## Description

The present invention relates to oral delivery systems. More particularly the invention relates to enhancing the absorption of active substances by administering these substances bound to vitamin B12 (VB12) or an analogue thereof.

The oral route of administration is perhaps the most preferable means of delivering an antigen or pharmaceutically active agent to man. This route does however suffer from the major disadvantage that there is generally poor uptake of antigens or pharmaceutically active agents by the gastrointestinal tract and some agents may be destroyed by prolonged exposure to proteolytic enzymes. In this regard, attemps to orally immunize man or animals in the past have met with limited success. Effective vaccination has generally only been achieved by the administration of large quantities of antigen or by combining parenteral priming with oral boosting. Recent work by us utilizing a number of molecules with the ability to bind to the intestinal mucosa has demonstrated effective oral immunization using low doses of these binding proteins or by coupling various antigens or haptens to these carriers. Uptake and delivery to the circulation of these molecules from the intestine seemed to be due to receptor-mediated endocytosis.

It has been known for some time that a number of specific uptake mechanisms exist in the gut for uptake of dietary molecules. Thus there are specific uptake mechanisms for monosaccharides, disaccharides, amino acids and vitamins. Most of these uptake mechanisms depend upon the presence of a specific protein or enzyme such as monosaccharidase or disaccharidase situated in the mucosal lamina propria which binds to the molecule and transports it into the cells lining the lamina propria.

Two notable exceptions to these uptake mechanisms are found with iron transport and VB12 uptake. In both these cases a specific binding protein is released into the intestine, which binds to its ligand in the lumen of the gut.

Thus, during iron uptake in the intestine transferrin is released from the stomach, binds to iron and is in turn bound by a receptor on the duodenal mucosa. The receptor-transferrin-iron complex is then taken up by receptor-mediated endocytosis.

Similarly, the absorption of physiological amounts of VB12 by the gut requires that it be complexed with a naturally occurring transport protein known as intrinsic factor (IF) (1-5). This protein is released into the lumen of the stomach by parietal cells in the fundus. Once bound to intrinsic factor, the VB12.IF complex interacts with a membrane bound receptor for IF located on the terminal ileum of the small intestine. The receptor-IF-VB12 complex is then internalized by a process of receptor mediated endocytosis (RME). Allen and Majerus (7) demonstrated that it is possible to chemically modify VB12, couple it to a resin and use the VB12-resin to affinity purify IF. This finding suggested to us that it may be possible to couple large macromolecules (such as the resin used by Allen and Majerus) to VB12 and to still preserve its ability to interact specifically with intrinsic factor. By coupling molecules to VB12 in such a way as to preserve the ability of VB12 to interact with intrinsic factor it was hoped that we could use the natural uptake mechanism for VB12 and various molecules coupled to it, to deliver various proteins, drugs or other pharmaceutically active molecules to the circulation. FR-A-2111895, GB-A-1123853, GB-A-1152461 and CH-A-467277 disclose vitamin B12 complexed with active substances.

It is thus the object of this invention to utilize the VB12 uptake mechanism to transport active substances such a drugs, hormones, antigenic material and the like, covalently coupled to VB12 or an analogue thereof, from the intestinal lumen into the circulation.

In a first embodiment the invention provides a complex which comprises at least one active substance linked to at least one carrier molecule which is VB12 or an analogue thereof wherein the ability of the carrier to undergo the binding reactions necessary for uptake and transport of VB12 in a vertebrate host and the activity of the active substance are substantially maintained.

In the context of the present invention, the term active substance includes all, part, an analogue, homologue, derivative or combination thereof, of a hormone, bio-active peptide, therapeutic agent, antigen or hapten.

Preferred active substances for delivery according to the invention include: hormones and bioactive peptides such as LHRH, insulin, testosterone, interferon, PMSG, HCG and inhibin; therapeutic agents such as neomycin, salbutamol, pyrimethamine, penicillin G, methicillin, carbenicillin, pethidine, xylazine, ketamine hydrochloride, mephenesin and iron dextran; antigens or haptens including allergens, proteins, polysaccharides and secretory products such as grass pollens (for instance barley and couch), weed pollens (e.g. clover, dock) tree pollens (e.g. ash, cyprus), plant pollens (e.g. broom), epithelia (e.g. cat hair, dog hair, pig hair) and house dust mite, wheat chaff and kapok; a protein derived from or immunogens against influenza, measles, Rubella, smallpox, yellow fever, diphtheria, tetanus, cholera, plague, typhus, BCG, tuberculosis causing agents, Haemophilus influenzae, Neisseria catarrhalis, Klebsiella pneumoniae, pneumococci, strep-

tococci; a secretory product derived from diphtheria, tetanus, cholera, plague, typhus, tuberculosis causing agents, Haemophilus influenzae, Neisseria catarrhalis, Klebsiella pneumoniae, pneumococci, streptococci, Streptococcus mutans, or is derived from a malarial parasite or the causitive agent of coccidiosis in chickens.

Preferred analogues of VB12 include cyanocobalamin (CN-Cbl), aquocobalamin, adenosylcobalamin, methylcobalamin, hydroxycobalamin, cyanocobalamin carbanalide, and 5-o-methylbenzylcobalmin [(5-OMeBza)CN-Cbl] as well as the desdimethyl, monoethylamide and the methylamide analogues of all of the above. Also included are the various analogues and homologues of cobalamide such as coenzyme B12 and 5'-deoxyadenosylcobalamin. Other analogues include chlorocobalamin, sulfitocobalamin, nitrocobalamin, thiocyanatocobalamin, benzimidazole derivatives such as; 5,6-dichlorobenzimidazole, 5-hydroxybenzimidazole, trimethylbenzimidazole, as well as adenosylcyanocobal amin [(Ade)CN-Cbl], cobalamin lactone, cobalamin lactam and the anilide, ethylamide, monocaboxylic and dicarboxylic acid derivatives of VB12 or its analogues.

Preferred derivatives of VB12 include the mono-, di- and tricarboxylic acid derivatives or the propionamide derivatives of VB12. Carriers may also include analogues of VB12 in which the cobalt is replaced by zinc or nickel. The corrin ring of VB12 or its analogues may also be substituted with any substituent which does not effect its binding to 1F.

In a preferred embodiment of the invention there is provided a complex comprising the lys-6 form of LHRH and VB12.

The complexes of this invention, of coupled active substances can be used to deliver these substances to any uni-or multicellular organism with a requirement for, and a specific transport mechanism for VB12. For example, bacteria resistant to a particular antibiotic where the resistance is mediated by the loss of ability to transport the antibiotic inside the cell, could be overcome by this procedure. A VB12-antibiotic complex could thus be effectively delivered inside the bacterial cell via the VB12 transport mechanism. This could lead to an ability to reutilize a number of antibiotics whose current use has become limited by development of bacterial resistance. Delivery of active substances, of the type described above, could be achieved in a wide variety of organisms, particularly parasites of humans or animals.

In another embodiment the invention provides a process for the production of a complex comprising, at least one active substance linked to at lease one carrier molecule, said carrier molecule being VB12 or an analogue thereof, wherein the ability of the carrier to undergo the binding reactions necessary for uptake and transport of VB12 in a vertebrate host and the activity of the active substance are substantially maintained which process comprises one or more of the following steps:

a) reacting the active substance with the carrier to form said complex ;

b) chemically modifying the active substance to provide at least one functional group capable of forming a chemical linkage, and reacting the active substance and carrier to form said complex;

c) chemically modifying the carrier to provide at least one functional group capable of forming a chemical linkage and reacting the active substance and carrier to form said complex;

d) chemically modifying the active substance and the carrier to provide functional groups capable of forming a chemical linkage, and reacting the active substance and carrier to form said complex;

e) reacting the active substance with at least one cross-linking agent and reacting the active substance and the carrier molecule to form said complex;

f) reacting the carrier with at least one cross-linking agent and reacting the active substance and carrier to form said complex;

g) reacting the active substance and carrier with at least one cross-linking agent and reacting the active substance and carrier to form said complex.

A preferred process of the invention comprises;

(i) preparing the mono-acid derivative of VB12 by mild acid hydrolysis, and purifying the derivative;

(ii) chemically modifying an active substance to provide at least one functional group capable of forming a chemical linkage; and

(iii) reacting the modified active substance and mono-acid derivative of VB12 to form said complex.

The cross-linking agent may contain a bond which is cleavable by acid, base, periodate or free sulfhydrylgroups. Example of cross-linking agents include N-(4-azidophenylthio)phthalimide, 4,4'-dithiobisphenylazide, dithiobis-(succinimidylpropionate), dimethyl-3,3'-dithiobispropionimidate.2HCl, 3,3'-dithiobis-(sulfosuccinimidylpropionate), ethyl-4-azidophenyl-1,4-dithiobutyrimidate.HCl, N-succinimidyl-(4-azidophenyl)-1,3'-dithiopropionate, sulfosuccinimidyl-2-(m-azido-o-nitrobenzamido)-ethyl-1,3'-dithiopropionate, sulfosuccinimidyl-2-(p-azidosalicylamido)-ethyl-1,3'dithiopropionate, N-succinimidyl-3-(2-pyridyldithio)propionate, sulfosuccinimidyl-(4-azidophenyldithio)-propionate, and 2-iminothiolane. Preferred cross-linking agents are disuccinimidyl tartrate and bis-[2-(succinimidyloxycarbonyloxy)-ethyl]sulfone.

Suitably, cross-linking of the carrier and active substance may be achieved by acid hydrolysis of the amide groups of the propionamide side chains adjacent to rings A, B and C of VB12 and coupling to suitable groups of the active substance.

In a further embodiment of the invention there is provided a medicament which comprises a complex according to the invention together with a pharmaceutically acceptable carrier or diluent.

Examples of pharmaceutically acceptable carriers and diluents include typical carriers and diluents such as sodium bicarbonate solutions and similar diluents which neutralize stomach acid or have similar buffering capacity, glycols, oils, oil-in-water or water-in-oil emulsions, and include medicaments in the form of emulsions, gels,pastes and viscous colloidal dispersions. The medicament may be presented in capsule, tablet, slow release or elixir form or as a gel or paste. Furthermore, the medicament may be provided as a livestock feed or as food suitable for human consumption.

The invention also provides an antibacterial formulation comprising a complex according to the invention, in which the active substance is an antibacterial active substance together with a carrier or diluent therefor.

In another embodiment the invention provides a method of enhancing a host vertebrate's response to an orally administered active substance which method comprises the oral administration of an effective amount of said active substance as a complex according to the invention, or of a medicament according to the invention.

The invention also provides a method of selectively modulating the magnitude and/or type of immune response to an antigen or hapten, which method comprises orally administering an effective amount of said antigen or hapten as a complex according to the invention, or of a medicament according to the invention.

The invention also provides a method of delivering an active substance to any unicellular or multicellular organism, including bacteria, protozoa, or parasites, which has a requirement for VB12 as well as a specific uptake mechanism for the same, which method comprises administering a complex of the invention to the organism. In this manner bacteria which are resistant to an antibiotic due to the loss of their ability to transport the antibiotic into the cell could be once again made sensitive to the antibiotic by coupling the antibiotic to VB12 and using the natural VB12, uptake system of the bacteria to deliver the antibiotic into the cell. In this fashion a number of antibiotics whose use has been discontinued due to the occurrence of bacterial resistance could regain pharmacological significance.

In a further embodiment of the invention there is provided a method of delivering an active substance across the blood/brain barrier or across the placenta into a developing foetus by administering a complex of the invention. Delivery of such substances would occur through the natural VB12 uptake mechanisms at these barriers.

## Materials

Bovine serun albumin (BSA), VB12, p-nitrophenol, LHRH acetate salt, and neomycin sulfate were all purchased from Sigma Chemical Co. St Louis, Mo. USA.
1-ethyl-3-(dimethylaminopropyl)carbodiimide HCl (EDAC) was obtained from BIORAD Labs, California, while N,N'dicyclohexylcarbodiimide (DCC) was purchased from Fluka.

## PREPARATION 1

### Monocarboxyl-Derivative of VB12

The acid derivative of VB12 can readily be prepared by hydrolysing native VB12 for 72h in 0.4M HCl at room temperature. The reaction is stopped by passing the hydrolystate down an ion-exchange column of DOWEX® AGI-X8. The flow through containing the monoacid VB12 is lyophilized and resuspended in 0.2M pyridine and adjusted to pH9.05 with 1M ammonium hydroxide. The solution is then passed down a Sephadex® QAE A25 previously equilibrated with 0.2M pyridine and the monoacid eluted with a gradient from 0.4M pyridine to 0.4M, 0. 16M acetic acid. The fractions containing the purified mono-acid are pooled and lyophilized.

The following examples illustrate preferred embodiments of the invention and should not be construed as limiting theron. The monocarboxyl VB12 can be covalently crosslinked to any amino containing compound by the use of a suitable carbodiimide.

## EXAMPLE 1

VB12-BSA

VB12-BSA complex was formed by mixing an equal weight of COOH-B12 with BSA in distilled water, the pH was adjusted to 6.5 with 1M NaOH and an equal weight of solid EDAC was added to the solution and allowed to react overnight. Free, unreacted COOH-B12 was removed by chromatography on Sephadex G-25, followed by repeated ethanol precipitation of the VB12-BSA complex.

EXAMPLE 2

VB12-Lys-6-LHRH

Monocarboxyl VB12 plus 1.5 equivalents of n-hydroxysuccinamide were dissolved in cold (4°C) dimethyl formamide (DMF). To this solution was added 1.1 equivalents of dicyclohexylcarbodiimide (DCC) in DMF. The solutions were warmed to room temperature and allowed to react for 1 hour. Lys-6-LHRH dissolved in DMF containing triethylamine was added and allowed to react overnight. The resultant complex was separated from the free reactants by chromatography on Sephadex G-25 followed by reverse phase HPLC.

EXAMPLE 3

VB12-Neomycin

The total acid hydrolysate of VB12 was adjusted to pH6.5 with NaOH, an equal weight of neomycin sulfate was added to the solution followed by an equal weight of EDAC. The conjugation was allowed to proceed overnight after which the conjugate was separated from unreacted reagents by chromatography on G-25 and reverse phase HPLC.

All reactions and purification procedures were monitored by thin layer chromatography. The degree of VB12 substitution of BSA was determined by spectrophotometric scanning of the conjugate using 0.D.278 extinction values of 0.6 and 11.5, for 1mg/ml solutions of BSA and VB12, respectively, and an O.D.361 of 20.4 for VB12.

Conjugate administration

Female C57B1/6J mice (18-22g) were obtained from the Animal Resources Centre (Perth, Western Australia). All mice received conjugate preparations in 0.5ml of 0.1M carbonate/bicarbonate buffer pH9.5 using a specially prepared feeding needle. Mice were fed on days 0 and 14. On day 21 the mice were bled from the orbital plexus. Antibody titres of serum were determined by ELISA using alkaline phosphatase conjugated anti-mouse serum.

EXAMPLE 4

Stimulation of serum antibodies following oral administration of VB12-BSA complex

The possible potential for VB12 to deliver protein molecules, covalently linked to it, from the intestine to the circulation was investigated. The immune response generated to this complex was compared to that generated by the protein fed alone or together with VB12, or to the protein injected intramuscularly.

As seen in Table 1, feeding mice with microgram quantities of BSA or FGG coupled to VB12 resulted in the stimulation of significant serum antibody responses to the BSA or FGG respectively. Feeding of either protein in similar amounts or in a 50-fold excess either mixed with VB12 or without VB12 resulted in the stimulation of no anti-BSA or anti-FGG antibodies. Feeding of these VB12-protein complexes was also capable of stimulating good cellular immunity (as measured by the footpad assay for DTH)

TABLE 1

Immune response to orally presented VB12-BSA or VB12-FGG complex

| Oral Immunogen | Serum Antibody Response * | Footpad Response + |
|---|---|---|
| BSA (50µg) | <4 | 0 |
| BSA (2500µg) | <4 | nd |
| VB12 | <4 | 0 |
| VB12+BSA | <4 | 0 |
| VB12-BSA | 1351±198 | 17.3±5 |
| FGG | <4 | 0 |
| VB12+FGG | <4 | 0 |
| VB12-FGG | 1584±647 | 23.3±6 |
| FGG+FCA s.c. | 16504±3047 | 27.4±4 |

* The reciprocal of the antiserum dilution that gave an ELISA reading of 0.5 after 45min. at 37$^0$C on day 21 after initial feeding. Each value represents the mean of 15 mice ±1 standard deviation. Mice received two feedings of antigen (50µg) on days 1 and 14. On day 21 mice were bled from the retro-orbital plexus and the antibody titres measured by ELISA as described previously (Russell-Jones et al., 1984). Each protein molecule was substituted with an average of 5 VB12 groups.

\+ Footpad swelling was measured in mm using a microcaliper. All groups received a 50µg priming dose of antigen followed by challenge with 10µg of the immunizing antigen in the right foot and 10µg of ovalbumin in the left footpad. Swelling was measured after 24h.

EXAMPLE 5

Oral delivery of VB12-LHRH as a means of stimulating ovulation

Although a number of hormones such as oestrogen and progesterone are actively absorbed upon oral administration, there are may other which have little effect when given per os. Noteable amongst these hormones is the peptide hormone luteinizing hormone releasing hormone (LHRH), or gonadotrophin releasing hormone (GnRH). This hormone is normally secreted by the anterior pituitary and is responsible for the control of release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Parenteral injections of LHRH have previously been shown to be effective in stimulating FSH and LH release, however orally presented LHRH has little effect. Many studies have been performed on varying the sequence of LHRH, with the result that a number of agonists and antagonists have now been identified. Perhaps one of the most powerful agonists identified to date is the D-Lys-6 analogue of LHRH (D-Lys-6.LHRH). As the epsilon amino group on the lysine of this analogue is readily accessible for peptide cross-linking it was

decided to use the DCC method to link monocarboxyl VB12 to D-Lys6.LHRH and to test its efficacy upon oral administration.

The D-lys-6 analogue of LHRH was synthesized by us and purified by reverse phase HPLC. The purified analogue was coupled to monocarboxyl VB12 using DCC as described in Example 2. The conjugated product was purified by Sephadex G-25 chromatography in 10% acetic acid, followed by HPLC Chromatography.

Mature C57B1/6J female mice were treated in the following fashion:- On day 0 all mice received a subcutaneous (s/c) superovulating dose of pregnant mare serum gonadotraphin (PMSG) to stimulate the growth of ovarian follicles. After 48 hours mice received various doses of LHRH, Lys-6-LHRH or saline. On day 3 mice were sacrificed and examined for ovulation. Ovulation was assessed by examining for the presence of corpora haemorrhagica on the ovaries using a stereoscopic microscope at 80X power.

The results below show that by coupling Lys-6-LRH to VB12 it is possible to deliver the analogue orally and to still observe a biological effect as exemplified by its ability to stimulate ovulation in developing follicles. The inability of this preparatin to exert its effect when injected intravenously presumably reflects the rapid clearance of free VB12 when it is not complexed to transcobalamin II.

TABLE 2

Demonstration of the biological activity of Lys-6-LHRH

| Treatment | | | Number of mice |
|---|---|---|---|
| Day 0 | Day 2 | | ovulating |
| PMSG 8IU | Lys-6-LHRH | 50µg iv | 3/4 |
| PMSG 8IU | LHRH | 50µg iv | 1/4 |
| PMSG 8IU | Saline | 250µl iv | 0/4 |
| PMSG 4IU | Lys-6-LHRH | 50µg iv | 3/3 |
| PMSG 4IU | LHRH | 50µg iv | 1/3 |
| PMSG 4IU | Saline | 250µl iv | 0/3 |

TABLE 3

Demonstration of the ability of VB12 to deliver the Lys-6- LHRH orally

| Treatment | | | Number of mice |
|---|---|---|---|
| Day 0 | Day 2 | | ovulating |
| PMSG 8IU | VB12-Lys-6-LHRH | 50µg iv | 0/5 |
| PMSG 8IU | VB12-Lys-6-LHRH | 50µg/os | 3/5 |
| PMSG 8IU | LHRH | 50µg/os | 1/5 |
| PMSG 8IU | Saline | 250µl/os | 0/5 |

TABLE 4

Dose response to orally presented VB12-Lys-6-LHRH

| Treatment | | | Number of mice |
|---|---|---|---|
| Day 0 | Day 2 | | ovulating |
| PMSG 8IU | VB12-Lys-6-LHRH | 50µg/os | 4/5 |
| PMSG 8IU | VB12-Lys-6-LHRH | 25µg/os | 3/5 |
| PMSG 8IU | VB12-Lys-6-LHRH | 12µg/os | 5/5 |
| PMSG 8IU | VB12-Lys-6-LHRH | 6µg/os | 2/5 |
| PMSG 8IU | LHRH | 50µg/os | 1/5 |
| PMSG 8IU | LHRH | 25µg/os | 1/5 |
| PMSG 8IU | LHRH | 12µg/os | 0/5 |
| PMSG 8IU | LHRH | 6µg/os | 0/5 |
| PMSG 8IU | HCG | 10IU iv | 5/5 |
| PMSG 8IU | Saline | 250µl/os | 0/5 |

EXAMPLE 6

A number of drugs including the antibiotic, neomycin, are highly effective antibiotics when injected parenterally, however they are completely ineffective when given orally as they cannot be transported

across the intestinal epithelium. It was therefore decided to see if VB12 could act as a carrier for an antibiotic (neomycin) which normally has no effect upon a systemic infection when the antibiotic was given orally.

Neomycin was covalently linked to VB12 as described in Example 3 and fed to mice infected with S. typhimurium.

Oral administration of neomycin, or neomycin plus VB12 was not able to eliminate systemic infection with S. typhimurium. When neomycin was coupled to VB12, however, a significant quantity of the conjugate was transported across the intestinal epithelium and was capable of eliminating a systemic Salmonella infection. Table 3 shows that mice infected with S. typhimurium could be saved by either feeding VB12.neomycin conjugate (1mg total dose) or by the i.m. injection of neomycin or VB12.neomycin (both 1mg total dose). All other treatments failed to prevent death due to infection. In addition, the extent to which orally presented VB12.neomycin was capable of clearing infective particles from the liver and spleen of experimental animals suggests that, at least for this dosage, VB12.neomycin is comparable to i.m. injection of neomycin alone or the neomycin.VB12 conjugate (Table 5).

TABLE 5

Bactericidal properties of VB12-neomycin conjugates

| Treatment | Route | Survivors (day 10) | |
|---|---|---|---|
| | | Number | Percentage |
| Saline | oral | 0 | 0 |
| Neomycin | oral | 0 | 0 |
| VB12 | oral | 0 | 0 |
| Neomycin+VB12 | oral | 0 | 0 |
| Neomycin-VB12 | oral | 2 | 100 |
| Saline | i.m. | 0 | 0 |
| Neomycin | i.m. | 2 | 100 |
| Neomycin-VB12 | i.m. | 2 | 100 |

Male C57B1/6J mice (/group) were fed $1x10^6$ S. typhimurium on day 0. On day 3 mice received either saline, VB12, VB12 + neomycin (Neomycin+VB12), VB12 coupled to neomycin (Neomycin-VB12), or neomycin alone. A total dose of 1mg was administered as five smaller doses each separated by 12 hours. Neomycin was coupled to VB12 and the conjugate purified as outlined in Example 3.

It is possible to covalently couple VB12 to proteins (FGG and BSA), hormones (LHRH) and antibiotics (neomycin) and to utilize the natural active uptake mechanism for VB12 to transport these molecules from the lumen of the gut into the systemic circulation while retaining full immunogenicity and/or biological activity of the molecules coupled to VB12. The importance of these findings lie in the potential use of VB12 as a specific carrier of highly potent hormones, antibiotics and vasoactive peptides which currently must be repeatedly administered by injection at considerable costs and inconvenience.

The present invention provides a simple and novel technique for the specific oral presentation of various molecules previously incapable of being transported across the gut in significant amounts or in producing a significant systemic immune response upon oral feeding of various antigens. These antigens would not normally elicit an immune response when fed unless very large quantities of antigen were administered. Similarly,various active molecules which are normally only poorly absorbed from the intestine can be covalently linked to VB12 and so render them susceptible to intestinal uptake.

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## Claims

1. A complex comprising at least one active substance other than a single amino acid, 3,5-diodotyrosine, ferrous malonate, a nucleotide or inosin, in which the active substance is linked to at least one carrier molecule, said carrier molecule being vitamin B12 or an analogue thereof, wherein the ability of the carrier to undergo the binding reactions necessary for uptake and transport of vitamin B12 in a vertebrate host and the activity of the active substance are substantially maintained.

2. A complex according to Claim 1, wherein the active substance is selected from: all, part, analogue, homologues, derivatives or combinations thereof of a hormone, a bioactive peptide or therapeutic agent.

3. A complex according to Claim 2, eherein the active substance is a hormone selected from LHRH, insulin, testosterone, interferon, PMSG, HCG, or inhibin.

4. A complex according to Claim 2, wherein the active substance is the lys-6 form of LHRH.

5. A complex according to Claim 2, wherein said active substance is a therapeutic agent selected from neomycin, salbutamol, cloridine, pencicillin G, methicillin, carbenicillin, pethidine, xylazine, ketamine hydrochloride, mephenesin or iron dextran.

6. A complex according to Claim 1, wherein the substance is selected from all, part, analogues, homologues, derivatives or combinations thereof of an antigen or hapten.

7. A complex according to Claim 6, wherein said antigen or hapten is an allergen, protein, polysaccharide or secretory product.

8. A complex according to Claim 6, wherein said antigen or hapten is selected from: grass pollen, weed pollen, tree pollen, plant pollen, cat hair, dog hair, pig hair or, other epithelia, house dust mite, wheat chaff, kapok; a protein derived from or immunogens against influenza, measles, Rubella, smallpox, yellow fever, diphteria, tetanus, cholera, plague, typhus, BCG tuberculosis causing agents, Haemophilus influenza, Neisseria caterrhalis, Klebsiella pneumoniae, pneumococci, streptococci ; a secretory product derived from diphteria, tetanus, cholera, plague, typhus, tuberculosis causing agents, Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, streptococci, Streptococcus mutans, or is derived from a malarial parasite or the causitive agent of coccidiosis in chickens.

9. A complex according to Claim 1, wherein the carrier is: cyanocobalamin, aquocobalamin, adenosylcobalamin, methylcobalamin, hydroxycobalamin, cyanocobalamin carbanalide, 5-o-methylbenzylcobalmin, the desdimethyl, monoethylamide and the methylamide analogues all of the above, analogues and homologues of cobamamide, coenzyme B12, 5'-deoxyadenosylcobalamine, chlorocobalamin, sulfitocobalamin, nitrocobalamin, thiocyanatocobalamin, benzimidazole derivatives, adenosylcyanocobalmin, cobalamin lactone, cobalamin lactam and the anilide, ethylamide, propionamide, monocaboxylic and dicarboxylic acid derivatives of vitamin B12 or its analogues.

10. A complex according to claim 1, wherein the carrier is a vitamin $B_{12}$ analogue in which the Co is replaced by Ni or Zn.

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## Claims

1. A complex comprising at least one active substance other than a single amino acid, 3,5-diodotyrosine, ferrous malonate, a nucleotide or inosin, in which the active substance is linked to at least one carrier molecule, said carrier molecule being vitamin B12 or an analogue thereof, wherein the ability of the carrier to undergo the binding reactions necessary for uptake and transport of vitamin B12 in a vertebrate host and the activity of the active substance are substantially maintained.

2. A complex according to Claim 1, wherein the active substance is selected from: all, part, analogue, homologues, derivatives or combinations thereof of a hormone, a bioactive peptide or therapeutic agent.

3. A complex according to Claim 2, eherein the active substance is a hormone selected from LHRH, insulin, testosterone, interferon, PMSG, HCG, or inhibin.

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6. A complex according to Claim 1, wherein the substance is selected from all, part, analogues, homologues, derivatives or combinations thereof of an antigen or hapten.

7. A complex according to Claim 6, wherein said antigen or hapten is an allergen, protein, polysaccharide or secretory product.

8. A complex according to Claim 6, wherein said antigen or hapten is selected from: grass pollen, weed pollen, tree pollen, plant pollen, cat hair, dog hair, pig hair or, other epithelia, house dust mite, wheat chaff, kapok; a protein derived from or immunogens against influenza, measles, Rubella, smallpox, yellow fever, diphteria, tetanus, cholera, plague, typhus, BCG tuberculosis causing agents, Haemophilus influenza, Neisseria caterrhalis, Klebsiella pneumoniae, pneumococci, streptococci ; a secretory product derived from diphteria, tetanus, cholera, plague, typhus, tuberculosis causing agents, Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, streptococci, Streptococcus mutans, or is derived from a malarial parasite or the causitive agent of coccidiosis in chickens.

9. A complex according to Claim 1, wherein the carrier is: cyanocobalamin, aquocobalamin, adenosylcobalamin, methylcobalamin, hydroxycobalamin, cyanocobalamin carbanalide, 5-o-methylbenzylcobalmin, the desdimethyl, monoethylamide and the methylamide analogues all of the above, analogues and homologues of cobamamide, coenzyme B12, 5'-deoxyadenosylcobalamine, chlorocobalamin, sulfitocobalamin, nitrocobalamin, thiocyanatocobalamin, benzimidazole derivatives, adenosylcyanocobalmin, cobalamin lactone, cobalamin lactam and the anilide, ethylamide, propionamide, monocaboxylic and dicarboxylic acid derivatives of vitamin B12 or its analogues.

10. A complex according to claim 1, wherein the carrier is a vitamin $B_{12}$ analogue in which the Co is replaced by Ni or Zn.

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11. A complex according to claim 1, wherein the carrier is a vitamin $B_{12}$ analogue in which the corrin ring is substituted with a substituent which does not effect binding to intrinsic factor.

12. A process for the production of a complex according to claim 1, which process comprises one or more of the following steps:
a) reacting the active substance with the carrier to form said complex:
b) chemically modifying the active substance to provide at least one functional group capable of forming a chemical linkage, and reacting the active substance and carrier to form said complex;
c) chemically modifying the carrier to provide at least one functional group capable of forming a chemical linkage and reacting the active substance and carrier to form said complex;
d) chemically modifying the active substance and the carrier to provide functional groups capable of forming a chemical linkage, and reacting the active substance and carrier to form said complex;
e) reacting the active substance with at least one cross-linking agent and reacting the active substance and the carrier molecule to form said complex;
f) reacting the carrier with at least one cross-linking agent and reacting the active substance and carrier to form said complex;
g) reacting the active substance and carrier with at least one cross-linking agent and reacting the active substance and carrier to form said complex.

13. A process according to claim 12, comprising:
(i) preparing the mono-acid derivative of vitamin B12 by mild acid hydrolysis, and purifying said derivative;
(ii) chemically modifying an active substance to provide at least one functional group capable of forming a chemical linkage; and
(iii) reacting the modified active substance and mono-acid derivative of vitamin B12 to form said complex.

14. A process according to Claim 12, wherein the carrier is prepared by acid hydrolysis of the amide groups of the propionamide side chains adjacent to rings A, B and C of vitamin $B_{12}$ and chemically cross-linked to suitable groups of the active substance.

15. A process according to claim 12, wherein the cross-linking agent is a cleavable cross-linking agent containing a disulfide bond.

16. A process according to claim 12, wherein the cross-linking agent is cleavable by acid.

17. A proces according to claim 12, wherein the cross-linking agent is cleavable by periodate.

18. A process according to claim 12, wherein the cross-linking agent is cleavable by base.

19. A process according to claim 12, wherein the cross-linking agent is N-(4-azidophenylthio)phthalimide, 4,4'-dithiobisphenylazide, dithiobis(succinimidylpropionate), dimethyl-3,3'-dithiobispropionimidate.2HCl, 3,3'-dithiobis(sulfosuccinimidylpropionate), ethyl-4-azidophenyl-1,4-dithiobutyrimidate.HCl, N-succinimidyl-(4-azidophenyl)-1,3'-dithiopropionate, sulfosuccinimidyl-2-(m-azido-o-nitrobenzamido)-ethyl-1,3'-dithiopropionate, sulfosuccinimidyl-2-(p-azidosalicylamido)-ethyl-1,3'-dithiopropionate, N-succinimidyl-3-(2-pyridyldithio)propionate. sulfosuccinimidyl-(4-azidophenyldithio)-propionate, or 2-iminothiolane.

20. A process according to claim 12, wherein the cross-linking agent is disuccinimidyl tartrate.

21. A proces according to claim 12, wherein the cross-linking agent is bis-[2-(succinimidyloxycarbonyloxy)-ethyl]-sulfone.

22. A medicament which comprises a complex according to claim 1, together with a pharmaceutically acceptable carrier or diluent therefor.

23. A medicament according to claim 22, wherein said medicament is in capsule, tablet, slow release, elixir, gel or paste form or is enteric coated.

24. An antibacterial formulation comprising a complex according to claim 1, in which the active substance is an antibacterial active substance together with a carrier or diluent therefor.

**Revendications**

1. Complexe comprenant au moins une substance active autre qu'un simple acide aminé, la 3,5-diiodotyrosine, le malonate ferreux, un nucléotide ou l'inosine, dans lequel la substance active est liée à au moins une molécule porteuse, ladite molécule porteuse étant la vitamine B12 ou un de ses analogues, dans lequel l'aptitude du porteur à subir les réactions de liaison nécessaires à la fixation et au transport de la vitamine B12 chez un hôte vertébré et l'activité de la substance active sont sensiblement conservées.

2. Complexe selon la revendication 1, dans lequel la substance active est choisie parmi, la totalité, une partie, un analogue, des homologues, des dérivés, ou leurs combinaisons, d'une hormone, d'un peptide bioactif ou d'un agent thérapeutique.

3. Complexe selon la revendication 2, dans lequel la substance active est une hormone choisie parmi l'hormone de libération de la lutéinostimuline, l'insuline, la testostérone, l'interféron, la gonadotrophine du sérum de jument gravide, la gonadotrophine corionique humaine ou l'inhibine.

4. Complexe selon la revendication 2, dans lequel la substance active est la forme lys-6 de l'hormone de libération de la lutéinostimuline.

5. Complexe selon la revendication 2, dans lequel ladite substance active est un agent thérapeutique choisi parmi la néomycine, la salbutamol, la cloridine, la pénicilline G, la méthicilline, la carbénicilline, la péthidine, la xylazine, le chlorhydrate de kétamine, la méphénésine et le fer-dextrane.

6. Complexe selon la revendication 1, dans lequel la substance est choisie parmi la totalité, une partie, des analogues, des homologues, des dérivés, ou leurs combinaisons, d'un antigène ou d'un haptène.

7. Complexe selon la revendication 6, dans lequel ledit antigène ou haptène est un allergène, une protéine, un polysaccharide ou un produit sécrétoire.

8. complexe selon la revendication 6, dans lequel ledit antigène ou haptène est choisi parmi : le pollen d'herbe, le pollen de mauvaise herbe, le pollen d'arbre, le pollen de plante, le poil de chat, le poil de chien, le poil de porc ou d'autres épithéliums, l'acarien de poussière domestique, la balle de blé, le kapok, une protéine dérivée de, ou des immunogènes contre, la grippe, la rougeole, la rubéole, la variole, la fièvre jaune, la diphtérie, le tétanos, le choléra, la peste, le typhus, les agents causaux de la tuberculose à BCG, Haemophilus influenzae, Neisseria catarrhalis, Klebsiella pneumoniae, les pneumocoques, les streptocoques; un produit sécrétoire dérivé de la diphtérie, du tétanos, du choléra, de la peste, du typhus, les agents causaux de la tuberculose, de Haemophilus influenzae, de Neisseria catarrhalis, de Klebsiella pneumoniae, des streptocoques, de Streptococcus mutans, ou est dérivé d'un parasite paludéen ou de l'agent causal de la coccidiose chez le poulet.

9. Complexe selon la revendcation 1, dans lequel le porteur est ; la cyanocobalamine, l'aquocobalamine, l'adénosylcobalamine, la méthylcobalamine, l'hydroxycobalamine, le cyanocobalamine-carbanalids, la 5-o-méthylbenzylcobalamine, les analogues dédiméthyle, monoéthylamide et méthylamide des composés ci-dessus, les analogues et homologues du cobamamide, la co-enzyme B12, la 5'-désoxy-adénosylcobalamine, la chlorocobalamine, la sulfitocobalamine, la nitrocobalamine, la thiocyanatocobalamine, les dérivés de benzimidazole, l'adénosylcyanocobalamine, la cobalamine-lactone, le cobalamine-lactame et les dérivés anilide, éthylamide, propionamide, acides monocarboxyliques et dicarboxyliques de la vitamine B12 ou de ses analogues.

10. Complexe selon la revendication 1, dans lequel le porteur est un analogue de vitamine B12, dans lequel le Co est remplacé par Ni ou Zn.

11. Complexe selon la revendication 1, dans lequel le porteur est un analogue de vitamine B12 dans lequel le noyau corrine est substitué par un substituant qui n'effectue pas la liaison au facteur intrinsèque.

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12. Procédé de production d'un complexe selon la revendication 1, ce procédé comprenant une ou plusieurs des étapes suivantes :
a) réaction de la substance active avec le porteur pour former ledit complexe;
b) modification chimique de la substance active pour donner au moins un groupe fonctionnel capable de former une liaison chimique, et réaction de la substance active et du porteur pour former ledit complexe;
c) modification chimique du porteur pour donner au moins un groupe fonctionnel capable de former une liaison chimique, et réaction de la substance active et du porteur pour former ledit complexe;
d) modification chimique de la substance active et du porteur pour donner des groupes fonctionnels capables de former une liaison chimique, et réaction de la substance active et du porteur pour former ledit complexe;
e) réaction de la substance active avec au moins un agent de réticulation et réaction de la substance active et de la molécule porteuse pour former ledit complexe;
f) réaction du porteur avec au moins un agent de réticulation et réaction de la substance active et du porteur pour former ledit complexe;
f) réaction de la substance active et du porteur avec au moins un agent de réticulation et réaction de la substance active et du porteur pour former ledit complexe.

13. Procédé selon la revendication 12, comprenant :
(i) la préparation du dérivé mono-acide de vitamine B12 par hydrolyse acide ménagée et la purification dudit dérivé;
(ii) la modification chimique d'une substance active pour donner au moins un groupe fonctionnel capable de former une liaison chimique; et
(iii) la réaction de la substance active modifiée et du dérivé mono-acide de vitamine B12 pour former ledit complexe.

14. Procédé selon la revendication 12, dans lequel le porteur est préparé par hydrolyse acide des groupes amide des chaînes latérales propionamide adjacentes aux noyaux A, B et C de la vitamine B12 et réticulés chimiquement à des groupes convenables de la substance active.

15. Procédé selon la revendication 12, dans lequel l'agent de réticulation est un agent de réticulation éliminable contenant une liaison disulfure.

16. Procédé selon la revendication 12, dans lequel l'agent de réticulation est éliminable par un acide.

17. Procédé selon la revendication 12, dans lequel l'agent de réticulation est éliminable par un periodate.

18. Procédé selon la revendication 12, dans lequel l'agent de réticulation est éliminable par une base.

19. Procédé selon la revendication 12, dans lequel l'agent de réticulation est le N-(4-azidophénylthio)-phtalimide, l'azoture de 4,4'-dithiobisphényle, le dithiobis(propionate de succinimidyle), le dichlorhydrate de diméthyl-3,3'-dithiobispropionimidate, le 3,3'-dithiobis(propionate de sulfosuccinimidyle), le chlorhydrate d'éthyl-4-azidophényl-1,4-dithiobutyrimidate, le (4-azidophényl)-1,3'-dithiopropionate de N-succinimidyle, le 2-(m-azido-o-nitrobenzamido)éthyl-1,3'-dithiopropionate de sulfosuccinimidyle, le 2-(p-azidosalicylamido)éthyl-1,3'-dithiopropionate de sulfosuccinimidyle, le 3-(2-pyridyldithio)propionate de N-succinimidyle, le (4-azidophényldithio)propionate de sulfosuccinimidyle ou le 2-iminothiolane.

20. Procédé selon la revendication 12, dans lequel l'agent de réticulation est le tartrate de disuccinimidyle.

21. Procédé selon la revendication 12, dans lequel l'agent de réticulation est la bis-[2-(succinimidyloxycarbonyloxy)éthyl]sulfone.

22. Médicament qui comprend un complexe selon la revendication 1, ainsi qu'un véhicule ou diluant pharmaceutiquement acceptable.

23. Médicament selon la revendication 22, dans lequel ledit médicament est sous forme de capsule, de comprimé, retard, d'élixir, de gel ou de pâte, ou à enrobage entérique.

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24. Formulation antibactérienne comprenant un complexe selon la revendication 1, dans laquelle la substance active est une substance active antibactérienne, ainsi qu'un véhicule ou un diluant.

**Ansprüche**

1. Komplex, der wenigstens einen von einer einzelnen Aminosäure unterschiedlichen Wirkstoff, 3,5-Diodotyrosin, Fe(II)-Malonat, ein Nucleotid oder Inosin enthält, wobei der Wirkstoff mit wenigstens einem Trägermolekül verknüpft ist, dieses Vitamin B12 oder ein Analoges davon darstellt, wobei die Fähigkeit des Trägers, die für die Aufnahme und den Transport von Vitamin B12 in einem Wirbeltier-Wirt erforderlichen Bindungsreaktionen einzugehen und die Aktivität des Wirkstoffs im wesentlichen aufrechterhalten werden.

2. Komplex nach Anspruch 1, worin der Wirkstoff zur Gänze oder teilweise ein Hormon, ein bioaktives Peptid oder ein Therapeutikum bzw. ein entsprechendes Analoges, Homologes, Derivate oder Gemische davon darstellt.

3. Komplex nach Anspruch 2, worin der Wirkstoff ein Hormon ist, ausgewählt unter LHRH, Insulin, Testosteron, Interferon, PMSG, HCG oder Inhibin.

4. Komplex nach Anspruch 2, worin der Wirkstoff die Lys-6-Form von LHRH ist.

5. Komplex nach Anspruch 2, worin der Wirkstoff ein Arzneimittel ist, ausgewählt unter Neomycin, Salbutamol, Cloridin, Penicillin G, Methicillin, Carbenicillin, Pethidin, Xylazin, Ketaminhydrochlorid, Mephenesin oder Fe-Dextran.

6. Komplex nach Anspruch 1, worin der Wirkstoff zur Gänze oder teilweise ein Antigen oder Hapten bzw. ein entsprechendes Analoges, Homologes, Derivate oder Gemische davon darstellt.

7. Komplex nach Anspruch 6, worin das Antigen oder Hapten ein Allergen, Protein, Polysaccharid oder Abscheidungsprodukt ist.

8. Komplex nach Anspruch 6, worin das Antigen oder Hapten ausgewählt ist unter Gras-, Unkraut-, Baum- oder Pflanzenpollen, Katzen-, Hunde- oder Schweinehaar oder anderen Epithelbildungen, Hausstaubmilben, Weizenspreu, Kapok; Immunogene gegen Grippe, Masern, Röteln, Pocken, Gelbfieber, Diphtherie, Tetanus, Cholera, Pest, Typhus, BCG-Tuberkulose verursachende Agentien, Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, pneumococci, streptococci sowie daraus hergestellte Proteine; im Zusammenhang mit Diphtherie, Tetanus, Cholera, Pest, Typhus und Tuberkulose verursachenden Agentien sowie mit Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, streptococci, Streptococcus mutans oder mit Malariaparasiten oder den Erregern von Hühnercoccidiose erhaltene Abscheidungsprodukte.

9. Komplex nach Anspruch 1, worin der Träger Cyanocobalamin, Aquocobalamin, Adenosylcobalamin, Methylcobalamin, Hydroxycobalamin, Cyanocobalamincarbanalid, 5-o-Methylbenzylcobalamin, die Desdimethyl-, Monoethylamid- und Methylamidanalogen all dieser Verbindungen, die Analogen und Homologen von Cobamamid, Coenzym B12, 5'-Deoxyadenosylcobalamin, Chlorocobalamin, Sulfitocobalamin, Nitrocobalamin, Thiocyanatocobalamin, Benzimidazolderivate, Adenosylcyanocobalamin, Cobalaminlacton, Cobalaminlactam und die Anilid-, Ethylamid-, Propionamid-, Monocarbonsäure- und Dicarbonsäurederivate von Vitamin B12 bzw. ihre Analogen darstellt.

10. Komplex nach Anspruch 1, worin der Träger ein Vitamin $B_{12}$-Analoges ist, bei dem Kobalt durch Nickel oder Zink ersetzt ist.

11. Komplex nach Anspruch 1, worin der Träger ein Vitamin $B_{12}$-Analoges ist, bei dem der Corrinring durch einen Substituenten substituiert ist, der keine Bindung an den Intrinsic Faktor bewirkt.

12. Verfahren zur Herstellung eines Komplexes nach Anspruch 1, das eine oder mehrere der folgenden Stufen umfaßt:
    a) Umsetzung des Wirkstoffs mit dem Träger zur Bildung des Komplexes;

b) chemische Abwandlung des Wirkstoffs zur Bildung wenigstens einer funktionellen Gruppe, die zur Bildung einer chemischen Bindung befähigt ist, und Umsetzung des Wirkstoffs mit dem Träger zur Bildung des Komplexes;
c) chemische Abwandlung des Trägers zur Bildung wenigstens einer funktionellen Gruppe, die zur Bildung einer chemischen Bindung befähigt ist, und Umsetzung des Wirkstoffs mit dem Träger zur Bildung des Komplexes;
d) chemische Abwandlung des Wirkstoffes und des Trägers zur Bildung von funktionellen Gruppen, die zur Bildung einer chemischen Bindung befähigt sind, und Umsetzung des wirkstoffs mit dem Träger zur Bildung des Komplexes;
e) Umsetzung des Wirkstoffs mit wenigstens einem Vernetzungsmittel und Umsetzung des Wirkstoffs mit dem Trägermolekül zur Bildung des Komplexes;
f) Umsetzung des Trägers mit wenigstens einem Vernetzungsmittel und Umsetzung des Wirkstoffs mit dem Träger zur Bildung des Komplexes;
g) Umsetzung des Wirkstoffs und des Trägers mit wenigstens einem Vernetzungsmittel und Umsetzung des Wirkstoffs mit dem Träger zur Bildung des Komplexes.

13. Verfahren nach Anspruch 12, das folgende Stufen umfaßt:
(i) Herstellung des Monosäurederivats von Vitamin B12 durch milde Säurehydrolyse und Reinigung des Derivats;
(ii) chemische Abwandlung eines Wirkstoffs zur Bildung wenigstens einer funktionellen Gruppe, die zur Bildung einer chemischen Bindung fähig ist und
(iii) Umsetzung des abgewandelten Wirkstoffs mit dem Monosäurederivat von Vitamin $B_{12}$ zur Bildung des Komplexes.

14. Verfahren nach Anspruch 12, worin der Träger hergestellt wird durch Säurehydrolyse der Amidgruppen der an die Ringe A, B und C von Vitamin $B_{12}$ angrenzenden und chemisch mit geeigneten Gruppen des Wirkstoffs vernetzten Propionamid-Seitenketten.

15. Verfahren nach Anspruch 12, worin das Vernetzungsmittel ein eine Disulfidbindung enthaltendes spaltbares Vernetzungsmittel ist.

16. Verfahren nach Anspruch 12, worin das Vernetzungsmittel durch eine Säure spaltbar ist.

17. Verfahren nach Anspruch 12, worin das Vernetzungsmittel durch Perjodat spaltbar ist.

18. Verfahren nach Anspruch 12, worin das Vernetzungsmittel durch eine Base spaltbar ist.

19. Verfahren nach Anspruch 12, worin das Vernetzungsmittel N-(4-Azidophenylthio)phthalimid, 4,4'-Dithiobisphenylazid, Dithiobis-(succinimidylpropionat), Dimethyl-3,3'-dithiobispropionimidat.2HCl, 3,3'-Dithiobis(sulfosuccinimidylpropionat), Ethyl-4-azidophenyl-1,4-dithiobutyrimidat.HCl, N-Succinimidyl-(4-azidophenyl)-1,3'-dithiopropionat, Sulfosuccinimidyl-2-(m-azido-o-nitrobenzamido)-ethyl-1,3'-dithiopropionat, Sulfosuccinimidyl-2-(p-azidosalicylamido)-ethyl-1,3'-dithiopropionat, N-Succinimidyl-3-(2-pyridyldithio)propionat, Sulfosuccinimidyl-(4-azidophenyldithio)-propionat oder 2-Iminothiolan ist.

20. Verfahren nach Anspruch 12, worin das Vernetzungsmittel Disuccinimidyltartrat ist.

21. Verfahren nach Anspruch 12, worin das Vernetzungsmittel Bis-/2-(succinimidyloxycarbonyloxy)-ethyl/-sulfon ist.

22. Arzneimittel, das einen Komplex gemäß Anspruch 1 zusammen mit einem pharmazeutisch verträglichen Träger bzw. Verdünnungsmittel enthält.

23. Arzneimittel nach Anspruch 22, worin das Arzneimittel in Kapsel-, Tabletten-, Slow release-, Elixier-, Gel- oder Pastenform vorliegt oder mit einer für die verzögerte Freisetzung vorgesehenen Beschichtung versehen ist.

24. Antibakterielle Formulierung, die einen Komplex gemäß Anspruch 1 enthält, bei dem der Wirkstoff ein antibakterieller Wirkstoff zusammen mit einem Träger oder Verdünnungsmittel ist.