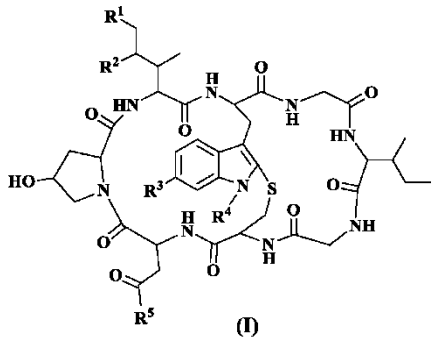
Claims

1. A non-natural amatoxin-antibody conjugate, comprising a toxin moiety having a structural formula (I) or a pharmaceutically acceptable salt thereof, and a biomacromolecule moiety A having a binding affinity to a target,



(I)

wherein:

R^1 is H, -OH or -O-L-A;

R^2 is H or -OH;

R^3 is OC_{1-6} alkyl;

R^4 is H or -L-A;

R^5 is $-NH_2$, -OH, -NH-L-A or -O-L-A;

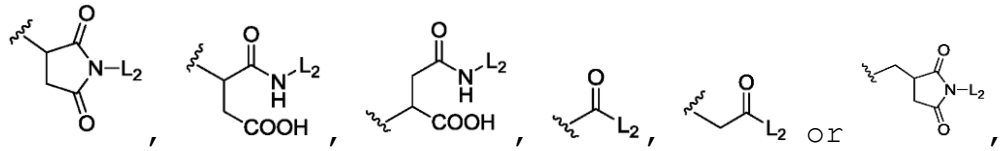
wherein O is an oxygen atom, N is a nitrogen atom and H is a hydrogen atom;

wherein the L comprises the following structure:

$$-L_1-[L_2]_m-[AA]_n-L_3-$$

wherein

L_1 is a linker connecting to the biomacromolecule moiety A, wherein L_1 is selected from the group consisting of:



wherein a wavy line represents the connection to A;

L_2 is a spacer connecting L_1 to AA, wherein L_2 is selected from:

a substituted or unsubstituted C1-C6 alkyl,

a substituted or unsubstituted C3-C20 cycloalkyl,

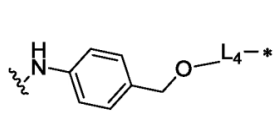
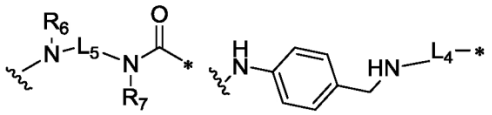
a substituted or unsubstituted C3-C20 heterocycloalkyl,

a substituted or unsubstituted C5-C20 aryl,

a substituted or unsubstituted C5-C20 heteroaryl, or

-(CH_2CH_2O)a-, wherein a is an integer selected from 1 to 20; m is an integer selected from 1-6;

L_3 is a structural fragment connecting to the toxin moiety, wherein L_3 comprises

or any linking group that connects to the toxin moiety,

wherein in L3

L4 is a carbonyl group or a single bond,

R6 and R7 are each independently selected from hydrogen or C1-C6 alkyl,

L5 is C2-C12 alkyl;

AA is a structural fragment consisting of 1 to 6 amino acids, and n is 0 or 1; and wherein only one of R^1, R^4 and R^5 contains an -L-A structure.

2. The non-natural amatoxin-antibody conjugate of claim 1, wherein A comprises an antibody or its antigen-binding fragment thereof, an antibody-like protein or a nucleic acid aptamer.

3. The non-natural amatoxin-antibody conjugate of claim 2, wherein the antibody or its antigen-binding fragment thereof comprises a chimeric antibody, a deimmunized antibody, a humanized antibody, a human antibody, a bispecific antibody, a triabody, a nanobody or their antigen-binding fragments thereof.

4. The non-natural amatoxin-antibody conjugate of claim 2 or 3, wherein the antigen-binding fragment is selected from the group consisting of Fab, F(ab'), Fd, Fv, a single-chain Fv or a disulfide-linked Fv(dsFv).

5. The non-natural amatoxin-antibody conjugate of claim 1, wherein the substituted comprises a substitution with a hydroxyl group, a sulfydryl group, halogen, a carboxyl group,

an amino group, a phosphate group, a nitro group, a cyano group, a sulfo group, or a further substituted or unsubstituted C1-C6 alkyl.

6. The non-natural amatoxin-antibody conjugate of claim 5, wherein the further substituted comprises a substitution with a hydroxyl group, a sulfydryl group, halogen, a carboxyl group, an amino group, a phosphate group, a nitro group, a cyano group, or a sulfo group.

7. The non-natural amatoxin-antibody conjugate of any one of claims 1-6, wherein the amino acids are L- amino acids selected from glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, tryptophan, serine, tyrosine, cysteine, methionine, asparagine, glutamine, threonine, aspartate, glutamate, lysine, arginine or histidine.

8. The non-natural amatoxin-antibody conjugate of claim 7, wherein the amino acids are selected from phenylalanine, citrulline, valine, lysine, serine, glutamate, aspartate or glycine.

9. A pharmaceutical composition comprising the non-natural amatoxin-type antibody conjugate as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9, wherein the pharmaceutical composition is an anti-lung cancer drug, an anti-renal cancer drug, an anti-urethral cancer drug, an anti-colorectal cancer drug, an anti-prostate cancer drug, an anti-glioblastoma drug, an anti-ovarian cancer drug, an anti-pancreatic cancer drug, an anti-breast cancer drug, an anti-melanoma drug, an anti-liver cancer drug, an anti-bladder cancer drug, an anti-malignant lymphoma drug, an anti-leukemia drug, an anti-gastric cancer drugs or an anti-esophageal cancer drug.

11. The use of the non-natural amatoxin-type antibody conjugate as claimed in any one of claims 1 to 8 or a pharmaceutical composition of claim 9 or 10 in the preparation of a medicament for treating a tumor or cancer.