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(71) Applicants *(for all designated States except US)*: **PLIVA Hrvatska d.o.o.** [HR/HR]; Ulica grada Vukovara 49, 10000 Zagreb (HR). **BUCKS, Teresa Anne** [GB/GB]; c/o Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAPLAR, Vesna** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **FRKANEC, Leo** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **JOKIC, Milan** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **MAKAREVIC, Janja** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **PORTADA, Tomislav** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **ZINIC, Mladen** [HR/HR]; c/o Rudjer Boskovic Institute, Bijenicka 54, 10000 Zagreb (HR). **JELCIC, Zelimir** [HR/HR]; c/o PLIVA Hrvatska d.o.o., IP Dept, Ulica grada Vukovara 49, 10000 Zagreb (HR).

(74) Agents: **BUCKS, Teresa, Anne** et al.; Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

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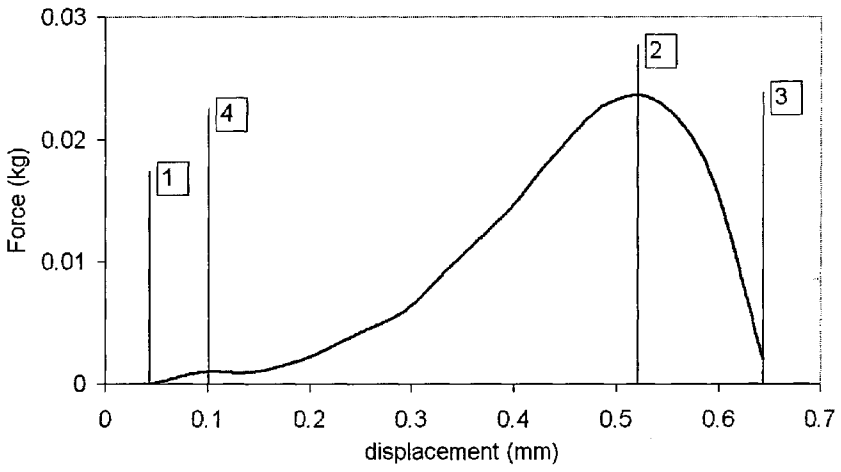

FIGURE 1

(57) Abstract: The invention relates to gel composition comprising a gelating agent and a solvent. The gelating agent is a compound of general formula (I): wherein: R^1 is hydrogen or C_{1-14} alkyl; R^3 is OH or a group; R^4 is hydrogen or C_{1-6} alkyl, optionally substituted with OR^9, COR^9 or $COOR^9$; R^9 is hydrogen, C_{1-6} alkyl or benzyl; R^2 is hydrogen, C_{1-6} alkyl or benzyl, either of which may optionally be substituted with OH or, when R^3 is R^2 may also be R^7; R^7 is a 5 or 6 membered aromatic or heteroaromatic ring system which is optionally further substituted with C_{1-6} alkyl, benzyl or hydroxy; or a salt thereof.

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GEL COMPOSITIONS

The present invention relates to compounds which are capable of forming gels when mixed with an appropriate solvent and to methods of preparing these compounds. The invention also relates to the gels formed by the compounds, methods for making them, compositions comprising the gels and to the use of the gels in various application.

Supramolecular hydrogels are used in many applications including food and cosmetic thickeners, formation of contact lenses, vehicles for drug delivery and tissue replacement matrices. They are of particular interest as drug delivery vehicles because of their generally favourable biocompatibility. Because of their high water content they are particularly attractive for the delivery of delicate bioactive agents such as proteins.

Gels may be either chemical or physical gels. Chemical gels consist of solid components which are covalently linked to one another and gel formation is irreversible. Physical gels are generally formed from smaller subunits which are linked non-covalently into a network. Physical gels tend to be thermoreversible.

Hydrogels may be formed either by polymers or by low molecular weight gelators (LMWGs). In gels formed by LMWGs, the molecules are assembled in well ordered arrays and the gels are thermoreversible and strong. In addition, they tend to have low minimal gelation concentrations and high tolerance towards salts and other additives.

There are many examples of documents relating to hydrogels formed from chemically cross-linked hydrophilic polymers. In EP-A-0212959, a hydrogel is formed from a cross-linked polymerised hydrophilic polymer with an olefinic bond, an amino acid polymer, a cross-linking agent and a lower alcohol.

WO-A-97/05185 relates to macromers which can be ionically or covalently cross-linked to form hydrogels. The macromers are block co-polymers which have hydrophilic blocks and blocks which are more hydrophobic.

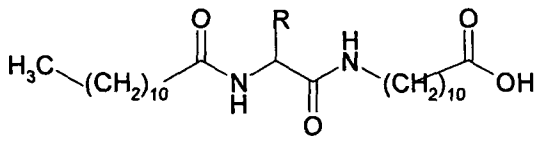
WO-A-03/089506 also relates to hydrogels as well as to hydrogel foams and superporous hydrogels. These hydrogels are said to consist of two or more interpenetrating polymer networks which provide enhanced elasticity and mechanical strength properties.

WO-A-2004/104021 again relates to hydrogels which, in this case, are intended to provide controlled release of active agents by utilising repeat sequence protein polymers.

There are also, however, a number of documents which relate to the formation of hydrogels from LMWGs. The art is reviewed by Maaike de Loos, Ben L. Feringa, and Jan H. van Esch, Design and Application of Self-Assembled Low Molecular Weight Hydrogels *Eur. J. Org. Chem.* 2005, 3615–3631; and by Estroff LA. Hamilton AD., in Water gelation by small organic molecules *Chemical Reviews* **104(3),** 1201-1217, 2004.

Fages *et al*, *Top Curr Chem* (2005) 256, 77–131, describe urea derivatives which are capable of forming gels when dissolved in various organic solvents. Some of the ureido amino acid derivatives are also capable of forming gels in water, Wang *et al, Chem. Commun.*, 2003, 310–311.

In our earlier publications (Caplar *et al*, *Eur. J. Org. Chem.*, **2004(19)**, 4048-4059 and D'Aléo *et al*, *Chem. Commun., **2004**, 190-191*) we discuss hydrogelator compounds formed by combining 11-aminoundecanoioc acid, lauric acid and aromatic and aliphatic amino acid units in the same molecule. These molecules were low molecular weight compounds derived from amino acids and connected through amide bonds with long aliphatic chains ending in a carboxylic acid functional group and have the general formula:

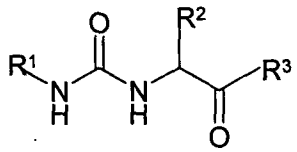


wherein R can be isopropyl, isobutyl, benzyl or phenyl.

Similarly, we report that chiral bis(amino acid)oxalyl amides and chiral bis(amino alcohol)oxalyl amide are capable of forming hydrogels (Makarević *et al*, *Chem.Eur.J.* 2001, 7, 3328 – 3341, Makarević *et al*,. *Croat. Chem. Acta.* 2004, 77, 403-414).

The present invention relates to novel non-polymeric compounds which, in water, are able to form hydrogels without the need for chemical cross-linking. In addition, the compounds are also able to form gels in solvents other than water, including organic solvents and oils. It is thought that the gels are formed by the self-assembly of the molecules into nanofibrous networks.

In the present invention there is provided a gel composition comprising a gelating agent and a solvent, characterised in that the gelating agent is a compound of general formula (I):

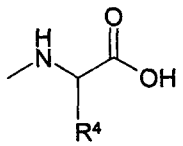


(I)

wherein:

R^1 is hydrogen or C_{1-14} alkyl;

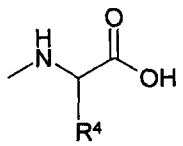
R^3 is OH or a group:



R^4 is hydrogen or C_{1-6} alkyl, optionally substituted with OR^9, COR^9 or $COOR^9$;

R^9 is hydrogen, C_{1-6} alkyl or benzyl;

R^2 is hydrogen, C_{1-6} alkyl or benzyl, either of which may optionally be substituted with OH or, when R^3 is



R^2 may also be R^7;

R^7 is a 5 or 6 membered aromatic or heteroaromatic ring system which is optionally further substituted with C_{1-6} alkyl, benzyl or hydroxy;

or a salt thereof.

When the compounds of general formula (I) or their salts are dissolved in solvent, it is believed that a gel is formed by means of individual molecules of the compounds forming chains and these chains becoming entangled to form nanofibrous networks. However, the effectiveness of the invention is not dependent on the correctness of this supposition.

Some compounds of general formula (I) are known in the art. For example, US 6,090,250 relates to chiral surfactants of general formula:

R_1-Y-A-X-[-C(ab)-]$_n$-Z

where R_1 can be C_4-C_{18} linear or branched alkyl alkyl;
Y can be NH
A can be CO
X can be NH
Z can be COO^-
one of a and b is an amino acid side chain and the other is hydrogen;
n can be 1.

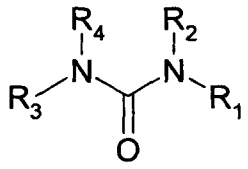
Ulsperger *et al*, *Seifen, Oele, Fette Wasche,* (1962), **88**, 666-671 relates to surfactants, for example the sodium salt of N-octylaminocarbonyl-L-alanine.

US 2,871,225 discloses a method for preparing polypeptides from a compound of formula:

RNHCONHCH(R')COOH.

WO 2005/107812 relates to a topical or transdermal composition of an anticholinergic or antispasmodic agent which also comprises a urea containing compounds as a penetration enhancing agent.

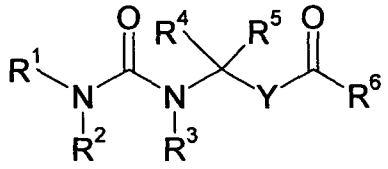
The urea containing compounds have the formula:



where R_1, R_2, R_3 and R_4 are very broadly defined. The preferred form of the composition is a gel but the urea containing compounds are not gelating agents.

JP07304755 teaches that L-leucine-*N*-[*N*-(aminocarbonyl)-L-leucyl] methyl ester can be used as a reagent in the preparation of compounds which are inhibitors of human renin.

WO 01/14328 relates to compounds of general formula:



Where R^1 can be hydrogen or alkyl;

R^2, R^3 and R^5 can be hydrogen;

R^4 can be hydrogen or optionally substituted alkyl, aryl etc.

R^6 can be NR^dR^e; where R^d is H and R^e can be alkyl substituted with COOH.

The compounds are said to be cell adhesion inhibitors and there is no suggestion in this document that they could be used to form gels.

The compounds of general formula (I), and especially their salts, have the advantages that they can form gels in both water and organic solvents and that the properties of the gels can easily be manipulated by adjusting the temperature, pH or the type and amount of solvent present.

In the present invention, the term "gel forming compound" refers to any molecule, whether a small organic molecule (such as the compounds of general formula (I)) or a polymer, which forms a gel when dissolved by heating, with either an aqueous or a non-aqueous solvent, and allowed to cool to room temperature

In the present specification "C_1-C_6 alkyl" refers to a straight or branched saturated hydrocarbon chain having one to six carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, t-butyl and n-hexyl.

The terms "aromatic moiety" and "aryl" in the context of the present specification refer to an aromatic ring system having from 5 to 10 ring carbon atoms and containing one or two rings. Examples of aromatic moieties are benzene, naphthalene and biphenyl ring systems.

"Heteroaromatic" and "heteroaryl" refer to aromatic ring systems as defined above but in which one or more ring atoms is replaced by a nitrogen, oxygen or sulphur atom. Examples of heteroaromatic ring systems include pyridine, quinoline, isoquinoline, quinazoline, thiazole, benzthiazole, benzoxazole, benzimidazole, indole, indazole and imidazole ring systems.

Salts of the compounds of general formula (I) are preferably pharmaceutically acceptable and include salts of inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, hemisulfate, thiocyanate, persulfate, salts of phosphoric and sulfonic acids; and salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanoate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, pamoate, pectinate, 3-phenylpropionate, picrate, pivalate, propionate, lactobionate, pivolate, camphorate,

undecanoate and succinate, salts of organic sulfonic acids such as methanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, camphorsulfonate, 2-naphthalenesulfonate, benzenesulfonate, *p*-chlorobenzenesulfonate and *p*-toluenesulfonate.

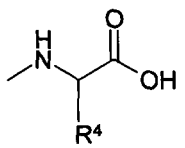
If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein. Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

In the gel compositions of the invention, the compound of general formula (I) is suitably the sole gelating agent; i.e. no other gelating agent is present.

The solvent may be an aqueous solvent such as water, sodium chloride solution or aqueous acetic acid or a mixture of water with an organic solvent such as DMSO or another suitable organic solvent.

In the gel, suitable compounds of general formula (I) are those in which, independently or in any combination:

R^1 is hydrogen, or unsubstituted C_{1-14} alkyl, more preferably hydrogen or C_{1-12} alkyl; and
R^2 is hydrogen, C_{1-4} alkyl optionally substituted with OH or, when R^3 is a group:

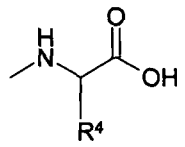


R^2 is R^7

R^7 is phenyl or a 5- or 6- membered nitrogen containing heteroaromatic ring system, either of which is optionally substituted with OH or benzyl.

In more suitable gel compositions of the present invention, in the compound of general formula (I) R^2 is hydrogen or methyl optionally substituted with hydroxy, imidazolyl, 1-benzylimidazolyl, or hydroxyphenyl.

In compounds of general formula (I), when R^3 is a group:



it is preferred that R^4 is hydrogen, methyl, ethyl or benzyl, any of which is optionally substituted with OR^9 or $COOR^9$;

R^9 is hydrogen, methyl, ethyl or benzyl;

More suitably, R^4 is hydrogen, methyl or ethyl wherein the methyl or ethyl groups may optionally be substituted COOH or COO-benzyl.

Preferred salts of compounds of general formula (I) are the hydrochloride salts.

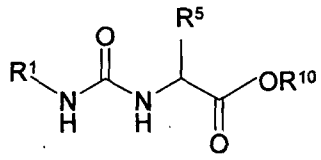
Particularly suitable compounds of general formula (I) include

1. *N*-ethylaminocarbonyl-glycine;
2. *N*-Decylaminocarbonyl-L-alanine;
3. *N*-Decylaminocarbonyl-L-valine;
4. *N*-Decyilaminocarbonyl-L-leucine;
5. *N*-Decylaminocarbonyl-L-tyrosine;
6. *N*-ethylaminocarbonyl-L-alanyl-L-alanine;
7. *N*-Butylaminocarbonyl-L-alanyl-L-alanine;
8. *N*-Butylaminocarbonyl-glicyl-glycine;
9. *N*-hexylaminocarbonyl-L-alanyl-glycine;
10. *N*-octylaminokarbonyl-L-alanyl-glycine;
11. *N*-dodecylaminocarbonyl-L-alanyl-glycine;
12. *N*-Heptylaminocarbonyl-L-alanyl-L-alanine;
13. *N*-Nonylaminocarbonyl-L-alanyl-L-alanine;
14. *N*-Dodecylaminocarbonyl-L-alanyl-L-alanine;

15. *N*-Octylaminocarbonyl-glycyl-glycine;
16. *N*-Decylaminocarbonyl-glycyl-glycine;
17. *N*-Nonylaminocarbonyl-glycyl-L-alanine;
18. *N*-Heptylaminocarbonyl-L-seryl-L-alanine;
19. *N*-Octylaminocarbonyl-L-seryl-L-alanine;
20. *N*-Nonylaminocarbonyl-L-seryl-L-alanine;
21. *N*-decylaminocarbonyl-glycyl-L-glutamic acid;
22. *N*γ –Benzyl, Nα-decylaminocarbonyl-L-hystidyl-glycine;
23. *N*-Aminocarbonyl-L-alanyl-glycine;

and salts thereof.

Compounds of general formula (I) in which R^3 is OH and R^1 is not hydrogen may be prepared from the corresponding esters of general formula (II):



(II)

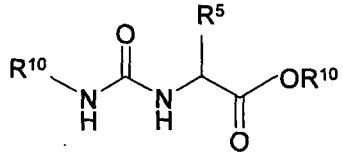
wherein R^1 is as defined for general formula (I), R^5 is either R^2 as defined in general formula (I) or, when R^2 contains a hydroxyl group, a protected version of R^2, and R^{10} is C_{1-6} alkyl or benzyl. The conversion of the ester group to a carboxylic acid may be achieved by any known method, for example by hydrogenolysis in which a solution of the ester is hydrogenated over a suitable catalyst (typically palladium/carbon) or alternatively by hydrolysis using a base such as lithium hydroxide.

Suitable protection and deprotection methodologies may be found, for example, in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc and when R^5 is a protected version of R^2, the protecting group is chosen so that it can be removed at the same time as the R^{10} moiety. Typically therefore, R^5 is benzyl ether.

Typically, hydrolysis is used for alkyl esters and hydrogenolysis for benzyl esters.

Esters of general formula (II) are new and they form a further aspect of the invention.

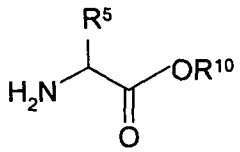
Compounds of general formula (I) in which R^3 is OH and R^1 is hydrogen may be prepared from the corresponding esters of general formula (IIa):



(IIa)

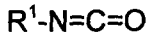
wherein R^5 is as defined above and the two R^{10} groups may be the same or different and are as defined above for general formula (II). The removal of the R^{10} groups may be achieved by any known method, for example by hydrogenolysis, in which a solution of the ester is hydrogenated over a suitable catalyst (typically palladium/carbon) or, alternatively by hydrolysis using a base such as lithium hydroxide.

An ester of general formula (II) or (IIa) may be prepared by the reaction of an amino acid ester of general formula (III):

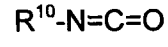


(III)

wherein R^5 and R^{10} are as defined for general formula (II);
or a salt of such an ester, typically a hydrochloride or *p*-toluenesulfonate salt;
with an isocyanate of general formula (IV) or (IVa):



(IV)



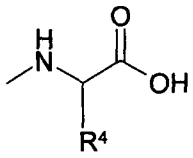
(IVa)

wherein R^1 is as defined for general formula (I) and R^{10} is as defined for general formula (II).

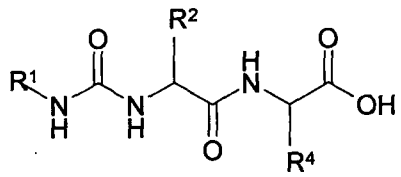
The reaction may be conducted in a dry organic solvent, for example dichloromethane and in the presence of a tertiary amine, typically triethylamine.

Compounds of general formula (III) and isocyanates of general formula (IV) and (IVa) are readily available or may be prepared using known methods by a person of skill in the art.

Compounds of formula (I) in which R^3 is:



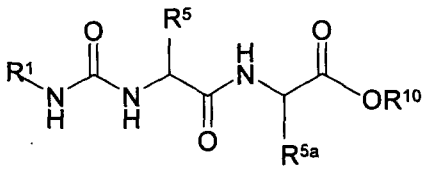
wherein R^4 is as defined above can be written as compounds of general formula (Ia):



(Ia)

wherein R^1, R^2, R^3 and R^4 are as defined for general formula (I).

These compounds of general formula (Ia) in which R^1 is not hydrogen may be prepared from the corresponding esters of general formula (VI):



(VI)

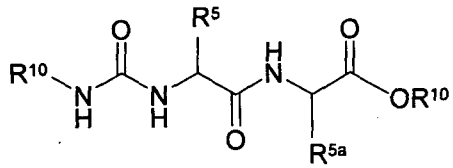
wherein R^1 is as defined for general formula (I), R^5 and R^{5a} are respectively either R^2 and R^4 as defined in general formula (I) or, when R^2 or R^4 contains a hydroxyl or carboxylic acid group, a protected version of R^2 or R^4; and R^{10} as defined for general formula (II). The

conversion of the ester group to a carboxylic acid may be achieved by any known method, for example by hydrogenolysis, in which a solution of the ester is hydrogenated over a suitable catalyst (typically palladium/carbon) or, alternatively by hydrolysis using a base such as lithium hydroxide.

Suitable protection and deprotection methodologies may be found, for example, in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc and when R^5 is a protected version of R^2 or R^4 the protecting group is chosen so that it can be removed at the same time as the R^{10} moiety. Typically therefore, R^5 is a benzyl ether or ester.

Typically, hydrolysis is used for alkyl esters and hydrogenolysis for benzyl esters.
Esters of general formula (VI) are new and they form a further aspect of the invention.

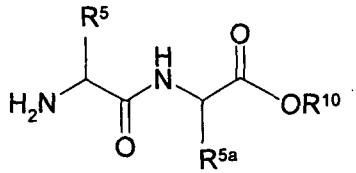
Compounds of general formula (Ia) in which R^1 is hydrogen may be prepared from the corresponding esters of general formula (VIa):



(VIa)

wherein R^5 and R^{5a} are as defined above for general formula (VI) and the two R^{10} groups may be the same or different and are as defined above for general formula (II). The removal of the R^{10} groups may be achieved by any known method, for example by hydrogenolysis, in which a solution of the ester is hydrogenated over a suitable catalyst (typically palladium/carbon) or, alternatively by hydrolysis using a base such as lithium hydroxide

An ester of general formula (VI) or (VIa) may be prepared by the reaction of a dipeptide ester of general formula (VII):

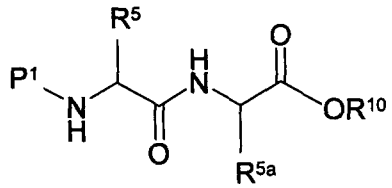


(VII)

wherein R^5 and R^{5a} are as defined for general formula (VI) and R^{10} is as defined for general formula (II);

or a salt of such an ester, typically a trifluoroacetate, hydrochloride or *p*-toluenesulfonate salt; with an isocyanate of general formula (IV) or (IVa) as defined above. The reaction may be conducted in a dry organic solvent, for example dichloromethane and in the presence of a tertiary amine, typically triethylamine.

Compounds of general formula (VII) or their salts may be prepared by deprotecting a protected dipeptide ester of general formula (VIII)



(VIII)

wherein R^5 and R^{5a} are as defined for general formula (VI), R^{10} is as defined for general formula (II) and and P^1 is an amine protecting group such as *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Z) or any other suitable protecting group. The method for removal of the protecting group will depend upon the particular protecting group which is used. For example, hydrogenation over a suitable catalyst, for example palladium or platinum, is particularly appropriate when P^1 is Z but when P^1 is BOC, it is more easily removed by stirring with trifluoroacetic acid and in this case, the compound of general formula (VII) will be a trifluoroacetate ester salt.

Suitable protection and deprotection methodologies may be found, for example, in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, published by John

Wiley & Sons Inc and therefore protected dipetide esters of general formula (VIII) may easily be prepared by a person of skill in the art.

As already discussed, compounds of general formula (I) and acid addition salts of these compounds are capable of forming gels when dissolved in water or other solvents.

Therefore, in a further aspect of the invention, there is provided a process for preparing a gel of the first aspect of the invention comprising mixing a compound of formula (I) or a salt thereof with a solvent. Heating and then cooling the solution are necessary for gel formation.

The solvent may be an aqueous solvent such as water, sodium chloride solution or aqueous acetic acid or a mixture of water with an organic solvent such as DMSO or another suitable organic solvent.

Where the compound of general formula (I) or a composition containing the compound is intended to be administered to a subject in a dry form, a gel may be formed *in situ* and in such a case, the aqueous solvent may be a physiological fluid, for example stomach acid or saliva.

Alternatively, however, the solvent may be an organic solvent such as DMSO, ethanol, *n*-decanol, propylene glycol, polyethylene glycol, tetrahydrofuran, dichloromethane, acetonitrile, toluene, *p*-xylene, or tetraline. The compound of the present invention are also capable of forming gels in oils such as glycerine, oleic acid, octyldodecanol and cocoyl caprylocaprate, which is sold under the trade mark Cetiol® LC (Cognis).

Many of the compounds of general formula (I) have extremely good gelation properties and relatively low concentrations are needed to cause gelation, although clearly the concentration required depends on the solvent. Typically, when in an aqueous solvent, the compound of general formula (I) or the salt thereof is present in a concentration of at least 0.2 mg/mL, but more preferably at least 1 mg/mL and in ascending order of preference at least 2, 3, 4, 5, 6, 7, 8, 9, 10 mg/mL or at larger suitable concentrations.

The concentration of the compound needed to form a gel (minimal gelation concentration or

MGC) varies according to the solvent and will, for example be different for an aqueous solution of sodium chloride and pure water. For an aqueous solution of, for example, sodium chloride or acetic acid, the MGC also varies according to the concentration of the solution. For the purposes of the present specification, MGC was determined visually by the vial inversion method in which sample vials were put in an inverted position and the MGC was defined as the concentration just before the gel started to flow. In practice, this requires the elastic modulus of the gel to be greater than about 65 Pa.

The MGC also depends upon the pH of the solvent used. The compounds of the invention can form gels in solutions which have acidic and neutral pH but are not so effective in alkaline solution, and particularly at pH 10 and above. More preferably, the pH of the solution is 7 or less.

Another advantageous property of gels formed by the compounds of general formula (I) and their salts is that they are able to flow when subjected to stresses above a threshold level, for example when extruded through an orifice or cannula, when packed into a delivery site using a spatula or when sprayed onto a delivery site. The threshold stresses of the gels are typically in the range of 1k Pa to 100 kPa. When subjected to stresses below the threshold level, however, the gels remain immobile.

These properties mean that the gel can be injected into a mould or extruded from a nozzle tip to form, for instance, line or sheet structures to cover a desired surface, which may be, for example, a skin surface or the surface of a body cavity.

The ease with which the gels can be formed into desired shapes means that they are ideally suited for purposes such as support matrices for tissue replacement as they can be applied to and conform to sites on or in tissue including tissue surfaces and defined cavities such as intravertebral spaces.

The gels formed by the compounds of the present invention are stable at room temperature for several months, they have high water content and therefore exhibit excellent biocompatibility and they are therefore ideal for pharmaceutical and cosmetic use. Furthermore, the

mucoadhesive and drug release properties of the gels can be adjusted by the degree of gelation, which is affected by the concentration above the minimal gelation concentration (MGC).

Therefore, in a further aspect of the invention, there is provided a composition comprising:

i. a compound of formula (I) or a salt thereof; and

ii. an active agent.

The compositions may additionally comprise a solvent, in which case they may be in gel form. In some cases, however, the composition may be a dry composition which is intended to form a gel *in situ*.

The compositions may be pharmaceutical compositions, in which case the active agent is a pharmaceutically or biologically active substance. Alternatively, however, they may be intended for the administration of other active agents, for example, dietary supplements.

The active agent is preferably water soluble and the solvent is preferably water or an aqueous solvent. Some active substances will show lesser solubility in aqueous hydrogelator systems than others and these water insoluble active substances can also be dispersed or suspended in the hydrogel with the aid of suitable suspending or viscosity enhancing agents.

A complete listing of useful water soluble, pharmaceutically active substances is not possible. However, representative are the following examples of the pharmacologically active substances that are preferred: anaesthetics (such as benoxinate, bupivacaine, dibucaine hydrochloride, dyclonine hydrochloride, etidocaine cocaine, hexylcaine, lidocaine, mepivacaine, naepaine, phenacaine hydrochloride, piperocaine, prilocaine, proparacaine hydrochloride, and tetracaine hydrochloride), analgesics (such as aspirin, acetaminophen and diflunisal), angiogenesis inhibitors, antiallergic agents, antibiotics (such as bacitracin, carbenicillin, cefazolin, cefoxitin, cephaloridine, chloramphenicol, chibrorifamycin, n-formamidoylthienamycin, gramicidin, neomycincolistin, penicillin G, polymyxin B, tetracyclines, vancomycin, and sulfonamides), anticancer, anticoagulants (such as heparin, bishydroxycoumarin, and warfarin), antidepressants (amitriptyline, chlordiazepoxide

perphenazine, doxepin, imipramine and protriptyline), antidiabetic agents (such as acetohexamide, chlorpropamide insulin, tolazamide and tolbutamide), antiepileptic agents, antifungal (such as amphotericin B, miconazole, natamycin, nystatin and tlucytosine), antihypertensive agents (such as spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine), anti-infective, anti-inflammatory (such as betamethasone, cortisone, dexamethasone sodium phosphate, fluorometholone, hydrocortisone, hydrocortisone acetate, dexamethasone, indomethacin, methylprednisolone, medrysone, prednisolone, preunisone, preunisolone sodium phosphate, triamcinolonesulindac, and its salts and analogs), antimicrobial, antipyretics, antiarrhythmic agents, antithrombotics, antituberculous agents, antitussive expectorants, antiulcer agents, antiviral (such as acyclovir, adenosine arabinoside (Ara-A), interferon, 5-iodo-2'-deoxyuridine and trifluorothymidine), bone resorption inhibitors, cholinergic or adrenergic agonists and antagonists, cardiotonics, cytostatic, haemostatics, fibrinolytics, muscle relaxants (such as melphalan, danbrolene, cyclobenzoprine, methocarbamol and diazepam), narcotic antagonists, sedatives, thrombolytics and wound healing agents. For example, the following highly water soluble drugs are suitable for delivery by hydrogels: buflomedil pyridoxalphosphate, diltiazem hydochloride, riboflavin sodium phosphate.

The drug delivery systems of the present invention may be designed to release appropriate biologically active substances. As biologically active substances should be intended for example proteins and their fragments, peptides and polynucleotides, growth factors, enzymes, vaccines and substances used in the treatment of diseases associated with genetic defects. Particular water soluble polypeptides which may be used include, for example, angiotensins, adrenocorticotrophic hormone (ACTH), bacitracins, bombesin antagonists, bradykinin, calcitonin, colistins, growth hormone, growth hormone releasing factor, endomorphins, enkephalins, glucagon, gastrin, gramicidines, insulin, interferon, luliberin or luteinizing hormone releasing hormone (LH-RH), LH-RH agonists or antagonists, monoclonal antibodies, tetragastrin, pentagastrin, urogastrone, prolactin, renin, secretin, oxytocin, polymyzins, somatostatin, tyrocidin, transforming growth factor antagonists, soluble vaccines, and vasopressin.

The compositions of the invention may also contain other agents, such as preservatives and buffering agents.

Suitable water soluble preservatives which may be employed in the drug delivery systems of the present invention include ascorbate, benzalkonium chloride, benzylalcohol, chlorobutanol, sodium bisulfite, sodium thiosulfate, parabens, phenylethanol, phenylmercuric borate and thimerosal. These agents may be present in amounts of from 0.001 to 5% by weight and preferably 0.01 to 2%.

Suitable water soluble buffering agents are alkali or alkali earth carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and the like, such as sodium phosphate, citrate, borate, acetate, bicarbonate and carbonate. These agents may be present in amounts sufficient to maintain a pH of the system of referably from 4 up to 8. The buffering agent therefore may be much as 5% by weight of the total composition.

Routes of administration of hydrogel-based drug delivery systems prepared in accordance with the present invention include, but are not limited to: inoculation or injection (e.g., intra-articular, intra-aural, intra-mammary, intra-muscular, intra-peritoneal, subcutaneous, etc.), topical application (e.g., on areas, such as eyes, ears, in or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g., vaginal and other epthelial linings, gastrointestinal mucosa, etc.). The compositions formulated using hydrogel matrices may include previously known pharmaceutical carriers or excipients, adjuvants, etc.

Compositions of the present invention are particularly advantageous as the gel formed by the compound of formula (I) or a salt thereof and a solvent is an ideal matrix for the sustained release of the active agent. The basic principle is to dissolve a water-soluble drug in solution that is then absorbed by the hydrogel. The drug is then released by diffusion. The release of water-soluble drug, entrapped in a hydrogels, occur only after water penetrates the networks to swell the gel and dissolve the drug, followed by diffusion along the aqueous pathways to the surface of the device. Drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through continuously swelling hydrogels. A

major element of the release of the active agent is related to the migration of its molecules through channels formed by the gel forming molecules, which may occur by one of two mechanisms, bulk flow and diffusion. The rate of diffusion of an active agent through a gel is modified by tortuosity (λ), which is defined by the equation:

$$\lambda = \left(\frac{D}{D^*}\right)^{1/2}$$

Where D is the diffusion coefficient in water and D* is the apparent diffusion coefficient in gel. Diffusion coefficients were observed to be in order of 10^{-6} (cm^2/sec). Tortuosity summarises the hindrance imposed by gel network structures and is also sensitive to the viscosity of the matrix and to molecular size. In practice, this means that increasing the elastic modulus of the gel or the size of the active agent molecule decreases the rate at which the active agent is released from the drug matrix. The elastic modulus of gels formed from compounds of general formula (I) or their salts is relatively easy to manipulate as it is affected by the solvent, the pH and the concentration of the compound of general formula (I) or its salt.

The thixotropic nature of the gels, which is discussed above, also means that compositions containing them can be formed required shapes, for instance tablets, lozenges, transdermal patches or suppositories. They can also easily be loaded into capsules.

The composition may be intended for topical, transdermal, rectal, buccal or sublingual administration and may be a pharmaceutical composition, in which the active agent is a biologically active compound. Alternatively, however, the composition may be a cosmetic composition intended for topical administration, in which case the active agent may be a cosmetically acceptable compound, for example a natural product or a vitamin.

The solvent in topical, transdermal, rectal, buccal or sublingual compositions may be either an aqueous solvent, a mixture of an aqueous and organic solvent or pharmaceutical oil such as glycerine, oleic acid, octyldodecanol or cocoyl caprylocaprate (Cetiol® LC). Oleic acid is a particularly useful oily solvent in such compositions because it has been found to reduce the irritation associated with many transdermal and topical products which is caused by other ingredients of the composition.

In transdermal pharmaceutical compositions, for example, penetration enhancing agents such as alcohols or glycols are known to cause skin irritation but oleic acid has been shown to reduce this (US 6,319,913). In addition, oleic acid is itself a penetration enhancing agent and so is particularly suitable solvent for transdermal products.

A composition for application to the skin may be also made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

Some topical and transdermal products take the form of patches which must adhere to the skin and it is therefore necessary for gels which form the basis of such products to exhibit appropriate values of adhesion and mechanical strength. The ability of an adhesive to form a bond with the skin is directly related to the tack of the adhesive, where tack is defined as the ability of an adhesive to form a bond after brief contact with light pressure. Insufficient tack may prevent attachment to the skin, whereas if the tack is too high, adhesive residue may be left on the skin after removal or the gel may cause dermal irritation. It is therefore preferable for a gel to have a probe tack value of at least 0.25 N as if it is lower than this, the skin adhesiveness is insufficient and the gel is likely to peel off with even a small amount of movement. Adhesives with high tack may form strong bonds with the skin on initial application and may therefore be difficult to remove and if the probe tack value of the gel exceeds 1.2 N, skin irritation is likely to occur (US 6,914,169).

The compositions may also be formulated for oral administration and they may be pharmaceutical compositions, in which case the active agent is a biologically active compound. Alternatively, however, they may be intended for the administration of, for example, dietary supplements.

The compounds of the first aspect of the invention are particularly useful for the formation of oral compositions as they are capable of retaining their gel structure at low pH and therefore are ideal for use as matrices for the sustained release of active agents in the stomach.

The solvent for the oral compositions may be an aqueous solvent, an organic solvent, a mixture of aqueous and organic solvents or oil and may be chosen according to the active compound. For example, hydrophobic compounds are preferably formulated in a gel which includes a hydrophobic solvent whereas for hydrophilic compounds an aqueous solvent may be preferred. Alternatively, the composition may be formulated without a solvent since the compound of general formula (Ia), (Ib) or salt thereof is capable of forming a gel in the stomach so that a matrix is formed around the active agent *in situ*.

Formulations for oral administration in the present invention may be presented as: discrete units such as capsules, sachets or tablets each containing predetermined amounts of the compound of general formula (Ia), (Ib) or salt thereof and active agent; as a powder or granules; as a gel composition in an aqueous liquid or a non-aqueous liquid etc.

Oral compositions, whether pharmaceutical or not, may also include an acceptable carrier.

For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound of general formula (Ia), (Ib) or salt thereof and active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in

a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored.

Other formulations suitable for oral administration include lozenges comprising the compound of general formula (Ia), (Ib) or salt thereof and the active agent in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound of general formula (Ia), (Ib) or salt thereof and the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia.

The compositions of the invention may be formed simply by mixing the compound of general formula (I) or a salt thereof with an active compound and optionally adding a solvent. This method forms yet another aspect of the present invention.

Other uses for gels formed by compounds of general formula (I) or their salts include thickeners for foodstuffs or cosmetic compositions.

Further aspects of the invention therefore comprise:

the use of a compound of general formula (I) in the preparation of a gel;

the use of a compound of general formula (I) in the preparation of a gel-forming composition, wherein the gel-forming composition comprises a compound of general formula (I) and an active agent;

the use of a compound of general formula (I) in the preparation of a pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of general formula (I), and a biologically active agent;

the use of a compound of general formula (I) as a gastroprotective agent for an acid sensitive biologically active agent;

the use of a compound of general formula (I) as an agent for controlling the rate of release of

an active agent from a composition;

the use of a compound of general formula (I) in the preparation of a cosmetic composition, wherein the cosmetic composition comprises a cosmetically acceptable compound; and

the use of a compound of general formula (I) in the preparation of a dietary supplement.

The invention will now be described in greater detail with reference to the following examples and to the drawing in which:

FIGURE 1 is a typical curve of tack probe measurement: force (in g) vs distance (or displacement in mm).

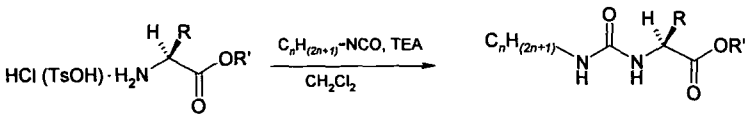
Example 1 – Chemical Synthesis of Compounds 1-23

General

Reagents were purchased from Aldrich, Bachem, Fluka, Kemika, Merck and Sigma, and were used without further purification. All solvents were purified and dried according to standard procedures. The reactions were monitored by thin-layer chromatography (t.l.c.) on Merck Kieselgel HF254 plastic sheets and spots were made visible using a UV lamp (254 nm) or I_2 vapors. Prepared compounds were purified chromatographically by preparative T.L.C. using silica gel *Merck* HF_{254} and by column chromatography using silica 0.063-0.2 mm (Merck). Reaction yields are not optimised. NMR spectra were recorded on a Bruker Avance spectrometer at 300/75 MHz with tetramethylsylane (TMS) as an internal standard. Chemical shifts (δ) were given in ppm, coupling constants (J) in Hz. Spin multiplicities; s (singlet), d (doublet), t (triplet), q (quadruplet), p (pentet) and m (multiplet). IR spectra were taken in KBr pellets on a ABB Bomen MB 102 FTIR-spectrometer, wave numbers (ν) are reported in cm^{-1}. Optical rotations were measured on an Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell at 589 nm, concentrations were given in g/100 ml.

1. Preparation *N* - alkylcarbonyl - amino acid methyl or benzyl esters

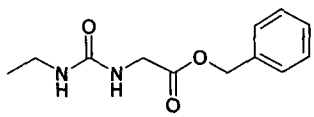
The title compounds were prepared by the reaction of alkyl isocyanate with appropriate amino ester:



1.1. *General procedure for the preparation methyl or benzyl esters of N-alkylaminocarbonyl - amino acids* ***(Esters 1 to 5)***

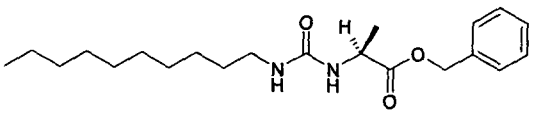
To a suspension of amino acid methyl or benzyl ester hydrochloride or *p*-toluensulfonate in dry CH_2Cl_2, TEA and $C_nH_{2n+1}NCO$ were added and the reaction mixture was stirred at room temperature over night. The product was partitioned between CH_2Cl_2 and water. Organic layer was washed with water, 5% HCl and 5 % $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The product was purified by crystallisation or by preparative t.l.c. chromatography.

1.1.1. Benzyl *N*-ethylaminocarbonyl - glycine (Ester 1)



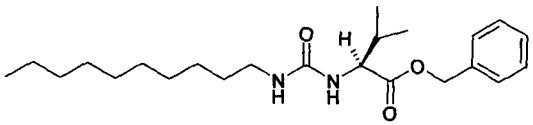
According to the general procedure 1.1.: HGlyOBzl·TsOH (0.611 g, 1.811 mmol), C_2H_5NCO (0.158 ml, 1.996 mmol), TEA (0.300 ml, 2.152 mmol), CH_2Cl_2 (10 ml) after crystallisation from CH_2Cl_2-ether-light petroleum - yield: 0.427 g, 99.8 %; ^{1}H NMR ($CDCl_3$): 7.39 – 7.28 (5 H, m, CH_{Bzl}), 5.97-5.67, 5.66 – 5.36 (2 x 1 H, 2 m, CONH), 5.17 – 5.10 (2 H, m, $CH_{2\ (Bzl)}$), 4.05 – 3.94 (2 H, m, $CH_{2,\ Gly}$), 3.25 – 3.11 (2 H, m, $CH_{2,\ Et}$), 1.16 – 1.03 (3 H, m, $CH_{3,\ Et}$); ^{13}C NMR: 171.5, 158.6 (CO), 135.4, (C_{Bzl}), 128.6, 128.4, 128.2 (CH_{Bzl}), 66.9 ($CH_{2,\ Bzl}$), 42.2 ($CH_{2,\ Gly}$), 35.1 (CH_2N_{Et}), 15.4 ($CH_{3,\ Et}$); IR: 3397, 3383, 3292, 3265, 1738, 1726, 1677, 1625, 1577.

1.1.2. Benzyl *N*-decylaminocarbonyl – L-alanine (Ester 2)



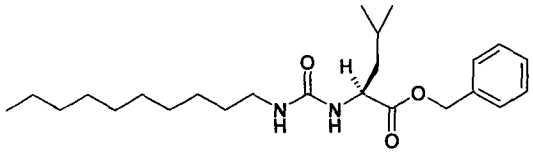
According to the general procedure 1.1.: L HAlaOBzl·TsOH (0.975 g, 2.774 mmol), $C_{10}H_{21}NCO$ (0.610 ml, 2.929 mmol, TEA (0.387 ml, 2.777 mmol), CH_2Cl_2 (30 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.5) – yield : 0.592 g, 58.9 %; ^{1}H NMR ($CDCl_3$): 7.39 – 7.29 (5 H, m, CH_{Bzl}), 5.37, 4.98 (2 x 1 H, 2 s br, NH_{Ala}, NH_{decyl}), 5.18, 5.12 (2 x 1 H, 2 d, J = 12.4, $CH_{2,\ Bzl}$), 4.58 - 4.48 (1 H, m, CH^*_{Ala}), 3.18 – 3.07 (2 H, m, CH_2N_{decyl}), 1.51 – 1.16 (16 H, m, $CH_{2,\ decyl}$), 1.37 (1 H, d, J = 7.2, $CH_{3\ (\beta,\ Ala)}$), 0.87 (3 H, t, J = 7.0, $CH_{3,\ decyl}$); ^{13}C NMR ($CDCl_3$): 173.9, 157.2 (CO), 135.1 (C_{Bzl}), 128.1, 127.8, 127.5 (CH_{Bzl}), 66.4 ($CH_{2,\ Bzl}$), 48.4 (CH^*_{Ala}), 40.1 (CH_2N_{decyl}), 31.4, 29.7, 29.09, 29.07, 28.9, 28.8, 26.4, 22.2 ($CH_{2,\ decyl}$), 18.5 ($CH_{3\ (\beta,\ Ala)}$), 13.6 ($CH_{3,\ decyl}$); IR: 3347, 1740, 1628, 1566.

1.1.3. Benzyl *N*-decylaminocarbonyl – L-valine (Ester 3)



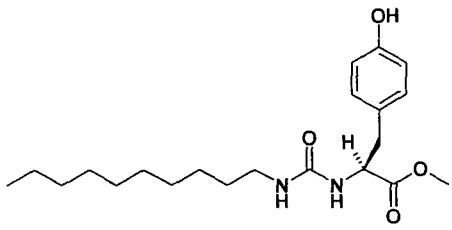
According to the general procedure 1.1.: L HValOBzl·TsOH (0.510 g, 1.344 mmol), $C_{10}H_{21}NCO$ (0.300 ml, 1.440 mmol), TEA (0.190 ml, 1.363 mmol), CH_2Cl_2 (20 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.5) – yield : 0.469, 89.3 %; ^{1}H NMR ($CDCl_3$): 7.35 – 7.29 (5 H, m, CH_{Bzl}), 5.78 (1 H, d, J = 8.7, NH_{Val}), 5.54 (1 H, t, J = 5.5, NH_{decyl}), 5.19, 5.08 (2 x 1 H, 2 d, J = 12.3, $CH_{2,\ Bzl}$), 4.48 (1 H, dd, J = 8.7, J = 4.9, CH^*_{Val}), 3.21 – 3.03 (2 H, m, CH_2N_{decyl}), 2.22 – 2.05 (1 H, m. $CH_{\beta,\ Val}$), 1.51 – 1.17 (16 H, m, $CH_{2,\ decyl}$), 0.92, 0.82 (2 x 3 H, 2 d, J = 6.8, $CH_{3\ (\gamma,\ Val)}$), 0.87 (3 H, t, J = 6.7, $CH_{3,\ decyl}$); ^{13}C NMR ($CDCl_3$): 173.5, 158.3 (CO), 135.3 (C_{Bzl}), 128.3, 128.0, 127.9 (CH_{Bzl}), 66.5 ($CH_{2,\ Bzl}$), 57.8 (CH^*_{Val}), 40.2 (CH_2N_{decyl}), 31.1 ($CH_{\beta,\ Val}$), 31.7, 30.0, 29.40, 29.38, 29.2, 29.1, 26.7, 22.4 ($CH_{2,\ decyl}$), 18.9, 17.4 ($CH_{3\ (\gamma,\ Val)}$), 13.9 ($CH_{3,\ decyl}$); IR: 3350, 1742, 1634, 1570.

1.1.4. Benzyl *N*-decylaminocarbonyl – L-leucine (Ester 4)



According to the general procedure 1.1.: L HLeuOBzl·TsOH (1.142 g, 2.902 mmol), $C_{10}H_{21}NCO$ (0.64 ml, 3.073 mmol, TEA (0.405 ml, 2.906 mmol), CH_2Cl_2 (30 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.5) – yield: 0.798, 68.0 %; $[\alpha]_D$ – 5 (c 5.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 7.39 – 7.28 (5 H, m, CH_{Bzl}), 5.36 (1 H, d, J = 8.5, NH_{Leu}), 5.18, 5.10 (2 x 1 H, 2 d, J = 12.4, $CH_{2,\ Bzl}$), 5.13 – 5.01 [1 H, m, NH_{decyl} (partly overlap with $\underline{CH_{2,\ Bzl}}$)], 4.53 (1 H, dd, J = 8.5, J = 5.1, CH^*_{Leu}), 3.21 – 3.01 (2 H, m, CH_2N_{decyl}), 1.78 – 1.16 (19 H, m, $CH_{\beta,\ Leu}$, $CH_{2\ (\gamma,\ Leu)}$, $CH_{2,\ decyl}$), 0.91, 0.89 (2 x 3 H, 2 d, J = 6.4, $CH_{3\ (\delta,\ Leu)}$), 0.87 (3 H, t, J = 6.8, $CH_{3,\ decyl}$); ^{13}C NMR ($CDCl_3$): 174.7, 157.9 (CO), 135.4 (C_{Bzl}), 128.4, 128.1, 127.9 (CH_{Bzl}), 66.7 ($CH_{2,Bzl}$), 51.5 (CH^*_{Leu}), 41.7 40.4 (CH_2N_{decyl} and $CH_{2,\ \beta,\ Leu}$), 37.7, 30.0, 29.46, 29.43, 29.24, 29.17, 26.8, 22.5 ($CH_{2,\ decyl}$), 24.6 ($CH_{\beta,\ Leu}$), 22.7, 21.8 ($CH_{3,\ \delta,\ Leu}$), 14.0 ($CH_{3,\ decyl}$); IR:3367, 1743, 1636, 1569

1.1.5. Methyl *N*-decylaminocarbonyl – L-tyrosine (Ester 5)

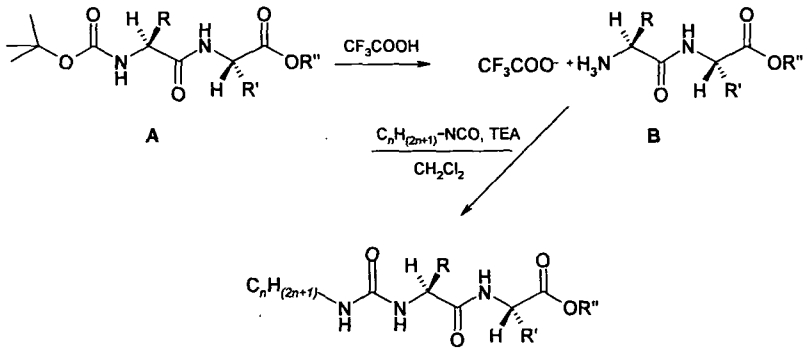


According to the general procedure 1.1.: L HTyrOMe·HCl (1.193 g, 5.149 mmol), $C_{10}H_{21}NCO$ (1.15 ml, 5.521 mmol), TEA (0.720ml, 5.166 mmol), CH_2Cl_2 (33 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.5) – yield: 1.078, 55.3 %; $[\alpha]_D$ + 34 (c 1, CH_2Cl_2 – EtOH, 3 : 2); ^{1}H NMR (DMSO-d_6): 9.23 (1 H, s, OH), 6.92, 6.66 (4 H, 2 dt, J = 8.5, J = 2.1, CH_{Ph}), 6.06 (1 H, t, J = 5.7, NH_{decyl}), 6.03 (1 H, d, J = 8.3, NH_{Tyr}), 4.36 – 4.26 (1 H, m, CH^*_{Tyr}), 3.58 (3 H, s, OCH_3), 2,93 (2 H, dt, J = 5.7, J = 6.5, CH_2N_{decyl}), 2.82 (1 H, dd, J = 13.8, J = 5.9, $CH_{A\ (\beta,\ Tyr)}$), 2.75 (1 H, dd, J = 13.8, J = 7.4, $CH_{B\ (\beta,\ Tyr)}$), 1.37 – 1.14 (16 H, m, $CH_{2,\ decyl}$), 0.85 (3 H, t, J = 6.7, $CH_{3,\ decyl}$); ^{13}C NMR (DMSO d_6): 173.7, 157.8 (CO), 156.5, 127.4 (C_{Ph}), 130.5, 115.5 (CH_{Ph}), 54.7 (CH^*_{Tyr}), 52.0 (OCH_3),

39.5, 37.4 (CH_2N_{decyl} and $CH_{2\ (\beta,\ Tyr)}$), 31.8, 30.4, 29.53, 29.45, 29.26 29.18, 26.8, 22.6 ($CH_{2,\ decyl}$), 14.4 ($CH_{3,\ decyl}$); IR: 3347, 1750, 1638, 1582, 1514.

2. Preparation of benzyl or methyl ester of *N*-alkylcarbonyl – dipeptide

The title compounds were prepared by the reaction of alkyl isocyanate with appropriate *N*-deprotected dipeptide **B.**

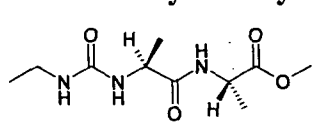


2.1. *General procedure for the preparation of methyl or benzyl esters of N - alkylcarbonyl – dipeptide* ***(Esters 6-22).***

a) A solution of appropriate dipeptide **A** in CF_3COOH was stirred for 30 min. at 0°C and for 1.5 h. at room temperature. The solvent was evaporated and and the traces of CF_3COOH were removed by coevaporation with benzene. The product was dried for 1 h under reduced pressure and dissolved in dry CH_2Cl_2 or dry EtOAc.

b) To this solution of *N* – deprotectide dipeptide **B**, TEA and $C_nH_{2n+1}NCO$ were added and the reaction mixture was stirred at room temperature over night. The product was partitioned between organic solvent and water. Organic layer was washed with water, 5% HCl and 5 % $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The products were purified by crystallisation or by preparative t.l.c. chromatography on silica gel or on silica gel column.

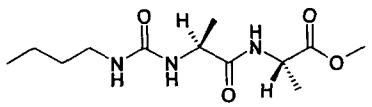
2.1.1. Methyl *N*-ethylaminocarbonyl – L – alanyl – L - alanine (Ester 6)



According to the general procedure 2.1.: a) Boc-Ala-Ala-OMe·(0.490 g, 1,786 mmol), CF_3COOH (3 ml); b) C_2H_5NCO (0.155 ml, 1.958 mmol), TEA (0.250 ml, 1.794 mmol),

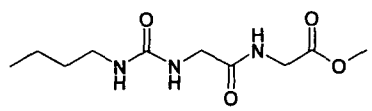
CH_2Cl_2 (10 ml) after purification on silica gel column – yield: 0.212 g, 48.4 %; ^{1}H NMR (DMSO-d_6): 8.33 (1 H, d, J =7.0, NH_{Ala}), 6.01 (1 H, t, J = 5.5, NH_{Et}), 5.98 (1 H, d, J = 7.8, NH_{Ala}), 4.33 – 4.14 (2 H, m, CH^*_{Ala}), 3.62 (3 H, s, $CH_{3,\ OEt}$), 2.95 (2 H, dt, J = 6.4, J = 5.5, CH_2N), 1.27 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 1 14 (3 H, d, J = 7.2, $CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 7.0, $CH_{3,\ Et}$); ^{13}C NMR ($CDCl_3$): 173.3, 172.2, 157.5 (CO), 50.9 ($CH_{3,\ OMe}$), 47.9, 46.7 (CH^*_{Ala}), 33.5 (CH_2N), 17.2, 15.8 ($CH_{3\ (\beta,\ Ala)}$), 13.8 ($CH_{3,\ Et}$); IR: 3340, 3278, 1744, 1650, 1624, 1578, 1559.

2.1.2. Methyl *N*-butylaminocarbonyl – L – alanyl – L - alanine (Ester 7)



According to the general procedure 2.1.:b) H-Ala-Ala-OMe·CF_3COOH (0.430 g, 1.492 mmol), C_4H_9NCO (0.185 ml, 1.642 mmol), TEA (0.208 ml, 1.492 mmol), EtOAc (20 ml) after crystallisation (CH_2Cl_2 – MeOH - light petroleum) – yield: 0.236 g, 57.9 %; ^{1}H NMR (DMSO-d_6): 8.33 (1 H, d, J = 7.1, NH), 6.02 (1 H, t, J = 5.6, NH), 5.96 (1 H, J = 8.2, NH), 4.32 - 4.12 (2 H, m, CH^*_{Ala}), 3.61 3 H, s, ($CH_{3,\ OMe}$), 2.95 (2 H, q, J = 6.2, CH_2N), 1.27 (3 H, d, J = 7.3, $CH_{3,\ \beta}$), 1.21 (3 H, d, J = 7.0, $CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.9, $CH_{3,\ Bu}$); ^{13}C NMR (DMSO-d_6): 173.7, 173.4, 157.8 (CO), 52.3 ($CH_{3,\ OMe}$), 48.5, 47.8 (CH^*_{Ala}), 39.2 (CH_2N), 32.5, 19.95 ($CH_{2,\ Bu}$), 19.98, 17.3 ($CH_{3\ (\beta,\ Ala)}$), 14.1 ($CH_{3,\ Bu}$); IR; 3349, 3327, 3285, 1742, 1652, 1617, 1560.

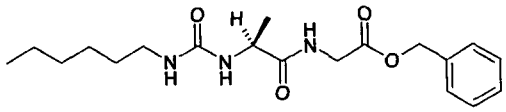
2.1.3. Methyl *N*-butylaminocarbonyl glycyl glycine (Ester 8)



According to the general procedure 2.1.:b) H-Gly-Gly-OMe·HCl (0.860 g, 4.709 mmol), C_4H_9NCO (0.520 ml, 4.616 mmol), TEA (0.650 ml, 4.663 mmol), EtOAc (20 ml) after crystallisation (CH_2Cl_2 – MeOH - light petroleum) – yield: 0.260 g, 22.5 %; ^{1}H NMR (DMSO-d_6):): 8.22 (1H, t, J =5.8, NH_{Gly}), 6.11 (1H, t, J =5.6, NH_{Bu}), 6.03 (1H, t, J =5.6, NH_{Gly}), 3.85 (1H, d, 2 J =5.8, $CH_{2,\ Gly}$), 3.67 (1H, d, J = 5.6, $CH_{2,\ Gly}$), 3.63 (3 H, s, $CH_{3,\ OMe}$), 3.30 (2 H, dt, J = *5.9,* J = 6.4, CH_2N_{Bu}), 1.41 – 1.19 (4 H, m, $CH_{2,\ Bu}$), 0.87 (3 H, t, J = 7.0,

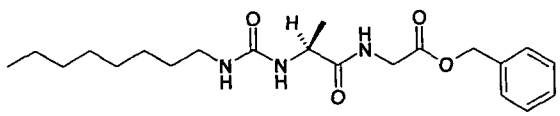
$CH_{3,\ Bu}$); ^{13}C NMR ($CDCl_3$): 171.3, 170.2, 158.8 (CO), 51.9 ($CH_{3,\ OMe}$), 43.6, 40.9, 39.7 (CH_2N_{Bu} and $CH_{2,\ Gly}$), 32.4, 19.9 ($CH_{2,\ Bu}$), 13.8 ($CH_{3,\ Bu}$).

2.1.4. Benzyl *N* - hexylaminocarbonyl – L – alanyl - glycine (Ester 9)



To a solution of H-Ala-Gly-OBzl·CF_3COOH (0.677 g, 1.933 mmol) and TEA (0.270 ml, 1.937 mmol) in dry CH_2Cl_2 (20 ml), $C_6H_{13}NCO$ (0.308. ml, 2.126 mmol) was added and the reaction mixture was stirred at room temperature. Because the reaction mixture was in gel state, dry EtOAc (15 ml) was added and the mixture was stirred overnight at 40 °C. After cooling gel was formed, this transformed to the fibrous precipitate after standing two days at room temperature. The precipitate was filtered off and washed with water to give: 0.617 g, 87.8 %; $[\alpha]_D$ – 150 (c 1, CH_2Cl_2 : MeOH, 1:1); ^1H NMR (DMSO-d_6):): 8.37 (1 H, t, J = 5.9 NH_{Gly}), 7.39 – 7.29 (5 H, m, CH_{Bzl}), 6.05 – 5.98 (2 H, m, $NH_{hexyl,\ Ala}$), 5.12 (2 H, s, $CH_{2\ (Bzl)}$), 4.19 (1 H, dq, J = 7.1, J = 7.7 CH^*_{Ala}), 3.93, 3.85 (2 H, 2 dd, J = 5.9, J = 17.2, $CH_{2,\ Gly}$), 2.95 (2 H, dt, J = 6.5, J = 5.8, CH_2N_{hexyl}), 1.39 – 1.18 (6 H, m, $CH_{2,\ hexyl}$), 1 13 (3 H, d, J = 7.0, $CH_{3\ (\beta,\ Ala)}$), 0.85 (3 H, t, J = 6. 8, $CH_{3,\ hexyl}$); ^{13}C NMR ($CDCl_3$): 174.5, 169.1, 157.8 (CO), 134.7 (C_{Bzl}), 128.1, 128.0, 127.7 (CH_{Bzl}), 66.5 ($CH_{2,\ Bzl}$), 48.8 (CH^*_{Ala}), 40.9, 39.9 ($CH_{2,\ Gly}$ and CH_2N_{hexyl}), 31.1, 29.7, 26.1, 22.1, ($CH_{2,\ hexyl}$), 18.4 ($CH_{3\ (\beta,\ Ala)}$), 13.5 ($CH_{3,\ hexyl}$); IR: 3369, 3326, 3290, 1734, 1654, 1625, 1570.

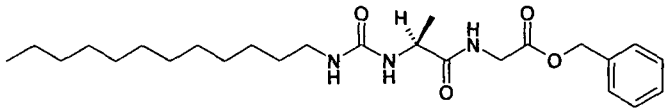
2.1.5. Benzyl *N*-octylaminocarbonyl – L – alanyl - glycine (Ester 10)



To a solution of H-Ala-Gly-OBzl·CF_3COOH (0.677 g, 1.933 mmol) and TEA (0.270 ml, 1.937 mmol) in dry CH_2Cl_2 (20 ml), $C_8H_{17}NCO$ (0.412. ml, 2.335 mmol) was added. Because by stirring over night gel was formed, additional amount of dry CH_2Cl_2 (5 ml) and dry EtOAc (10 ml) were added. The jelly mixture was stirred over night. The solvent was evaporated at the reduced pressure and the product was purified by preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – MeOH, 100:2) to give: 0.565 g, 74.7 %; $[\alpha]_D$ – 120 (c 1, CH_2Cl_2 : MeOH,

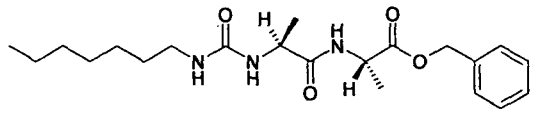
1:1); ^{1}H NMR (DMSO-d_6): 8.37 (1 H, t, J = 5.9, NH_{Gly}), 7.42 – 7.28 (5 H, m, CH_{Bzl}), 6.05 – 5.98 (2 H, m, $NH_{octyl,\ Ala}$), 5.12 (2 H, s, $CH_{2,\ Bzl}$), 4.19 (1 H, dq, J = 7.1, J = 7.6 CH^*_{Ala}), 3.93, 3.85 (2 H, 2 dd, J = 6.0, J = 17.2, $CH_{2,\ Gly}$), 2.95 (2 H, q, J = 6.5, CH_2N_{octyl}), 1.38 – 1.19 (12 H, m, $CH_{2,\ octyl}$), 1 13 (3 H, d, J = 7.0, $CH_{3\ (\beta,\ Ala)}$), 0.85 (3 H, t, J = 6. 8, $CH_{3,\ octyl}$); ^{13}C NMR ($CDCl_3$): 174.9, 169.4, 158.1 (CO), 135.0 (C_{Bzl}), 128.4, 128.3, 128.1 (CH_{Bzl}), 66.8 ($CH_{2,\ Bzl}$), 49.0 (CH^*_{Ala}), 41.2, 40.1 ($CH_{2,\ Gly}$ and CH_2N_{octyl}), 31.7, 30.2, 29.2, 29.1, 26.8, 22.5, ($CH_{2,\ octyl}$), 18.9 ($CH_{3\ (\beta,\ Ala)}$), 13.9 (, $CH_{3,\ octyl}$); IR: 3311, 1735, 1645, 1624, 1561.

2.1.6. Benzyl *N*-dodecylaminocarbonyl – L – alanyl - glicyne (Ester 11)



To a solution of H-Ala-Gly-OBzl·CF_3COOH (0.677 g, 1.933 mmol) and TEA (0.270 ml, 1.937 mmol) in dry CH_2Cl_2 (20 ml), $C_{12}H_{25}NCO$ (0.512. ml, 2.125 mmol) was added. Because by the stirring over night gel was formed, additional amount of dry CH_2Cl_2 (10 ml) and dry EtOAc (5 ml) were added. The reaction mixture was stirred over night. The solvent was evaporated and the precipitate was filtered off and washed with water to give: 0.480 g, 55.5 %; $[\alpha]_D$ – 90 (c 1, CH_2Cl_2 : MeOH, 1:1); ^{1}H NMR (DMSO-d_6): 8.38 (1 H, t, J = 5.8 NH_{Gly}), 7.39 – 7.29 (5 H, m, CH_{Bzl}), 6.02 (1 H, d, J = 8.1, NH_{Ala}), 6.01 (1 H, t, J = 5.9, NH $_{dodecyl}$), 5.12 (2 H, s, $CH_{2,\ Bzl}$), 4.25 –4.13 (1 H, m, CH^*_{Ala}), 3.94, 3.85 (2 H, 2 dd, J = 5.8, J = 17.2, $CH_{2,\ Gly}$), 2.95 (2 H, dt, J = 5.9, J = 6.3, $CH_2N_{dodecyl}$), 1.38 – 1.18 (20 H, m, $CH_{2,\ dodecyl}$), 1.14 (3 H, d, J = 7.0, $CH_{3\ (\beta,\ Ala)}$), 0.85 (3 H, t, J = 6.6, $CH_{3,\ dodecyl}$); ^{13}C NMR($CDCl_3$): 174.5, 169.1, 157.8 (CO), 134.7 (C_{Bzl}), 128.1, 128.0, 127.7 (CH_{Bzl}), 66.5 ($CH_{2,\ Bzl}$), 48.8 (CH^*_{Ala}), 40.9, 39.9 ($CH_{2,\ Gly}$ and $CH_2N_{dodecyl}$), 31.4, 29.8, 29.2, 29.0, 28.9, 26.5, 22.2 ($CH_{2,\ dodecyl}$), 18.4 (CH^*_{Ala}), 13.6 ($CH_{3,\ dodecyl}$); IR: 3313, 1735, 1655, 1623, 1560.

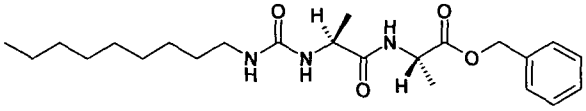
2.1.7. Benzyl *N*-heptylaminocarbonyl – L- alanyl – L - alanine (Ester 12)



According to the general procedure 2.1.: a) Boc-Ala-Ala-OBzl·(0.533 g, 1.521 mmol), CF_3COOH (3 ml); b) $C_7H_{15}NCO$ (0.260 ml, 1.613 mmol), TEA (0.440 ml, 3.157 mmol),

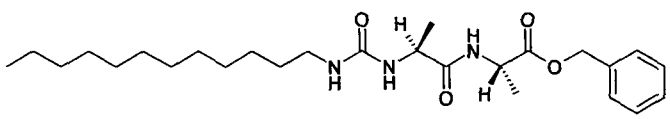
CH_2Cl_2 (10 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 4) – yield: 0.428 g, 71.9 %: ^{1}H NMR ($CDCl_3$): 7.85 (1 H, d, J = 6.6, NH_{Ala}), 7.38 – 7.27 (5H, m, CH_{Bzl}), 6.31, 5.70 (2 x 1 H, 2 s br, NH_{Ala} and NH_{heptyl}), 5.16, 5.07 (2 H, 2 d, 2 J = 12.4, $CH_{2, Bzl}$), 4.63 – 4.55 (1 H, m, CH^*_{Ala}), 4.48 (2 x 1 H, 2 p, J = 7.2, CH^*_{Ala}), 3.15 – 3.01 (2 H, m, CH_2N_{heptyl}), 1.48 – 1.15 (10 H, m. $CH_{2, heptyl}$), 1.39, 1.30 (2 x 3 H, 2 d, 2 J = 7.2, $CH_{3\ (\beta, Ala)}$), 0.85 (3 H, t, J = 7.0, $CH_{3, heptyl}$); ^{13}C NMR ($CDCl_3$): 174.0, 171.8, 157.8 (CO), 135.0 (C_{Bzl}), 128.0, 127.8, 127.6 (CH_{Bzl}), 66.4 ($CH_{2, Bzl}$), 48.7, 47.8 (CH^*_{Ala}), 39.8 (CH_2N_{heptyl}), 31.3, 29.8, 28.6, 26.5, 22.1 ($CH_{2, heptyl}$), 18.9, 16.9 ($CH_{3\ (\beta, Ala)}$), 13.5 ($CH_{3, heptyl}$); IR: 3320, 3273, 1732, 1647, 1626, 1560.

2.1.8. Benzyl *N*-nonylaminocarbonyl – L- alanyl – L - alanine (Ester 13)



According to the general procedure 2.1.: a) Boc-Ala-Ala-OMe·(0.533 g, 1.521 mmol), CF_3COOH (3 ml); b) $C_9H_{19}NCO$ (0.310 ml, 1.593 mmol), TEA (0.440 ml, 3.157 mmol), CH_2Cl_2 (10 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100: 4) – yield: 0.169 g, 26.5 %: ^{1}H NMR ($CDCl_3$): 7.49 (1 H, s br, NH_{Ala}), 7.38 – 7.28 (5 H, m, CH_{Bzl}), 5.98, 5.39 (2 x 1 H, 2 s br, NH_{Ala} and NH_{nonyl}), 5.17, 5.09 (2 H, 2d, 2 J = 12.3, $CH_{2, Bzl}$), 4.50 (2 H, p., J = 7.1, CH^*_{Ala}), 3.15 – 3.02 (2 H, m, CH_2N_{nonyl}), 1.51 – 1.10 (14 H, m. $CH_{2, nonyl}$), 1.39, 1.31 (2 x 3H, 2 d, 2 J = 7.1, $CH_{3\ (\beta, Ala)}$), 0.86 (3 H, t, J = 7.0, $CH_{3, nonyl}$); ^{13}C NMR ($CDCl_3$): 173.6, 171.9, 157.6 (CO), 134.9 (C_{Bzl}), 128.1, 127.9, 127.6 (CH_{Bzl}), 66.5 ($CH_{2, Bzl}$), 49.9, 47.8 (CH^*_{Ala}), 39.9 (CH_2N_{nonyl}), 31.4, 29.8, 29.1, 28. 9, 28.8, 26.5, 22.1 ($CH_{2, nonyl}$), 18.7 ,17.1 ($CH_{3\ (\beta, Ala)}$), 13.6 ($CH_{3, nonyl}$); IR: 3344, 3323, 3279, 1744, 1649, 1628, 1553.

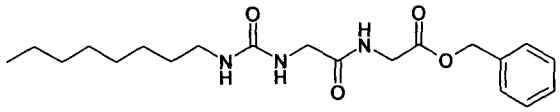
2.1.9. Benzyl *N* – dodecylaminocarbonyl – L- alanyl – L - alanine (Ester 14)



According to the general procedure 2.1.: a) Boc-Ala-Ala-OMe·(0.533 g, 1.521 mmol), CF_3COOH (3 ml); b) $C_{12}H_{25}NCO$ (0.390 ml, 1.618 mmol), TEA (0.640 ml, 4.592 mmol), CH_2Cl_2 (60 ml) after crystallization – yield: 0.280 g, 39.9 %; ^{1}H NMR (DMSO-d_6): 8.37 (1 H,

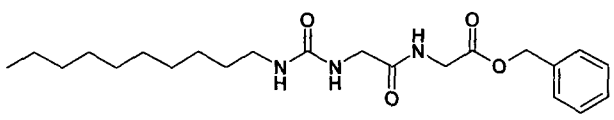
t, J = 7.1, NH_{Ala}), 7.41 – 7.27 (5 H, m, CH_{Bzl}), 6.02 (1 H, t, J = 5.6, NH), 5.98 (1 H, d, *J* = 8.3, NH), 5.13, 5.08 (2 H, 2 d, 2 *J* = 12.6, $CH_{2,\ Bzl}$), 4.32 (1 H, p, *J* = 7.1, CH^*_{Ala}), 4.20 (1 H, dq., *J* = 7.1, *J* = 7.7, CH^*_{Ala}), 3.00 -2.88 (2 H, m, $CH_2N_{dodecyl}$), 1.39 – 1.15 (20 H, m. $CH_{2,\ dodecyl}$),1.30, 1.10 (2 x 3 H, 2 d, 2 *J* = 7.1, $CH_{3\ (\beta,\ Ala)}$), 0.85 (3 H, t, *J* = 6.6, $CH_{3,\ dodecyl}$); ^{13}C NMR (DMSO-d_6): 173.8, 172.8, 157.7 (CO), 136.4 (C_{Bzl}), 128.8, 128.4, 128.2 (CH_{Bzl}), 68.3 ($CH_{2,\ Bzl}$), 48.5, 48.0 (CH^*_{Ala}), 39.6 ($CH_2N_{dodecyl}$), 31.8, 30.4, 29.53, 29.49, 29.27, 29.19, 26.8, 22.6 ($CH_{2,\ dodecyl}$), 20.0, 17.2 ($CH_{3\ (\beta,\ Ala)}$), 14.4 ($CH_{3,\ dodecyl}$); IR: 3357, 3321, 3286, 1741, 1730, 1651, 1617, 1569, 1557.

2.1.10. Benzyl *N* – octylaminocarbonyl – glycyl - glycine (Ester 15)



To a suspension of H-Gly–Gly–OBzl·TsOH (2.011 g, 5.098 mmol) and TEA (0.80 ml, 5.740 mmol) in dry CH_2Cl_2 (20 ml) and dry EtOAc (50 ml), $C_8H_{17}NCO$ (1.06 ml, 6.009 mmol) was added and the reaction mixture was stirred 4 h. at room temperature and heated for reflux over night. After cooling to the room temperature, precipitate was filtered off and washed with water to give 1.750 g, 90.9 %; ^1H NMR (DMSO-d_6): 8.27 (1 H, t, *J* = 5.9, NH_{Gly}), 7.39 – 7.28 (5 H, m, CH_{Bzl}), 6.11 (1 H, t, *J* = 5.6, NH), 6.05 (1 H, t, *J* = 5.6, NH), 5.13 (2 H, s, $CH_{2,\ Bzl}$), 3.91 (2 H, d, *J* = 5.9, $CH_{2,\ Gly}$), 3.68 (2 H, d, *J* = 5.6, $CH_{2,\ Gly}$), 2.97 (2 H, dt, *J* = 5.6, *J* = 6.1, CH_2N_{octyl}), 1.41 – 1.4 (12 H, m. $CH_{2,\ octyl}$), 0.86 (3 H, t, *J* = 7.0, $CH_{3,\ octyl}$); ^{13}C NMR (DMSO-d_6): 171.2, 170.2, 158.3 (CO), 136.4 (C_{Bzl}), 128.9, 128.5, 128.4 (CH_{Bzl}), 66.3 ($CH_{2,\ Bzl}$), 43.1, 41.1 ($CH_{2,\ Gly}$), 39.8 (CH_2N_{octyl}), 31.7, 30.4, 29.25, 29.18, 26.9, 22.6 ($CH_{2,\ octyl}$), 14.4 ($CH_{3,\ octyl}$); IR: 3350, 3310, 1738, 1661, 1625, 1581, 1544, 1514.

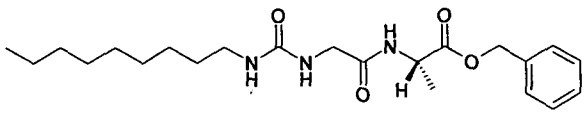
2.1.11. Benzyl *N* – decylaminocarbonyl – glicyl - glycine (Ester 16)



To a suspension of H-Gly–Gly–OBzl·TsOH (1.850 g, 4.690 mmol) and TEA (0.730 ml, 5.237 mmol) in dry CH_2Cl_2 (20 ml) and dry EtOAc (50 ml), $C_{10}H_{21}NCO$ (1.20 ml, 5.761 mmol) was added and the reaction mixture was stirred 1 h. at room temperature and heated for reflux for 4h. After cooling to the room temperature, precipitate was filtered of and washed with water

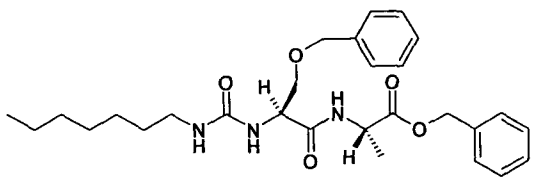
to give: 1.723 g, 90.6 %; ^{1}H NMR (DMSO-d_6): 8.26 (1 H, t, J = 5.9, NH_{Gly}), 7.44 – 7.27 (5 H, m, CH_{Bzl}), 6.12 (1 H, t, J = 5.6, NH), 6.05 (1 H, t, J = 5.6, NH), 5.13 (2 H, s, $CH_{2,\ Bzl}$), 3.91 (2 H, d, J = 5.9, $CH_{2,\ Gly}$), 3.68 (2 H, d, J = 5.6, $CH_{2,\ Gly}$), 3.01 – 2 92 (2 H, m, CH_2N_{decyl}), 1.41 – 1.15 (16 H, m. $CH_{2,\ decyl}$), 0.85 (3 H, t, J = 6.5, $CH_{3,\ decyl}$); ^{13}C NMR (DMSO-d_6): 170.7, 169.7, 157.9 (CO), 135.9 (C_{Bzl}), 128.4, 128.0, 127.8 (CH_{Bzl}), 65.8 ($CH_{2,\ Bzl}$), 42.7, 40.6 ($CH_{2,\ Gly}$), 39.3 (CH_2N_{decyl}), 31.3, 29.9, 29.03, 28.96, 28.80, 27.68, 26.4, 22.1 ($CH_{2,\ decyl}$), 13.9 ($CH_{3,\ decyl}$); IR: 3349, 3310, 1738, 1661, 1625, 1581, 1545.

2.1.12. Benzyl N – nonylaminocarbonyl - glycyl- L- alanine (Ester 17)



According to the general procedure 2.1.: a) Boc-Gly-Ala-OMe·(0.983 g, 2.922 mmol), CF_3COOH (1.5 ml); b) $C_9H_{19}NCO$ (0.625 ml, 3.213 mmol), TEA (0.815 ml, 5.847 mmol), CH_2Cl_2 (26 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 5) – yield: 0.157 g, 14.8 %: ^{1}H NMR ($CDCl_3$): 7.59 (1 H, d, J = 7.1, NH_{Ala}), 7.40 – 7.28 (5 H, m, CH_{Bzl}), 6.09 (1 H, t, J = 5.5, NH_{Gly}), 5.51 (1 H, t, J = 5.3, NH_{nonyl}), 5.17, 5.10 (2 x 1H, 2 d, 2 J = 12.3, $CH_{2,\ Bzl}$), 4.56 (1 H, p, J = 7.1, CH^*_{Ala}), 3.92 (2H, d, J = 5.5, $CH_{2,\ Gly}$), 3.16 - 3.05 (2 H, m, CH_2N_{nonyl}), 1.52 – 1.15 (14 H, m, $CH_{2,\ nonyl}$), 1.40 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.6, $CH_{3,\ hexyl}$); ^{13}C NMR ($CDCl_3$): 172.6, 171.1, 158.8 (CO), 135.4 (C_{Bzl}), 128.6, 128.4, 128.0 (CH_{Bzl}), 67.0 ($CH_{2,\ Bzl}$), 48.3 (CH^*_{Ala}), 43.8, 40.5 ($CH_{2,\ Gly}$ and CH_2N_{Bzl}), 31.9, 30.3, 29.6, 29.4, 29.3, 27.0, 22.7 ($CH_{2,\ nonyl}$), 17.7 ($CH_{3\ (\beta,\ Ala)}$), 14.1 ($CH_{3,\ nonyl}$); IR: 3311, 1734, 1654, 1624, 1560.

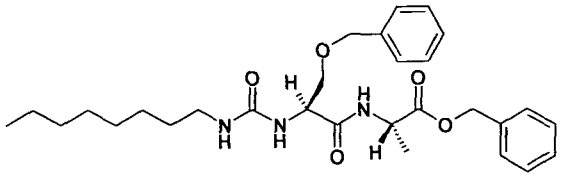
2.1.13. Benzyl O-benzyl, N-heptylaminocarbonyl-L-seryl-L-alanine (Ester 18)



According to the general procedure 2.1.: a) Boc-L-Ser (Bzl)-L-Ala-OMe·(0.761 g, 1.667 mmol), CF_3COOH (4 ml); b) $C_7H_{15}NCO$ (0.300 ml, 1.861 mmol), TEA (0.465 ml, 3.336 mmol), CH_2Cl_2 (5 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.4) – yield: 0.685 g, 82.6 %; ^{1}H NMR ($CDCl_3$): 7.39 (1 H, d, J = 7.2, NH_{Ala}), 7.36 –

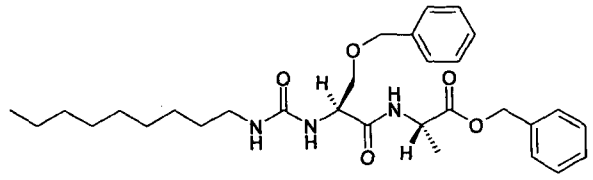
7.23 (10 H, m, CH_{Bzl}), 5.71 (1 H, d, J = 5.9, NH_{Ser}), 5.17, 5.10 (2 H, 2 d, 2 J = 12.3, $CH_{2,\ Bzl}$), 4.62 – 4.43 (4 H, m, CH^*_{Ala}, CH^*_{Ser} and $CH_{2\ (Bzl\text{-}Ser,)}$), 3.81 (1 H, dd, J = 4.3, J = 9.3, $CH_{A\ (\beta,\ Ser)}$), 3.51 (1 H, dd, J = 7.2, J = 9.3, $CH_{B\ (\beta,\ Ser)}$), 3.11 (2 H, t, J = 6.9, CH_2N_{heptyl}), 1.53 – 1.17 (10 H, m, $CH_{2,\ heptyl}$), 1.37 (3 H, d, J = 7.2,$CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.7, $CH_{3,\ heptyl}$); ^{13}C NMR ($CDCl_3$): 172.3, 171.3, 157.9 (CO), 137.5, 135.4 (C_{Bzl}), 128.6, 128,4, 128.2, 127.8 (CH_{Bzl}), 73.3, 70.5 ($OCH_{2\ (Bzl\text{-}Ser)}$ and $CH_{2\ (\beta,\ Ser)}$), 67.1 ($CH_{2,\ Bzl}$), 53.1 (CH^*_{Ser}), 48.4 (CH^*_{Ala}), 40.6 (CH_2N_{heptyl}), 33.9, 31.8, 30.2, 29.0, 26.9, 22.6 ($CH_{2,\ heptyl}$), 18.0 ($CH_{3,\ Ala}$), 14.1 ($CH_{3,\ heptyl}$);

2.1.14. Benzyl O-benzyl, N-octylaminocarbonyl-L-seryl-L-alanine (Ester 19)



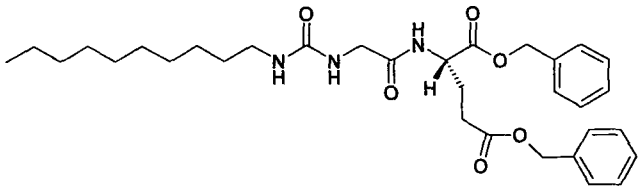
According to the general procedure 2.1.: a) Boc-L-Ser (Bzl)-L-Ala-OMe·(0.761 g, 1.667 mmol), CF_3COOH (4 ml); b) $C_8H_{17}NCO$ (0.330 ml, 1.871 mmol), TEA (0.465 ml, 3.336 mmol), CH_2Cl_2 (5 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.4) – yield: 0.840 g, 98.5 %; ^1H NMR ($CDCl_3$): 7.51 (1 H, d, J = 7.3, NH_{Ala}), 7.39 – 7.18 (10 H, m, CH_{Bzl}), 5.97 – 5.83 (1 H, m, NH_{Ser}), 5.39 (1 H, s br, NH_{nonyl}), 5.15, 5.08 (2 H, 2 d, 2 J = 12.3, $CH_{2,\ Bzl}$), 4.65 – 4.55 (1 H, m, CH^*_{Ser}), 4.54 (1 H, p, J = 7.2, CH^*_{Ala}), 4.46 (2 H, s, $CH_{2\ (Bzl\text{-}Ser,)}$), 3.76 (1 H, dd, J = 4.5, J = 9.3, $CH_{A\ (\beta,\ Ser)}$), 3.52 (1 H, dd, J = 7.1, J = 9.3, $CH_{B\ (\beta,\ Ser)}$), 3.16 –3.04 (2 H, m, CH_2N_{octyl}), 1.50 – 1.16 (12 H, m, $CH_{2,\ octyl}$), 1.36 (3 H, d, J = 7.2, $CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.7, $CH_{3,\ octyl}$); ^{13}C NMR ($CDCl_3$):172.3, 171.5, 158.0 (CO), 137.6, 135.4 (C_{Bzl}), 128.6, 128.41, 128.39, 128.1, 127.7 (CH_{Bzl}), 73.2, 70.7 ($CH_{2\ (Bzl\text{-}Ser)}$ and $CH_{2\ (\beta,\ Ser)}$), 67.0 ($CH_{2,\ Bzl}$), 53.0 (CH^*_{Ser}), 48.4 (CH^*_{Ala}), 40.5 (CH_2N_{octyl}), 31.8, 30.3, 29.4, 29.3, 27.0, 22.7 ($CH_{2,\ octyl}$), 18.0 ($CH_{3,\ Ala}$), 14.1 ($CH_{3,\ octyl}$);

2.1.15. Benzyl O-benzyl, N-nonylaminocarbonyl-L-seryl-L-alanine (Ester 20)



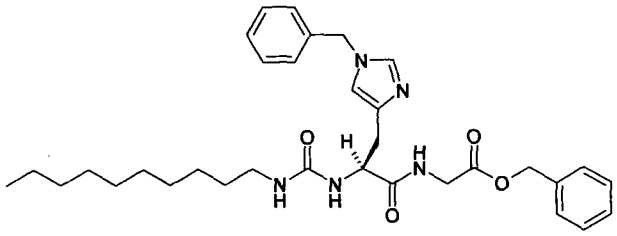
According to the general procedure 2.1.: a) Boc-L-Ser (Bzl)-L-Ala-OMe·(0.761 g, 1.667 mmol), CF_3COOH (4 ml); b) $C_9H_{19}NCO$ (0.360 ml, 1850 mmol), TEA (0.465 ml, 3.336 mmol), CH_2Cl_2 (5 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 0.4) – yield: 0.875 g, 99.9 %; ^1H NMR ($CDCl_3$): 7.49 (1 H, d, J = 7.2, NH_{Ala}), 7.37 – 7.22 (10 H, m, CH_{Bzl}), 5.96 – 5.84 (1 H, s br, NH_{Ser}), 5.36 (1 H, s br, NH_{nonyl}), 5.15, 5.09 (2 H, 2 d, 2 J = 12.3, $CH_{2,\ Bzl}$), 4.64 -4 57 (1 H, m, CH^*_{Ser}), 4.57 (1 H, p, J = 7.2, CH^*_{Ala}), 4.48, 4.45 (2 H, 2 d, J = 11.9, $CH_{2\ (Bzl\text{-}Ser)}$), 377 (1 H, dd, J = 4.4, J = 9.3, $CH_{A\ (\beta,\ Ser)}$), 3.51 (1 H, dd, J = 7.2, J = 9.3, $CH_{B\ (\beta,\ Ser)}$), 3.15 –3.04 (2 H, m, CH_2N_{nonyl}), 1.51 – 1.15 (14 H, m, $CH_{2,\ nonyl}$), 1.36 (3 H, d, J = 7.2,$CH_{3\ (\beta,\ Ala)}$), 0.87 (3 H, t, J = 7.1, $CH_{3,\ nonyl}$); ^{13}C NMR ($CDCl_3$): 172.3, 171.4, 158.0 (CO), 137.7, 135.4 (C_{Bzl}), 128.6, 128.4, 128,1, 127.8 (CH_{Bzl}), 73.3, 70.6, 67.0 ($CH_{2\ (Bzl\text{-}Ser)}$, $CH_{2\ (\beta,\ Ser)}$,$OCH_{2,\ Bzl}$), 53.1 (CH^*_{Ser}), 48.4 (CH^*_{Ala}), 40.5(CH_2N_{nonyl}), 31.9, 30.2, 29.6, 29.4, 29.3, 27.0, 22.7 ($CH_{2,\ nonyl}$), 18.0 ($CH_{3,\ Ala}$), 14.1 ($CH_{3,\ nonyl}$);

2.1.16. Dibenzyl *N*-decylaminocarbonyl glycyl-L-glutamate (Ester 21)



According to the general procedure 2.1.: a) Boc-Gly Glu-$(OBzl)_2$·(1.063 g, 2.198 mmol), CF_3COOH (4 ml), CH_2Cl_2 (1 ml); b) $C_{10}H_{21}$-NCO (0.520 ml, 2.497 mmol), TEA (0.612 ml, 4.391 mmol), CH_2Cl_2 (22 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100:4) – yield: 1.018 g, 81.6 %; ^1H NMR ($CDCl_3$): 7.42 – 7.19 (11 H, m, CH_{Bzl} and NH), 5.61 (1 H, s br, NH_{Glu}), 5.12, 5.07 (2 x 2 H, 2 s, $CH_{2,\ Bzl}$), 4.62 (1 H, dt, J = 5.1, J = 7.8, CH^*_{Glu}), 3.91, 3.82 (2 H, 2 d, J = 16.7, $CH_{2,\ Gly}$), 3.11 (1 H, t, J = 7.0, CH_2N_{decyl}), 2.51 – 1.89 (4 H, m, $CH_{2,\ Glu}$), 1.51 – 0.97 (18 H, m, $CH_{2,\ decyl}$), 0.87 (3 H, t, J = 6.6, $CH_{3,\ decyl}$); ^{13}C NMR ($CDCl_3$):172.4, 171.3, 170.9, 158.3 (CO), 135.6, 135.0 (C_{Bzl}), 128.5, 128.4, 128.3, 128.2, 128.09, 128.08 (CH_{Bzl}), 67.2, 66.4 ($CH_{2,\ Bzl}$), 51.7 (CH^*_{Glu}), 43.9 ($CH_{2,\ Gly}$), 40.5 (CH_2N_{decyl}), 31.8, 30.1, 30.0, 29.50, 29.48, 29.28, 29.21, 26.8, 22.6 ($CH_{2,\ decyl}$ and $CH_{2,\ Glu}$), 14.0 ($CH_{3,\ decyl}$);

2.1.17. Benzyl *N*γ-benzyl, *N*α-decylaminocarbonyl-L-histidylglycine (Ester 22)

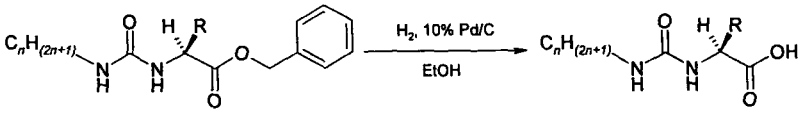


According to the general procedure 2.1.: a) Boc-L-His(Bzl)-Gly-OBzl·(0.525 g, 1.066 mmol), CF_3COOH (3 ml); b) $C_{10}H_{21}NCO$ (0.240 ml, 1.152 mmol), TEA (0.300 ml, 2.152 mmol), CH_2Cl_2 (10 ml) after preparative t.l.c. chromatography on silica gel (CH_2Cl_2 – EtOH, 100 : 5) – yield: 0.180 g, 29.3 %; ^{1}H NMR ($CDCl_3$): 7.63 (1 H, t, J=5.2, NH_{Gly}), 7.37, 6.74 (2 x 1 H, 2 s, CH_{His}), 7.42 – 7.03 (10 H, m, CH_{Bzl}), 6.36 (1 H, d, J = 6.3, NH_{His}), 5.13, 4.99 (2 x 2 H, 2 s, $CH_{2,\ Bzl}$), 4.94 (1 H, t, J = 5.4, NH_{decyl}), 4.59 – 4.47 (1 H, m, CH^*_{His}), 4.06 (1 H, dd, J = 5.9, J = 18.3 $CH_{A,\ Gly}$), 3.92 (1 H, d, J = 5.0, J = 18.3 $CH_{B,\ Gly}$), 3.19 – 3.06 (3 H, m, CH_2N_{decyl} and $CH_{A\ (\beta,\ His)}$), 2.91 (1 H, dd, J = 5.4, J = 14.6, $CH_{B\ (\beta,\ His)}$), 1.54 - 1.13 (16 H, m, $CH_{2,\ decyl}$), 0.87 (3 H, t, J = 6.6, $CH_{3,\ decyl}$); ^{13}C NMR ($CDCl_3$): 172.8, 169.5, 158.2 (CO), 138.2, 135.7, 135.2 (C_{His} and C_{Bzl}), 129.8,128.8, 128.5, 128.3, 128.2, 128.1, 127.3, 127.2, 117.5 (C_{His} and CH_{Bzl}), 66.8 ($OCH_{2,\ Bzl}$), 54.4 (CH^*_{His}), 50.8 ($NCH_{2,\ Bzl}$), 41.1 ($CH_{2,\ Gly}$), 40.4 (CH_2N_{decyl}), 31.8, 30.0, 29.5, 29.4, 29.23, 29.18, 26.8, 22.5 ($CH_{2,\ decyl}$ and $CH_{2\ (\beta,\ His)}$), 14.0 ($CH_{3,\ decyl}$);

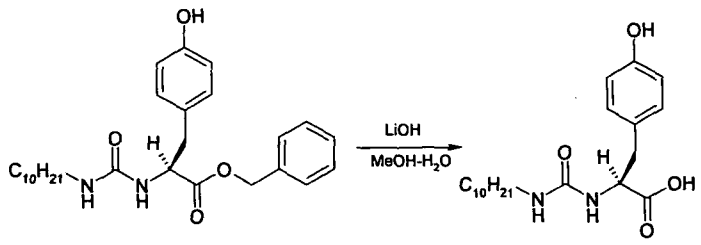
3. Preparation *N* - alkylaminocarbonyl - amino acid

The title carboxylic acids were prepared:

a) by the hydrogenolysis of corresponding benzyl esters



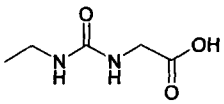
b) by the hydrolysis of methyl ester



3.1. *General procedure for the preparation N - alkylaminocarbonyl - amino acid (Compounds 1-4) from corresponding benzyl esters*

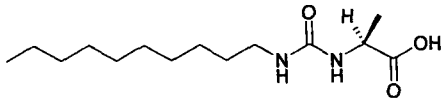
To a solution benzyl esters, Esters 1-4, in EtOH and CH_2Cl_2, 10% Pd/C was added and the reaction mixture was hydrogenated at 0.24 – 0.37 MPa and room temperature for 20 h. The catalyst was filtered of and the solvent was evaporated.

3.1.1. *N*-ethylaminocarbonyl glycine (Compound 1)



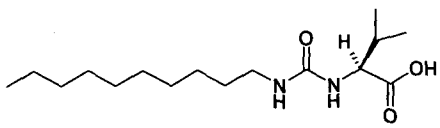
According to the general procedure 3.1.: Ester **1** (0.316 g, 1.337 mmol), EtOH (50 ml), CH_2Cl_2 (1 ml), 10% Pd/C (0.065 g), 0.24 MPa (H_2) – yield: 0.195 g, 99.8 % ; ^{1}H NMR (DMSO-d_6): 12.38 (1 H, s br, COOH), 6.15 – 5.97 (2 H, m, CONH), 3.67 (2 H, s br, $CH_{2,\ Gly}$), 3.06 – 2.94 (2 H, m, CH_2N_{Et}), 0.98 (3 H, t, J = 7.1, $CH_{3,\ Et}$); ^{13}C NMR (CD_3OD): 172.2, 158.8 (CO), 40.3 ($CH_{2,\ Gly}$), 33.6 (CH_2N_{Et}), 13.5 (CH_3); IR; 3349, 3143, 1730, 1698, 1590.

3.1.2. *N*-Decylaminocarbonyl-L-alanine (Compound 2)



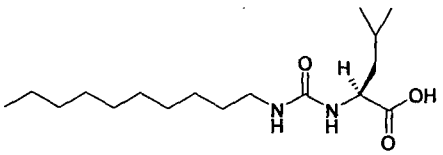
According to the general procedure 3.1.:Ester **2** (0.187 g, 0.516 mmol), 10 % Pd/C (0.040 g), EtOH (50 ml), 0.37 MPa – yield: 0.140 g, 99.6 %; $[\alpha]_D$ + 3 (c 1.3, EtOH); ^{1}H NMR (DMSO-d_6): 12.43 (1 H, s, COOH), 6.05 (1 H, t, J = 7.8, NH_{Ala}), 5.95 (1 H, t, J = 5.7, NH_{decyl}), 4.07 (1 H, p, J = 7.3, CH^*_{Ala}), 2.95 (2 H, q, J = 6.3, CH_2N_{decyl}), 1.39 – 1.13 (16 H, m. $CH_{2,\ decyl}$), 1.21 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.5, $CH_{3,\ decyl}$); ^{13}C NMR (MeOD): 177.6, 160.9 (CO), 50.1 (CH^*_{Ala}), 41.2 (CH_2N_{decyl}), 33.4, 31.6, 31.06, 31.02, 30.82, 30.78, 28.3, 24.1 ($CH_{2,\ decyl}$), 19.1 ($CH_{3,\ Ala}$), 14.8 ($CH_{3,\ decyl}$); IR: 3366, 3322, 1716, 1628, 1564.

3.1.3 *N*-Decylaminocarbonyl-L-valine (Compound 3)



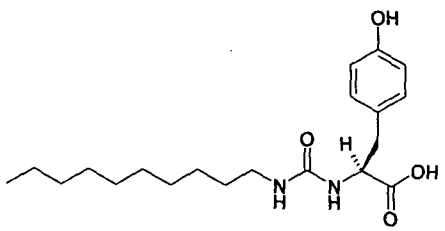
According to the general procedure 3.1.: Ester **3** (0.450 g, 1.152 mmol), EtOH (20 ml), 10 % Pd/C (0.038 g), 0.37 MPa – yield: 0.333 g, 96.2 %; ^{1}H NMR (DMSO-d_6): 12.45 (1 H, s, COOH), 5.98 (1 H, d, J = 9.2, NH_{Val}), 6.00 (1 H, t, J = 5.4, NH_{decyl}), 4.02 (1 H, dd, *J* = 5.0, *J* = 9.0, CH^*_{Val}), 3.02 – 2.89 (2 H, m, CH_2N_{decyl}), 2.06 – 1.92 (1 H, m, $CH_{\beta, Val}$), 1.42 – 1.13 (16 H, m, $CH_{2, decyl}$), 0.86, 0.82 (2 x 3H, 2 d, 2 *J* = 6.9, $CH_{3\ (\beta, Val)}$), 0.86 (3 H, t, *J* = 6.4, $CH_{3, decyl}$); ^{13}C NMR (MeOD): 176.4, 161.3 (CO), 50.5 (CH^*_{Val}), 41.2 (CH_2N_{decyl}), 32.4 ($CH_{\beta, Val}$), 33.4, 31.6, 31.1, 31.0, 30.79, 30.77, 28.2, 24.0 ($CH_{2, decyl}$), 20.0, 18.2 ($CH_{3\ (\beta, Val)}$), 14.8 ($CH_{3, decyl}$); IR: 3356, 3287, 1709, 1591, 108.

3.1.4. *N*-Decylaminocarbonyl-L-leucine (Compound 4)



According to the general procedure 3.1.: Ester **4** (0.336 g, 0.830 mmol), 10 % Pd/C (0.070 g), EtOH (40 ml), 0.37 MPa – yield: 0.238 g, 91.1 %. ^{1}H NMR (DMSO-d_6): 12.39 (1 H, s, COOH), 6.00 (1 H, t, *J* = 8.6, NH_{Leu}), 5.91 (1 H, t, *J* = 5.6, NH_{decyl}), 4.10 (1 H, dt, *J* = 8.7, *J* = 5.7, CH^*_{Leu}), 2.96 (2 H, q, *J* = 6.2, CH_2N_{decyl}), 1.81 – 1.11 (19 H, m, $CH_{\gamma, Leu}$, $CH_{2\ (\beta, Leu)}$ and $CH_{2, decyl}$), 0.88, 0.86 (2 x 3H, 2 d, 2 *J* = 6.6, $CH_{3, Leu}$), 0.86 (3 H, t, *J* = 6.8, $CH_{3, decyl}$); ^{13}C NMR (DMSO-d_6):175.4, 157.8 (CO), 50.9 (CH^*_{Leu}),, 41.3 (CH_2N), 39.2 ($CH_{2, \beta, Leu}$), 31.4, 30.1, 29.16, 29.06, 28.97, 28.90, 28.81, 22.2 ($CH_{2, decyl}$), 26.4 ($CH_{\gamma, Leu}$), 22.9, 21.7 ($CH_{3, Leu}$), 14.0 ($CH_{3, decyl}$); IR: 3393, 3320, 1727, 1638, 1570.

3.2. *N*-Decylaminocarbonyl-L-tyrosine (Compound 5)



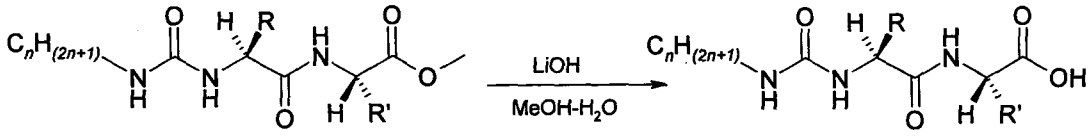
To a solution of Ester 5 (0.340 g, 0.898 mmol) in MeOH (4.0 ml) and CH_2Cl_2 (0.7 ml), 1M LiOH (2.7 ml, 2.700 mmol) was added and the reaction mixture was stirred at room temperature over night. Than, it was acidified to pH 7 and solvent was evaporated. Water was added and the solution was acidified with 5 % HCl to pH 3. The product was extracted with

EtOAc. Organic layer was dried (Na_2SO_4) and solvent evaporated to give 0.315 g, 96.2 %; ^1H NMR (MeOD): 6.92, 6.61 (4 H, 2 d, J = 8.4, CH_{Ph}), 4.20 (1 H, t, J = 4.5, CH^*_{Tyr}), 3.27 – 3.12 (2 H, m, $CH_{2\ (\beta,\ Tyr)}$), 2.91 (2 H, m, CH_2N_{decyl}), 1.43 – 1.07 (16 H, m, $CH_{2,\ decyl}$), 0.84 (3 H, t, J = 7.1, $CH_{3,\ decyl}$); ^{13}C NMR (MeOD): 174.0, 157.4 (CO), 155.8, 124.6 (C_{Ph}), 130.2, 114.3 (CH_{Ph}), 57.4 (CH^*_{Tyr}), 37. 4, 35.2 (CH_2N_{decyl} , $CH_{2\ (\beta,\ Tyr)}$), 31.2, 28.8, 28.7, 28.6, 28.4, 27,1, 25.7, 21.9 ($CH_{2,\ decyl}$), 12.7 ($CH_{3,\ decyl}$); IR: 3319, 1767, 1701, 1615

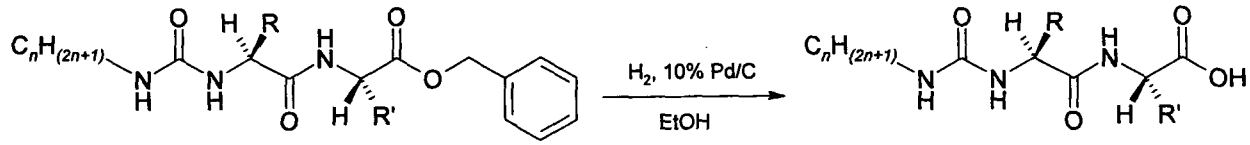
4. Preparation of *N* - alkylaminocarbonyl dipeptides

The title carboxylic acids were prepared:

a) by the hydrolyses of the corresponding methyl esters



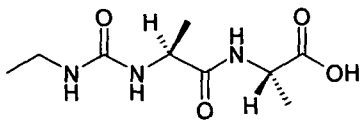
b) by the hydrogenolyses of the corresponding benzyl esters



4.1. *General procedure for the preparation of N – acylaminocarbonyl - dipeptide* ***(Compounds 6-8)*** *from methyl ester.*

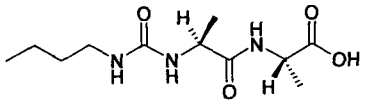
To a solution of methyl esters, **6 - 8**, in MeOH and CH_2Cl_2, 1M LiOH was added and the reaction mixture was stirred at room temperature over night. The reaction mixture was acidified to pH 7 and the solvent was evaporated. Water was added and the solution was acidified with 5 % HCl to pH 3. The crude product was filtered of and washed with water or if the products were not suitable for filtration they were extracted with EtOAc.

4.1.1 *N*-ethylaminocarbonyl-L-alanyl-L-alanine (Compound 6)



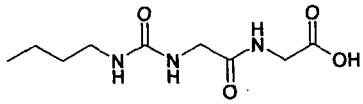
According to the general procedure 4.1.: **Ester 6** (0.096 g, 0.391 mmol), 1M LiOH (0.59 ml, 0.590 mmol), MeOH (1.59 ml), CH_2Cl_2 (0.2 ml) – yield: 0.046 g, 50.8 % ; ^1H NMR (CD_3OD): 4.17 (1 H, q, J = 7.3, CH^*_{Ala}), 4.05 (1 H, q, J = 7.1, CH^*_{Ala}), 2.92 (2 H, q, J = 7.2, CH_2N_{Et}), 1.19 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 1 10 (3 H, d, J = 7.1, $CH_{3\ (\beta,\ Ala)}$), 0.88 (3 H, t, J = 7.2, $CH_{3,\ Et}$); ^{13}C NMR (CD_3OD): 173.0, 172.9, 157.3 (CO), 47.6, 46.3 (CH^*_{Ala}), 32.8 (CH_2N_{Et}), 16.1, 14.8 ($CH_{3\ (\beta,\ Ala)}$, 12.8 ($CH_{3,\ Et}$); IR: 3349, 1730, 1698, 1625, 1590.

4.1.2. *N*-Butylaminocarbonyl-L-alanyl-L-alanine (Compound 7)



According to the general procedure 4.1.: **Ester 7** (0.064 g, 0.234 mmol), 1M LiOH (0.35 ml, 0.350 mmol), MeOH (2.0 ml), CH_2Cl_2 (0.5 ml) – yield: 0.044 g, 72.5 %; ^1H NMR (CD_3OD): 4.20 (1 H, q, J = 7.2, CH^*_{Ala}), 4.09 (1 H, q, J = 6.9, CH^*_{Ala}), 2.92 (2H, t, J = 6.5, CH_2N_{Bu}), 1.34 - 1.08 (4H, m, $CH_{2,\ Bu}$), 1.22 (3H, d, J = 7.4, $CH_{3\ (\beta,\ Ala)}$), 1.14 (3H, d, J = 7.1, $CH_{3\ (\beta,\ Ala)}$), 0.75 (3H, t, J = 7.1, $CH_{3,\ Bu}$); ^{13}C NMR (CD_3OD): 176.2, 170.1, 160.6 (CO), 50.8 and 49.5 (CH^*_{Ala}), 40.9 (CH_2N_{Bu}), 33.7, 21.3($CH_{2,\ Bu}$), 19.4 and 18.0 ($CH_{3\ (\beta,\ Ala)}$), 14.4 ($CH_{3,\ Bu}$).

4.1.3. N – Butylaminocarbonyl glycyl glycine (Compound 8)

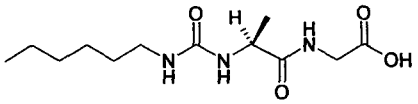


According to the general procedure 4.1.: **Ester 8** (0.108 g, 0.440 mmol), 1M LiOH (0.6 ml, 0.600 mmol), MeOH (1.6 ml), CH_2Cl_2 (0.2 ml) – yield: 0.064 g, 62.9 %; ^1H NMR (CD_3OD): 3.88 (2 H, s, $CH_{2,\ Gly}$), 3.78 (2 H, s, $CH_{2,\ Gly}$), 3.07 (2 H, t, J = 7.0, CH_2N_{Bu}), 1.44 – 1.38, 1.34 – 1.27 (4 H, 2 m, $CH_{2,\ Bu}$), 0.88 (3 H, t, J = 7.3, $CH_{3,\ Bu}$); ^{13}C NMR (CD_3OD): 171.6, 171.0, 159.0 (CO), 42.4, 39.9 ($CH_{2,\ Gly}$), 39.0 (CH_2N), 31.4, 19.1 ($CH_{2,\ Bu}$), 12.2 ($CH_{3,\ Bu}$); IR: 3355, 3301, 1702, 1663, 1625, 1594, 1553.

4.2. General procedure *for the preparation of N-alkylaminocarbonyl - dipeptide (Compounds 9-21) from corresponding benzyl esters*

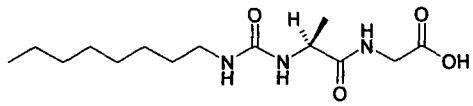
To a solution benzyl ester of *N*-alkylcarbonyl-dipeptide **9 - 21** in EtOH and CH_2Cl_2, 10% Pd/C was added and the reaction mixture was hydrogenated at 0.17 – 0.41 MPa and room temperature for 20 h. The catalyst was filtered of and the solvent was evaporated.

4.2.1. *N*-hexylaminocarbonyl-L-alanyl glycine (Compound 9)



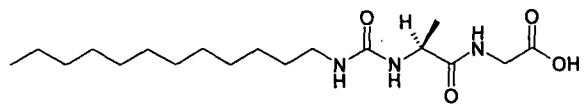
According to the general procedure 4.2.: **Ester 9** (0.205 g, 0.564 mmol), 10 % Pd/C (0.045 g), EtOH (30 ml), 0.41 MPa – yield: 0.153 g, 99.2 %; ^{1}H NMR (DMSO – d_6): 12.54 (1 H, s, COOH), 8.21 (1 H, t, J = 5.9, NH_{Gly}), 6.03 (1 H, t, J = 5.8, NH_{hexyl}), 6.01 (1 H, d, J = 8.4, NH_{Ala}), 4.25 – 4.11 (1 H, m, CH^*_{Ala}), 3.77, 3.71 (2H, 2 dd, J = 5.9, J = 19.4, $CH_{2,\,Gly}$), 2.95 (2 H, dt, J = 6.4, J = 5.8, CH_2N_{hexyl}), 1.41 – 1.67 (8 H, m, $CH_{2,\,hexyl}$), 1.15 (3 H, d, J = 7.0,$CH_{3(\beta,\,Ala)}$), 0.86 (3 H, t, J = 6.7, $CH_{3,\,hexyl}$); ^{13}C NMR (MeOD): 173.7, 169.8, 157.3 (CO), 47.8 (CH^*_{Ala}), 38.7, 38.0 ($CH_{2,\,Gly}$ and CH_2N_{hexyl}), 29.7, 28.2, 24.6, 20.7 ($CH_{2,\,hexyl}$), 16.1 ($CH_{3\,(\beta,\,Ala)}$), 11.4 ($CH_{3,\,hexyl}$);

4.2.2. *N*-octylaminokarbonyl -L-alanyl glycine (Compound 10)



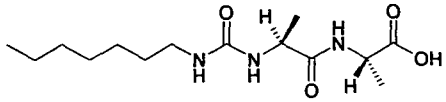
According to the general procedure 4.2.: **Ester 10** (0.147 g, 0.375 mmol), 10 % Pd/C (0.030 g), EtOH (35 ml), 0.37 MPa – yield: 0.110 g, 97.2 %; ^{1}H NMR (MeOD):4.26 (1 H, q, J = 7.1, CH^*_{Ala}), 3.94, 3.87 (2H, 2 d, J = 17.9, $CH_{2,\,Gly}$), 3.18 –3.01 (2 H, m, CH_2N_{octyl}), 1.65 – 1.17 (8 H, m, $CH_{2,\,octyl}$), 1.33 (3 H, d, J = 7.2, $CH_{3\,(\beta,\,Ala)}$), 0.89 (3 H, t, J = 6.7, $CH_{3,\,octyl}$); ^{13}C NMR (MeOD): 175.5, 174.4, 158.2 (CO), 48.6 (CH^*_{Ala}), 38.8 ($CH_{2,\,Gly}$), 30.8, 29.1, 28.26, 28.21, 25.8, 21.5 (CH_2N_{octyl}), 16.8 ($CH_{3\,(\beta,\,Ala)}$), 12.2 ($CH_{3,\,octyl}$);

4.2.3. *N*-dodecylaminocarbonyl-L-alanyl glycine (Compound 11)



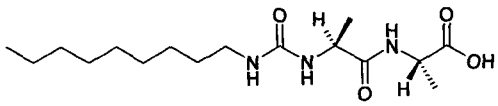
According to the general procedure 4.2.: **Ester 11** (0.132 g, 0.295 mmol), 10 % Pd/C (0.026 g), EtOH (30 ml), 0.17 MPa – yield: 0.094 g, 89.2 %; ^{1}H NMR (DMSO-d_6): 12.45 (1 H, br s, COOH), 8.13 - 8.09 (1 H, m. NH_{Gly}), 5.95 (1 H, t, J = 5.8, NH_{Gly}), 5.94 (1 H, d, J = 7.6, NH_{Ala}), 4.15 – 4.08 (1 H, m, CH^*_{Ala}), 3.69, 3.65 (2 H, 2 dd, J = 5.8, J = 17.5, $CH_{2,\ Gly}$), 2.95 – 2.82 (2 H, m, $CH_2N_{dodecyl}$), 1.30 – 1.11 (20 H, m, $CH_{2,\ dodecyl}$), 1 08 (3 H, d, J = 7.0, $CH_{3(\beta,\ Ala)}$), 0.78 (3 H, t, J = 7.0, $CH_{3,\ dodecyl}$); ^{13}C NMR (DMSO-d_6): 173.6, 171.1, 157.3 (CO), 48.3 (CH^*_{Ala}), 40.5 (CH_2N_{Gly}), 39.1 ($CH_2N_{dodecyl}$), 31.3, 29.9, 29.02, 28.98, 28.77, 28.67, 26.4, 22.1 ($CH_{2,\ dodecyl}$), 19.6 ($CH_{3\ (\beta,\ Ala)}$) 13.9 ($CH_{3,\ dodecyl}$); IR: 3367, 3316, 3287, 1708, 1627, 1564.

4.2.4. *N*-Heptylaminocarbonyl-L-alanyl-L-alanine (Compound 12)



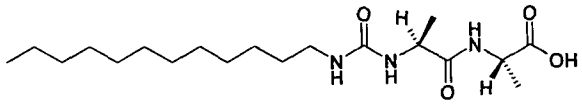
According to the general procedure 4.2.: **Ester 12** (0.188 g, 0.480 mmol), 10 % Pd/C (0.039 g), EtOH (30 ml), 0.37 MPa – yield: 0.138 g, 95.4 %; ^{1}H NMR (DMSO-d_6): 12.50 (1 H, s br., COOH), 8.18 (1 H, d, J = 7.3, NH_{Ala}), 6.02 (1 H, t, J = 5.6, NH_{heptyl}), 5.97 (1 H, t, J = 8.2, NH_{Ala}), 4.18 (2 H, p, J = 7.3, 2 CH^*_{Ala}), 2.99 – 2.89 (2 H, m, CH_2N_{heptyl}), 1.39 – 1.18 (10 H, m. $CH_{2,\ heptyl}$), 1.26, 1.36 (2 x 3 H, 2 d, 2 J = 7.0, $CH_{3(\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.7, $CH_{3,\ heptyl}$); ^{13}C NMR (MeOD): 173.0, 172.8, 157.3 (CO), 47.5, 46.2 (CH^*_{Ala}), 38.0 (CH_2N_{heptyl}), 30.0, 28.3, 27.2, 24.9, 20.7 ($CH_{2,\ heptyl}$), 16.1, 14.7 ($CH_{3\ (\beta,\ Ala)}$), 11.5 ($CH_{3,\ heptyl}$); IR: 3343, 3271, 1714, 1631, 1565.

4.2.5. *N*-Nonylaminocarbonyl-L-alanyl-L-alanine (Compound 13)



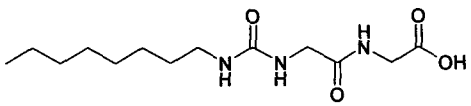
According to the general procedure 4.2.: **Ester 13** (0.138 g, 0.329 mmol), 10 % Pd/C (0.031 g), EtOH (20 ml), 0.37 MPa – yield:. 0.102 g, 94.1 %; ^{1}H NMR (MeOD): 4.22 (1 H, q, J = 7.3, CH^*_{Ala}), 4.10 (1 H, q, J = 7.0, CH^*_{Ala}), 2.94 (2 H, t, J = 6.8, CH_2N_{nonyl}), 1.37 – 1.04 (14 H, m. $CH_{2,\ nonyl}$), 1.24, 1.16 (2 x 3H, 2 d, 2 J = 7.0, $CH_{3(\beta,\ Ala)}$), 0.74 (3 H, t, J = 6.6, $CH_{3,\ nonyl}$); ^{13}C NMR (MeOD): 176.2, 176.1, 160.6 (CO), 50.8, 49.5 (CH^*_{Ala}), 41.2 (CH_2N_{nonyl}), 33.3, 31.6, 31.0, 30.8, 30.7, 28.2, 24.0 ($CH_{2,\ nonyl}$), 19.4, 19.0 ($CH_{3(\beta,\ Ala)}$), 14.7 ($CH_{3,\ nonyl}$); IR: 3345, 3317, 3270, 1715, 1652, 1629, 1561.

4.2.6. *N*-Dodecylaminocarbonyl-L-alanyl-L-alanine (Compound 14)



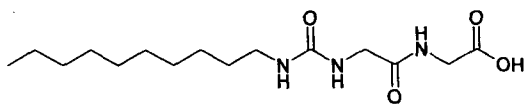
According to the general procedure 4.2.: **Ester 14** 0.178 g (0.386 mmol), 10 % Pd/C (0.035 g), EtOH (120 ml) and CH_2Cl_2 (3 ml), 0.37 MPa – yield: 0.115 g, 80.3 %.: ^{1}H NMR (MeOD-DMSO-d_6): 4.48 (H, q, J = 7.3, CH^*_{Ala}), 4.35 (H, q, J = 7.1, CH^*_{Ala}), 3.19 (2 H, t, J = 6.9, $CH_2N_{dodecyl}$), 1.65 – 1.29 (20 H, m. $CH_{2,\ dodecyl}$), 1.49, 1.40 (2 x 3 H, 2 d, 2 J = 7.1, $CH_{3\ (\beta,\ Ala)}$), 0.98 (3 H, t, J = 6.7, $CH_{3,\ dodecyl}$); ^{13}C NMR (MeOD-DMSO-d_6 -50 °C): 48.0, 46.7 (CH^*_{Ala}), 38.5 ($CH_2N_{dodecyl}$), 30.4, 28.6, 28.06, 28.03, 28.01, 27.8, 27.7, 25.3, 21.0 ($CH_{2,\ dodecyl}$), 16.4, 15.3 ($CH_{3\ (\beta,\ Ala)}$), 11.7 ($CH_{3,\ dodecyl}$); IR: 3347, 3315, 3270, 1715, 1653, 1629, 1565.

4.2.7. *N*-Octylaminocarbonyl glycyl glycine (Compound 15)



According to the general procedure 4.2.: **Ester 15** (0.157 g, 0.416 mmol), 10 % Pd/C (0.033 g), EtOH (50 ml), 0.37 MPa – yield: 0.105 g, 87.9 %: ^{1}H NMR (MeOD):3.93, 3.83 2 x (2 H, 2 s, $CH_{2,\ Gly}$), 3.11 (2 H, t, J = 7.0, CH_2N_{octyl}), 1.58 – 1.20 (12 H, m. $CH_{2,\ octyl}$), 0.90 (3 H, t, J = 6.9, $CH_{3,\ octyl}$); ^{13}C NMR (MeOD-DMSO-d_6, 50 °C): 44.6, 41.5 ($CH_{2,\ Gly}$), 33.1 (CH_2N_{octyl}), 31.4, 30.6, 30.5, 28.2, 23.8 ($CH_{2,\ octyl}$), 14.7 ($CH_{3,\ octyl}$);

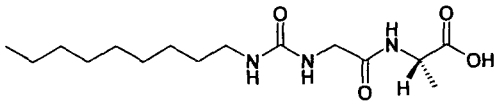
4.2.8. *N*-Decylaminocarbonyl glycyl glycine (Compound 16)



According to the general procedure 5.2.: **Ester 16** (0.245 g, 0.604 mmol), 10 % Pd/C (0.050 g), EtOH (60 ml), 0.37 MPa – yield: 0.182 g, 95.5 %; ^{1}H NMR (DMSO-d_6): 12.57 (1 H, s br., COOH), 8.09 (1 H, t, J = 5.8, NH_{Gly}), 6.12 (1 H, t, J = 5.6, NH_{Gly}), 6.03 (1 H, t, J = 5.0, NH_{decyl}), 3.76 (2 H, d, J = 5.8, $CH_{2,\ Gly}$), 3.66 (2 H, d, J = 5.6, $CH_{2,\ Gly}$), 2.99 – 2.94 (2 H, m, CH_2N_{decyl}), 1.38 – 1.18 (16 H, m, $CH_{2,\ decyl}$), 0.86 (3 H, t, J = 7.0, $CH_{3,\ decyl}$); ^{13}C NMR (DMSO-d_6): 171.1, 170.5, 157.9 (CO), 42.7, 40.5 ($CH_{2,\ Gly}$), 39.3 (CH_2N_{decyl}), 31.3, 29.9,

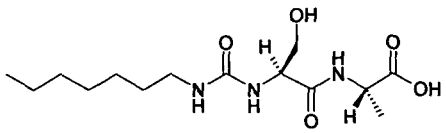
29.0, 28.9, 28.8, 28.7, 26.4, 22.0 ($CH_{2,\ decyl}$), 13.9 ($CH_{3,\ decyl}$); IR: 3347, 3300, 1701, 1663, 1624, 1597.

4.2.9. *N*-Nonylaminocarbonyl-glycyl-L-alanine (Compound 17)



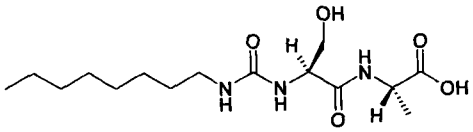
According to the general procedure 5.2.: **Ester 17** (0.130 g, 0.358 mmol), 10 % Pd/C (0.030 g), EtOH (20 ml), 0.37 MPa – yield: 0.103 g, 91.3 %; ^{1}H NMR (MeOD):4.41 (1 H, q, J = 7.0, CH^*_{Ala}), 3.85, 3.78 (2H, 2 d, J = 17.0, $CH_{2,\ Gly}$), 3.11 (2 H, t, J = 7.0, $CH_{2,}N_{nonyl}$), 1.54 – 1.21 (14 H, m, $CH_{2,\ nonyl}$), 1.40 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 0.89 (3 H, d, J = 7.0, $CH_{3,\ nonyl}$); ^{1}H NMR (DMSO – d_6): 12.58 (1 H, s, COOH), 8.10 (1 H, d, J = 7.3, NH_{Ala}), 6.12 (1 H, t, J = 5.5, NH_{Gly}), 5.98 (1 H, t, J = 5.1, NH_{nonyl}), 4.27 –4.14 (1 H, m, CH^*_{Ala}), 3.73 – 3.56 (2H, m, $CH_{2,\ Gly}$), 3.01 –2.80 (2 H, m, $CH_2N_{\ nonyl}$), 1.41 – 1.16 (17 H, m, $CH_{2,\ nonyl}$ and $CH_{3(\beta,\ Ala)}$), 0.86 (3 H, t, J = 6.5, $CH_{3,\ nonyl}$); ^{13}C NMR (MeOD): 172.9, 169.7, 158.0 (CO), 49.3 (CH^*_{Ala}), 41.1, 38.2 ($CH_{2,\ Gly}$ and CH_2N_{nonyl}), 30.1, 28.3, 27.7, 27.5, 27.4, 25.0, 20.8, ($CH_{2,\ nonyl}$), 14.9 ($CH_{3(\beta,\ Ala)}$), 11.5 ($CH_{3,\ nonyl}$); IR: 3391, 3316, 1736, 1703, 1655, 1615, 1561.

4.2.10. *N*-Heptylaminocarbonyl-L-seryl-L-alanine (Compound 18)



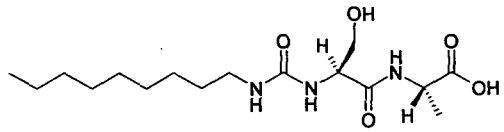
According to the general procedure 5.2.: **Ester 18** (0.157 g, 0.315 mmol), 10 % Pd/C (0.065 g), EtOH (35 ml), CH_2Cl_2 (2 ml), 0.37 MPa – yield: 0.057 g, 56.9 %; ^{1}H NMR (DMSO – d_6): 12.69 (1 H, s, COOH), 8.18 (1 H, d, J = 7.3, NH_{Ala}), 6.33 (1 H, t, J = 5.7, NH_{heptyl}), 6.13 (1 H, d, J = 8.0, NH_{Ser}), 4.92 (1 H, s br, OH), 4.34 (1 H, p, J = 7.3, CH^*_{Ala}), 4.28 (1 H, dt, J = 5.1, J = 8.0, CH^*_{Ser}), 3.66 (1 H, dd, J = 5.3, J = 10.5, $CH_{A\ (\beta,\ Ser)}$), 3.59 (1 H, dd, J = 5.1, J = 10.5, $CH_{B\ (\beta,\ Ser)}$), 3.08 (2 H, dt, J = 5.7, J = 6.6, CH_2N_{heptyl}), 1.54 – 1.19 (10 H, m, $CH_{2,\ heptyl}$), 1.38 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 0.97 (3 H, t, J = 6.7, $CH_{3,\ heptyl}$); ^{13}C NMR (DMSO – d_6): 174.2, 171.0, 157.8 (CO), 62.8 ($CH_{2,\ \beta,\ Ser}$), 55.2 (CH^*_{Ser}), 47.6 (CH^*_{Ala}), 39.3 (CH_2N_{heptyl}), 31.4, 30.1, 28.6, 26.5, 22.2 ($CH_{2,\ heptyl}$), 17.6 ($CH_{3\ (\beta,\ Ala)}$), 14.1 ($CH_{3,\ heptyl}$);

4.2.11. *N*-Octylaminocarbonyl-L-seryl-L-alanine (Compound 19)



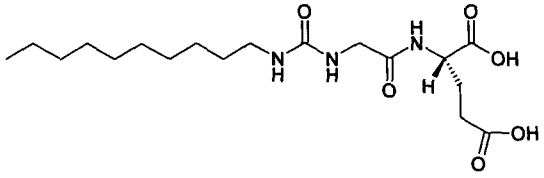
According to the general procedure 5.2.: **Ester 19** (0.136 g, 0.266 mmol), 10 % Pd/C (0.030 g), EtOH (25 ml), CH_2Cl_2 (2 ml), 0.37 MPa – yield: 0.046 g, 52.2 %; ^{1}H NMR (DMSO – d_6): 12.52 (1 H, s, COOH), 8.00 (1 H, d, J = 7.3, NH_{Ala}), 6.14 (1 H, t, J = 5.6, NH_{octyl}), 5.94 (1 H, d, J = 7.7, NH_{Ser}), 4.71 (1 H, s br, OH), 4.16 (1 H, p, J = 7.3, CH^*_{Ala}), 4.15 - 4.03 (1 H, m, CH^*_{Ser}), 3.48 (1 H, dd, J = 5.4, J = 10.6, $CH_{A\ (\beta,\ Ser)}$), 3.41 (1 H, dd, J = 5.1, J = 10.6, $CH_{B\ (\beta,\ Ser)}$), 2.95 –2.81 (2 H, m, CH_2N_{octyl}), 1.32 – 1.09 (12 H, m, $CH_{2,\ octyl}$), 1.20 (3 H, d, J = 7.3, $CH_{3\ (\beta,\ Ala)}$), 0.79 (3 H, t, J = 6.5, $CH_{3,\ octyl}$); ^{13}C NMR (DMSO – d_6): 174.5, 171.4, 158.1 (CO), 63.1 ($CH_{2\ (\beta,\ Ser)}$), 55.5 (CH^*_{Ser}), 47.9 (CH^*_{Ala}), 33.8 (CH_2N_{octyl}), 31.7, 30.4, 29.23, 29.18, 26.9, 22.6 ($CH_{2,\ octyl}$), 17.9 ($CH_{3\ (\beta,\ Ala)}$), 14.4 ($CH_{3,\ octyl}$);

4.2.12. *N*-Nonylaminocarbonyl-L-seryl-L-alanine (Compound 20)



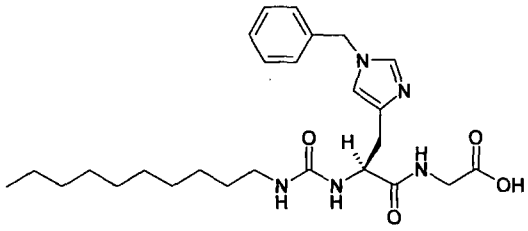
According to the general procedure 5.2.: **Ester 20** (0.198 g, 0.377 mmol), 10 % Pd/C (0.040 g), EtOH (30 ml), CH_2Cl_2 (2 ml), 0.37 MPa – yield: 0.061 g, 46.9 %; ^{1}H NMR (DMSO – d_6): 12.56 (1 H, s, COOH), 8.00 (1 H, d, J = 7.2, NH_{Ala}), 6.14 (1 H, t, J = 5.6, NH_{nonyl}), 5.94 (1 H, d, J = 7.9, NH_{Ser}), 4.73 (1 H, s br, OH), 4.16 (1 H, p, J = 7.2, CH^*_{Ala}), 4.11 – 4.07 (1 H, m, CH^*_{Ser}), 3.47 (1 H, dd, J = 5.2, J = 10.5, $CH_{A\ (\beta,\ Ser)}$), 3.41 (1 H, dd, J = 4.9, J = 10.5, $CH_{B\ (\beta,\ Ser)}$), 2.93 –2.85 (2 H, m, CH_2N_{nonyl}), 1.33 – 1.11 (14 H, m, $CH_{2,\ nonyl}$), 1.20 (3 H, d, J = 7.2, $CH_{3(\beta,\ Ala)}$), 0.70 (3 H, t, J = 6.6, $CH_{3,\ nonyl}$); ^{13}C NMR (DMSO – d_6):174.5, 171.4, 158.1 (CO), 63.1 ($CH_{2\ (\beta,\ Ser)}$), 55.5 (CH^*_{Ser}), 47.9 (CH^*_{Ala}), 31.8, 30.4, 29.5, 29.2, 29.1, 26.9, 22.6 ($CH_{2,\ nonyl}$), 17.9 ($CH_{3\ (\beta,\ Ala)}$), 14.4 ($CH_{3,\ nonyl}$);

4.2.13. *N*-decylaminocarbonyl-glycyl-L-glutamic acid (Compound 21)



According to the general procedure 5.2.: **Ester 21** (0.216 g, 0.380 mmol), 10 % Pd/C (0.045 g), EtOH (20 ml), CH_2Cl_2 (1 ml), 0.41 MPa– yield: 0.142 g, 96.3 %; ^{1}H NMR (MeOD): 4.64 – 4.51 (1 H, m, CH^*_{Glu}), 4.06 – 3.80 (2 H, m, $CH_{2,\ Gly}$), 3.29 – 3.11 (2 H, m, (CH_2N), 2.61 – 1.92 ($CH_{2,\ Glu}$), 1.67 – 1.14 (18 H, m, $CH_{2,\ decyl}$), 0.98 (3 H, t, J = 6.5, $CH_{3,\ decyl}$)); ^{13}C NMR (MeOD): 176.6, 175.1, 174.9, 174.86 (CO), 53.2 (CH^*_{Glu}), 44.5 ($CH_{2,\ Gly}$), 41.5 (CH_2N_{decyl}), 33.3, 31.4, 31.3, 31.2, 31.0, 30.75, 30.71, 28.2, 24.0, ($CH_{2,\ decyl}$ and $CH_{2,\ Glu}$), 14.8 ($CH_{3,\ decyl}$);

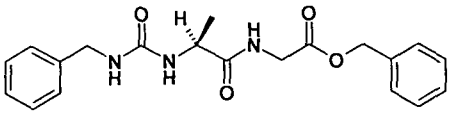
4.2.14. *N*γ-Benzyl, *N*α-decylaminocarbonyl-L-hystidyl-glycine (Compound 22)



To a solution of **Ester 22** (0.580 g, 1.007 mmol) in CH_2Cl_2 (2 ml) and EtOH (80 ml), 10 % Pd/C (0.150 g) was added and the reaction mixture was hydrogenated at 0.39 MPa for 24 h and at room temperature. The result is a solution or granular gel in the solvent. If the gel is formed, this mixture was heated to 45 °C and filtered of. Undissolved material (black gel) was washed with EtOH and the mixture EtOH - CH_2Cl_2 of the same temperature until all product was dissolved. The filtrate was evaporated to give solid, foamy product: 0.321 g, 65.6 % (Hydrogenation must be repeated if all quantity of the ester **22** was not transformed to the carboxylic acid, because the catalyst can be entrapped by the gelation of the product. Some traces of fully deprotected compound could be detected by the NMR spectra). NMR (MeOD): 8.98, 7.46 (2 x 1 H, 2 s, CH_{His}), 7.47 – 7.26 (5 H, m, CH_{Bzl}), 5.39 (2 H, s, $CH_{2,\ Bzl}$), 4.67 – 4.50 (1 H, m, CH_{His}^*), 3.94. 3.84 (2 x 1 H, 2 d, J = 17.6 $CH_{2,\ Gly}$), 3.25 – 2.91 (4 H, m, CH_2N_{decyl} and $CH_{2,\ His}$), 1.49 - 1.07 (16 H, m, $CH_{2,\ decyl}$), 0.87 (3 H, t, J = 6.7, $CH_{3,\ decyl}$)); ^{13}C NMR (MeOD): 173.1, 172.0, 171.5 (CO), 135.6, 132.1, 121.9 (C_{His} and C_{Bzl}), 130.6, 130.4, 129.9, (C_{His} and CH_{Bzl}), 54.30 (CH_{His}^*), 54.27 ($NCH_{2,\ Bzl}$), 42.1, 41.4, 33.2, 31.4, 30.90, 30.87, 30.67, 30.60, 29.5, 28.2, 23.9 ($CH_{2,\ Gly}$, $CH_{2,\ decyl}$ and $CH_{2,\ \beta\ (His)}$), 14.7 ($CH_{3,\ decyl}$);

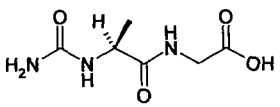
5. Preparation of other dipeptide derivatives

5.1. Benzyl *N*-benzylaminocarbonyl-L-alanyl-glycine (Ester 23)



To a solution of H-Ala-Gly-OBzl·CF_3COOH (0.677 g, 1.933 mmol) and TEA (0.270 ml, 1.937 mmol) in dry CH_2Cl_2 (20 ml), BzlNCO (0.261. ml, 2.113 mmol) was added. Because by the stirring over night gel was formed, additional amount of dry CH_2Cl_2 (10 ml) was added and the reaction mixture stirred overnight. The solvent was evaporated and the precipitate filtered off and washed with water to give: 0.580 g, 81.2 %; $[\alpha]_D$ – 145 (c 1, CH_2Cl_2 : MeOH, 1:1); ^{1}H NMR (DMSO-d_6): 8.37 (1 H, t, J = 5.9, NH_{Gly}), 7.36 – 7.12 (10 H, m, CH_{Bzl}), 6.47 (1 H, t, J = 6.0, NH_{Bzl}), 6.16 (1 H, d, J = 7.9, NH_{Ala}), 5.06 (2 H, s, $OCH_{2,\ Bzl}$), 4.21 – 4.15 (1 H, m, CH^*_{Ala}), 4.14 (2H, d, J = 5.9, $CH_{2,\ Gly}$), 3.88 (1 H, dd, J = 6.0, J = 17.5, $NCH_{A,\ Bzl}$), 3.82 (1 H, dd, J = 5.9, J = 17.5, $NCH_{B,\ Bzl}$), 1 11 (3 H, d, J = 7.0, $CH_{3\ (\beta,\ Ala)}$); ^{13}C NMR ($CDCl_3$): 173.8, 169.6, 157.3 (CO), 140.6,135.9 (C_{Bzl}), 128.4, 128.2, 128.0, 127.9, 127.0, 126.6 (CH_{Bzl}), 65.8 ($CH_{2,\ Bzl}$), 48.4 (CH^*_{Ala}), 42.8, 40.6 ($CH_{2,\ Gly}$ and CH_2N_{Bzl}), 19.6 ($CH_{3\ (\beta,\ Ala)}$); IR: 3335, 3289, 1763, 1737, 1656, 1650, 1624, 1589, 1561.

5.2 *N*-Aminocarbonyl-L-alanyl-glycine (Compound 23)



To a solution of **Ester 23** (0.098 g, 0.265 mmol) in EtOH (30 ml), 10 % Pd/C (0.020 g) was added and the reaction mixture was hydrogenated at 0.37 MPa and room temperature for 20 h. The catalyst was filtered of and the solvent was evaporated to give: 0.042 g, 83.7%;
^{1}H NMR (MeOD): 4.33-4.20 (1 H, m CH^*_{Ala}), 3.92 (2 H, s, $CH_{2,\ Gly}$), 1.34 (3 H, d, J = 6.5, $CH_{3\ (\beta,\ Ala)}$);

Example 2 – Gelation of Compounds 1-23

Compounds 1-23 were tested for gelation in water. A weighed amount of a test compound was dissolved in a measured volume of water. In a typical experiment, measured volumes of

water (100-250 μL) were added by means of a syringe to the 10mg of test compound in a septum-capped test tube (1.25 x 180 mm). After water addition, the mixture was heated to boiling point, and the resulting solution was then allowed to cool by immersing the test tube in a water bath (20 ± 2°C). If the formation of a gel was observed (visual observation), the procedure was repeated until the test tube could be inverted without noticeable flow.

Most of Compounds 1-23 were only slightly soluble in water and therefore it is preferable for them to be dissolved in an organic solvent and then gelled with water.

Two compounds were particularly effective in gelating a mixture of ethanol and water:
10 mg of Compound 13 gelates a mixture of 1.75 mL ethanol and 4.0 mL water;
10 mg of Compound 16 gelates a mixture of 1.98 mL ethanol and 4.2 mL water.

Compound 12 forms a gel-like structure, composed of micrometric, fibrilous aggregates.

Compound 22 hydrochloride salts is the most soluble of the compounds in water and 10 mg of Compound 22 hydrochloride gelates 5.4 mL water.

Example 3 – Gelation of Compounds in Oils

Gelation of Compound 22 hydrochloride (at 10 mg/1 mL) in various pharmaceutical oils (glycerine, oleic acid, octyldodecanol and Cetiol® LC) is shown in Table 1. Many transdermal and topical products show high incidences of adverse skin reactions such as scaling, pruritic erythema, and vesicobollous irritant and allergic contact dermatitis. The problem has also been approached by the additional inclusion of non-irritating ingredients such as glycerine. By gelation in glycerine the skin irritation caused by the drug-gel formulations can be completely avoided.

Oleic acid (cis-9-octadecenoic acid) is a monounsaturated fatty acid and makes up 55-85% of olive oil. The ability of oleic acid to lessen the irritation caused by other penetration enhancing agents and/or other formulation components to a greater extent than oleyl alcohol has been described previously (United States Patent 6,319,913 Penetration enhancing and irritation reducing systems). The gelled combination of oleic acid with a gelling agent (a

supramolecular hydrogelator), such as referred here, and/or other irritation reducing agents, can result in drug formulations that produce markedly reduced levels of skin irritation.

Table 1 – Gelation of Compound 22 hydrochloride in Pharmaceuticial Oils at 10mg/mL

Pharmaceutical Oil	Gelation state
Glycerine	Gel
Oleic Acid	Sol
Octyldodecanol	Sol
Cetiol® LC	Sol

Compound 22 hydrochloride formed a gel in glycerine at a concentration of 10 mg/mL, although at this concentration it did not form a gel in the other pharmaceutical oils tested.

Example 4 – Textural Analysis (Probe tack; adhesion to steel)

The interaction of solvent with the gel forming compounds and its distribution within the gel system are critical for the gel's mechanical strength, and also its ability to control drug release. Desirable gels for bioadhesive systems would be those that exhibited high values of the work of adhesion and high mechanical strength. The ability of the adhesive to form a bond to the skin is directly related to the probe tack of the adhesive. Tack is the ability of an adhesive to form a bond after brief contact with light pressure. Insufficient tack may prevent attachment to the skin, whereas excessive tack may leave adhesive residue on removal or cause dermal irritation. If the probe tack value of gel is less than 0.25 N, then the skin adhesiveness of gel becomes insufficient, so that it is likely to peel off even upon a little movement. Adhesives with a very high tack could form strong initial bonds with the skin upon application and thus may be difficult to remove. If the probes tack value of gel exceeds the 1.2 N value, the skin irritation increases so much that rashes in the skin and pains upon peeling are likely to occur.

Method

In a tack test an adhesive covered substrate is pressed against a flat (steel) punch for a short time at a fixed pressure and then the joint is pulled apart. The force and energy involved in the detachment process are measured. As the two surfaces are moved apart the force increases

rapidly to a maximum and then, for strong adhesion, tends to drop to a nearly constant value where it remains until final detachment. For weaker adhesion the force decreases rapidly to zero (detachment) after the maximum. In the strong adhesion case the adhesive forms voids and then fibrillates during the stress plateau with much energy dissipated in drawing out the fibrils. Measurements of probe tack using an inverted probe machine (Texture Analyzer TA-XTPlus, Stable Micro Systems) were based on the method described in ASTM D2979-01 *Standard Test Method for Pressure-Sensitive Tack of Adhesives Using an Inverted Probe Machine*. Namely, by using the probe tack tester defined in ASTM D 2979-01, after one bottom face of a cylinder (probe) made of steel having a diameter of 12.5 mm and a gel layer surface are brought into contact with each other at a contact load of 4.9 ± 0.01 N for a contact time of 10.0 ± 0.01 seconds, the probe is separated from the adhesive layer surface in the perpendicular direction of the latter at a separating speed of 0.5 ± 0.1 mm/s. The probe tack value refers to the force [N] required at the time of separation. In this test, conducted at room temperature, the approach pre-test speed was 1 mm/second and the dwell time was 10 second, with the applied force of 4.9 N and contact area of 122.7 mm^2; test speed 0.5 mm/second. Figure 1 shows a typical curve of tack probe measurement: force (in g) vs. distance (or displacement in mm). Probe tack (or Adhesive Peak Force) is the maximum force (point 2 in Figure 1) required to break adhesive bond; in g or Newton (or g/cm^2 or N/mm^2). The average force at maximum is average of 10 repeated measurements. Adhesion throughout the contact surface was achieved only for a short period of time, as indicated by the shape of the curve. The area under the curve of tack force vs. length (displacement or time) was integrated to determine the work of fracture of the adhesive bond (gel to steel). Other parameters that can be derived from the probe tack measurements are: a) area of adhesive work (area between anchors 1 and 3); b) stringiness of the product (distance between anchors 1 and 3); c) cohesiveness of the product relative to the adhesiveness to the probe (area 2:3 over area 1:2); and, d) initial adhesive strength (gradient 1:4).

Tables 2 show the effect of acidity on the tack force of Compound 22 by comparing the effect on the tack force of using as a solvent acetic acid of varying concentrations and therefore varying pH. The results from the table show that at a pH of 2.17, the tack force will make the

gel formed by Compound 22 hydrochloride show the tackiness at ordinary temperatures to permit easy temporary adhesion to adherends, suitable for use in bioadhesive systems

Table 2 – Effect of pH on tack force of Compound 22 (10 mg/mL)

Tack force, $F_{max, 1st}$ (N)

acetic acid/ water (% vol./ vol.)	0.01	0.1	1	10	20	30
pH	3.81	3.28	2.73	2.17	1.95	1.74
$F_{max,1}$ (N)	5.511	5.576	6.959	0.425	-	-

Example 13 – Textural Analysis (Extrusional Force)

The quality of gels as usable objects was checked by measuring the gel texture using the viscosity values. Viscosity often determines the flow of products and controls the productivity. The flowability of the gel (e.g. the ability to be extruded through a syringe) is the ability of the gel to be applied onto and conform to sites on or in tissue, including tissue surfaces and defined cavities (intravertebral spaces, tissue). In particular, the gel flow when subjected to stresses above a threshold level, for example when extruded through an orifice or cannula, when packed into a delivery site using a spatula, when sprayed onto the delivery site, or the like. The threshold stresses are typically in the range of several kPa. The compositions, however, will remain generally immobile when subjected to stresses below the threshold level. A minimum pressure gradient is required to extrude a given gel through orifice. Once this minimum pressure gradient is exceeded, the pressure gradient during gel extrusion is insensitive to the flow rate.

Method

Measurements of extrusion were based on flow rate determination using a capillary extrusion viscosimeter with a plunger (tube length: 6, tube diameter 12.5 mm) that was attached to a texture analyzer machine (Texture Analyzer TA-XTPlus, Stable Micro Systems), and it consists of a cylindrical steel flow cell that has a steel bottom with a small size orifice (1mm in diameter). The pre-test speed was 1.5 mm/second, and test speed 2 mm/second. The trigger force was set at 0.00981 N. The force and stress required to extrude the gel through the orifice at the constant speed was measured and the results are shown in Table 3.

The results also indicate gel-to-sol transformation and shear thinning or consistency lost through shearing. In other words, they became less viscous as the shear rate increased, which facilitated the flow of the formulations. The concentration of ingredients in the formula has to be adjusted in order to express flowability through the needle after drug incorporation.

These pre-formed hydrogel materials are promising as injectables and their use could have important clinical consequences, because they can be injected non-invasively using a small gauge needle, minimizing soft tissue dissection and the risk of implant migration.

Table 3 – Extrusional Force/Stress for hydrogels based on Compound 22 hydrochloride salt

Extrusional force/ stress

Compound 22 x HCl concentration wt./ vol.% water	**Average Force value (N)**	**Average stress value (kPa)**
2.5	7.020	57.20
2	9.708	79.11
1.5	1.366	11.13
1	0.695	5.66
1	0.745	6.07
0.5	0.165	1.34
0.33	0.312	2.54
0.25	0.213	1.74
0.2	0.140	1.14
2.5	7.020	57.20

Example 14 – Compound 22 hydrogel compounded with water soluble drug

The chosen model drug, water soluble, is valacyclovir. The example hydrogel compounds contain the constant amount of Compound 22 (1 wt./vol. %) and various contents of valacyclovir form 0.5 up to 5 (wt./vol. %) in water. In this concentration range the gelation has been observed.

The prefferable concentration range would be for Compound 22 from 0.2 (wt./vol. %) up to 10 (wt./vol. %) in water, and the prefferable concentration of valacyclovir form 0.2 up to 10 (wt./vol. %) in water.

Example 15 – Tackiness of Compound 22 hydrogel compounded with water insoluble drug

The chosen model drug that is water insoluble was ibuprofen. The example hydrogel compounds contain the constant amount of Compound 22 (1 wt./vol. %) and various contents of ibuprofen form 0.02 up to 2 (wt./vol. %) in water. In this concentration range the gelation has been observed. The observed tackiness is given in Table 4.
The prefferable concentration range would be for Compound 22 from 0.2 (wt./vol. %) up to 10 (wt./vol. %) in water, and the prefferable concentration of ibuprofen form 0.02 up to 2 (wt./vol. %) in water.

Table 4 – Effect of insoluble drug content on tack force of Compound 22 (10 mg/mL)

Ibuprofen(wt./vol.)	Compound 22 (wt./vol. %)	**Force, $F_{max, 1st}$ (N)**
0.02	1	**6.32**
0.05	1	**4.97**
0.1	1	**7.59**
0.2	1	**5.13**

Example 16 – Diffusion in Compound 22 hydrogel compounded with water insoluble drug

The release rate of drug from formulated hydrogel bases should be diffusion controlled, which can be described by the simplified Higuchi diffusion equation [Higuchi, W. Analysis of data on the medicament release from ointments. J. Pharm. Sci. 1962, 51 (8), 802–804.):

$Q= 2\ C_o\ (Dt/\pi)^{1/2}$

when the drug is completely dissolved in the vehicle, Q=the cumulative amount of drug released into the receptor phase, C_o=is the initial drug concentration in the vehicle, D=the

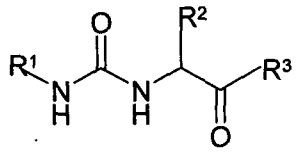
diffusion coefficient of drug in the vehicle, and t=the time elapsed since the start of drug release.

Table 4 – Effect of in-soluble drug content on diffusional constant of Compound 22 (10 mg/mL)

Ibuprofen(wt./vol.)	Compound 22 (wt./vol. %)	$D_{effective}$ (cm^2/s)
0.02	1	1.01×10^{-6}
0.05	1	1.67×10^{-6}
0.1	1	-
0.2	1	-

CLAIMS

1. A gel composition comprising a gelating agent and a solvent, characterised in that the gelating agent is a compound of general formula (I)

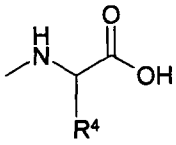


(I)

wherein:

R^1 is hydrogen or C_{1-14} alkyl;

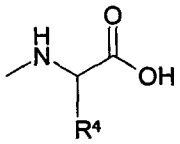
R^3 is OH or a group:



R^4 is hydrogen or C_{1-6} alkyl, optionally substituted with OR^9, COR^9 or $COOR^9$;

R^9 is hydrogen, C_{1-6} alkyl or benzyl;

R^2 is hydrogen, C_{1-6} alkyl or benzyl, either of which may optionally be substituted with OH or, when R^3 is



R^2 may also be R^7;

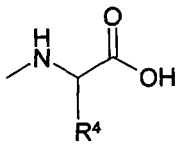
R^7 is a 5 or 6 membered aromatic or heteroaromatic ring system which is optionally further substituted with C_{1-6} alkyl, benzyl or hydroxy;

or a salt thereof.

2. A gel composition as claimed in claim 1 wherein in the compound of general formula (I), independently or in any combination:

R^1 is hydrogen, C_{1-12} alkyl; and

R^2 is hydrogen, C_{1-3} alkyl or benzyl optionally substituted with OH or, when R^3 is

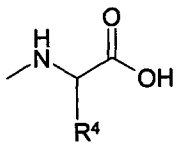


R^2 is R^7 wherein

R^7 is phenyl or a 5- or 6- membered nitrogen containing heteroaromatic ring system, either of which is optionally substituted with OH or benzyl.

3. A gel composition as claimed in claim 2, wherein in the compound of general formula (I) R^2 is hydrogen or methyl optionally substituted with hydroxy, imidazolyl, 1-benzylimidazolyl, phenyl or hydroxyphenyl.

4. A gel composition as claimed in any one of claims 1 to 3 wherein in the compound of general formula (I), R^3 is a group:



and R^4 is hydrogen, methyl, ethyl or benzyl, any of which is optionally substituted with OR^9 or $COOR^9$;

R^9 is hydrogen, methyl, ethyl or benzyl.

5. A gel composition as claimed in claim 4, wherein in the compound of general formula (I), R^4 is hydrogen, methyl or ethyl and the methyl or ethyl groups are optionally substituted COOH or COO-benzyl.

6. A gel composition as claimed in any one of claims 1 to 5 wherein the gelling agent is a hydrochloride salt of a compound of general formula (I).

7. A gel composition as claimed in any one of claims 1 to 5 comprising a gelling agent selected from:

N-ethylaminocarbonyl-glycine;

N-Decylaminocarbonyl-L-alanine;
N-Decylaminocarbonyl-L-valine;
N-Decyilaminocarbonyl-L-leucine;
N-Decylaminocarbonyl-L-tyrosine;
N-ethylaminocarbonyl-L-alanyl-L-alanine;
N-Butylaminocarbonyl-L-alanyl-L-alanine;
N – Butylaminocarbonyl-glycyl-glycine;
N-hexylaminocarbonyl-L-alanyl- glycine;
N-octylaminokarbonyl-L-alanyl- glycine;
N-dodecylaminocarbonyl-L-alanyl- glycine;
N-Heptylaminocarbonyl-L-alanyl-L-alanine;
N-Nonylaminocarbonyl-L-alanyl-L-alanine;
N-Dodecylaminocarbonyl-L-alanyl-L-alanine;
N-Octylaminocarbonyl-glycyl-glycine;
N-Decylaminocarbonyl-glycyl-glycine;
N-Nonylaminocarbonyl-glycyl-L-alanine;
N-Heptylaminocarbonyl-L-seryl-L-alanine;
N-Octylaminocarbonyl-L-seryl-L-alanine;
N-Nonylaminocarbonyl-L-seryl-L-alanine;
N-decylaminocarbonyl - glycyl - L – glutamic acid;
*N*γ-Benzyl, Nα-decylaminocarbonyl-L-hystidyl-glycine;
N-Aminocarbonyl-L-alanyl-glycine;
or a salt thereof.

8. A process for preparing a gel composition as claimed in any one of claims 1 to 7, the process comprising:

a. mixing a compound of general formula (I) as defined in any one of claims 1 to 7 with a solvent; and

b. heating and then cooling the solution.

9. A gel composition as claimed in any one of claims 1 to 7 or a process as claimed in claim 8, wherein the solvent is

a) An aqueous solvent such as water, sodium chloride solution or aqueous acetic acid or a physiological fluid such as stomach acid or saliva;

b) A mixture of water with an organic solvent such as ethanol or DMSO;

c) An organic solvent such as DMSO, ethanol, *n*-decanol, propylene glycol, polyethylene glycol, tetrahydrofuran, dichloromethane, acetonitrile, toluene, *p*-xylene, or tetraline; or

d) Oil such as glycerine, oleic acid, octyldodecanol and cocoyl caprylocaprate.

10. A process or a gel as claimed in claim 8 or claim 9, wherein the solvent is an aqueous solvent and the compound of general formula (I) is present in a concentration of at least 0.2 mg/mL.

11. A composition comprising:

i. a compound of general formula (I) as defined in any one of claims 1 to 7; and

ii. an active agent.

12. A composition as claimed in claim 11, further comprising a solvent.

13. A composition as claimed in claim 11 or claim 12 which is formulated for topical, transdermal, rectal, buccal or sublingual administration.

14. A composition as claimed in claim 13 which is a pharmaceutical composition in which the active agent is a pharmaceutically or biologically active substance.

15. A composition as claimed in claim 13 which is a cosmetic composition intended for topical administration and in which the active agent is a cosmetically acceptable compound, for example an enzyme or a vitamin.

16. A composition as claimed in any one of claims 12 to 15 wherein the solvent is either an aqueous solvent, a mixture of an aqueous and an organic solvent or a pharmaceutical oil such as glycerine, oleic acid, octyldodecanol or cocoyl caprylocaprate .

17. A composition as claimed in any one of claims 12 to 16 which is formulated as a patch

which adheres to the skin.

18. A composition as claimed in claim 11 or claim 12 which is formulated for oral administration.

19. A composition as claimed in claim 18 which is a pharmaceutical composition and in which the active agent is a pharmaceutically or biologically active compound.

20. A compostion as claimed in claim 19 in which the active agent is a dietary supplement.

21. A composition as claimed in any one of claims 18 to 20, when dependent on claim 12, in which the solvent is an aqueous solvent, an organic solvent, a mixture of aqueous and organic solvents or an oil.

22. A composition as claimed in any one of claims 18 to 20 which does not comprise a solvent.

23. A composition as claimed in claim 14 or claim 19, wherein the pharmaceutically active substance is selected from anaesthetics (such as benoxinate, bupivacaine, dibucaine hydrochloride, dyclonine hydrochloride, etidocaine cocaine, hexylcaine, lidocaine, mepivacaine, naepaine, phenacaine hydrochloride, piperocaine, prilocaine, proparacaine hydrochloride, and tetracaine hydrochloride), analgesics (such as aspirin, acetaminophen and diflunisal), angiogenesis inhibitors, antiallergic agents, antibiotics (such as bacitracin, carbenicillin, cefazolin, cefoxitin, cephaloridine, chloramphenicol, chibrorifamycin, n-formamidoylthienamycin, gramicidin, neomycincolistin, penicillin G, polymyxin B, tetracyclines, vancomycin, and sulfonamides), anticancer, anticoagulants (such as heparin, bishydroxycoumarin, and warfarin), antidepressants (amitriptyline, chlordiazepoxide perphenazine, doxepin, imipramine and protriptyline), antidiabetic agents (such as acetohexamide, chlorpropamide insulin, tolazamide and tolbutamide), antiepileptic agents, antifungal (such as amphotericin B, miconazole, natamycin, nystatin and tlucytosine), antihypertensive agents (such as spironolactone, methyldopa, hydralazine, clonidine,

chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine), anti-infective, anti-inflammatory (such as betamethasone, cortisone, dexamethasone sodium phosphate, fluorometholone, hydrocortisone, hydrocortisone acetate, dexamethasone, indomethacin, methylprednisolone, medrysone, prednisolone, preunisone, preunisolone sodium phosphate, triamcinolonesulindac, and its salts and analogs), antimicrobial, antipyretics, antiarrhythmic agents, antithrombotics, antituberculous agents, antitussive expectorants, antiulcer agents, antiviral (such as acyclovir, adenosine arabinoside (Ara-A), interferon, 5-iodo-2'-deoxyuridine and trifluorothymidine), bone resorption inhibitors, cholinergic or adrenergic agonists and antagonists, cardiotonics, cytostatic, haemostatics, fibrinolytics, muscle relaxants (such as melphalan, danbrolene, cyclobenzoprine, methocarbamol and diazepam), narcotic antagonists, sedatives, thrombolytics and wound healing agents or buflomedil pyridoxalphosphate, diltiazem hydochloride, riboflavin sodium phosphate or a biologically active substance selected from proteins and their fragments, peptides and polynucleotides, growth factors, enzymes, vaccines and substances used in the treatment of diseases associated with genetic defects, for example angiotensins, adrenocorticotrophic hormone (ACTH), bacitracins, bombesin antagonists, bradykinin, calcitonin, colistins, growth hormone, growth hormone releasing factor, endomorphins, enkephalins, glucagon, gastrin, gramicidines, insulin, interferon, luliberin or luteinizing hormone releasing hormone (LH-RH), LH-RH agonists or antagonists, monoclonal antibodies, tetragastrin, pentagastrin, urogastrone, prolactin, renin, secretin, oxytocin, polymyzins, somatostatin, tyrocidin, transforming growth factor antagonists, soluble vaccines, and vasopressin.

24. A process for the preparation of a composition as claimed in any one of claims 11 to 23 comprising mixing a compound of general formula (I) as defined in any one of claims 1 to 7 with an active compound and optionally adding a solvent then heating and cooling the solution.

25. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 as a gelling agent in the preparation of a gel.

26. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 in

the preparation of a gel-forming composition, wherein the gel-forming composition comprises a compound of general formula (I) as defined in any one of claims 1 to 7 and an active agent.

27. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 in the preparation of a pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of general formula (I) as defined in any one of claims 1 to 7 and a biologically active agent.

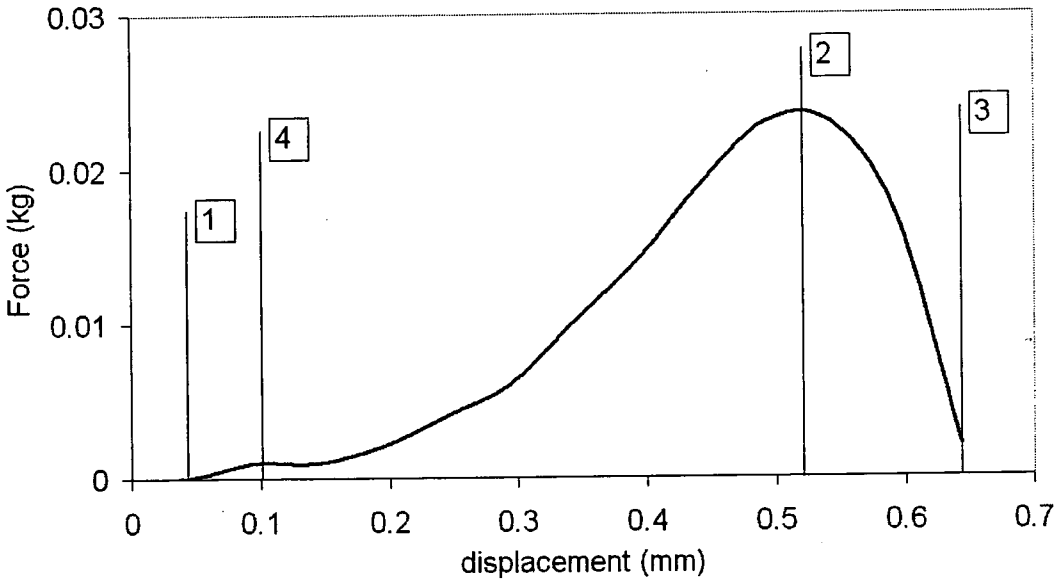
28. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 as a gastroprotective agent for an acid sensitive biologically active agent.

29. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 for controlling the rate of release of an active agent from a composition.

30. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 in the preparation of a cosmetic composition, wherein the cosmetic composition comprises a cosmetically acceptable compound.

31. The use of a compound of general formula (I) as defined in any one of claims 1 to 7 in the preparation of a dietary supplement.

FIGURE 1


0.03
0.02
0.01
0
Force (kg)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
displacement (mm)
1
2
3
4