspective view in Fig. 12 of the drawings, the manifold apparatus **100** is shown to be generally comprised of a base **102**, an open area lid **104**, a first gasket **106**, and a second gasket **108**. Unlike the first and second sheet gaskets (**18** and **20**) of the synthesis apparatus, the first and second gaskets (**106** and **108**) of the manifold apparatus **100** each have a continuous rectangular band shape with a large rectangular open area, with the second gasket **108** being more narrow in width than the first gasket **106**. Similar to the synthesis apparatus **10**, an attachment method is used in which the lid **104** is clipped onto the base **102**, with the first gasket **106** being sandwichedly interposed therebetween.

The base **102** has a rectangular box-like shape and includes opposing pairs of side walls **110** and end walls **112**, and a bottom **114**. Located at the top of the four walls (**110** and **112**) is a continuous planar lip **116** which provides a support for the first gasket **106** and the lid **104**. Present on the outside of each of the side and end walls (**110** and **112**) are clips **118** which are similar to the clips (**66** and **68**) of the synthesis apparatus **10**. A threaded aperture or outlet **120** for a tube fitting **121** (see Fig. 13) is located within one end wall **112**, near the bottom **114**, for connection to a vacuum source (not shown).

Although not depicted, for easy alignment of the gasket **106** and lid **104** upon the lip **116**, the lip **116** may be provided with a number of vertically protruding alignment pins (or similar structures), and the gasket **106** and lid

104 provided with corresponding apertures or cutouts which are mateably received by those pins.

Referring also now to the partially transparent view of Fig. 13, the base **102** has an interior space or chamber **122** (see Fig. 12) sized to accommodate a collection plate **123** of a dimensional area and array that is typical for a 96-well plate. The collection plate **123** may be of the deepwell variety as shown or it may be a smaller micro plate placed atop a support of appropriate height in order that effluent may be neatly received by the collection plate **123** during elution of solvent from the wells **24**.

As shown in Figs. 12 and 13, the lid **104** has a rectangular shape to match that of the base **102**. The lid **104** includes a planar underside **124**, pairs of opposing side surfaces **126** and end surfaces **127**, an upper surface **128**, and a rectangular open area **130**. Included on the side and end surfaces (**126** and **127**) are strike or catch elements **131** which are in vertical alignment with the clips **118** of the base **102**. The catch elements **131** and clips **116** together permit a secure fastening of the lid **104** upon the base **102** after the collection plate **123** has been placed within the base **102** and the first gasket **106** positioned upon the lip **116**.

Along the perimeter of the open area **120** of the lid **104** is present a narrow ledge or shelf **132** which is vertically recessed from the upper surface **126**. The open area **128** is sufficiently large to accept the lower block portion **32** of the synthesis block **12**, while the shelf **132** functions as a stop for the synthesis block **12** by providing a support upon which the block body lower surface **36** may rest. The second gasket **108** is interposed between the shelf **132** and the perimeter of the block body lower surface **36** to enable a hermetic seal therebetween.

Not shown is that the lid **104** might also be made of two halves each having planar surfaces fittable one on top of the other in order to be capable of sandwiching a gasket similar to gasket **108** - but having a greater width - therebetween. The wider gasket would extend from the shelf **132** to in between the two lid halves to be compressibly retained about the gasket perimeter. The retention causes the portion of the gasket present upon the shelf **132** to be properly seated at all times, whereas the narrower gasket **108** may, when not careful, be inadvertently dislodged.

As shown in Fig. 13, with the lid **104** in place atop the first gasket **106** and lip **112**, and the synthesis block **12** in position atop the second gasket **108** and shelf **132**, a vacuum tight chamber is created in which a pressure differential may be applied by a vacuum source via the outlet **120** and tube fitting **121** to forcibly elute any liquid contained in the wells **24** through the filter disks **48** and into the wells of the collection plate **123**. (As noted previously, in the case of synthesis block embodiment **412**, the elutions will occur into alternating columns of the wells of the collection plate **123/423**.)

It should be noted that a simplified manifold apparatus **100** might also be designed in which only a base portion **102** is present with no lid **104** and supporting shelf **130**. However, such would require that the synthesis block **12** have a greater than standard footprint size in order that the synthesis block **12** might span the extents between the side and end walls (**110** and **112**) of the base **102**. As mentioned previously, the employment of a standard footprint size for the synthesis block **12** (and upper and lower covers (**14** and **16**)) enables the block **12** (whether covered or uncovered) to be used in a number of automated operations in which standard sized holders are also employed.

For actual performance of a synthesis reaction, a carrier apparatus and a modified oven assembly are provided to enable convenient agitation and heating of the contents of multiple ones of the synthesis blocks **12** simultaneously. Shown in Fig. 14, and designated therein by the reference number **200**, is one of a variety of possible embodiments of the carrier apparatus. As will be described later, the carrier apparatus **200** is used in combination with the oven assembly **202** shown in Fig. 16 and is removably located therein.

Referring now to the perspective view in Fig. 14 of the drawings, in which the carrier apparatus **200** has been separated from oven assembly **202** (as will typically be done for loading of the synthesis blocks **12** therein), the carrier apparatus **200** is seen to be generally comprised of a tray **204**, a plurality of containment arm assemblies **206**, and a rotation assembly **208**. It will become evident that each of these components may have a design and appearance substantially different from that depicted and still perform the novel function, as explained below, to which they are concertedly directed.

The tray **204** as shown has a compartmentalized rectangular box-like shape and includes a platform **210**, and pairs of opposing side walls **212** and end walls **214**. The platform **210** is comprised of a number of contiguous ledges **216** which are present about the platform **210** perimeter and a crosspiece **218** which spans the median width of the platform **210**. Open areas **220** within the platform **210** reduce the amount of material comprising the carrier apparatus **200** and, more importantly, allow for a more uniform heat distribution about the synthesis apparatuses **10** when such are in place upon the platform **210** and heating is occurring within the oven assembly **202**. Towards these ends, it will be apparent that the crosspiece **218** might also be eliminated.

Still referring to Fig. 14, the two ledges **216** which are present along the end walls **214**, together with the crosspiece **218**, each include bores or apertures **222**, **224**, and **226**, respectively, which extend horizontally therethrough. These apertures (**222**, **224**, and **226**) are present in an in-line fashion for receipt and mounting of the rotation assembly **208**. As will be described shortly, the attachment of the rotation assembly **208** permits the carrier apparatus **200** to be rotated within the oven assembly **202** so that the contents of the synthesis apparatuses **10** may be agitated and mixed during heating.

The side walls **212** and end walls **214** of the platform **210**, together with separators **228**, assist in lateral containment and further define two compartmentalized spaces for the location of two of the synthesis apparatuses **10**. The tray **204** actually has a symmetrical, dual-sided nature. That is, the tray **204**, including the platform **210**, has the same appearance as shown as when the carrier apparatus **200** has been inverted (rotated) 180 degrees from the orientation of Fig. 12. Thus, and referring now to the transparent end view shown in Fig. 15, two synthesis apparatuses **10** (the alternative embodiment **310** is actually depicted) may be placed upon each side of the platform **210** to permit heating and agitation of as many as four of the synthesis apparatuses **10** simultaneously.

The synthesis apparatuses **10** are held in cage-like fashion upon one or both sides of the platform **210** during rotation by the four containment arm assemblies **206**. As shown in Fig. 12, each containment arm assembly **206** includes a clasp arm **230** having a first end **232** and a second end **234**. The clasp arm **230** is hingedly connected at the first end **232** to a first upright extension portion **236** via a hinge joint **238**. When lowered to the horizontal position (as three of the clasp arms **230** are depicted in Fig. 14), the second end **234** is caused to rest upon a second upright extension portion **240**. The second upright extension portion **240** is provided with a clip type latch **242**, while upon the clasp arm **230** there is present a corresponding catch **244** so that the clasp arm **232** may be securely fastened to the second upright extension portion **240**.

In the preferred embodiment, the clasp arms **232** are contoured such that a depending or protruding portion **246** may be inserted into the upper cover **14** of a synthesis apparatus **10**, the upper cover **14** having a recessed top surface **54**, as noted previously, which allows such insertion. Thus, the clasp arms **230** provide some measure of lateral containment and stability during rotation in addition to the primary vertical containment which is afforded.

With continued reference to Fig. 14, the rotation assembly **208** is seen to include a carrier shaft **248** of typical rod-like appearance with a first end **250** and a second end **252**. An engagement head **254** is located at the second end **252** and includes a pin **256** which projects therefrom. A pair of retention collars **258** are mounted upon the outside of each of the end walls **214** of the tray **204** to enable secure attachment of the carrier shaft **248** to the tray **204**.

During assembly of the carrier apparatus **200**, the first end **250** of the carrier shaft **248** is inserted through the apertures **222**, **224**, and **226**, and the carrier shaft **248** is made to be immobile relative to the tray **204** with a set screw **260** located within each retention collar **258**. The arrangement provides that any rotation of the carrier shaft **248** about a rotation axis **261** also causes rotation of the tray **204** therewith. Thus, the carrier shaft **248** is not free to rotate irrespective of the tray **204**.

As previously stated, the components comprising the carrier apparatus **200** may take a number of forms in order to provide the function of providing an efficient housing for rotation of multiple ones of the synthesis apparatuses **10** inside of the oven apparatus **202**. (Most apparent, of course, is that a carrier apparatus such as **200** may be designed to hold any number of synthesis apparatuses **10**, and not just four as shown.)

The tray **204**, for example, need not have a platform **210** of the particular appearance depicted. A suitable "platform" might be comprised of but a single narrow "crosspiece" that would extend longitudinally in the direction of what is presently shown (in Fig. 14) as the two end walls **214**. From this longitudinally extending platform could then be attached the containment arm assemblies **206** via horizontal extension portions perpendicularly attached to the platform. Side walls and end walls such as **212** and **214** may be absent altogether.

It is also apparent, for example, that only two containment arm assemblies such as **206** might be present wherein those containment assemblies would be mounted to provide that a longer clasp arm having a length of that of the tray **204**, rather than that of the tray **204** width, would be utilized. This longer clasp arm would be contoured to have two protruding sections for insertion into two of the synthesis apparatuses **10**, and would extend between comparable first and second upright extension portions mounted in the location of the end walls **214** as opposed to the side walls **212** as presently depicted.

It is further apparent that the containment arm assemblies **206** need not be comprised of the particular combination of elements depicted, or even be used at all. For example, rather than the combination of elements shown, a simpler latching arrangement might be used in which a large, arcuate wire-type clip is mounted upon one side wall **212** to bear down upon a synthesis apparatuses **10** with a correlating catch on the opposing side wall for attachment thereto.

With regard to the rotation assembly **208**, it would be apparent that a carrier shaft **248** of the length depicted need not be utilized. That is, rather than a single long shaft **248** which passes through the entire length of the tray **204**, two shorter shaft portions might be utilized which extend outward only from the end walls **214**.

Referring now to the perspective view of Fig. 16, the oven assembly **202** within which the carrier apparatus **200** is caused to be rotated is primarily conventional in nature and includes an oven body **262** and a windowed oven door **264**. A pair of opposing first and second side walls **266** and **268**, respectively, are insulated, as is the remainder of the oven body **262** and the oven door **264.** A drive motor **270** delivers rotational force through a drive linkage **272** to an abbreviated drive shaft **274**. A control panel **276** includes a number of controls to adjust such factors as the oven temperature, rotation speed, and power on and off. Such a control panel as **276** may also be provided remotely from the oven body **262** (e.g., with an electrical tether) to reduce the likelihood of spark ignition. Vacuum and gas inlets **278** and **280**, respectively, are also present to provide for an inert atmosphere capability.

An interior cavity **282** is defined by the oven body **262** and the oven door **264** and is suitably large enough such that the carrier assembly **200** may rotate within the interior cavity **282** about the rotation axis **261** without interference. The manner in which the carrier assembly **200** is attached within the interior cavity **282** in order to accomplish such rotation now follows.

With continued reference to Fig. 16, and especially to the close-up partial views depicted therein, the drive shaft **274**, which extends horizontally a short distance into the interior cavity **282** from the second side wall **268**, is provided with a fixed bearing cup **284**. The bearing cup **284** includes a hollow chamber **286** having a plurality of slots **287** within which the engagement head **254** and pin **256** of the carrier shaft **248** are capable of being received. The chamber **286** and any one of the slots **287** provides a form of key hole, with the engagement head **254** and protruding pin **256** being inserted in key-like fashion so that the carrier shaft **248** may be supported and caused to rotate as the drive shaft **274** is turned.

In-line with the drive shaft **274** and extending into the interior cavity **282** from the opposing first side wall **266** is a bearing seat **288** which offers support for the first end **250** of the carrier shaft **248**. The bearing seat **280** has the form of a shaft with a depression **290** suitably sized so that the carrier shaft **248** may be supportably cradled therein as the carrier shaft **248** rotates.

The arrangement described provides that the carrier apparatus **200** is rotated about the rotation axis **261** while still being removable as necessary to give convenient access to the synthesis apparatuses **200** carried thereby.

It would be apparent that a multitude of other rotation interfaces might be used as well, including such interfaces as might provide for a carrier apparatus **200** that is fixed within the interior cavity **282**. Any number of rotational force transfer systems might also be used in conjunction with the drive motor **270**, including geared, sprocket and chain, etc.

In addition to the above mentioned examples, it is to be understood that various other modifications and alterations with regard to the types of materials used, their method of joining and attachment, and the shapes, dimensions and orientations of the components as described may be made without departing from the invention. Accordingly, the above disclosure is not to be considered as limiting and the appended claims are to interpreted as encompassing the entire spirit and scope of the invention.

INDUSTRIAL APPLICABILITY

The synthesis apparatus **10** (and still including the alternative embodiments **310** and **412**) of the present invention is designed to be used for any chemical synthesis procedure in which it is expedient that numerous, individual micro-scale reactions occur simultaneously and where filtration may be a necessary step during the synthesis process or workup procedure. The synthesis block **12**, in conjunction with the manifold apparatus **100**, also finds use for multiple, simultaneous micro-scale chromatographic purifications (and workups/extractions), as described below. Non-chemistry related uses include parallel culturing of microorganisms, particularly anaerobic organisms, among other uses.

The synthesis apparatus **10** will be found to be especially useful with respect to solid phase organic synthesis where chemical linkers and starting structures are bound to polymer resin supports in order to permit chemical coupling or transformation in that conveniently bound form. The synthesis apparatus **10** is similarly expected to find use in myriad other chemical syntheses in which a heterogenous reaction mixture is present due to insoluble salts or resins, such as might be employed for catalysis, and/or where precipitated by-products or end-products are anticipated, and wherein filtration is also necessary at some point in a reaction process.

As noted, a further use of the synthesis and manifold apparatuses (**10** and **100**) is for purification purposes. Thus, each well **24** may serve as a miniature column for chromatographic purification of chemical mixtures on silica gel, alumina, and various affinity resins as are commonly employed in the art of column chromatography. Depending on the difficulty of the separation contemplated, elution of the chromatography solvent might be gravity-wise or elution may be assisted with a reduced pressure via the manifold apparatus **110**. The invention (**10** and **100**) may also be used for simple ion exchange resin purposes and solid phase extraction as well.

Use of the synthesis and manifold apparatuses (**10** and **100**) is simple. A typical solid phase synthesis procedure might be as follows: The outlet spouts **40** of the wells **24** are sealed by placing the second sheet gasket **20** within the lower cover **16** and then clipping the lower cover **16** and sheet gasket **20** onto the synthesis block **12**. (In the case of the alternative embodiment **310**, the reinforcement assembly **372** will have first been attached to the skirt **26** of the synthesis block **312** and then the lower cover **316** clipped onto the upper collar **374** - rather than onto the synthesis block **312** itself.) The resin-bound starting chemical structure, solvent, and any air-stable reagents are then added to any number or all of the wells **24** using, for example, a multichannel pipette.

The first gasket sheet **18** and upper cover **14** are then clipped upon the synthesis block **12** (or the lower collar **376** in the case of embodiment **310**) to seal the tops of the wells **24**. Air-sensitive reagents may then be safely added via syringe through the holes **70** of the upper cover **14**. (Provision of an inert atmosphere and pressure equalization with an inert gas inlet tube and needle may or may not be required.) The synthesis apparatus **10** is then subjected to agitation and also heat treatment, as required, using the carrier apparatus **200** and associated oven assembly **202**.

Use of the carrier apparatus **202** and associated oven assembly **202** is also simple. One or two of the synthesis apparatuses **10** are placed upon one side of the platform **210** of the carrier apparatus **200** and the appropriate clasp arms **230** are latched in place. The carrier apparatus **200** is then inverted and up to two (for the embodiment shown) additional synthesis apparatuses **10** are placed on the second side of the platform **210** and the corresponding clasp arms **230** are again latched.

The carrier apparatus **200** is then transferred to the oven assembly **202**. The engagement head **254** is first inserted within the bearing cup **284** and the first end **250** of the carrier shaft **248** laid within the bearing seat **288**. The oven door **264** is closed and rotation and heating is commenced for the time period necessary.

Upon completion of the particular reaction step or synthesis, and after removal from the oven assembly **202** and carrier apparatus **200**, the synthesis apparatus **10** is inverted so that the lower cover **16** and second sheet gasket **20** may be removed, the independent cover removal system providing that the upper cover **14** remains tightly in place. With the collection plate **123** positioned within the manifold apparatus **100** as previously described, the manifold apparatus **100** is inverted and placed over the synthesis block **12** so that the collection plate **123** is caused to be placed over the outlet spouts **40** and the synthesis block **12** is caused to be placed within the open area **128** and upon the shelf **130** of the lid **104**. The combined assembly is then turned right side up. Alternatively, in the case of many solvents, the liquid contents are sufficiently held back by a partial vacuum due to the tops of the wells **24** remaining sealed such that the inversion procedure is not necessary to prevent escape of material from the orifices **48** of the wells **24** as the synthesis block **12** is simply placed directly over the collection plate **123** after removal of the bottom cover **16**.

The upper cover **14** and first sheet gasket **18** are then removed and a vacuum is applied as necessary. Solvent is typically used to rinse the resin support, and any washings or product-containing effluent drains neatly into the collection plate **123**.

In some instances, it may be desired not to use a vacuum method for elution of the liquid contained within the wells **24**, in which case centrifugation (e.g., "swinging bucket") and pressurization methods might be used.

The described synthesis and manifold apparatuses (**10** and **100**), and the associated carrier apparatus **200** and oven assembly **202**, enable the researcher to be more efficient and permit, for example, the rapid simultaneous synthesis of numerous analogs of a particular chemical compound to speed submission of samples for biological testing and evaluation in the pharmaceutical field.

For the foregoing reason, and for numerous others as set forth previously herein, it is expected that the industrial applicability and commercial utility of the present invention will be extensive and long lasting.

IN THE CLAIMS

What is claimed is:

1. An apparatus for multiple, simultaneous synthesis, comprising:

a synthesis block, said synthesis block including a plurality of wells arranged in ordered array, each well having an inlet portion and an outlet spout, said synthesis block further having a periphery;

a first sheet gasket sealable upon the inlet portions;

a second sheet gasket sealable upon the outlet spouts;

an upper cover for pressured engagement with said first sheet gasket;

a lower cover for pressured engagement with said second sheet gasket; and

attachment means for releasably and independently attaching each one of said upper and lower covers to said periphery.

2. The apparatus of claim 1 wherein:

each well further includes a well bottom in fluid communication with the outlet spouts, and a filter element, the filter element seated upon the well bottom.

3. The apparatus of claim 1 wherein:

said upper cover includes a plurality of apertures in axial alignment with the wells.

4. The apparatus of claim 1 wherein:

said attachment means includes said synthesis block having at least one protruding structure located on the periphery for attachment of said upper and lower covers.

5. The apparatus of claim 4 wherein:

there is one such protruding structure in the nature of a laterally extending skirt, the skirt being continuous about the periphery.

6. The apparatus of claim 4 wherein:

said attachment means further includes each of said upper and lower covers having a plurality of clips for latching onto the at least one protruding structure.

7. The apparatus of claim 4 wherein:

said attachment means further includes a reinforcement assembly having an upper collar and a lower collar for opposable sandwiching of the at least one protruding structure, said upper and lower covers attached to the collars.

8. The apparatus of claim 7 wherein:

the reinforcement assembly further includes holding means for removably holding the upper and lower collars upon the at least one protruding structure.

9. The apparatus of claim 8 wherein:

the holding means includes a plurality of finger screws.

10. The apparatus of claim 1 further including:

a manifold apparatus and said synthesis block further having a block body lower surface, the manifold apparatus including a base, a removable lid, a first gasket, a second gasket, and means for securing the lid to the base, the base having an open chamber sized to receive a collection plate, a top surface, and an outlet for applying a reduced pressure to the chamber, the lid having an open area bounded by a shelf, the first and second gaskets having a generally rectangular band shape, the first gasket interposable between the base top surface and the lid, the second gasket interposable between the shelf and the block body lower surface.

11. The apparatus of claim 1 further including:

agitation means for agitating at least one of said synthesis blocks with said upper and lower covers attached.

12. The apparatus of claim 11 wherein:

said agitation means includes a carrier apparatus, the carrier apparatus including a platform, the platform sized to receive the at least one covered synthesis block, retaining means for retaining the at least one covered synthesis block upon the platform, at least one shaft affixed to the platform and extending planarly therefrom, and rotational drive means for turning the shaft.

13. An apparatus for multiple, simultaneous synthesis, comprising:

a synthesis block, said synthesis block including a plurality of wells arranged in ordered array, each well having an inlet portion and an outlet spout, said synthesis block further having a periphery;

a first sheet gasket sealable upon the inlet portions;

a second sheet gasket sealable upon the outlet spouts;

an upper cover for pressured engagement with said first sheet gasket;

a lower cover for pressured engagement with said second sheet gasket;

a first collar and a second collar, said first and second collars opposably located about the periphery;

first attachment means for removably attaching the collars to the periphery;

second attachment means for releasably and independently attaching said upper and lower covers to said first and second collars.

14. The apparatus of claim 13 wherein:

said first attachment means includes a plurality of threaded rods.

15. The apparatus of claim 13 wherein:

said upper and lower covers have a dimensional footprint which corresponds to that of a standard microplate.

16. An integrally fashioned multi-well block for multiple, simultaneous synthesis, used in conjunction with an upper and lower cover, comprising:

a block body of a generally rectangular shape, said block body having an upper surface, a lower surface, and side surfaces;

a plurality of tube bores arranged in ordered array, said tube bores extending between the upper and lower surfaces;

a plurality of outlet spouts depending from the lower surface, each outlet spout in fluid communication with a said tube bore;

a plurality of inlet portions extending upwardly from the upper surface, each inlet portion in axial alignment with a said tube bore; and

attachment site structure means disposed upon the side surfaces approximately medially between the top and bottom surfaces for providing sites for the independent clampable attachment of said upper and lower covers thereto.

17. The multi-well block of claim 16 wherein:

each tube bore includes an open seat proximal to the lower surface, and a filter element, the filter element located upon the open seat.

18. The apparatus of claim 16 wherein:

said attachment site structure means is a laterally extending skirt, the skirt being continuous about the side surfaces.

19. The apparatus of claim 16 wherein:

each inlet portion includes a distinctly raised, thin-walled well rim.

20. The apparatus of claim 16 wherein:

said inlet portions are separated by rifts.

21. The apparatus of claim 16 wherein:

said tube bores are arrayed in a standard 96-well format.

22. The apparatus of claim 16 wherein:

said outlet spouts have a tapered Luer-tip shape

23. The multi-well block of claim 16 wherein:

said tube bores have a cross-sectional shape selected from the group of shapes consisting of round and rounded square, each outlet spout in general axial alignment with each tube bore.

24. The multi-well block of claim 16 wherein:

said tube bores have a cross-sectional shape selected from the group of shapes consisting of generally rectangular and oval, each outlet spout axially offset with respect to each tube bore to provide alignment of said outlet spouts with the odd-numbered columns of wells of a multi-well collection plate in a first orientation of said block, and alignment with the even-numbered columns of wells of the collection plate in a second orientation in which said block is turned 180 degrees from the first orientation.

25. The multi-well block of claim 24 wherein:

each tube bore has an inclined bottom surface portion, the lower aspect of which is in the direction of said outlet spouts.

26. A carrier apparatus for multiple, simultaneous synthesis, used in conjunction with at least one multi-well synthesis block covered with an upper cover and a lower cover, comprising:

a dual-sided platform, the platform having opposing first and second sides to receive at least one said covered block on the first side and at least another said covered block on the second side in a two-level array;

retaining means for retaining the at least one said covered block upon said platform;

at least one shaft affixed to said platform and extending planarly therefrom; and

interfacing means for the interfacing of said shaft with a means for rotating said shaft.

27. The apparatus of claim 26 wherein:

said retaining means includes a least one hinged arm assembly engageable with each upper cover.

28. The apparatus of claim 27 wherein:

the upper cover has a recessed top surface, the at least one arm assembly including a clasp arm contoured to have a depending portion insertable into the upper cover.

29. The apparatus of claim 26 wherein:

said interfacing means includes said shaft having a fixed engagement head with a projecting pin, and a drive shaft upon which is located a fixed bearing cup having a plurality of slots, the bearing cup receiving the engagement head in key-like fashion.

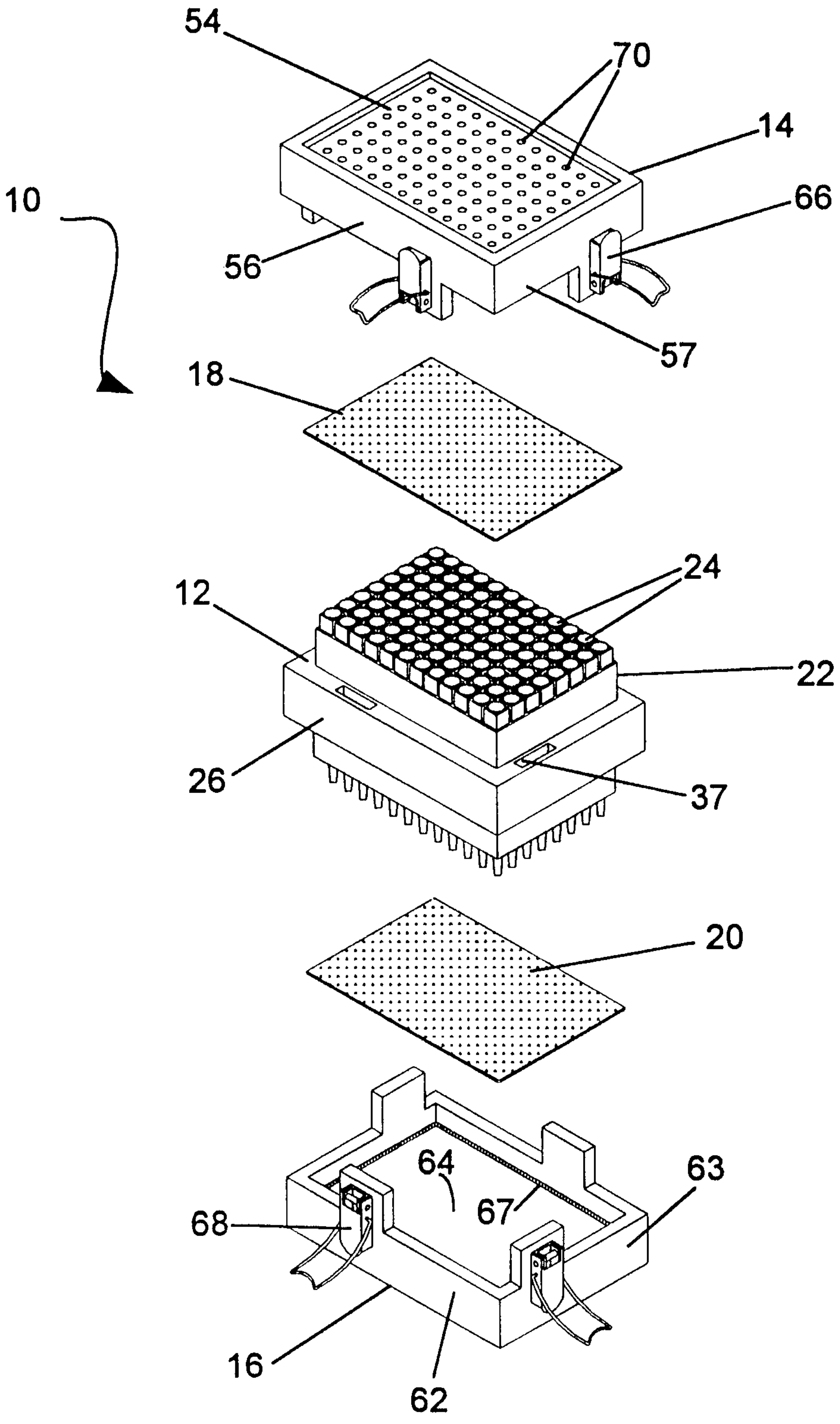


Fig. 1

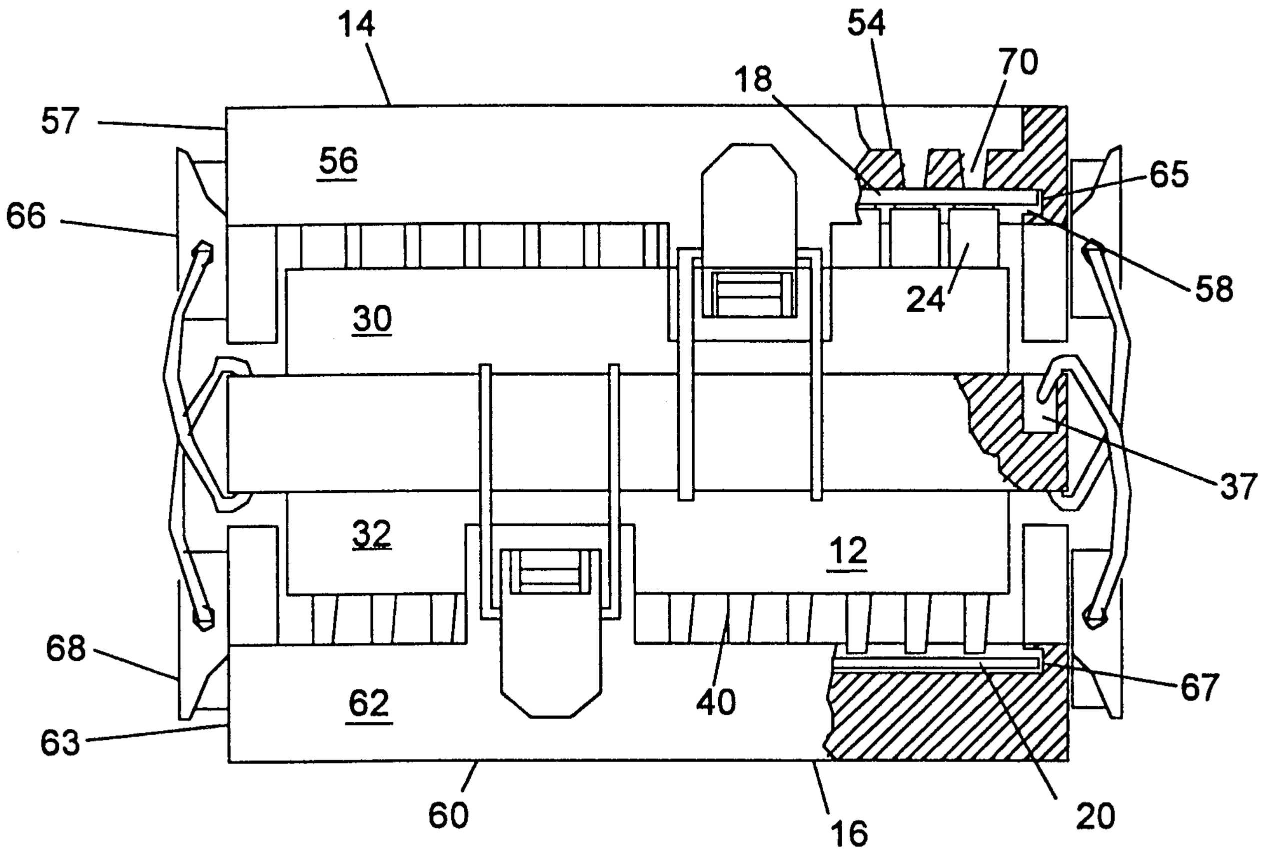


Fig. 2

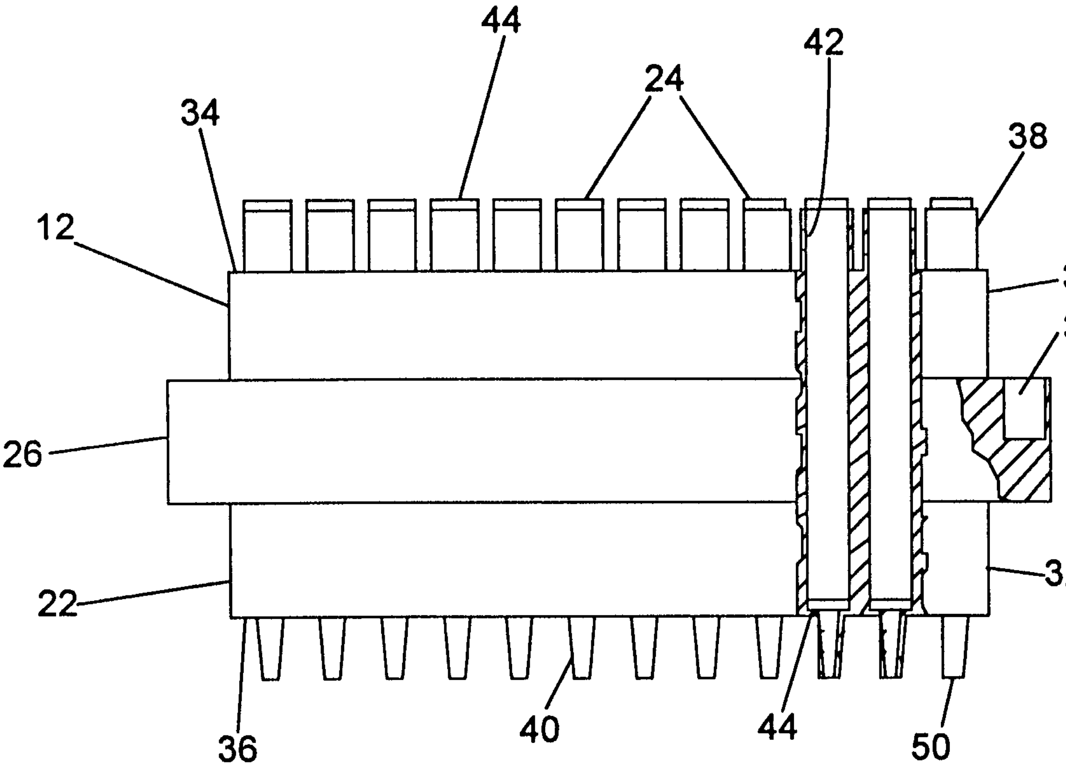


Fig. 3

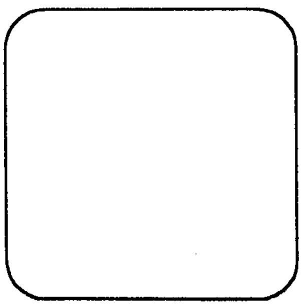


Fig. 3a

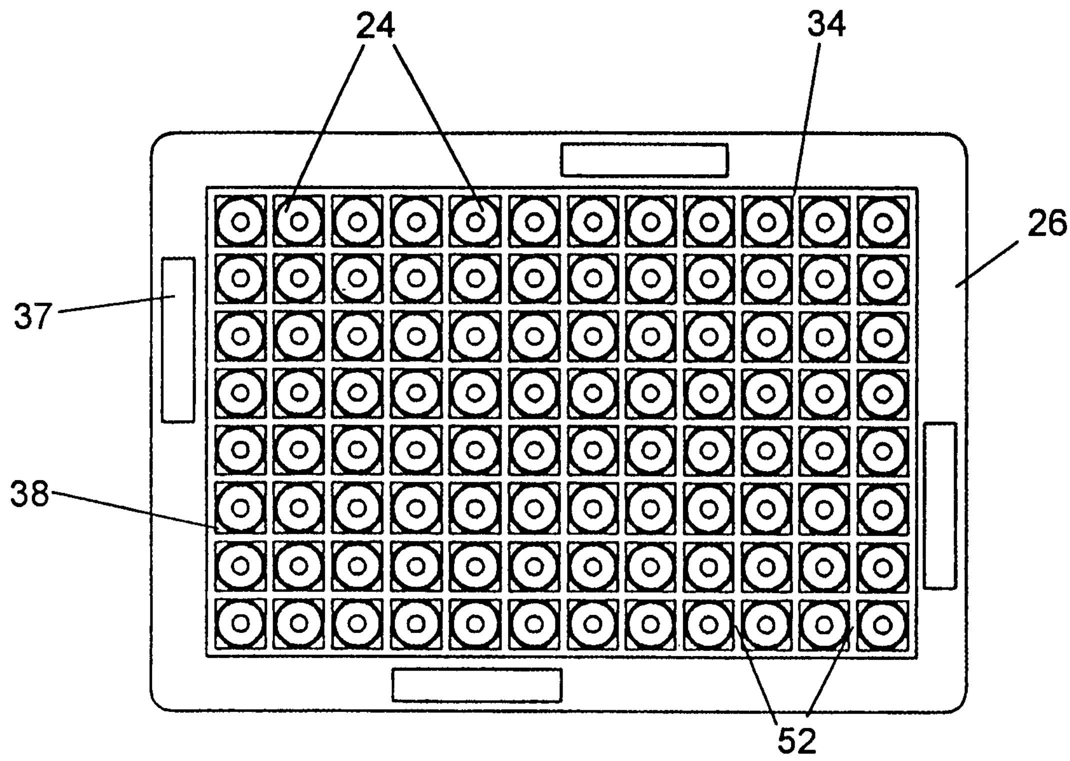


Fig. 4

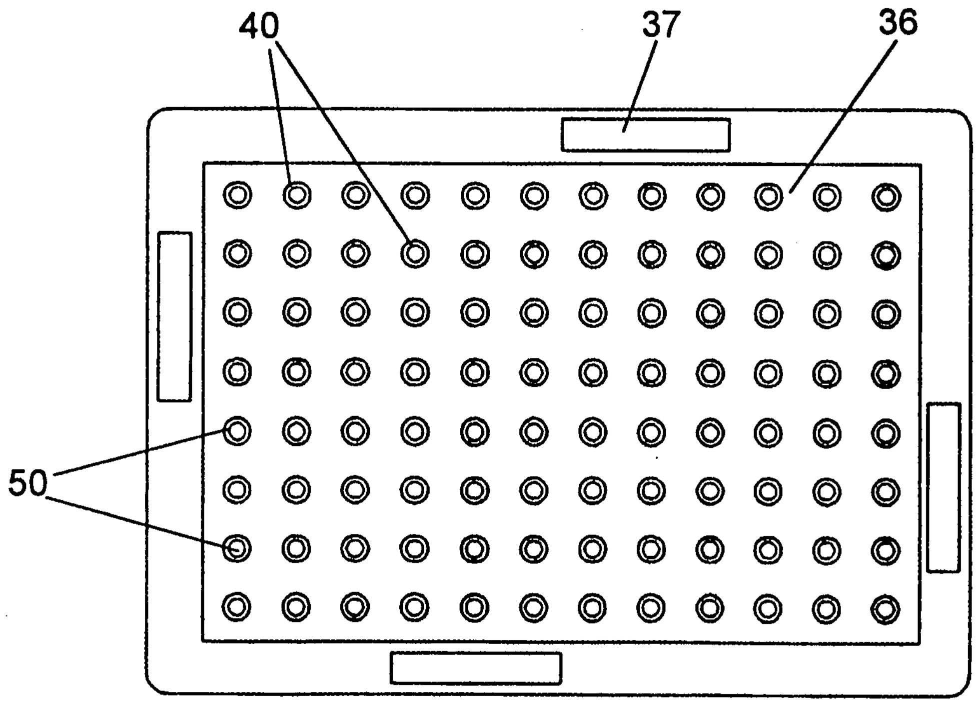


Fig. 5

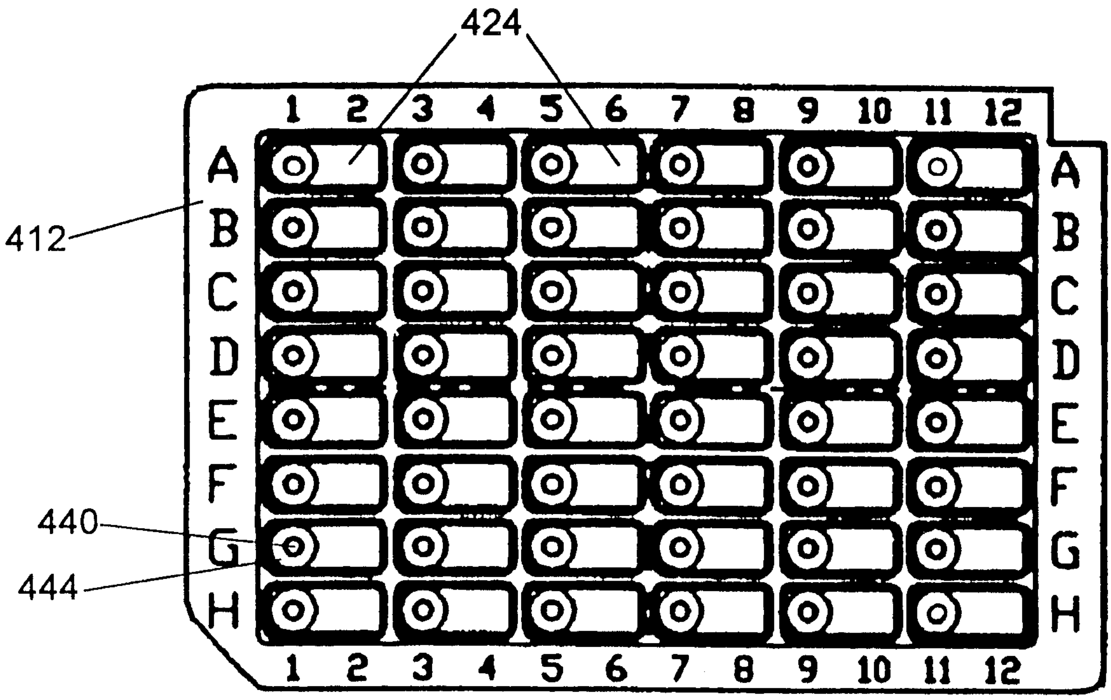

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Fig. 6

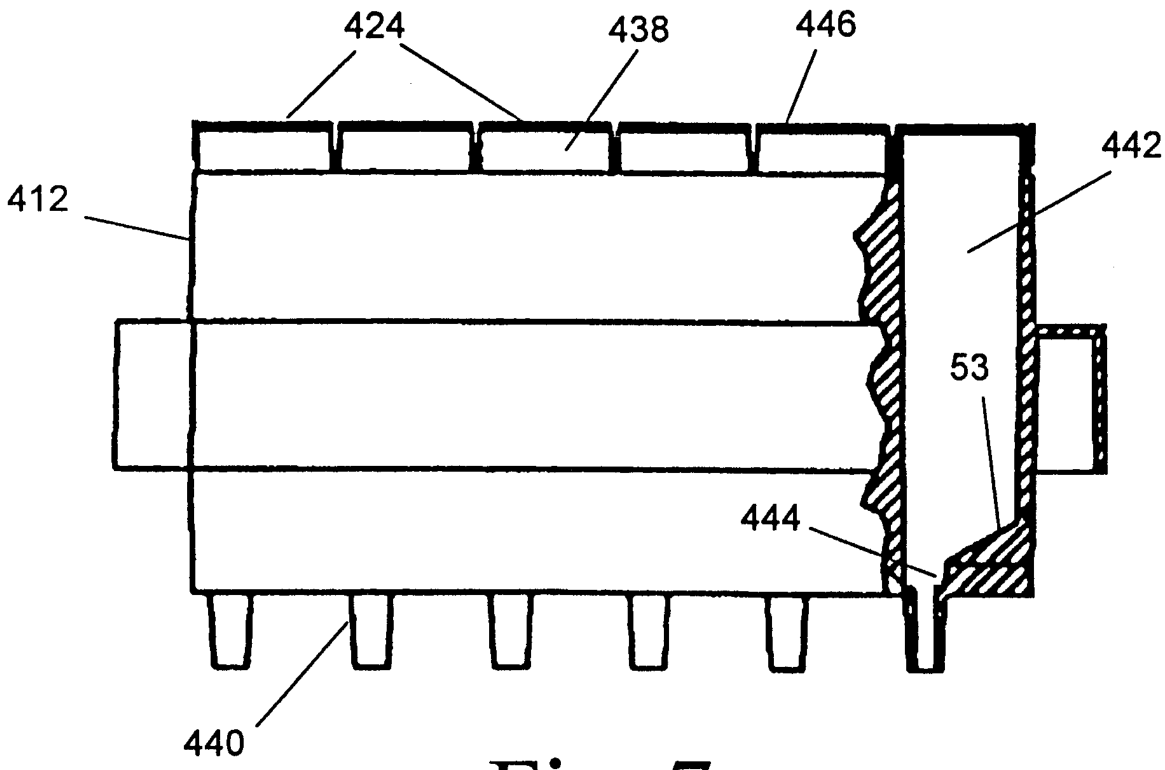
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Fig. 7

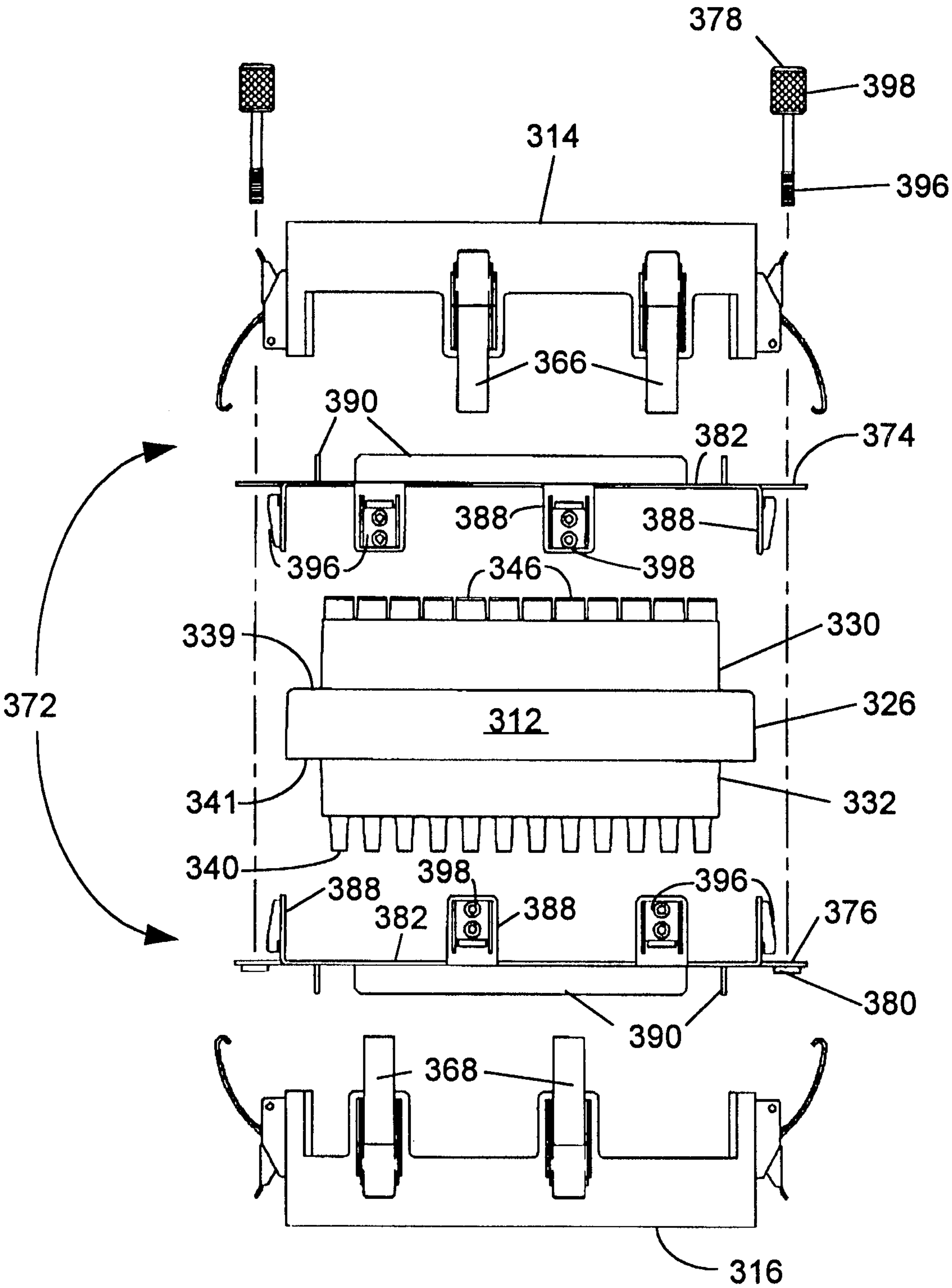
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Fig. 8

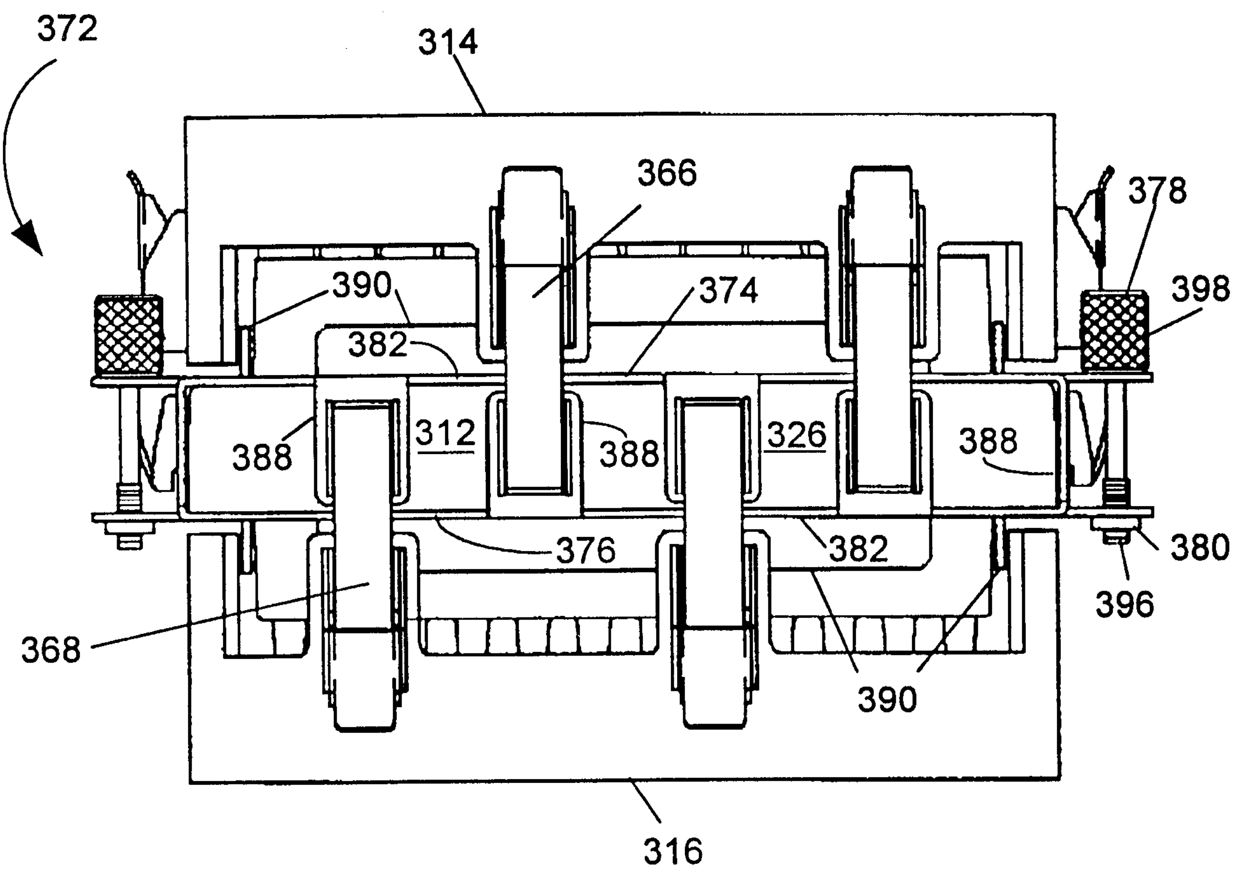
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Fig. 9

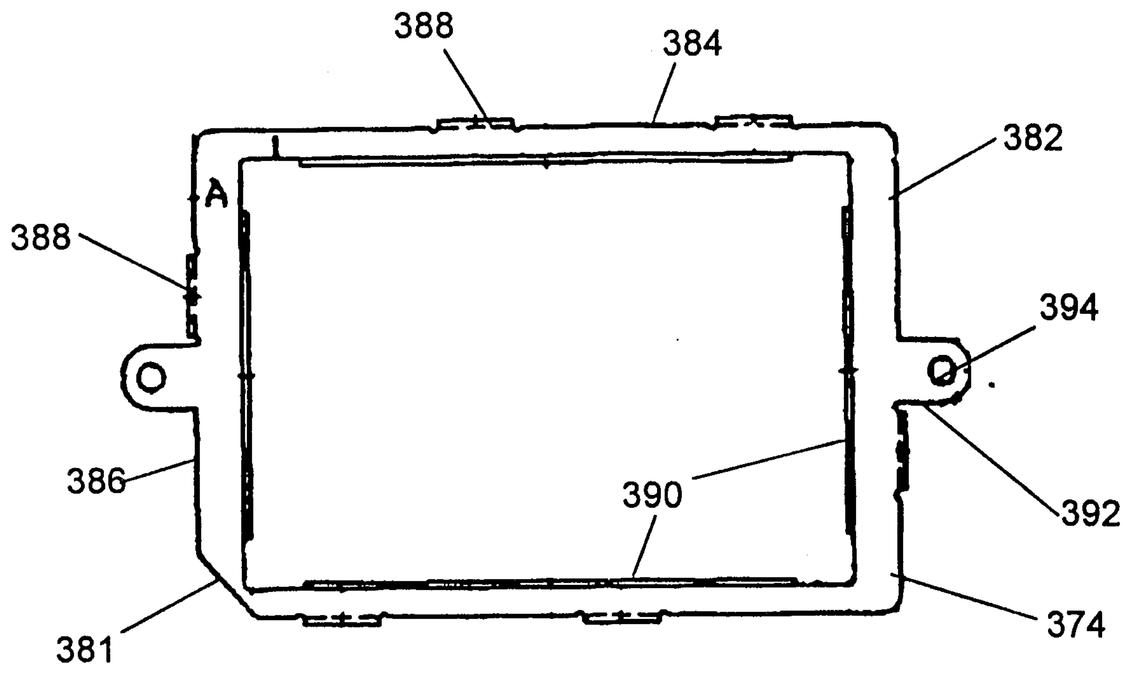
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Fig. 10

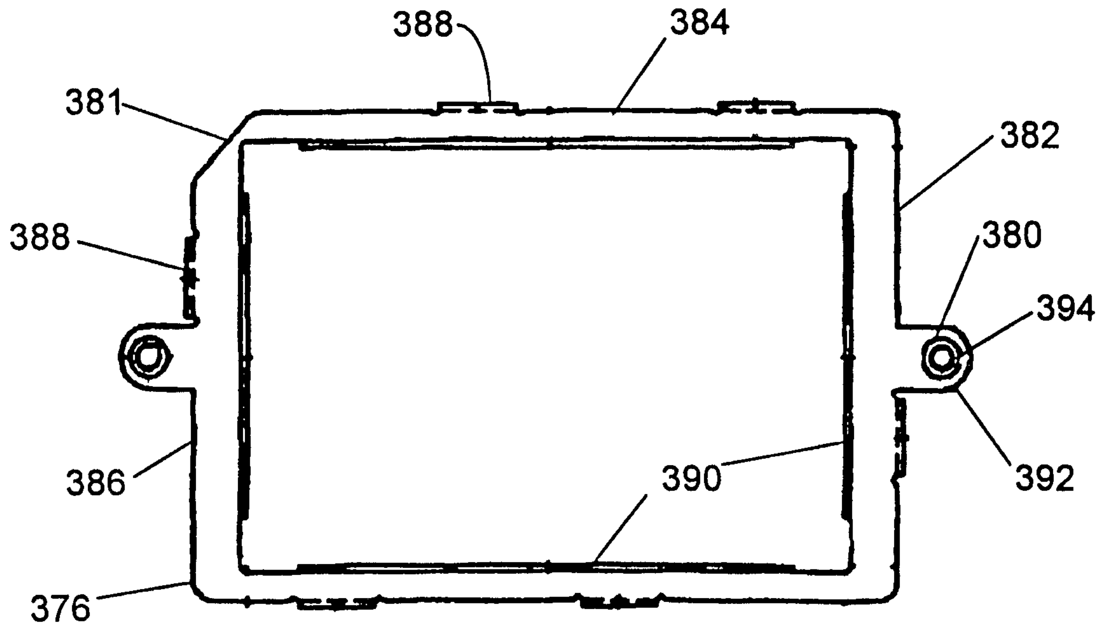
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Fig. 11

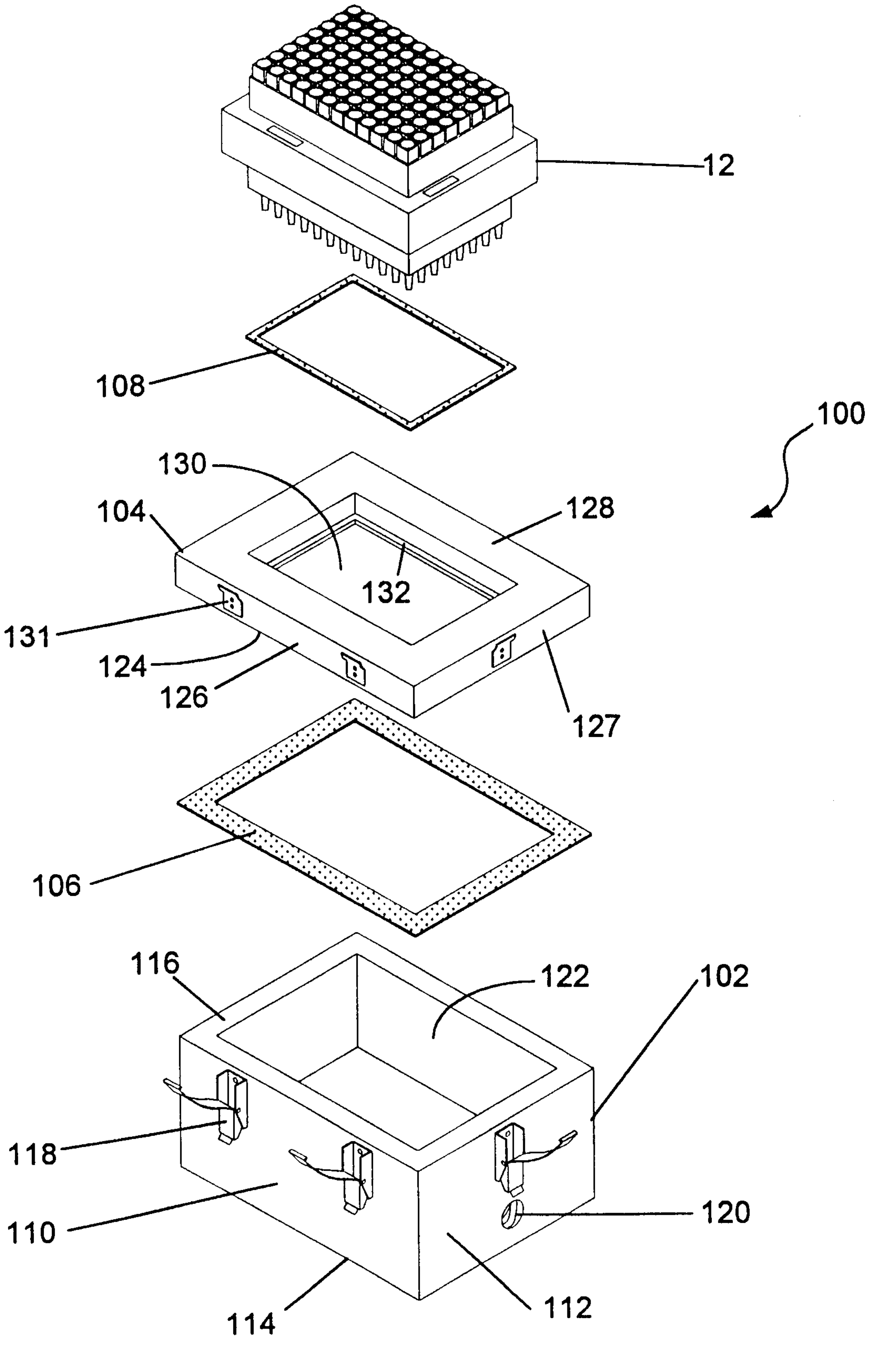
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Fig. 12

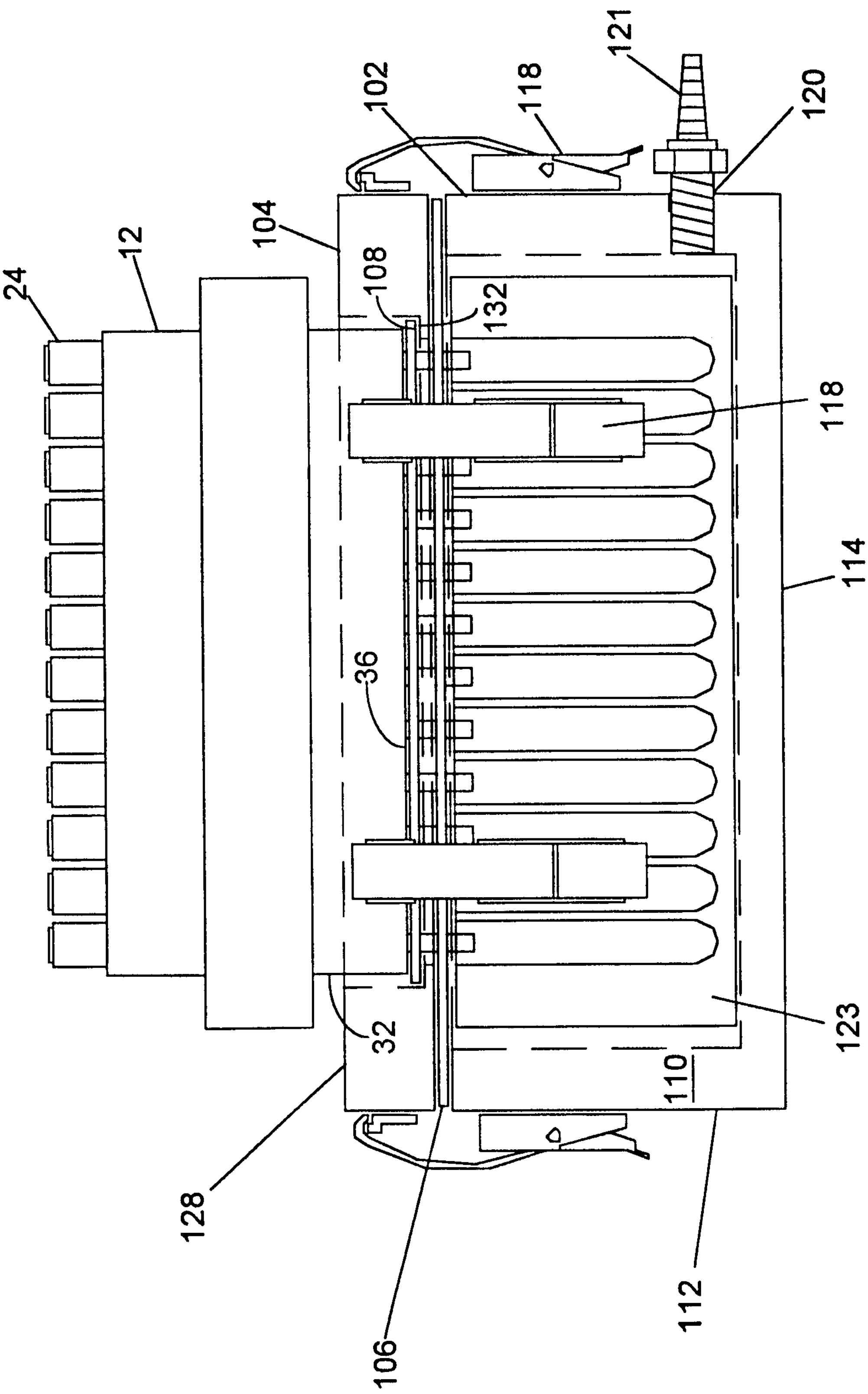
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Fig. 13

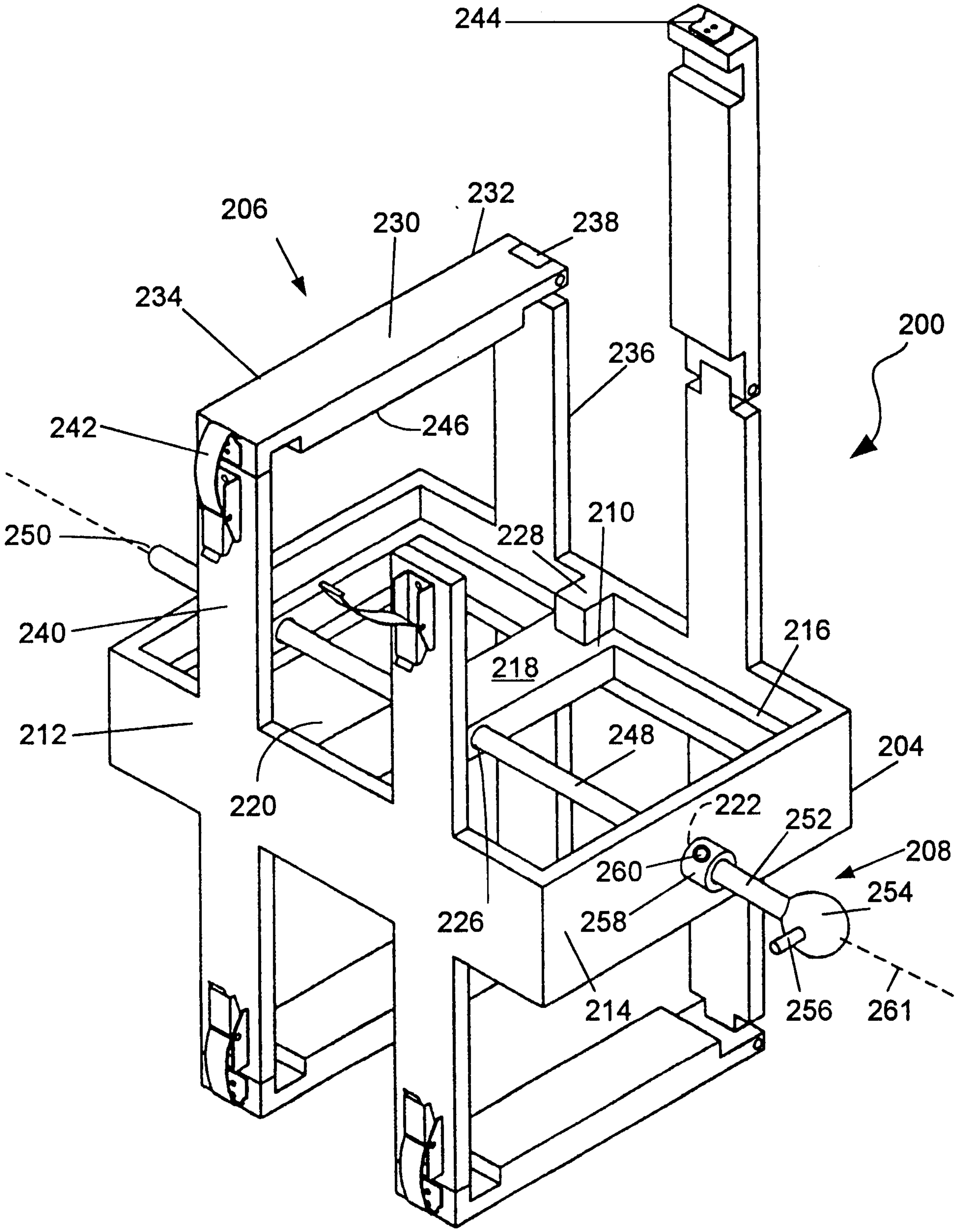
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Fig. 14

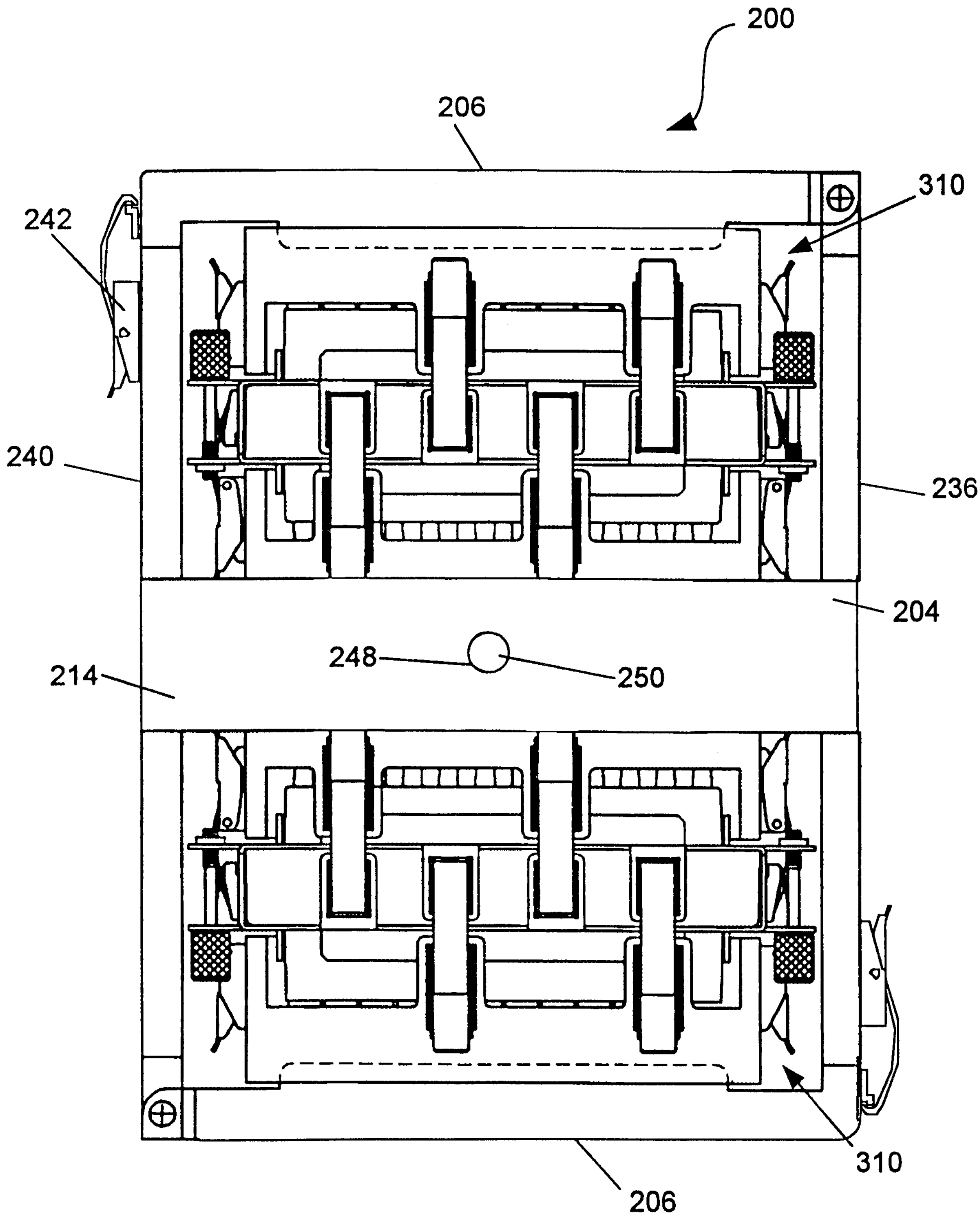

Fig. 15

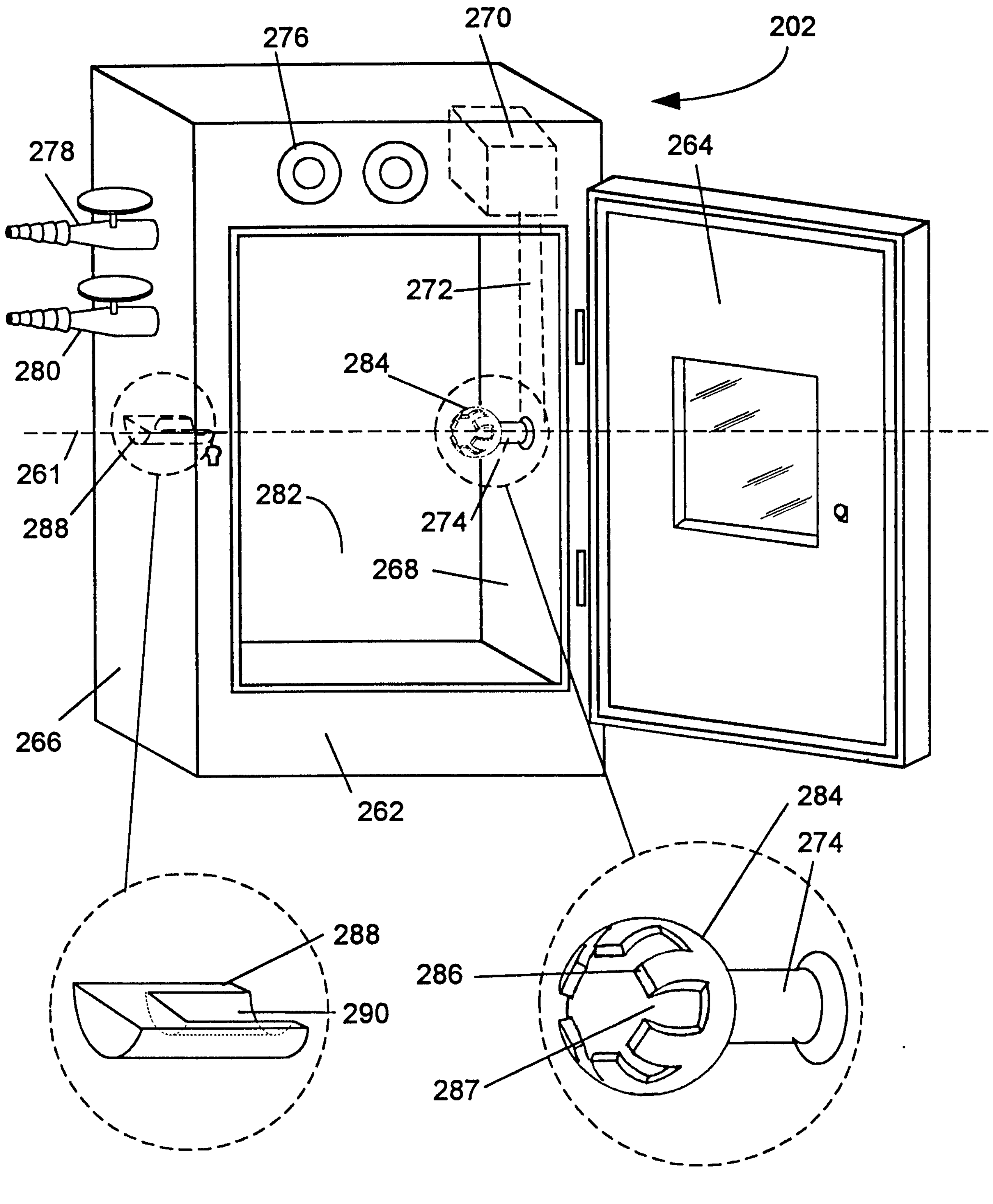
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Fig. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21228

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : B01L 9/00, 11/00
US CL : 422/99, 101, 102, 104, 196
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)

U.S. : 422/99, 101, 102, 104, 196; 211/4; 356/244, 246

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)

APS, STN search terms: reaction block, microplate, multi-well, synthesis, combinatorial, screening, micro scale.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,324,483 A (CODY et al) 28 June 1994, entire document.	1-25
Y	US 5,039,493 A (OPRANDY) 13 August 1991, entire document.	1-25
Y	US 4,902,481 A (CLARK et al) 20 February 1990, entire document.	1-25
Y	US 5,219,528 A (CLARK) 15 June 1993, entire document	1-25
Y	US 4,304,865 A (O'BRIEN et al) 08 December 1981, entire document.	1-25
Y	US 4,948,564 A (ROOT et al) 14 August 1990, entire document.	1-25

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 MARCH 1998	28 APR 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ALEXANDER MARKOFF
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,526,690 A (KIOVSKY et al) 02 July 1985, entire document.	1-25
Y	US 5,283,039 A (AYSTA) 01 February 1994, entire document.	1-25
Y	US 4,493,815 A (FERNWOOD et al) 15 January 1985	1-25
Y	US 4,787,988 A (BERTONCINI et al) 29 November 1988, entire document.	1-25
Y	US 5,108,704 A (BOWERS et al) 28 April 1992	1-25
Y	US 5,417,922 A (MARKIN et al) 23 May 1995, entire document.	26-29
Y	US 5,266,272 A (GRINER et al) 30 November 1993, entire document.	26-29
A	US 5,384,093 A (OOTANI et al) 24 January 1995, entire document.	26-29
A	US 5,082,631 (LENMARK et al) 21 January 1992, entire document.	26-29
Y	US 5,260,028 A (ASTLE) 09 November 1993, entire document.	26-29
Y, P	US 5,609,826 A (CARGILL et al) 11 March 1997, entire document.	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21228

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-25, drawn to an apparatus for multiple, simultaneous synthesis and a multi-well block for multiple, simultaneous synthesis.

Group II, claim(s) 26-29, drawn to a carrier apparatus.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The carrier apparatus of Group II, as claimed, lacks corresponding technical features of the synthesis block. Neither the block nor the apparatus of Group I require any carrier apparatus.