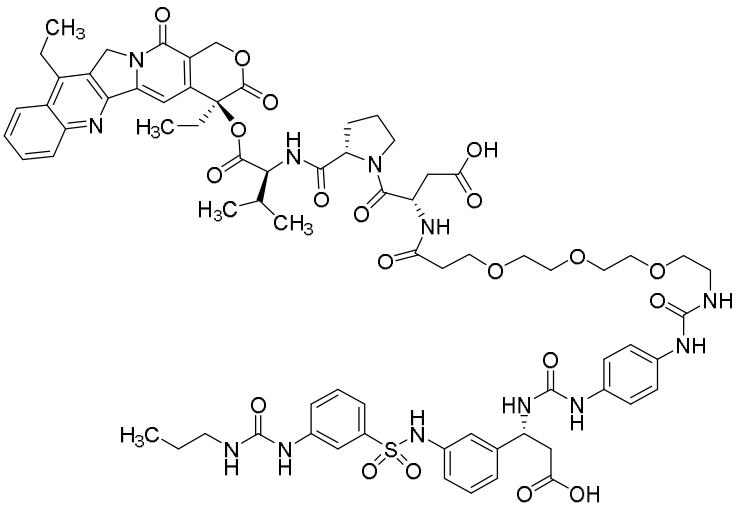
tumor microenvironment, where the moiety in the conjugate addressing $\alpha_v\beta_3$ integrin receptors retains its ability to bind to the $\alpha_v\beta_3$ integrin receptor and therefore provides tissue selectivity to such compounds. In addition, cleavability of the conjugates and drug release should be mediated by enzymes present and active in the tumor environment such as neutrophil elastase. Finally, the profile of the toxophore should match an extracellular cleavage and release mechanism in a way, that it should be highly permeable into tumor cells and tissues and not being a substrate of drug transporters.

Summary

[00017a] In one aspect, the present disclosure refers to a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, solvate, or solvate of a salt thereof.

[00017b] In another aspect, the present disclosure refers to the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof disclosed herein, or the salt disclosed herein, for use as a medicament.

[00017c] In another aspect, the present disclosure refers to a use of the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof disclosed herein, or the salt disclosed herein, in the manufacture of a medicament for treating hyperproliferative disorders.

[00017d] In another aspect, the present disclosure refers to a pharmaceutical combination comprising (i) the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof disclosed herein, or the salt disclosed herein, in combination with (ii) one or more pharmaceutically acceptable excipients.

[00017e] In another aspect, the present disclosure refers to the pharmaceutical combination as described herein for use in therapy.

[00017f] In another aspect, the present disclosure refers to a use of the pharmaceutical combination as described herein in the manufacture of a medicament for treating hyperproliferative disorders.

[00017g] In another aspect, the present disclosure refers to a use of the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof disclosed herein, or the salt disclosed herein, or the pharmaceutical combination as described herein, in the manufacture of a medicament for treating ophthalmological disorders.

[00018] The present invention relates to pharmaceutical compounds which are conjugates comprising an $\alpha_v\beta_3$ integrin antagonist, linking units which can be selectively cleaved by elastase, a polyethyleneglycol (PEG)

spacer and a cytotoxic element (toxophore). The conjugates have a tumor-specific action as a result of linkage to $\alpha_v\beta_3$ integrin antagonists via preferred linking units which can be selectively cleaved by elastase, i.e. by an enzyme which can especially be found in tumor stroma. The preferred linking units provide sufficient stability of the conjugate of cytostatic and $\alpha_v\beta_3$ integrin antagonist in biological media, e.g. culture medium or serum and, at the same time, the desired intracellular action within tumor tissue as a result of its specific enzymatic or hydrolytic cleavability with release of the cytostatic.

[00019] In particular, the compounds of the present invention show favorable features:

- Improved stability of the conjugates after replacement of thio urea by urea linkage
- Employment of 7-Ethyl camptothecin as a particularly suitable toxophore moiety
    - Beneficial impact e.g. on lactone ring stability (Drugs Fut 2002, 27(9), 869)
    - High cellular permeability and low efflux (as compared e.g. to SN38)
- Modified spacer with beneficial impact on solubility, integrin-binding affinity, elastase cleavability
- Tumor accumulation of toxophore after conjugate administration versus direct administration.
- Excellent therapeutic efficacy in various tumor models.

[00020] Towards this goal, 7-Ethyl camptothecin is particularly preferred as the toxophore moiety in above mentioned conjugates.

[00021] The present invention provides compounds of the formula (I)

CT – LI – SP – IA (I)

in which

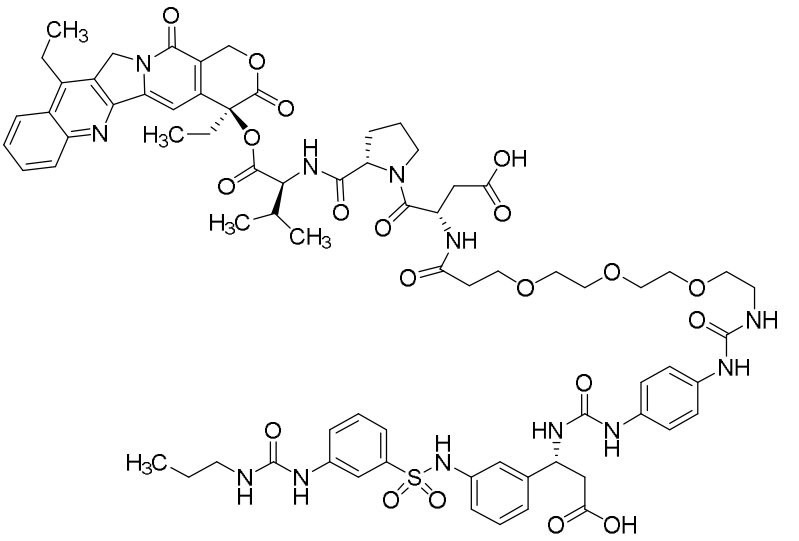
CT is a mono valent radical from the group of a cytotoxic radical, a radical of a cytostatic and a radical of a cytostatic derivative, which can each additionally carry hydroxyl, carboxyl or amino group

LI is a bivalent peptide radical of the formula: -L-Val – L-Pro – L-Asp-

SP is a group of the formula: $-C{=}O-(CH_2)_x-O-(CH_2-CH_2-O)_y-CH_2-CH_2-NH-C{=}O-$ with x = 1 - 5 and y = 0 - 15

What is claimed is:

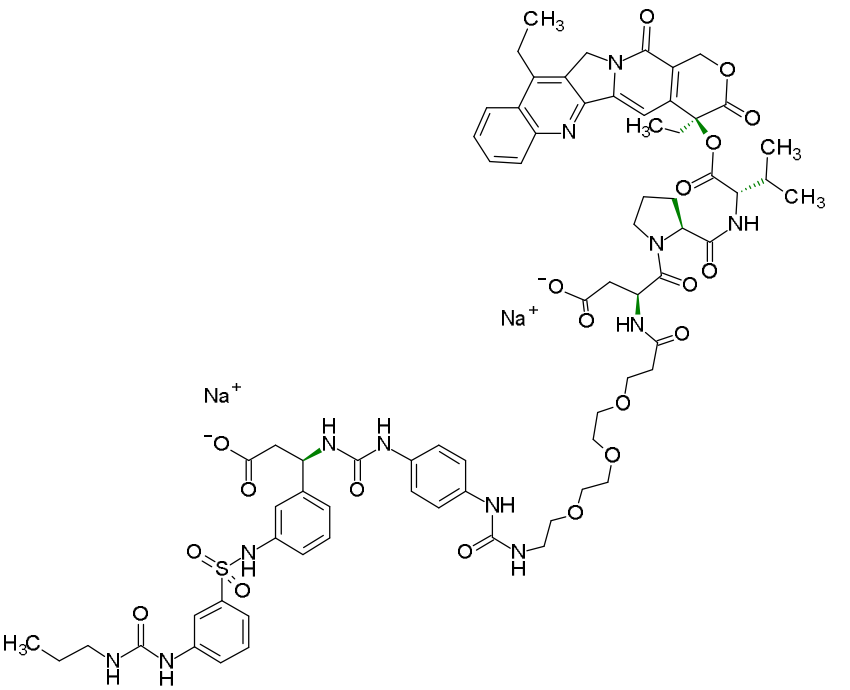
1. A compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, solvate, or solvate of a salt thereof.

2. The compound of claim 1, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof, that is:



3. The compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof, of claim 1, or the salt of claim 2, for use as a medicament.

4. Use of the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof, of claim 1, or the salt of claim 2, in the manufacture of a medicament for treating hyperproliferative disorders.

5. A pharmaceutical combination comprising (i) the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof, of claim 1, or the salt of claim 2, in combination with (ii) one or more pharmaceutically acceptable excipients.

6. The pharmaceutical combination of claim 5 for use in therapy.

7. Use of the pharmaceutical combination of claim 5 in the manufacture of a medicament for treating hyperproliferative disorders.

8. Use of the compound, or the pharmaceutically acceptable salt, solvate, or solvate of the salt thereof, of claim 1, or the salt of claim 2, or the pharmaceutical combination of claim 5, in the manufacture of a medicament for treating ophthalmological disorders.

9. The use as defined in claim 4 or 7, wherein the hyperproliferative disorder is a solid tumor of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, or parathyroid, or and their distant metastases.

10. The use as defined in claim 9, wherein the hyperproliferative disorder is a cancer.

11. The use as defined in claim 10, wherein the cancer is breast cancer, colon cancer, lung cancer, or renal cancer.