A NONAPEPTIDE WITH ANTI-TUMOUR ACTIVITY

The present invention relates to peptides or peptide like molecules and their uses in therapy, in particular as anti-tumour agents and also as adjuvants for vaccines including tumour vaccines.

Peptides and their derivatives have long been recognised as therapeutically interesting molecules. A wide variety of organisms use peptides as part of their host defence mechanism. Antimicrobial peptides have been isolated from species as diverse as bacteria and mammals. Generally, these peptides have a net positive charge and a propensity to form amphiphilic α-helix or β-sheet structures upon interaction with the outer phospholipid bilayer in bacterial cell membranes. In most cases the detailed molecular mechanisms of the antibiotic action are unknown, although some peptides categorised as class L (lytic) peptides are believed to interact with bacterial cell membranes, forming ion-channels, pores or other structures capable of destabilising the membrane.

Amongst the general class of lytic antimicrobial peptides, some have also been shown to have anti-tumour activity. Eukaryotic cell membranes of tumour cells develop properties similar to the cell membranes of prokaryotes and it has been postulated that this could provide a degree of selectivity of these lytic peptides for tumour cells *in vivo*. Some anti-tumour activity of peptides having amphiphilic character and a net positive charge has been described in WO 00/12542, WO 01/66147, WO 01/19852 and by Yang et al. in Journal of Peptide Science [2004], 10, pp 37-46 (PMID: 14959890). Generally anti-tumour activity requires larger peptides than can be designed for antibacterial uses. Balancing the need for good target cell cytotoxicity and *in vivo* selectivity presents particular problems in the generation of useful anti-tumour peptides, in part because there remains a high degree of similarity between the cell membrane of tumour and non-transformed cells. Nevertheless, the prevalence of cancer in human and animal populations and its role in mortality means there is a continuing need for new drugs which are effective against tumours. Elimination of a tumour or a reduction in its size or reducing the number of cancer cells circulating in the blood or lymph systems may be beneficial in a variety of ways; reducing pain or discomfort, preventing metastasis, facilitating operative intervention, prolonging life.

Summary

In one aspect, the present invention is directed to a compound having the formula of SEQ ID NO: 23 (LTX-315), or a salt, ester or amide thereof. In another aspect, the present invention is directed to the use of a compound of the present invention as a medicament. In another aspect, the present invention refers to the use of a compound of the present invention in the manufacture of a medicament in combination with a vaccine, as a vaccine adjuvant. In still another aspect, the present invention refers to a formulation comprising a compound of the present invention and at least one vaccine. In still another aspect, the present invention refers to a pharmaceutical pack comprising: at least one vaccine; and a compound of the present invention. In another aspect, the present invention refers to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a tumour, wherein the use comprises the step of administration of a pharmaceutically effective amount of said compound to a patient in need of same.

Detailed Description

During their investigations into the biological activity of peptides, the present inventors have identified a small group of molecules which exhibit particularly good activity

against a range of cancer types and good selectivity for cancerous cells over normal cells.

As is detailed below, one molecule (LTX-315) is particularly preferred and therefore according to ~~a first aspect of the present invention~~one example described herein there is provided a compound having the formula of SEQ ID NO: 23, or a salt, ester or amide thereof.

In one ~~aspect, the present invention provides~~example, disclosed herein is a compound, preferably a peptide, having the following characteristics:

a) consisting of 9 amino acids in a linear arrangement;

b) of those 9 amino acids, 5 are cationic and 4 have a lipophilic R group;

c) at least one of said 9 amino acids is a non-genetically coded amino acid or a modified derivative of a genetically coded amino acid; and optionally

d) the lipophilic and cationic residues are arranged such that there are no more than two of either type of residue adjacent to one another; and further optionally

e) the molecule comprises two pairs of adjacent cationic amino acids and one or two pairs of adjacent lipophilic residues.

The cationic amino acids, which may be the same or different, are preferably lysine or arginine but may be histidine or any non-genetically coded or modified amino acid carrying a positive charge at pH 7.0.

Suitable non-genetically coded cationic amino acids and modified cationic amino acids include analogues of lysine, arginine and histidine such as homolysine, ornithine, diaminobutyric acid, diaminopimelic acid, diaminopropionic acid and homoarginine as well as trimethylysine and trimethylornithine, 4-aminopiperidine-4-carboxylic acid, 4-amino-1-carbamimidoylpiperidine-4-carboxylic acid and 4-guanidinophenylalanine.

The lipophilic amino acids (i.e. amino acids with a lipophilic R group), which may be the same or different, all possess an R group with at least 7, preferably at least 8 or 9, more preferably at least 10 non-hydrogen atoms. An amino acid with a lipophilic R group is referred to herein as a lipophilic amino acid. Typically the lipophilic R group has at least one, preferably two cyclic groups, which may be fused or connected.

resulting in a peptidomimetic. The free amino or carboxy terminals of these molecules may be modified, the carboxy terminus is preferably modified to remove the negative charge, most preferably the carboxy terminus is amidated, this amide group may be substituted.

CCLLCCLLC (I) (SEQ ID NO: 1)

LCCLLCCLC (II) (SEQ ID NO: 2)

CLLCCLLCC (III) (SEQ ID NO: 3)

CCLLCLLCC (IV) (SEQ ID NO: 4)

CLCCLLCCL (V) (SEQ ID NO: 5)

A peptidomimetic is typically characterised by retaining the polarity, three dimensional size and functionality (bioactivity) of its peptide equivalent but wherein the peptide bonds have been replaced, often by more stable linkages. By 'stable' is meant more resistant to enzymatic degradation by hydrolytic enzymes. Generally, the bond which replaces the amide bond (amide bond surrogate) conserves many of the properties of the amide bond, e.g. conformation, steric bulk, electrostatic character, possibility for hydrogen bonding etc. Chapter 14 of "Drug Design and Development", Krogsgaard, Larsen, Liljefors and Madsen (Eds) 1996, Horwood Acad. Pub provides a general discussion of techniques for the design and synthesis of peptidomimetics. In the present case, where the molecule is reacting with a membrane rather than the specific active site of an enzyme, some of the problems described of exactly mimicking affinity and efficacy or substrate function are not relevant and a peptidomimetic can be readily prepared based on a given peptide structure or a motif of required functional groups. Suitable amide bond surrogates include the following groups: N-alkylation (Schmidt, R. et al., Int. J. Peptide Protein Res., 1995, 46,47), retro-inverse amide (Chorev, M and Goodman, M., Acc. Chem. Res, 1993, 26, 266), thioamide (Sherman D.B. and Spatola, A.F. J. Am. Chem. Soc., 1990, 112, 433), thioester, phosphonate, ketomethylene (Hoffman, R.V. and Kim, H.O. J. Org. Chem., 1995, 60, 5107), hydroxymethylene, fluorovinyl (Allmendinger, T. et al., Tetrahydron Lett., 1990, 31, 7297), vinyl, methyleneamino (Sasaki, Y and Abe, J. Chem. Pharm. Bull. 1997 45, 13), methylenethio (Spatola, A.F., Methods Neurosci, 1993, 13, 19), alkane (Lavielle, S. et. al., Int. J. Peptide Protein Res., 1993, 42, 270) and sulfonamido (Luisi, G. et al. Tetrahedron Lett. 1993, 34, 2391).

The peptidomimetic compounds of the present ~~invention~~ disclosure may have 9 identifiable sub-units which are approximately equivalent in size and function to the 9 cationic and

lipophilic amino acids. The term 'amino acid' may thus conveniently be used herein to refer to the equivalent sub-units of a peptidomimetic compound. Moreover, peptidomimetics may have groups equivalent to the R groups of amino acids and discussion herein of suitable R groups and of N and C terminal modifying groups applies, *mutatis mutandis*, to peptidomimetic compounds.

As is discussed in "Drug Design and Development", Krogsgaard *et al.*, 1996, as well as replacement of amide bonds, peptidomimetics may involve the replacement of larger structural moieties with di- or tripeptidomimetic structures and in this case, mimetic moieties involving the peptide bond, such as azole-derived mimetics may be used as dipeptide replacements. Peptidomimetics and thus peptidomimetic backbones wherein just the amide bonds have been replaced as discussed above are, however, preferred.

Suitable peptidomimetics include reduced peptides where the amide bond has been reduced to a methylene amine by treatment with a reducing agent e.g. borane or a hydride reagent such as lithium aluminium-hydride. Such a reduction has the added advantage of increasing the overall cationicity of the molecule.

Other peptidomimetics include peptoids formed, for example, by the stepwise synthesis of amide-functionalised polyglycines. Some peptidomimetic backbones will be readily available from their peptide precursors, such as peptides which have been permethylated, suitable methods are described by Ostresh, J.M. et al. in Proc. Natl. Acad. Sci. USA (1994) 91, 11138-11142. Strongly basic conditions will favour N-methylation over O-methylation and result in methylation of some or all of the nitrogen atoms in the peptide bonds and the N-terminal nitrogen.

Preferred peptidomimetic backbones include polyesters, polyamines and derivatives thereof as well as substituted alkanes and alkenes. The peptidomimetics will preferably have N and C termini which may be modified as discussed herein.

β and γ amino acids as well as α amino acids are included within the term 'amino acids', as are N-substituted glycines. The compounds of the ~~invention~~ disclosure include beta peptides and depsipeptides.

As discussed above, the compounds of the ~~invention~~ disclosure incorporate at least one, and preferably one, non-genetically coded amino acid. When this residue is denoted L', preferred compounds are represented by the following formulae:

LTX-323	30	K-Dip-K-K-W-W-K-K-W-NH_2
LTX-324	31	K-K-Dip-W-K-K-W-W-K-NH_2
LTX-325	32	k-w-w-k-k-dip-w-k-k-NH_2
LTX-326	33	R-R-*Bip*-W-R-R-W-W-R-NH_2
LTX-327	34	R-R-Dip-W-R-R-W-W-R-NH_2
LTX-329	35	k-k-bip-w-k-k-w-w-k-NH_2
LTX-331	36	k-k-Bip-w-k-k-w-w-k-NH_2
LTX-332	37	K-K-bip-W-K-K-W-W-K-NH_2
LTX-333	38	Dab-Dab-W-Dip-Dab-Dab-W-W-Dab-NH_2
LTX-334	39	K-K-W-1-Nal-K-K-W-W-K-NH_2
LTX-335	40	K-K-W-2-Nal-K-K-W-W-K-NH_2
LTX-336	41	K-K-W-Ath-K-K-W-W-K-NH_2
LTX-338	42	K-K-W-Phe(4-4'Bip)-K-K-W-W-K-NH_2

In which:

- the standard single letter code is used for the genetically coded amino acids
- lower case denotes D amino acids
- Dip is diphenylalanine
- Bip is biphenylalanine
- Orn is ornithine
- Dap is 2,3-diaminopropionic acid
- Dab is 2,4-diaminobutyric acid
- 1-Nal is 1-naphthylalanine
- 2-Nal is 2-naphthylalanine
- Ath is 2-amino-3-(anthracen-9-yl)propanoic acid
- Phe(4,4'Bip) is 2-amino-3-[1,1':4',1"-terphenyl-4-yl]propionic acid

All of the molecules described herein may be in salt, ester or amide form.

Thus, also provided according to the present ~~invention~~ disclosure is a compound selected from the group consisting of: LTX-301, LTX-303 – LTX-310, LTX-312 - LTX-321, LTX-323 – LTX-327, LTX-329, LTX-331 - LTX-336, and LTX-338, or a salt, ester or amide thereof. Thus, the present ~~invention~~ disclosure provides a compound having a formula selected from the group consisting of: SEQ ID NOs: 10 and 12-42, or a salt, ester or amide thereof.

The molecules are preferably peptides and preferably have a modified, particularly an amidated, C-terminus. Amidated peptides may themselves be in salt form and acetate forms are preferred. Suitable physiologically acceptable salts are well known in the art and include salts of inorganic or organic acids, and include trifluoracetate as well as acetate and salts formed with HCl.

The molecules described herein are amphipathic in nature, their 2° structure, which may or may not tend towards the formation of an α-helix, provides an amphipathic molecule in physiological conditions.

In a further ~~aspect~~ example is provided the compounds ~~of the invention~~disclosed herein, in particular the compounds of formulae I to V, especially the peptides of Table 1, for use in therapy, particularly for use as an anti-tumour or anticancer agent, the terms are used synonymously herein.

The compounds exhibit anti-tumour activity; in particular they exert a cytotoxic effect through a direct membrane-affecting mechanism. These molecules are lytic, destabilising or even perforating the cell membrane. This offers a distinct therapeutic advantage over agents which act on or interact with proteinaceous components of the target cells, e.g. cell surface receptors. While mutations may result in new forms of the target proteins leading to chemotherapeutic resistance, it is much less likely that radical changes to the lipid membranes could occur to prevent the cytotoxic effect.

Thus in a further ~~aspect~~ example is provided the compounds ~~of the invention~~disclosed herein for use in destabilising and/or permeabilising tumour cell membranes. By 'destabilising' is meant a perturbation of the normal three dimensional lipid bi-layer configuration including but not limited to membrane thinning, increased membrane permeability (typically not involving channels) to water, ions or metabolites etc.

The ~~invention~~ disclosure provides methods of treating tumours, both solid and nonsolid tumours, by administering the various compounds described herein. The amount administered should be effective to kill all or a proportion of the target cells or to prevent or reduce their rate of multiplication, or to inhibit metastasis or otherwise to lessen the harmful effect of the tumour on the patient. The clinician or patient should observe improvement in one or more of the parameters or symptoms associated with the tumour. Administration may also be prophylactic. The patient will typically be a human patient but non-human animals, such as domestic or livestock animals may also be treated.

Unlike the majority of agents which have protein targets, the molecules of the present ~~invention~~ disclosure can target a wide variety of cancers, as shown in the Examples hereto. Preferred cancer targets include lymphomas, leukemias, neuroblastomas and glioblastomas (e.g. from the brain), carcinomas and adenocarcinomas (particularly from the breast, colon, kidney, liver, lung, ovary, pancreas, prostate and skin) and melanomas. Breast cancer is an especially preferred target.

The peptides of the ~~invention~~ disclosure may be synthesised in any convenient way. Generally the reactive groups present (for example amino, thiol and/or carboxyl) will be protected during overall synthesis. The final step in the synthesis will thus be the deprotection of a protected derivative of the ~~invention~~disclosure.

In building up the peptide, one can in principle start either at the C-terminal or the N-terminal although the C-terminal starting procedure is preferred.

Methods of peptide synthesis are well known in the art but for the present ~~invention~~ disclosure it may be particularly convenient to carry out the synthesis on a solid phase support, such supports being well known in the art.

A wide choice of protecting groups for amino acids are known and suitable amine protecting groups may include carbobenzyloxy (also designated Z) t-butoxycarbonyl (also designated Boc), 4-methoxy-2,3,6-trimethylbenzene sulphonyl (Mtr) and 9-fluorenylmethoxy-carbonyl (also designated Fmoc). It will be appreciated that when the peptide is built up from the C-terminal end, an amine-protecting group will be present on the α-amino group of each new residue added and will need to be removed selectively prior to the next coupling step.

Carboxyl protecting groups which may, for example be employed include readily cleaved ester groups such as benzyl (Bzl), p-nitrobenzyl (ONb), or t-butyl (OtBu) groups as well as the coupling groups on solid supports, for example the Rink amide linked to polystyrene.

Thiol protecting groups include p-methoxybenzyl (Mob), trityl (Trt) and acetamidomethyl (Acm).

Preferred peptides of the ~~invention~~ disclosure may conveniently be prepared using the t-butyloxycarbonyl (Boc) protecting group for the amine side chains of Lys, Orn, Dab and Dap as well as for protection of the indole nitrogen of the tryptophan residues. Fmoc can be used for protection of the alpha-amino groups. For peptides containing Arg, 2,2,4,6,7-pentamethyldihydrobenzofurane-5-sulfonyl can be used for protection of the guanidine side chain.

A wide range of procedures exists for removing amine- and carboxyl-protecting groups. These must, however, be consistent with the synthetic strategy employed. The side chain protecting groups must be stable to the conditions used to remove the temporary α-amino protecting group prior to the next coupling step.

Amine protecting groups such as Boc and carboxyl protecting groups such as tBu may be removed simultaneously by acid treatment, for example with trifluoroacetic acid. Thiol protecting groups such as Trt may be removed selectively using an oxidation agent such as iodine.

References and techniques for synthesising peptidomimetic compounds and the other bioactive molecules of the ~~invention~~ disclosure are described herein and thus are well known in the art.

Formulations comprising one or more compounds of the ~~invention~~ disclosure in admixture with a suitable diluent, carrier or excipient constitute a further ~~aspect of the present invention~~example described herein. Such formulations may be for, *inter alia*, pharmaceutical (including veterinary) purposes. Suitable diluents, excipients and carriers are known to the skilled person.

While it is possible for the compounds of the present ~~invention~~ disclosure (or salts, esters or amides thereof) to be administered as pure compounds, it is preferable to present them as pharmaceutical formulations. Thus, formulations according to the present ~~invention~~ disclosure preferably comprise at least one compound, salt, ester or amide as defined above, together with at least one other therapeutic ingredient. Thus, the present ~~invention~~ disclosure extends to combination products incorporating the compound of the present ~~invention~~ disclosure (or a salt, ester or amide thereof) and at least one other therapeutic ingredient.

Methods of treating tumours which comprise administration to a human or animal patient one or more of the compounds as defined herein constitute a further ~~aspect of the present invention~~example described herein.

The compositions according to the ~~invention~~ disclosure may be presented, for example, in a form suitable for oral, topical, nasal, parenteral, intravenal, intratumoral, rectal or regional (e.g. isolated limb perfusion) administration. Administration is typically by a parenteral route, preferably by injection subcutaneously, intramuscularly, intracapsularly, intraspinaly, intratumouraly or intravenously.

The active compounds defined herein may be presented in the conventional pharmacological forms of administration, such as tablets, coated tablets, nasal sprays, solutions, emulsions, liposomes, powders, capsules or sustained release forms. Conventional pharmaceutical excipients as well as the usual methods of production may be employed for the preparation of these forms.

Organ specific carrier systems may also be used.

Injection solutions may, for example, be produced in the conventional manner, such as by the addition of preservation agents, such as p-hydroxybenzoates, or stabilizers, such as EDTA. The solutions are then filled into injection vials or ampoules.

Preferred formulations are those in which the peptides are dissolved in saline. Such formulations being suitable for use in preferred methods of administration, especially local administration, i.e. intratumoural, e.g. by injection or by perfusion/infusion of a preferably isolated (including partial isolation) limb, body region or organ.

Dosage units containing the active molecules preferably contain 0.1-10 mg, for example 1-5 mg of the anti-tumour agent. The pharmaceutical compositions may additionally comprise further active ingredients, including other cytotoxic agents such as other anti-tumour peptides. Other active ingredients may include different types of cytokines e.g. IFN-γ, TNF, CSF and growth factors, immunomodulators, chemotherapeutics e.g. cisplatin or antibodies or cancer vaccines.

In employing such compositions systemically, the active molecule is present in an amount to achieve a serum level of the bioactive molecule of at least about 5 µg/ml. In general, the serum level need not exceed 500 µg/ml. A preferred serum level is about

100 µg/ml. Such serum levels may be achieved by incorporating the bioactive molecule in a composition to be administered systemically at a dose of from 1 to about 10 mg/kg. In general, the molecule(s) need not be administered at a dose exceeding 100 mg/kg.

Also provided according to the present ~~invention~~ disclosure is a compound, salt, ester or amide according to the present ~~invention~~ disclosure in combination with an at least one vaccine.

As detailed below, experiments have shown that prophylactic vaccination with LTX-315-lysed tumour cells result in tumour growth inhibition and show that the compounds of the present disclosure~~invention~~ are highly effective as vaccine adjuvants, and thus the present ~~invention~~disclosure extends to the use of the compounds (or salts, esters or amides thereof) in combination with an at least one vaccine. Preferred vaccines include, but are not limited to, anti cancer vaccines containing at least one protein and/or peptide with amino acid sequences corresponding to immunogenic sequence(s) from tumour associated antigen(s) (TAA), preferred TAAs, but not limited to, are telomerase, survivin oncogenic p21 ras, abl, gip, gsp, ret, terk, and antivirus vaccines containing at least one protein and/or peptide with amino acid sequence(s) corresponding to immunogenic sequences from viral protein(s). In addition, tumour lysate can be used. Examples of preferred vaccines include vaccines, peptides, peptide fragments and immunogens taught by WO 92/14756, WO 00/66153 (NO 309798), WO 00/02581, WO 02/051994, WO 02/070679, WO 02/094312, WO 99/58552, and WO 99/58564.

Also provided according to the present ~~invention~~disclosure is the use of a compound, salt, ester or amide or combination according to the present ~~invention~~disclosure in the manufacture of a medicament, particularly in the manufacture of a medicament for the treatment of cancer and/or in the manufacture of a vaccine.

Preferably, the medicament is for the treatment of multidrug resistant (MDR) tumours.

Also provided according to the present invention is a pharmaceutical pack comprising:

(i) an at least one vaccine; and

(ii) a compound, salt, ester or amide according to the present invention.

With pharmaceutical packs, the at least one vaccine and the compound, salt, ester or amide can for administration separately (for example with a time delay of about, at least, or no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 45, 60, 90 or 120 minutes). The pharmaceutical pack can of course also comprise instructions for administration.

Also provided according to the present ~~invention~~disclosure is a method of treatment of a tumour, comprising the step of administering a pharmaceutically effective amount of a compound, salt, ester or amide or combination according to the present ~~invention~~disclosure to a patient in need of same.

Also provided according to the present ~~invention~~disclosure is a method of vaccination, comprising the step of administering a pharmaceutically effective amount of a compound, salt, ester or amide or combination according to the present ~~invention~~disclosure to a patient.

Also provided according to the present ~~invention~~disclosure is a method of manufacture of a medicament, comprising admixing a compound having the formula of SEQ ID NO: 23 (LTX-315) or a salt, ester or amide thereof with a pharmaceutically acceptable carrier, diluent or excipient.

Also provided according to the present ~~invention~~disclosure is a method of manufacture of a medicament, comprising admixing a compound having the formula of SEQ ID NO: 23 (LTX-315) or a salt, ester or amide thereof with tumour cells.

The invention will now be further described in the following Examples and with reference to the figures in which:

Figure 1 is a graph showing the percentage of red blood cell death in a series of experiments to test peptide LTX-315 at varying concentrations. X-axis shows peptide concentration (µg/ml). Y-axis shows % cell death;

Figure 2 shows tumour growth in mice re-inoculated with murine A20 B cell lymphoma cells compared with growth in the control animals from the initial study. Diamonds indicate controls from primary studies. Solid squares indicate re-inoculated mice;

Figure 3 shows tumour growth in individual mice re-inoculated with murine A20 B cell lymphoma cells having been initially treated with LTX-315. Squares indicate Mouse 1. Triangles (base at bottom) indicate Mouse 2. Triangles (base at top) indicate Mouse 3. Diamonds indicate Mouse 4;

Figure 4 shows tumour growth in mice re-inoculated with murine CT26WT colon carcinoma cells compared with growth in the control

CLAIMS

1. A compound of formula:

CCLLCCLLC	(I)	(SEQ ID No. 1) or
CLLCCLLCC	(III)	(SEQ ID No. 3);

wherein C represents a cationic amino acid and L represents an amino acid with a lipophilic R group and in which one of the amino acids having a lipophilic R group is a non-genetically coded amino acid, said compound optionally in the form of a salt, ester or amide.

2. A compound as claimed in claim 1 wherein each lipophilic R group has at least 9 non-hydrogen atoms.

3. A compound as claimed in claim 1 or claim 2 wherein each lipophilic R group has at least one cyclic group.

4. A compound as claimed in any preceding claim in which 1 to 3 of the amino acids with lipophilic R groups are tryptophan.

5. A compound as claimed in any preceding claim which incorporates a non-genetically coded amino acid selected from the group consisting of: 2-amino-3-(biphenyl-4-yl)propanoic acid (biphenylalanine), 2-amino-3,3-diphenylpropanoic acid (diphenylalanine), 2-amino-3-(anthracen-9-yl)propanoic acid, 2-amino-3-(naphthalen-2-yl)propanoic acid, 2-amino-3-(naphthalen-1-yl)propanoic acid, 2-amino-3-[1,1':4',1"-terphenyl-4-yl]-propionic acid, 2-amino-3-(2,5,7-tri-*tert*-butyl-1H-indol-3-yl)propanoic acid, 2-amino-3-[1,1':3',1"-terphenyl-4-yl]-propionic acid, 2-amino-3-[1,1':2',1"-terphenyl-4-yl]-propionic acid, 2-amino-3-(4-naphthalen-2-yl-phenyl)-propionic acid, 2-amino-3-(4'-butylbiphenyl-4-yl)propanoic acid, 2-amino-3-[1,1':3',1"-terphenyl-5'-yl]-propionic acid and 2-amino-3-(4-(2,2-diphenylethyl)phenyl)propanoic acid.

6. A compound as claimed in any preceding claim having the formula of SEQ ID NO: 23 (LTX-315), or a salt, ester or amide thereof.

7. A composition comprising a compound as claimed in any preceding claim, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

8. A composition comprising a compound as claimed in any one of claims 1 to 6 in combination with at least one other therapeutic ingredient.

9. Use of a compound as claimed in any one of claims 1 to 6 as medicament.

10. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament in combination with a vaccine, as a vaccine adjuvant.

11. A formulation comprising a compound as claimed in any one of claims 1 to 6 and at least one vaccine.

12. A pharmaceutical pack comprising:
    (i) at least one vaccine; and
    (ii) a compound as claimed in any one of claims 1 to 6.

13. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of a tumour, wherein the use comprises the step of administration of a pharmaceutically effective amount of said compound to a patient in need of same.

14. The formulation as claimed in claim 11, the pharmaceutical pack as claimed in claim 12, or the use as claimed in claim 10, wherein said vaccine is either a tumour lysate or an anti-cancer vaccine containing at least one protein and/or peptide with amino acid sequences corresponding to immunogenic sequence(s) from tumour associated antigen(s).

15. The formulation as claimed in claim 11, the pharmaceutical pack as claimed in claim 12 or the use as claimed in claim 10, wherein said vaccine is an anti-virus vaccine containing at least one protein and/or peptide with amino acid sequence(s) corresponding to immunogenic sequences from viral protein(s).

CLAIMS

1. A compound having the formula of SEQ ID NO: 23 (LTX-315), or a salt, ester or amide thereof.

2. A composition comprising a compound as claimed in claim 1, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

3. A composition comprising a compound as claimed in claim 1 in combination with at least one other therapeutic ingredient.

4. Use of a compound as claimed in claim 1 as a medicament.

5. Use of a compound as claimed in claim 1 in the manufacture of a medicament in combination with a vaccine, as a vaccine adjuvant.

6. A formulation comprising a compound as claimed in claim 1 and at least one vaccine.

7. A pharmaceutical pack comprising:
   (i) at least one vaccine; and
   (ii) a compound as claimed in claim 1.

8. Use of a compound as claimed in claim 1 in the manufacture of a medicament for the treatment of a tumour, wherein the use comprises the step of administration of a pharmaceutically effective amount of said compound to a patient in need of same.

9. The formulation as claimed in claim 6, the pharmaceutical pack as claimed in claim 7, or the use as claimed in claim 5, wherein said vaccine is either a tumour lysate or an anti-cancer vaccine containing at least one protein and/or peptide with amino acid sequences corresponding to immunogenic sequence(s) from tumour associated antigen(s).

10. The formulation as claimed in claim 6, the pharmaceutical pack as claimed in claim 7 or the use as claimed in claim 5, wherein said vaccine is an anti-virus vaccine

containing at least one protein and/or peptide with amino acid sequence(s) corresponding to immunogenic sequences from viral protein(s).