

free drug against nearby cancer cells with low copy number or undetectable levels of targeted antigen and bystander activity against more distant normal cells, which would lead to off-target toxicities, is context dependent. Thus, maximal bystander activity would typically be desired against solid tumors with the highest cancer cell heterogeneity, while lower bystander activity would typically be more desirable against more homogenous tumors, which have limited numbers of cancer cells with lower copy number compared to the bulk of the cancer cells or undetectable levels of targeted antigen, or those cancers where diffusion of free drug from the desired site of action is most likely, as would likely be the case for haematological malignancies (e.g., see Staudacher, A.H. and Brown, M.P. “Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required?” *Br. J. Cancer* (2017) **117**: 1736-1742).

SUMMARY OF THE INVENTION

[0006] In one aspect, the present disclosure provides a Ligand Drug Conjugate compound represented by Formula 1:

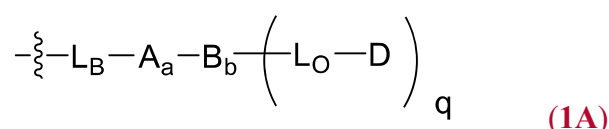


or a salt thereof, wherein

L is a Ligand Unit;

subscript p' is an integer ranging from 1 to 24;

each -LU-D' is a drug-linker moiety of Formula 1A:



or a salt thereof,

wherein the wavy line indicates covalent attachment to L;

L_B is a ligand covalent binding moiety;

A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is an optional secondary linker moiety;

or a salt thereof,

wherein the wavy line indicates covalent attachment to L;

L_B is a ligand covalent binding moiety;

A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence or presence of A, respectively;

B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence or presence of B, respectively;

L_O is an optional secondary linker moiety;

or a salt thereof, wherein

the hydrophobic auristatin F compound is conjugated to the remainder of the drug-linker moiety through its C-terminal component's carboxylic acid carbon atom;

Ar is phenyl, thienyl, 1-naphthyl, 2-naphthyl, or benzo[b]thiophen-3-yl;

R³ is independently selected from the group consisting of hydrogen and C₁-C₂ alkyl;

R¹ is C₁-C₉ alkyl, or

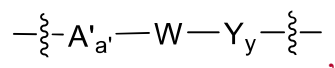
R¹ is (C₃-C₆ carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R₁ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group

and R⁴ is C₁-C₆ alkyl; and

R² is C₁-C₂ alkyl,

with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10, and R¹ and R² are not each methyl, wherein, when present, L_O has the formula of:



wherein the wavy line adjacent to Y indicates the site of covalent attachment to the hydrophobic auristatin F compound, and the wavy line adjacent to A' indicates the site of covalent attachment to the remainder of the drug linker moiety;

A' is a second optional Stretcher Unit;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively;

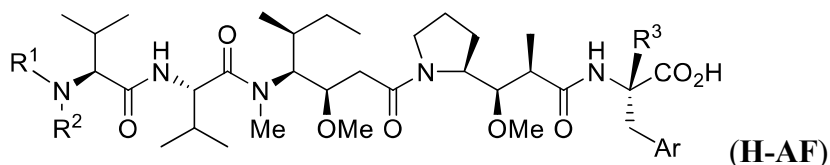
W is a peptide Cleavable Unit;

Y is a peptide Spacer Unit; and

subscript y is 0 or 1, indicating the absence or presence of Y, respectively.

One principle ~~embodiment~~example of the ~~invention~~disclosure provides for synthetically-accessible hydrophobically-modified auristatin F (AF) and AF-type compounds, collectively referred to as hydrophobic AF compounds, that are suitable for conjugation to the C-terminal component of the auristatin structure for providing ADCs having dual

MDR⁺ and tunable bystander activities against targeted cells, wherein the hydrophobic AF compounds are related to auristatin F by having the structure of Formula **H-AF**:



[0007] or a salt thereof, in particular, a pharmaceutically acceptable salt, wherein Ar is phenyl, thienyl, 1-naphthyl, 2-naphthyl or benzo[b]thiophen-3-yl, optionally substituted;

[0008] R² is C₁-C₂ alkyl;

[0009] R³ is independently selected from the group consisting of hydrogen and C₁-C₂ alkyl; and

[0010] R¹ is C₁-C₉ alkyl, which is inclusive of saturated C₁-C₉ alkyl and unsaturated C₃-C₉ alkyl, optionally substituted by a C₃-C₆ carbocyclyl to provide a (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

[0011] R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,

[0012] with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R¹, R² and R³ is between 3 and 10, and R¹, R² and R³ are not each methyl, or

[0013] wherein Ar is phenyl; R³ is hydrogen; R¹ is a first non-aromatic hydrophobic moiety; and R² is a second non-aromatic hydrophobic moiety, wherein R¹ and R² provide the hydrophobic auristatin F compound of Formula **H-AF** characterized by a clogP value of between about 4.4 to about 7.2, and

[0014] wherein the parent auristatin F compound has the structure of Formula **H-AF** in which R¹ and R² are methyl, R³ is hydrogen, and Ar is phenyl.

[0015] Other hydrophobic AF compounds that are related to auristatin F and are synthetically accessible have the internal valine residue of AF or a Formula **H-AF** compound replaced with another α -amino acid residue having a different hydrophobic α -carbon side chain provided that the cLogP of the hydrophobic AF compound from said replacement is or remains within the range of between about 4.4 to about 7.2.

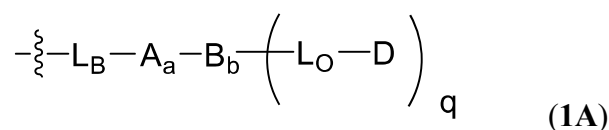
[0016] Still other hydrophobic AF compounds that are related to auristatin F have the structure of AF or any one of the previously described hydrophobically-modified AF compounds in which the N-methyl substituent of the Dil amino acid residue has been replaced with variable group R⁵, wherein R⁵ is C₂-C₆ alkyl or has the of formula -(C₂-C₆ alkylene)-X'-R⁶, wherein X' is an independently selected amide or carbamate functional group and R⁶ is C₁-C₆ alkyl and the remaining variable groups retain their previous meanings, with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R¹, R², R³ and R⁵ is between 3 and 10, or has been replaced with a more hydrophobic moiety provided that the cLogP from said replacement is or remains within the range of between about 4.4 to about 7.2,

[0017] Another principal embodimentexample of the inventiondisclosure provides for a Ligand Drug Conjugate (LDC) composition represented by Formula **1**:



[0018] or a salt thereof, in particular a pharmaceutically acceptable salt thereof, wherein L is a Ligand Unit; LU is a Linker Unit; and subscript p is a number ranging from 1 to 24; D' represents from 1 to 4 hydrophobic auristatin F Drug Units each of which is a hydrophobic AF drug of Formula **H-AF** conjugated to its C-terminal component, in particular through its carboxylic acid functional group, for each drug linker moiety of formula -LU-D', wherein in some aspectexample the Ligand Unit is an antibody or antigen-

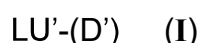
binding fragment thereof, thereby defining an antibody Ligand Unit of an Antibody Drug Conjugate (ADC), wherein the Ligand Unit is capable of selective binding to a targeted moiety of a targeted cell, which in some aspectexample is an antigen of a cancer cell, for subsequent release of free drug, wherein the targeted moiety is preferably capable of internalization along with bound Ligand Drug Conjugate compound into the targeted cell upon said binding to initiate intracellular release of free drug subsequent to said internalization, wherein each hydrophobic auristatin F drug linker moiety in a Ligand Drug Conjugate compound of the composition has the structure of Formula **1A**:



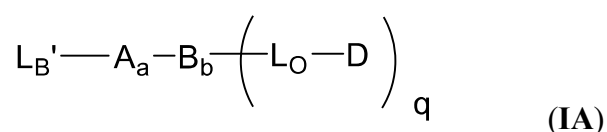
[0019] or a salt thereof, in particular a pharmaceutically acceptable salt thereof, wherein the wavy line indicates covalent attachment to L; L_B is an ligand covalent binding moiety, which is an antibody covalent binding moiety when L is an antibody Ligand Unit; A is a first optional Stretcher Unit; subscript a is 0 or 1 indicating the absence of presence of A, respectively; B is an optional Branching Unit; subscript b is 0 or 1, indicating the absence of presence of B, respectively; L_O is an optional secondary linker moiety; D is the hydrophobic AF Drug Unit; and subscript q is an integer ranging from 1 to 4, provided that subscript b is 1 when subscript q ranges from 2 to 4 and is 0 when subscript q is 1,

[0020] wherein the LDC compound has the structure of Formula **1** in which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24.

[0021] A related principle embodimentexample provides for a Drug Linker compound of Formula **I**:



[0022] or a salt thereof, in particular a pharmaceutically acceptable salt thereof, wherein LU' is a LU precursor; and D' represents from 1 to 4 hydrophobic AF Drug Units, each of which is a hydrophobic AF drug of Formula **H-AF** conjugated to its C-terminal component, in particular through its carboxylic acid functional group, wherein the Drug Linker compound is further defined by the structure of Formula **IA**:



[0023] wherein L_B' is a ligand covalent binding moiety precursor and the remaining variable groups are as defined for Formula 1A.

[0024] Those and other ~~embodiment examples~~ of the ~~invention disclosure~~ are described in more detail in the following "Detailed Description of the ~~Invention Disclosure~~" and "Claims".

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Figure 1. Variation of *in vitro* IC₅₀ values for auristatin free drugs on MDR-HL60 and MDR⁺ HL60/RV acute myeloid leukemia cells with increasing unbranched alkyl chain length replacing the N-terminal methyl of auristatin F (n = 1)

[0026] Figure 2. *In vivo* efficacies of hydrophobic auristatin F ADCs targeting CD70 against a nude mouse xenograft model bearing subcutaneous 786-O renal carcinoma tumors, which are MDR⁺, administered i.p. at doses of 0.5 and 1.5 mg/Kg.

[0027] Figure 3. *In vivo* efficacies of a hydrophobic auristatin F ADC targeting CD30 and comparator ADCs having MMAE and MMAF Drug Units against a nude mouse xenograft model bearing an admixed Karpas/KarpasBVR Hodgkin (MDR⁻/MDR⁺) lymphoma tumors, administered i.p. at doses of 3 mg/Kg.

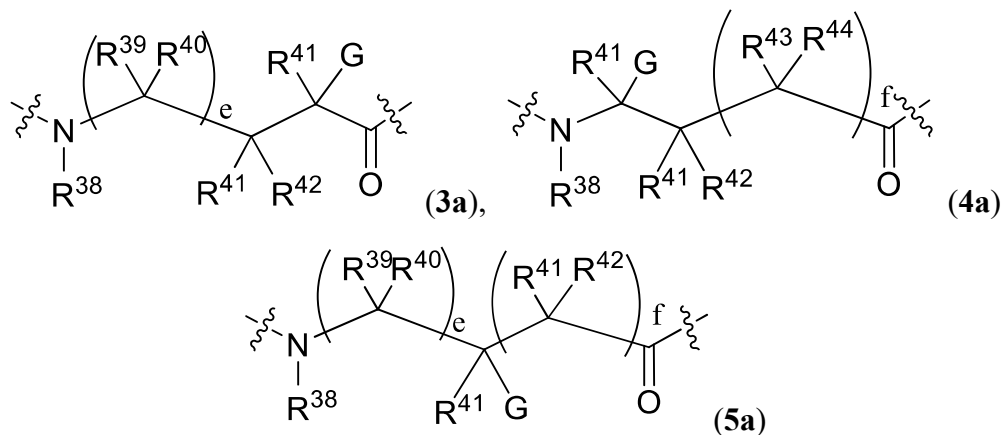
DETAILED DESCRIPTION OF THE INVENTION

[0028] General

[0029] The present invention is based, in part, on the unexpected finding that a hydrophobic auristatin F (AF) compound conjugated through its C-terminal carboxylic acid functional group provides an auristatin Antibody Drug Conjugate having immunologically-specific cytotoxic activity towards targeted cancer cells, which are characterized by higher copy number of the targeted antigen, and bystander activity against nearby cancer cells, which are characterized by a lower copy number or undetectable levels of the targeted antigen, and are sufficiently cytotoxic irrespective of the heterogeneity in MDR status of the tumor cells throughout the tumor. It was unpredictably found upon exposure of cancer cells to an ADC having conjugation to a hydrophobic AF compound, which is characterized by an increased hydrophobicity relative to AF in the parent ADC, that sufficient retention of MDR⁺ activity, previously observed for the parent ADC having conjugation to AF through its C-terminal carboxylic acid functional group, occurred with emergence of bystander activity and that the dual bystander and MDR⁺ activities were observed for a narrow range of that increase as a

embodiments, the PEG Unit contains a total of 4 to 24 contiguous ethyleneoxy monomer units.

[0346] In other of those embodiments, A₀/A₂ is an amine-containing acid residue having the structure of formula 3a, formula 4a or formula 5a:



[0347] wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the remainder of A, and the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to A'; subscripts e and f are independently 0 or 1; and

[0348] G is hydrogen, -OH, -OR^{PR}, -CO₂H, -CO₂R^{PR} or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of -OH, -OR^{PR}, -CO₂H, and -CO₂R^{PR}; and wherein R^{PR} is a suitable protecting group, or

[0349] G is N(R^{PR})(R^{PR}) or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

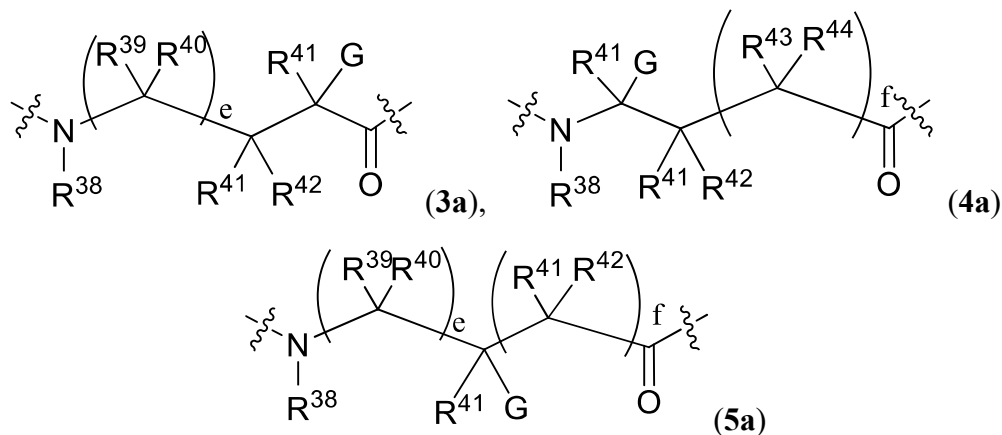
[0350] G is -N(R⁴⁵)(R⁴⁶), or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is -N(R⁴⁵)(R⁴⁶), wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

[0351] R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and

[0352] R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or

[0353] R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein,

[0488] 36. The Ligand Drug Conjugate composition of embodiment 34 or 35, wherein A_O is a second subunit of A that is present and is indicated as A₂, wherein A₂ is an amine-containing acid residue having the structure of formula 3a, formula 4a or formula 5a:



[0489] wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to [HE] of the first subunit of A, wherein [HE] is $-\text{C}(=\text{O})-$ and the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to L_O, wherein both attachments are through amide functional groups; subscripts e and f are independently 0 or 1; and

[0490] G is hydrogen, $-\text{OH}$, $-\text{OR}^{\text{PR}}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{\text{PR}}$ or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of $-\text{OH}$, $-\text{OR}^{\text{PR}}$, $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{R}^{\text{PR}}$; and wherein R^{PR} is a suitable protecting group, or G is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$ or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or G is $-\text{N}(\text{R}^{45})(\text{R}^{46})$, or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is $-\text{N}(\text{R}^{45})(\text{R}^{46})$, wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

[0491] R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein, or R⁴³, R⁴⁴ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R³⁹-R⁴² are as defined herein, or R⁴⁰ and R⁴¹, or R⁴⁰ and R⁴³, or R⁴¹ and R⁴³ to together with the carbon atom or heteroatom

[0498] wherein subscript e and f range from 0 to 6; subscripts e' and f' range from 1 to 6; the wavy line next to the nitrogen atom of the amine residue to which R³⁸ is attached indicates the site of covalent attachment to a first optional Stretcher Unit that is present or to A₀, wherein A₀ is an optional second subunit of A that when present is indicated as A₂; and the wavy line adjacent to the nitrogen atom of the other amine residue indicates the site of covalent attachment to W, wherein both attachments are through amide functional groups;

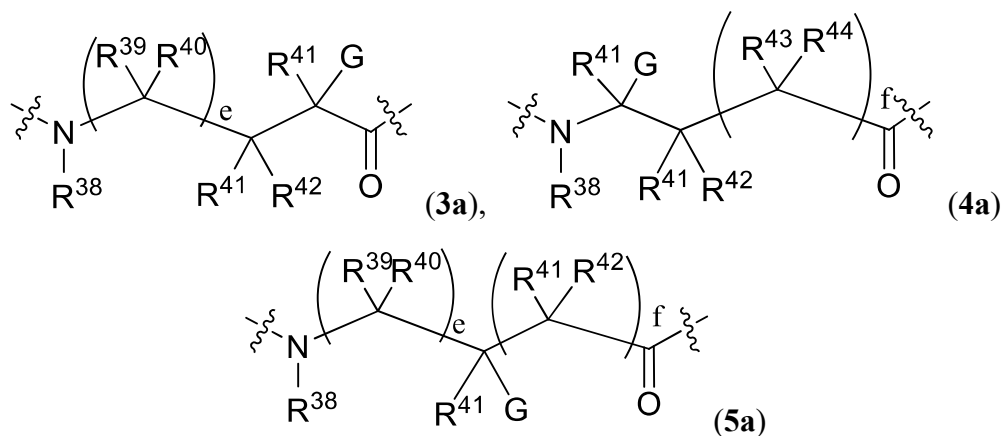
[0499] G is hydrogen, -OH, -OR^{PR}, -CO₂H, -CO₂R^{PR} or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of -OH, -OR^{PR}, -CO₂H, and -CO₂R^{PR}; and wherein R^{PR} is a suitable protecting group, or G is N(R^{PR})(R^{PR}) or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or G is -N(R⁴⁵)(R⁴⁶), or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is -N(R⁴⁵)(R⁴⁶), wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

[0500] R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein, or R⁴³, R⁴⁴ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R³⁹-R⁴² are as defined herein, or R⁴⁰ and R⁴¹, or R⁴⁰ and R⁴³, or R⁴¹ and R⁴³ together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C₅-C₆ carbocyclo or a C₅-C₆ heterocyclo, and R³⁹, R⁴⁴ and the remainder of R⁴⁰-R⁴³ are as defined herein,

[0501] or A' is an optionally substituted diamine residue, wherein one amino nitrogen atom is covalently attached to the remainder of A, and the other amino nitrogen atom is covalently attached to W, wherein both attachments are through amide functional groups.

[0502] 40. The Ligand Drug Conjugate composition of embodiment 39, wherein -A₂-A' - has the structure of:

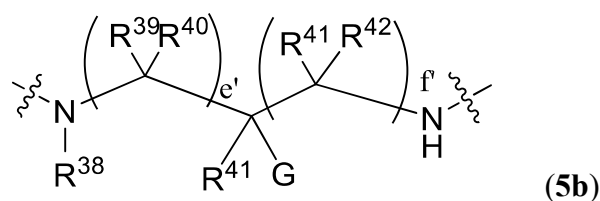
[0563] 69. The Drug Linker compound of embodiment 67 or 68, wherein A₀ is a second subunit of A that is present and is indicated as A₂, wherein A₂ is an amine-containing acid residue having the structure of formula 3a, formula 4a or formula 5a:



[0564] wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to [HE] of the first subunit of A, wherein [HE] is $-\text{C}(=\text{O})-$ and the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to L₀, wherein both attachments are through amide functional groups; subscripts e and f are independently 0 or 1; and

[0565] G is hydrogen, $-\text{OH}$, $-\text{OR}^{\text{PR}}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{\text{PR}}$ or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of $-\text{OH}$, $-\text{OR}^{\text{PR}}$, $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{R}^{\text{PR}}$; and wherein R^{PR} is a suitable protecting group, or G is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$ or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or G is $-\text{N}(\text{R}^{45})(\text{R}^{46})$, or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is $-\text{N}(\text{R}^{45})(\text{R}^{46})$, wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

[0566] R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein, or R⁴³, R⁴⁴ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R³⁹-R⁴² are as defined herein, or R⁴⁰ and R⁴¹, or R⁴⁰ and R⁴³, or R⁴¹ and R⁴³ together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or



[0572] wherein subscript e and f range from 0 to 6; subscripts e' and f' range from 1 to 6; the wavy line next to the nitrogen atom of the amine residue to which R³⁸ is attached indicates the site of covalent attachment to a first optional Stretcher Unit that is present or to A₀, wherein A₀ is an optional second subunit of A that when present is indicated as A₂; the wavy line adjacent to the nitrogen atom of the other amine residue indicates the site of covalent attachment to W, wherein both attachments are through amide functional groups;

[0573] G is hydrogen, -OH, -OR^{PR}, -CO₂H, -CO₂R^{PR} or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of -OH, -OR^{PR}, -CO₂H, and -CO₂R^{PR}; and wherein R^{PR} is a suitable protecting group, or G is N(R^{PR})(R^{PR}) or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or G is -N(R⁴⁵)(R⁴⁶), or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is -N(R⁴⁵)(R⁴⁶), wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

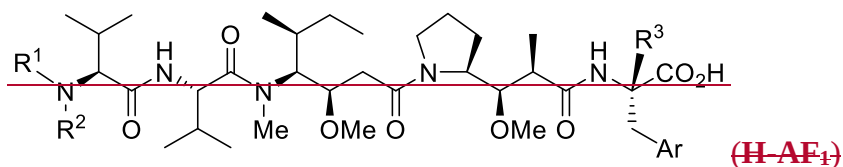
[0574] R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein, or R⁴³, R⁴⁴ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R³⁹-R⁴² are as defined herein, or R⁴⁰ and R⁴¹, or R⁴⁰ and R⁴³, or R⁴¹ and R⁴³ together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C₅-C₆ carbocyclo or a C₅-C₆ heterocyclo, and R³⁹, R⁴⁴ and the remainder of R⁴⁰-R⁴³ are as defined herein,

[0575] or A' is an optionally substituted diamine residue, wherein one amino nitrogen atom is covalently attached to the remainder of A, and the other amino nitrogen atom is covalently attached to W, wherein both attachments are through amide functional groups.

[0576] 73. The Drug Linker compound of embodiments 71, wherein -A₂-A' has the structure of:

WHAT IS CLAIMED IS:

1. ~~A compound, wherein the compound is a hydrophobic auristatin F compound of Formula **H-AF₁** having the structure of:~~



~~or a salt thereof, wherein~~

~~Ar is phenyl, thienyl, 1-naphthyl, 2-naphthyl or benzo[b]thiophen-3-yl;~~

~~R³ is independently selected from the group consisting of hydrogen and C₁-C₂ alkyl;~~

~~R¹ is C₁-C₉ alkyl, optionally substituted by a C₃-C₆ carbocyclyl to provide a (carbocyclyl) alkylene of up to 9 total carbon atoms, or~~

~~R¹ is (C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl; and~~

~~R² is C₁-C₂ alkyl,~~

~~with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R¹, R² and R³ is between 3 and 10 and R¹, R² and R³ are not each methyl, or~~

~~Ar is phenyl;~~

~~R³ is hydrogen;~~

~~R¹ is a first non-aromatic hydrophobic moiety; and~~

~~R² is a second non-aromatic hydrophobic moiety,~~

~~wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2.~~

2. ~~The compound of claim 1, wherein R² is methyl and R³ is hydrogen,~~

3. ~~The compound of claim 1, wherein R³ is hydrogen and Ar is phenyl.~~

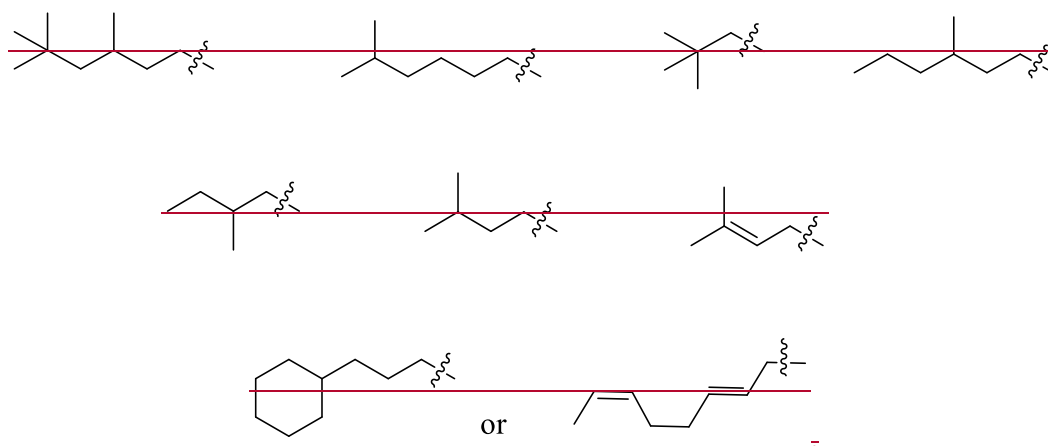
4. ~~The compound of claim 1, wherein R² is methyl; R³ is hydrogen; and Ar is phenyl.~~

5. ~~The compound of any one of claims 1 to 4, wherein R^1 is a saturated C_4 - C_9 alkyl, an unsaturated C_3 - C_9 alkyl or a carbocyclyl alkyl of up to 9 total carbon atoms.~~

6. ~~The compound of any one of claims 1 to 4, wherein R^1 is a branched C_3 - C_9 alkyl, in particular a branched C_4 - C_9 alkyl, or R^1 is $(C_2-C_6 \text{ alkylene})-X-R^4$, wherein X is a carbamate functional group and R^4 is t-butyl or $CH_2C=CH_2$.~~

7. ~~The compound of claim 6, wherein R^1 has the formula of $(CH_2)_{3-5}-N(R^7)-C(=O)-t\text{-Bu}$ wherein R^7 is hydrogen or $-CH_3$.~~

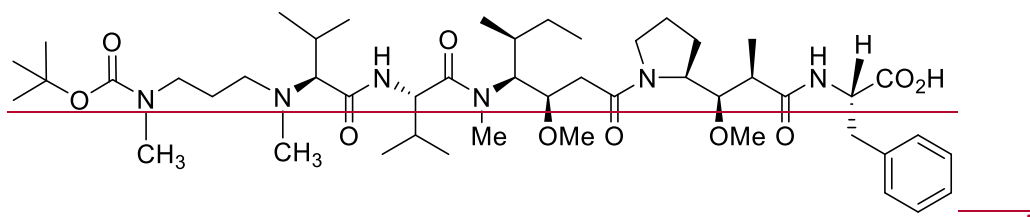
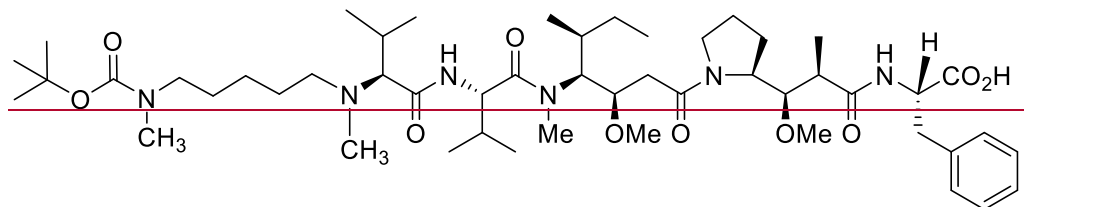
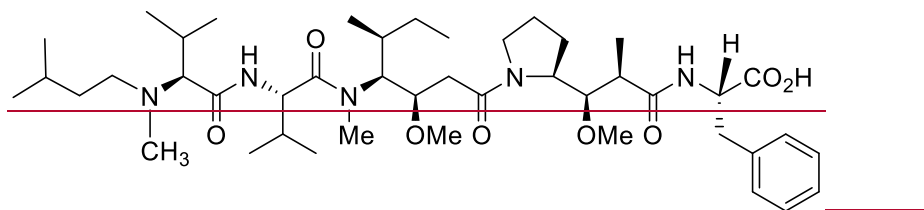
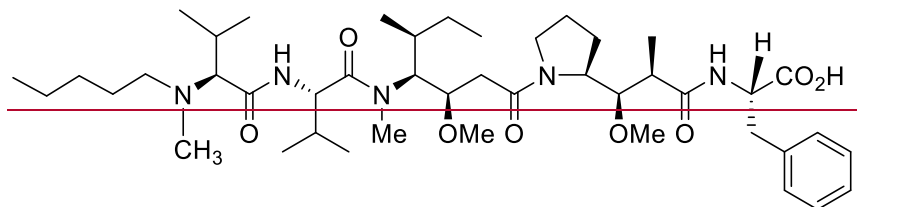
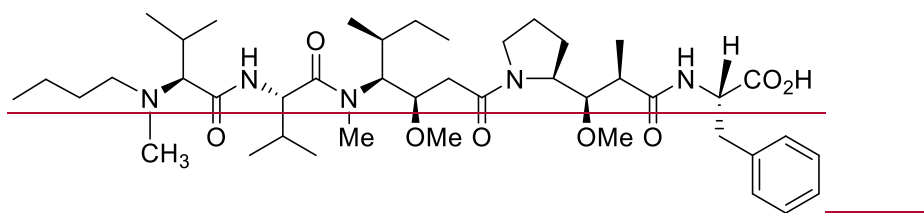
8. ~~The compound of any one of claims 6 wherein R^1 is a branched C_4 - C_9 alkyl having the structure of:~~



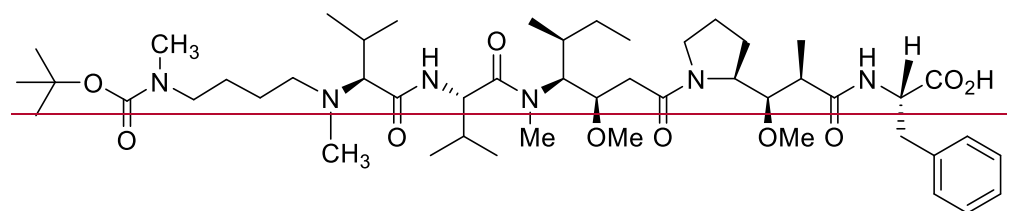
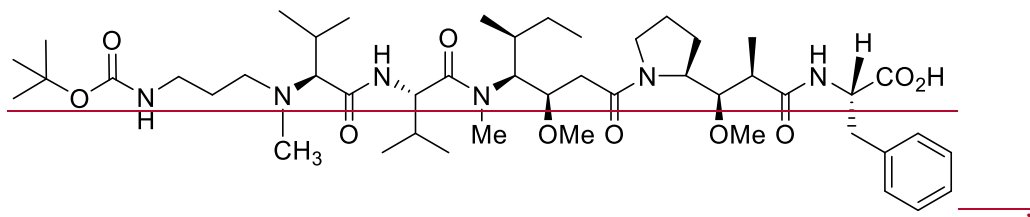
9. ~~The compound of any one of claims 1 to 4, wherein R^1 is $CH_2CH_2CH(CH_3)CH_2C(CH_3)_3$, $CH_2CH_2CH_2CH_2N(CH_3)-C(=O)-O-t\text{-Bu}$, $CH_2CH_2CH_2N(CH_3)-C(=O)-O-t\text{-Bu}$ or $CH_2CH_2CH_2NH-C(=O)-O-t\text{-Bu}$.~~

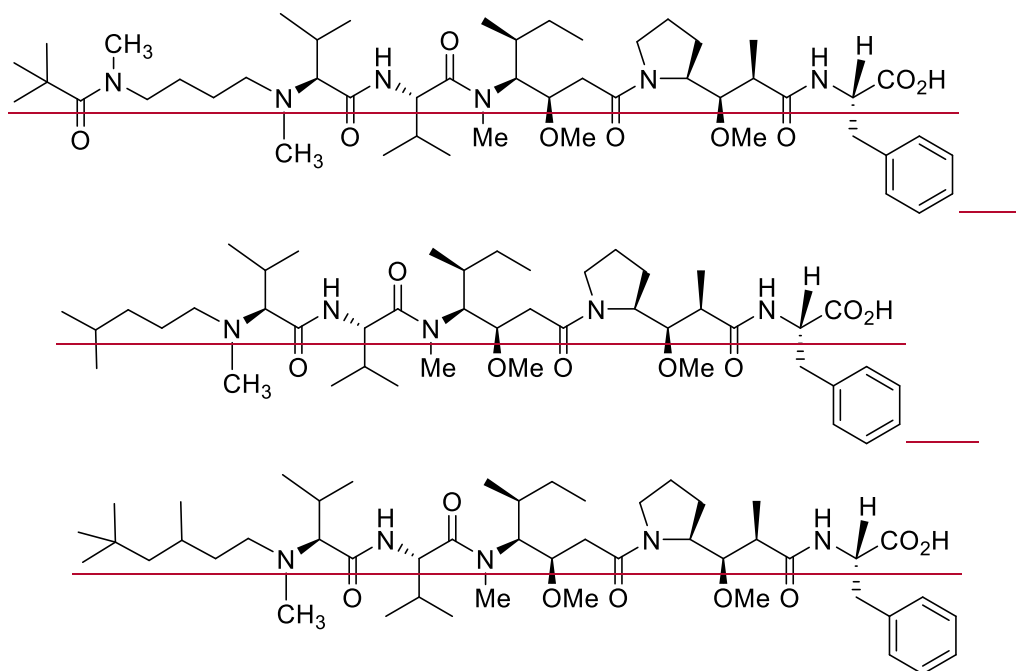
10. ~~The compound of any one of claims 1 to 4, wherein R^1 is $CH_2CH_2CH_2CH_2N(CH_3)-C(=O)-t\text{-Bu}$.~~

11. ~~The compound of claim 1, wherein the compound is:~~



5





or a salt thereof.

5

121. A Ligand Drug Conjugate composition-compound represented by Formula 1:



or a salt thereof, wherein

L is a Ligand Unit;

10

subscript p' is an integer ranging from 1 to 24;

LU is a Linker Unit; and

D' represents from 1 to 4 hydrophobic auristatin F Drug Units (D) in each drug linker moiety of formula LU-D';

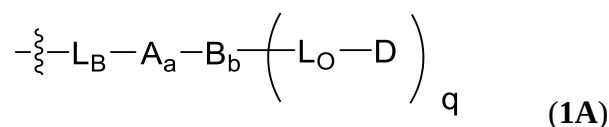
15

wherein each hydrophobic auristatin F Drug Unit is a hydrophobic auristatin F compound of any one of claims 1 to 11 conjugated through its C-terminal component's carboxylic acid functional group;

wherein the Ligand Unit is capable of selective binding to a targeted moiety of a targeted cell for subsequent release of the hydrophobic auristatin F compound;

20

wherein each -LU-D' is a drug-linker moiety in a Ligand Drug Conjugate compound of the composition has the structure of Formula 1A:



or a salt thereof,

wherein the wavy line indicates covalent attachment to L;

~~D is the hydrophobic AF Drug Unit;~~

~~L_B is an~~ ligand covalent binding moiety;

A is a first optional Stretcher Unit;

subscript a is 0 or 1, indicating the absence ~~of~~ or presence of A, respectively;

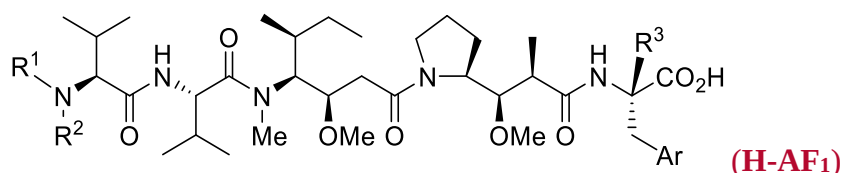
B is an optional Branching Unit;

subscript b is 0 or 1, indicating the absence ~~of~~ or presence of B, respectively;

L_O is an optional secondary linker moiety;

subscript q is an integer ranging from 1 to 4;

D is a hydrophobic auristatin F compound represented by the structure of:



or a salt thereof, wherein

the hydrophobic auristatin F compound is conjugated to the remainder of the drug-linker moiety through its C-terminal component's carboxylic acid carbon atom;

Ar is phenyl, thienyl, 1-naphthyl, 2-naphthyl, or benzo[b]thiophen-3-yl;

R³ is independently selected from the group consisting of hydrogen and C₁-C₂ alkyl;

R¹ is C₁-C₉ alkyl, or

R¹ is (C₃-C₆ carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R₁ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl; and

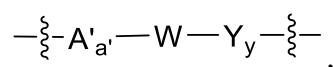
R² is C₁-C₂ alkyl,

with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10, and R¹ and R² are not each methyl,

~~wherein the Ligand Drug Conjugate compound has the structure of Formula 1 in~~

~~which subscript p is replaced by subscript p', wherein subscript p' is an integer ranging from 1 to 24,~~

~~in particular, wherein, when present, L_O is a secondary linker that is present and~~ has the formula of:



wherein the wavy line adjacent to Y indicates the site of covalent attachment ~~of L_O to~~ the hydrophobic auristatin ~~Drug Unit~~ F compound, and the wavy line adjacent to A' ~~to~~ indicates the site of covalent attachment ~~of L_O to~~ the remainder of the drug linker moiety;

A' is a second optional Stretcher Unit;

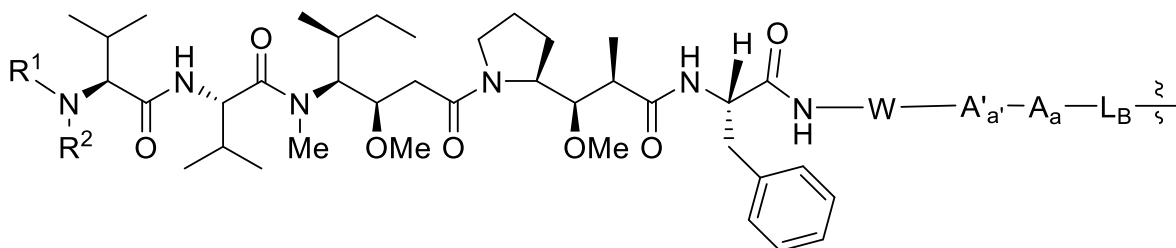
subscript a' is 0 or 1, indicating the absence or presence of A', respectively,

W is a peptide Cleavable Unit;

Y is a peptide Spacer Unit; and

subscript y is 0 or 1, indicating the absence or presence of Y, respectively.

132. The Ligand Drug Conjugate ~~composition compound~~ of claim 12, wherein each of ~~its-the~~ drug linker moieties has the structure of:



or a ~~salt thereof, in particular a~~ pharmaceutically acceptable salt thereof, wherein

R² is methyl; and

R¹ is C₃-C₉ alkyl, or

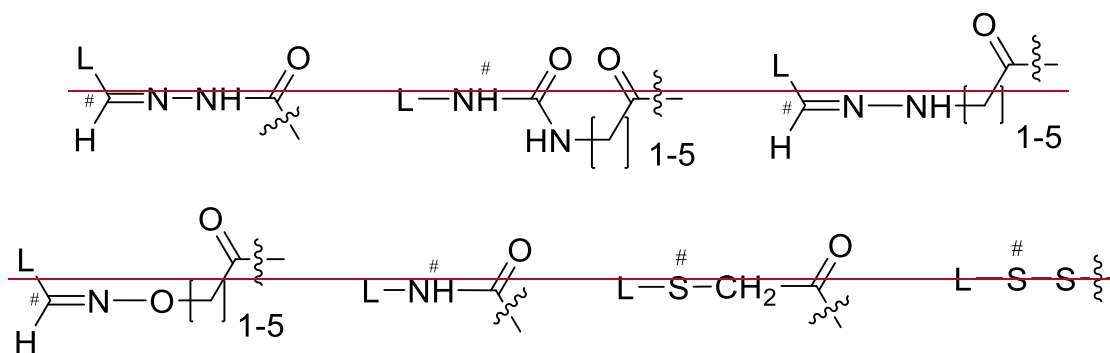
R¹ is optionally substituted by a C₃-C₆ ~~carbocyclyl to provide a~~ (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

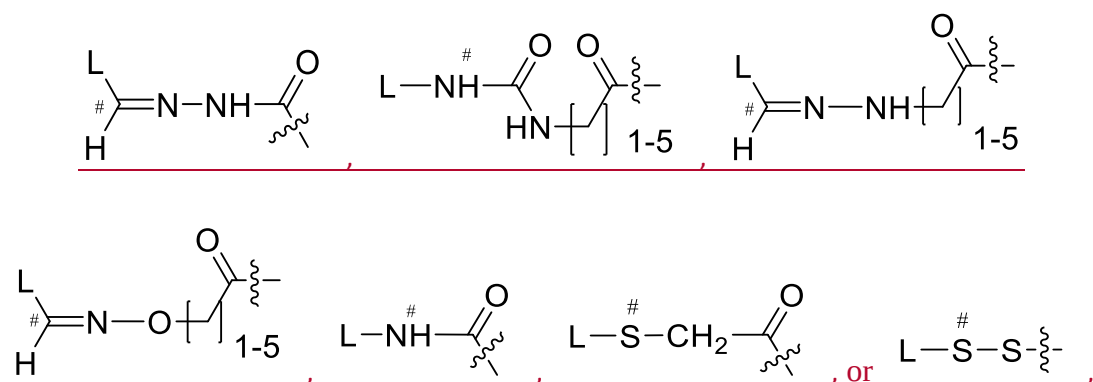
R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl;

with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10.

143. The Ligand Drug Conjugate ~~composition compound~~ of claim 132, wherein:

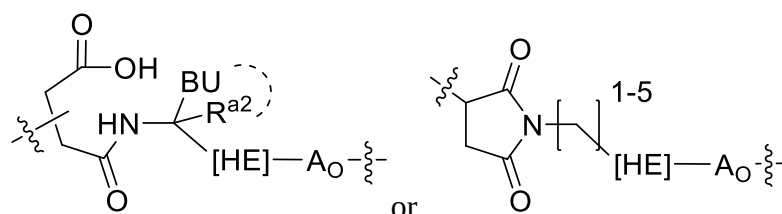
(a) L-L_B-A- ~~has or is comprised comprises of~~ one of the structures of:





wherein the nitrogen, carbon, or sulfur atom indicated by (#) ~~nitrogen, carbon or sulfur atom~~ is from the Ligand Unit; and wherein the wavy line indicates the site of covalent attachment to the remainder of the Ligand Drug Conjugate structure compound;

(b) wherein each $-L_B-A-$ in a plurality of drug linker moieties has the structure of:



~~or a salt thereof~~, wherein

the wavy line adjacent to A_0 indicates the site of covalent attachment to L_0 ; and the other wavy line indicates the site of covalent attachment to a sulfur atom of a Ligand Unit; A_0 is an optional second subunit of A;

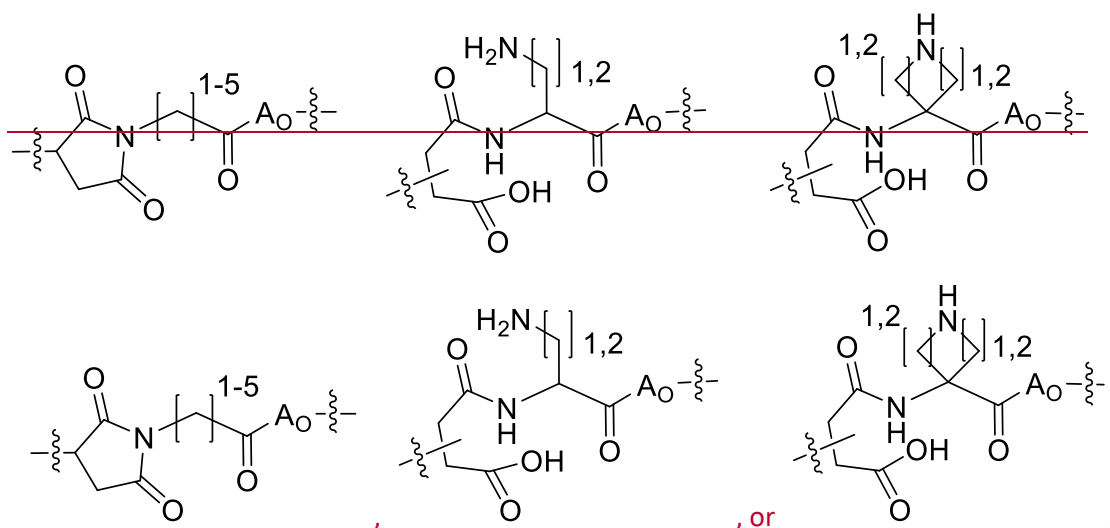
[HE] is an optional Hydrolysis Enhancing Unit, which is a component provided by A or a first subunit thereof; and

BU is an acyclic Basic Unit moiety comprising; ~~R^{a2} is an optionally substituted C_4-C_{12} alkyl group; and the dotted curved line indicates optional cyclization so that in the absence of said cyclization, BU is an acyclic Basic Unit having~~ a primary, secondary or tertiary amine as the basic functional group; ~~as the basic function group of the acyclic Basic Unit, or in the presence of said cyclization the dotted curved line is absent; and R^{a2} is a substituted C_1-C_{12} alkyl group; or~~

~~BU is a cyclized Basic Unit in which~~ R^{a2} and BU, together with the carbon atom to which both are attached, define an ~~optionally~~ or unsubstituted spiro C_3-C_{20} heterocycle Basic Unit moiety comprising an annular containing a skeletal basic nitrogen atom of a secondary or tertiary amine as the basic functional group ~~as the basic function group of the cyclic Basic Unit,~~

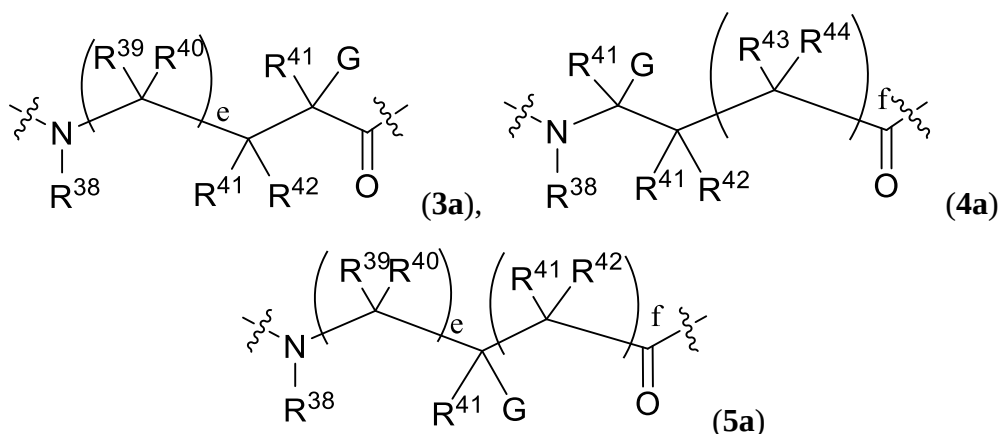
wherein the basic ~~nitrogen atom~~amine of the ~~acyclic~~Basic Unit or cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated, unprotonated, or suitably protected by a nitrogen protecting group; or

5 in particular, -L_B-A- in a plurality of drug linker moieties has the structure of: (c)
[HE] is -C(=O)-, and -L_B-A- has the structure of:



10 wherein A₀ is optional or a salt thereof.

154. The Ligand Drug Conjugate composition of claim **143**, wherein A₀ is a second subunit of A that is present and is indicated as A₂, wherein A₂ is an amine-containing acid residue having the structure of formula **3a**, formula **4a** or formula **5a**:



wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to [HE] of the first subunit of A, wherein [HE] is -C(=O)- and the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to L_O,
 20 wherein both attachments are through amide functional groups;

subscripts e and f are independently 0 or 1; and

G is hydrogen, -OH, -OR^{PR}, -CO₂H, -CO₂R^{PR} or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of -OH, -OR^{PR}, -CO₂H, and -CO₂R^{PR}; and wherein R^{PR} is a suitable protecting group, or

G is N(R^{PR})(R^{PR}) or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is -N(R⁴⁵)(R⁴⁶), or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is -N(R⁴⁵)(R⁴⁶), wherein one of R⁴⁵, R⁴⁶ is hydrogen or R^{PR}, wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C₁-C₆ alkyl;

R³⁸ is hydrogen or optionally substituted C₁-C₆ alkyl; and

R³⁹-R⁴⁴ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₅-C₂₀ heteroaryl, or

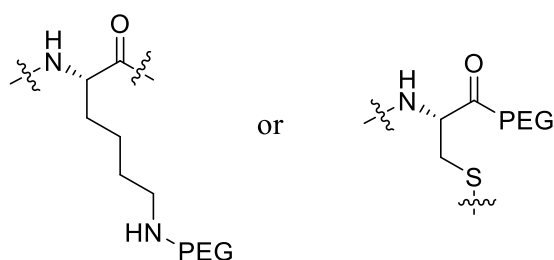
R³⁹, R⁴⁰ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R⁴¹-R⁴⁴ are as defined herein, or

R⁴³, R⁴⁴ together with the carbon atom to which both are attached define a C₃-C₆ carbocyclo, and R³⁹-R⁴² are as defined herein, or

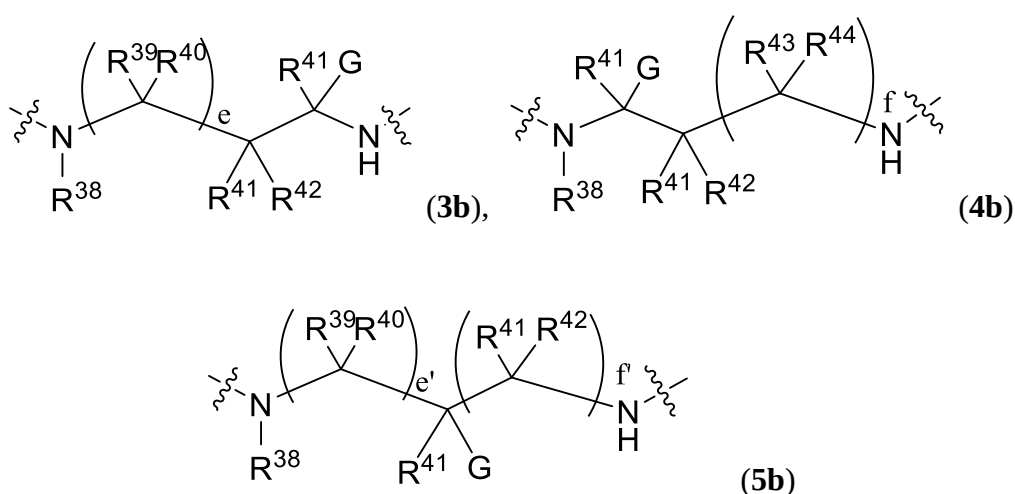
R⁴⁰ and R⁴¹, or R⁴⁰ and R⁴³, or R⁴¹ and R⁴³ together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C₅-C₆ carbocyclo or a C₅-C₆ heterocyclo, and R³⁹, R⁴⁴ and the remainder of R⁴⁰-R⁴³ are as defined herein,

or A_O is an α-amino or β-amino acid residue, wherein its amino nitrogen atom is covalently attached to the remainder of A, and its carboxylic acid carbonyl carbon is covalently attached to A', wherein both attachments are through amide functional groups,

or A_O is a second subunit of A that is present and is indicated as A₂ wherein A₂ is a β-amino acid residue having the structure of -NHCH₂CH₂C(=O)- or has the formula of -L^P(PEG)-, wherein L^P is Parallel Connector Unit having the structure of a tri-functional amine-containing acid residue and PEG is a PEG Unit, in particular, -L^P(PEG)- has the structure of:



wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the first subunit of A and the wavy line to the carbonyl carbon atom or the sulfur atom indicates the site of covalent attachment to A' of L_O, wherein A' is preferably an alkylene diamine residue having the structure of formula **3b**, formula **4b** or formula **5b**:



wherein subscript e and f range from 0 to 6;

subscripts e' and f' range from 1 to 6;

the wavy line next to the nitrogen atom of the amine residue to which R³⁸ is attached indicates the site of covalent attachment to a first optional Stretcher Unit that is present or to A₀, wherein A₀ is an optional second subunit of A that when present is indicated as A₂;

the wavy line adjacent to the nitrogen atom of the other amine residue indicates the site of covalent attachment to W,

wherein both attachments are through amide functional groups;

G is hydrogen, -OH, -OR^{PR}, -CO₂H, -CO₂R^{PR} or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is selected from the group consisting of -OH, -OR^{PR}, -CO₂H, and -CO₂R^{PR}; and wherein R^{PR} is a suitable protecting group, or

G is N(R^{PR})(R^{PR}) or an optionally substituted C₁-C₆ alkyl, wherein the optional substituent when present is N(R^{PR})(R^{PR}), wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is $-N(R^{45})(R^{46})$, or an optionally substituted C_1 - C_6 alkyl, wherein the optional substituent when present is $-N(R^{45})(R^{46})$, wherein one of R^{45} , R^{46} is hydrogen or R^{PR} , wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C_1 - C_6 alkyl;

5 R^{38} is hydrogen or optionally substituted C_1 - C_6 alkyl; and

R^{39} - R^{44} are independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_6 - C_{20} aryl, and optionally substituted C_5 - C_{20} heteroaryl, or

10 R^{39} , R^{40} together with the carbon atom to which both are attached define a C_3 - C_6 carbocyclo, and R^{41} - R^{44} are as defined herein, or

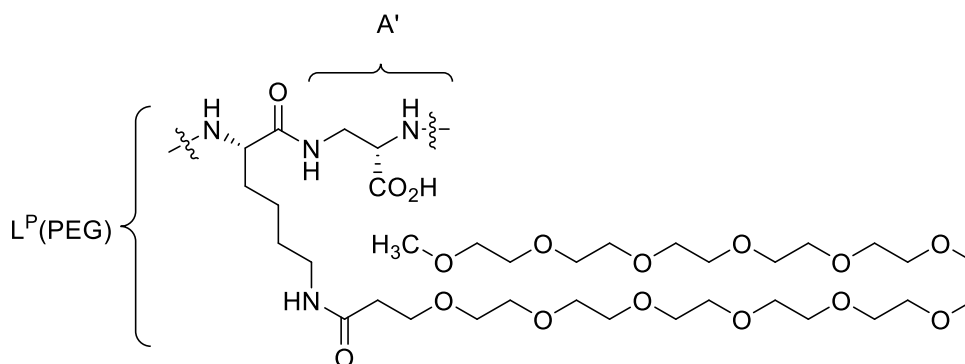
R^{43} , R^{44} together with the carbon atom to which both are attached define a C_3 - C_6 carbocyclo, and R^{39} - R^{42} are as defined herein, or

15 R^{40} and R^{41} , or R^{40} and R^{43} , or R^{41} and R^{43} to together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C_5 - C_6 carbocyclo or a C_5 - C_6 heterocyclo, and R^{39} , R^{44} and the remainder of R^{40} - R^{43} are as defined herein,

or A' is an optionally substituted diamine residue, wherein one amino nitrogen atom is covalently attached to the remainder of A , and the other amino nitrogen atom is covalently attached to W , wherein both attachments are through amide functional groups.

20

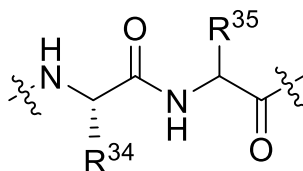
165. The Ligand Drug Conjugate composition of claim **154**, wherein $-A_2-A'$ has the structure of:



25 or a salt thereof, wherein the wavy line to the nitrogen atom of $L^P(PEG)$ indicates the site of attachment to the remainder of A and the wavy line to the nitrogen atom of A' indicates the site of attachment to W , wherein both attachments are through amide functional groups.

176. The Ligand Drug Conjugate ~~composition compound~~ of ~~any one of~~ claims 12 to 161, wherein

(a) W is an amino acid sequence ~~comprised-comprising of~~ a dipeptide ~~that provides a recognition site for a protease~~, wherein the dipeptide has the structure of:



~~or a salt thereof~~, wherein

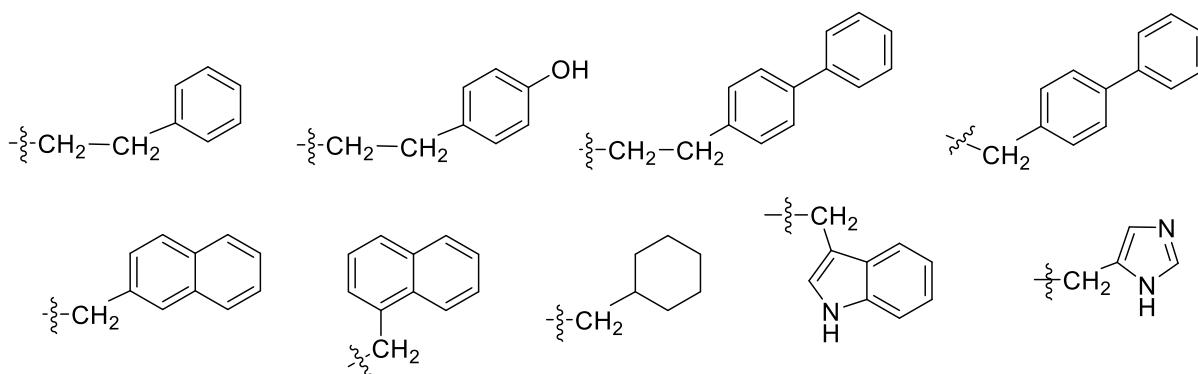
the wavy line at the dipeptide N-terminal-terminus indicates the site of covalent attachment ~~as-via~~ an amide bond to an ~~auristatin F compound AF Drug Unit~~ through its C-terminal component's carboxylic acid residue, ~~wherein the amide bond is cleavable by the protease to release the Drug Unit as free drug~~;

the wavy line at the dipeptide C-terminal-terminus indicates the site of covalent attachment to the remainder ~~W of the amino acid sequence~~ or to A, or a subunit thereof, as when A₀ is present as A₂;

R³⁴ is hydrogen, or the side chain of a naturally occurring α -amino acid except proline, in particular -CH₃, -C(CH₃)₂, -CH₂COOH, -CH₂CH₂COOH or -CH₂CH₂CH₂CH₂NH₂; and

R³⁵ is hydrogen, methyl, isopropyl, sec-butyl, benzyl, p-hydroxy-benzyl, -CH₂OH, -CH(OH)CH₃, -CH₂CH₂SCH₃, -CH₂C(=O)NH₂, -CH₂COOH, -CH₂CH₂C(=O)NH₂, -CH₂CH₂COOH, -CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NHC(=O)CH₃, -CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂NH-C(=O)CH₃, -CH₂CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂NHC(=O)NH₂, -CH₂CH₂CH₂CH₂NHC(=O)NH₂, -CH₂CH₂CH(OH)CH₂NH₂, 2-pyridylmethyl, 4-pyridylmethyl, phenyl or cyclohexyl, or

R³⁵ has the structure of one of:



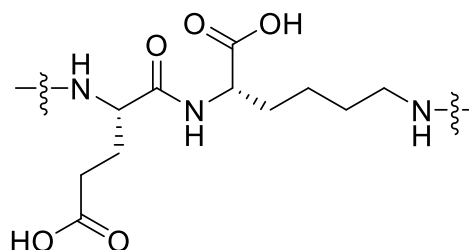
wherein the wavy line indicates the site of covalent attachment to the dipeptide backbone, or

(b) W is a glutamic acid residue, an aspartic acid residue, or a peptide sequence ~~comprised comprising of~~ an N-terminal glutamic acid residue or N-terminal aspartic acid residue, wherein W is covalently attached ~~to through its the hydrophobic AF Drug Unit C-terminal component's carboxylic acid residue through the glutamic acid or aspartic acid~~ amino nitrogen atom to the hydrophobic auristatin F compound C-terminal component's carboxylic acid residue, and wherein W is covalently attached through its and to the remainder of the peptide sequence or to A', which is an optional second Stretcher Unit that is present, through the glutamic acid or aspartic acid α -carboxyl carbon atom to A', wherein both attachments are through amide bonds,

~~wherein the amide bond to the C-terminal component is cleavable by a protease to release the Drug Unit as free drug, and~~

wherein A' is a C₂-C₁₂ alkylene diamine, in particular a C₂-C₆ or a C₂-C₄ alkylene diamine having a carboxylic acid substituent, wherein side chain so that the nitrogen atom of one of ~~its the~~ amines of A' is covalently attached ~~as via~~ an amide bond to W ~~the glutamic acid residue~~, and the nitrogen atom of the other amine of A' is covalently attached to A, or a subunit thereof, as when A₀ is present as A₂; or

~~(c) in particular, -A'-W-~~ has the structure of:



~~or a salt thereof,~~ wherein

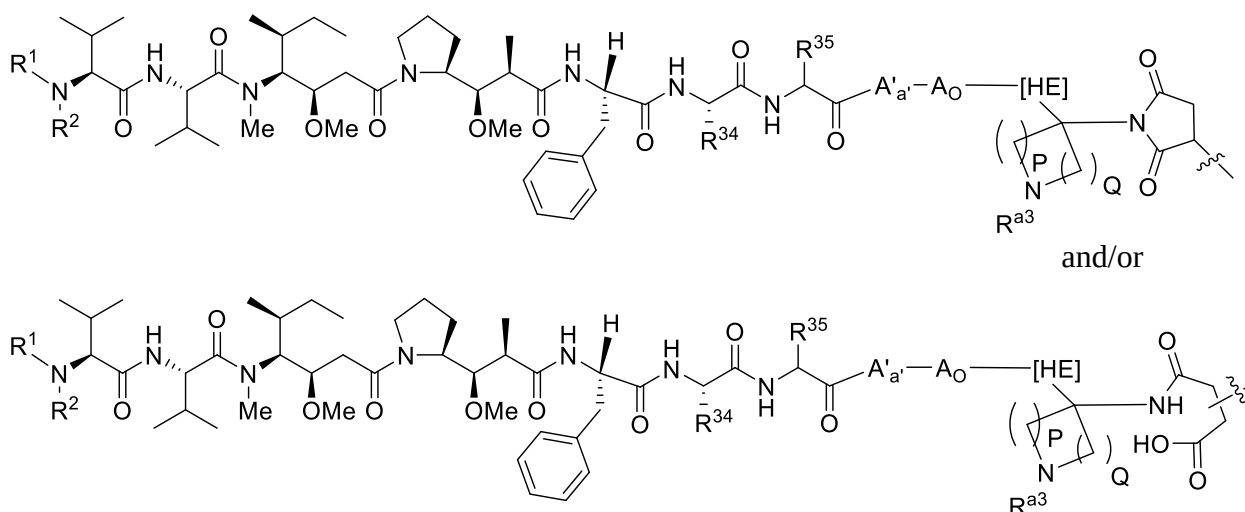
the wavy line adjacent to the glutamic acid alpha-amino nitrogen atom indicates the site of covalent attachment ~~as via~~ an amide bond to the hydrophobic auristatin F

compound AF Drug Unit through its C-terminal component's carboxylic acid residue,
~~wherein the amide bond is cleavable by the protease to release the Drug Unit as free drug;~~

and the wavy line adjacent the lysine epsilon amine nitrogen atom indicates the site of
 covalent attachment to ~~a first optional Stretcher Unit (A)~~ or subunit thereof as when A₀

~~that~~ is present as A₂.

187. The Ligand Drug Conjugate composition of claim **121**, wherein its drug linker
 moieties are represented by the structure(s) of:



or a salt thereof, wherein HE is an optional Hydrolysis Enhancing Unit;

A₀ is absent or is a second subunit of A;

A' is a second optional Stretcher Unit;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively;

subscript P is 1 or 2;

subscript Q ranges from 1 to 6;

R^{a3} is -H, optionally substituted C₁-C₆ alkyl, optionally substituted -C₁-C₄ alkylene-
 (C₆-C₁₀ aryl), or -R^{PEG1}-O-(CH₂CH₂O)₁₋₃₆-R^{PEG2}, wherein R^{PEG1} is C₁-C₄ alkylene, R^{PEG2} is
 -H or C₁-C₄ alkylene,

wherein the basic nitrogen bonded to R^{a3} is optionally protonated or is in a salt form,

R³⁴ is -CH₃, -C(CH₃)₂, -CH₂COOH, -CH₂CH₂COOH or -CH₂CH₂CH₂CH₂NH₂; and

R³⁵ is methyl, isopropyl, -CH₂C(=O)NH₂, -CH₂COOH, -CH₂CH₂C(=O)NH₂, -
 CH₂CH₂COOH, -CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NH-
 C(=O)CH₃, -CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂CH₂NHC(=NH)NH₂, -

CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂NH-C(=O)CH₃, -CH₂CH₂CH₂CH₂NH-C(=O)H,
 -CH₂CH₂CH₂NHC(=O)NH₂, -CH₂CH₂CH₂CH₂NHC(=O)NH₂ or -
 CH₂CH₂CH(OH)CH₂NH₂;

R² is methyl; and

5 R¹ is C₁-C₉ alkyl, optionally substituted by a C₃-C₆ carbocyclyl to provide a
 (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group
 and R⁴ is C₁-C₆ alkyl,

10 with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene)
 moieties of R¹ is between 4 and 10 and R¹ is not methyl, or

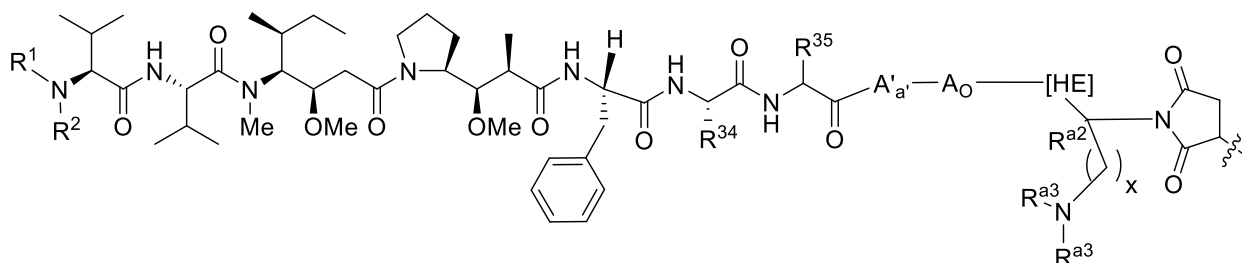
R¹ is a first non-aromatic hydrophobic moiety; and

R² is a second non-aromatic hydrophobic moiety,

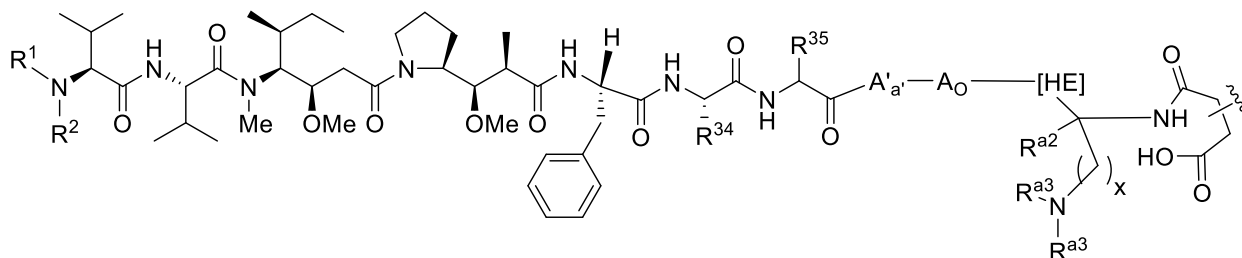
wherein the first and second hydrophobic moieties provide the hydrophobic AF
 compound characterized by a clogP value of between ~~about~~ 4.4 to ~~about~~ 7.2,

15 or

wherein its drug linker moieties are represented by the structure(s) of:



20 and/or



or a salt thereof,

wherein HE is an optional Hydrolysis Enhancing Unit,

25 AO is absent or is a second subunit of A;

A' is a second optional Stretcher Unit;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively;

subscript x is 1 or 2;

R^{a2} is hydrogen or $-CH_3$ or $-CH_2CH_3$;

R^{a3} , at each instance, is independently hydrogen, $-CH_3$ or $-CH_2CH_3$, or both R^{a3}

together with the nitrogen to which they are attached define an azetidiny, pyrrolidiny or
5 piperidiny heterocycl, in which a basic primary, secondary or tertiary amine so defined is
optionally protonated as an acid addition salt form,

R^{34} is $-CH_3$, $-C(CH_3)_2$, $-CH_2COOH$, $-CH_2CH_2COOH$ or $-CH_2CH_2CH_2CH_2NH_2$; and

R^{35} is methyl, isopropyl, $-CH_2C(=O)NH_2$, $-CH_2COOH$, $-CH_2CH_2C(=O)NH_2$, $-$
 CH_2CH_2COOH , $-CH_2CH_2CH_2NHC(=NH)NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH-$
10 $C(=O)CH_3$, $-CH_2CH_2CH_2NH-C(=O)H$, $-CH_2CH_2CH_2CH_2NHC(=NH)NH_2$, $-$
 $CH_2CH_2CH_2CH_2NH_2-$, $-CH_2CH_2CH_2CH_2NH-C(=O)CH_3$, $-CH_2CH_2CH_2CH_2NH-C(=O)H$,
 $-CH_2CH_2CH_2NHC(=O)NH_2$, $-CH_2CH_2CH_2CH_2NHC(=O)NH_2$ or $-$
 $CH_2CH_2CH(OH)CH_2NH_2$;

R^2 is methyl; and

15 R^1 is C_1 - C_9 alkyl, optionally substituted by a C_3 - C_6 carbocycl to provide a
(carbocycl)-alkylene- of up to 9 total carbon atoms, or

R^1 is $-(C_2$ - C_6 alkylene)- $X-R^4$, wherein X is an amide or carbamate functional group
and R^4 is C_1 - C_6 alkyl,

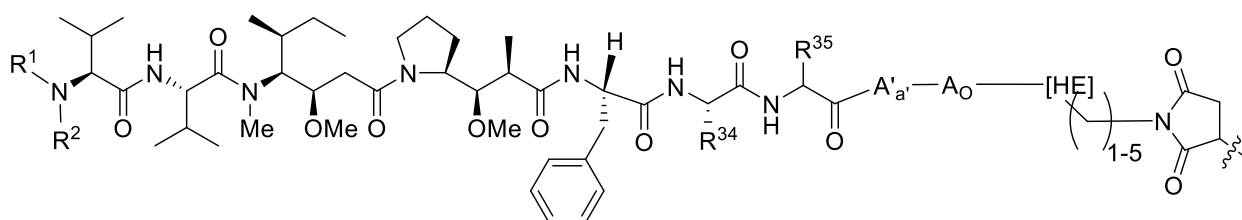
with the proviso that the total number of carbon atoms in the (carbocycl)alkyl(ene)
20 moieties of R^1 is between 4 and 10 and R^1 is not methyl, or

R^1 is a first non-aromatic hydrophobic moiety; and

R^2 is a second non-aromatic hydrophobic moiety,

wherein the first and second hydrophobic moieties provide the hydrophobic AF
compound characterized by a clogP value of between ~~about~~ 4.4 to ~~about~~ 7.2.

25 ~~198~~. The Ligand Drug Conjugate ~~composition compound~~ of claim ~~121~~, wherein a
plurality of its drug linker moieties are represented by the structure(s) of:



or a salt thereof, wherein

HE is an optional Hydrolysis Enhancing Unit, which is a component provided by A or a first subunit thereof;

A_O is an optional~~absent or is a~~ second subunit of A;

A' is a second optional Stretcher Unit;

subscript a' is 0 or 1, indicating the absence or presence of A';

R³⁴ is -CH₃, -C(CH₃)₂, -CH₂COOH, -CH₂CH₂COOH or -CH₂CH₂CH₂CH₂NH₂; and

R³⁵ is methyl, isopropyl, -CH₂C(=O)NH₂, -CH₂COOH, -CH₂CH₂C(=O)NH₂, -CH₂CH₂COOH, -CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NH-C(=O)CH₃, -CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂NH-C(=O)CH₃, -CH₂CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂NHC(=O)NH₂, -CH₂CH₂CH₂CH₂NHC(=O)NH₂ or -CH₂CH₂CH(OH)CH₂NH₂;

R² is methyl; and

R¹ is C₁-C₉ alkyl, or

R¹ is optionally substituted by a C₃-C₆ carbocyclyl to provide a (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,

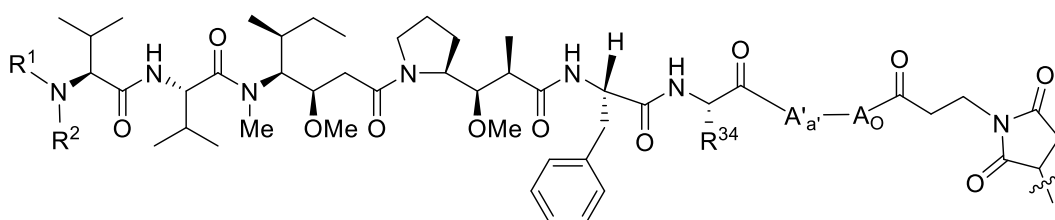
with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moieties of R¹ is between 4 and 10 and R¹ is not methyl, or

R¹ is a first non-aromatic hydrophobic moiety; and

R² is a second non-aromatic hydrophobic moiety,

wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2,

in particular, the plurality of its (b) each drug linker moieties moiety is represented by the structure of:



or a salt thereof, wherein

A₀ is absent or ~~is a second subunit of A having the structure of~~ an α-amino acid or a β-amino acid residue;

A' is ~~a second optional Stretcher Unit that is present having the structure of an optionally-present~~ substituted or unsubstituted C₂-C₆ alkylene diamine residue, ~~wherein one amino nitrogen atom is covalently attached to A₀, and the other amino nitrogen atom is covalently attached to the R³⁴-containing amino acid residue, wherein both attachments are through amide functional groups;~~

R³⁴ is -CH₂CO₂H or -CH₂CH₂CO₂H;

R² is methyl; and

R¹ is C₁-C₉ alkyl, or optionally substituted by

R¹ is a C₃-C₆ ~~carbocyclyl to provide a~~ (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,

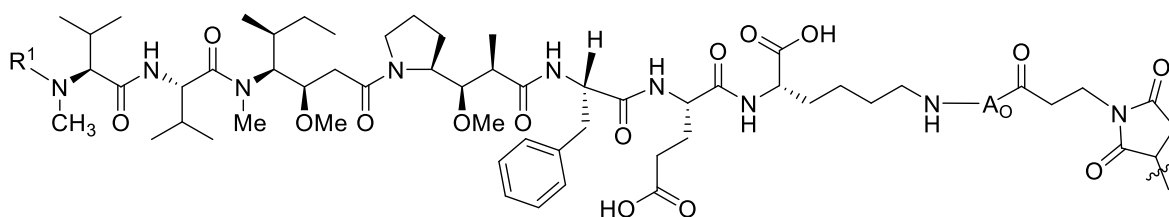
with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moieties of R¹ is between 4 and 10 and R¹ is not methyl, or

~~R¹ is a first non-aromatic hydrophobic moiety; and~~

~~R² is a second non-aromatic hydrophobic moiety,~~

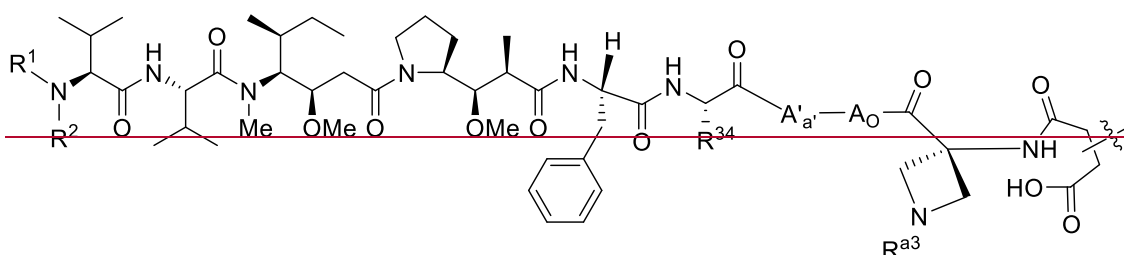
~~more particularly, the plurality of its (c) each drug linker moieties moiety~~ is

represented by the structure of:



~~or~~

~~wherein a plurality of its drug linker moieties is represented by the structure of:~~



or a salt thereof, wherein

~~R^{a3} is hydrogen, -CH₃ or -CH₂CH₃, wherein the secondary or tertiary amine so defined is optionally protonated as an acid addition salt form;~~

A_O is absent or is ~~a second subunit of A having the structure of~~ an α-amino acid or a β-amino acid residue; and

~~A' is a second optional Stretcher Unit that is present having the structure of an optionally substituted C₂-C₆ alkylene diamine residue, wherein one amino nitrogen atom is covalently attached to A_O, and the other amino nitrogen atom is covalently attached to the R³⁴-containing amino acid residue, wherein both attachments are through amide functional groups;~~

~~R³⁴ is -CH₂CO₂H or -CH₂CH₂CO₂H;~~

~~R² is methyl; and~~

R¹ is C₁-C₉ alkyl, or

~~R¹ is optionally substituted by a C₃-C₆ carbocyclyl to provide a (carbocyclyl)-alkylene- of up to 9 total carbon atoms, or~~

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,

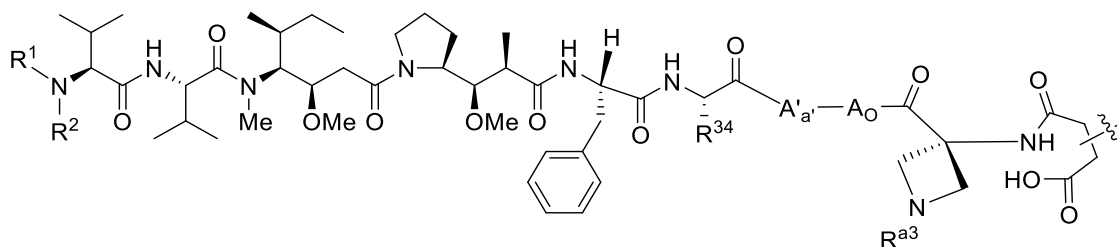
with the proviso that the total number of carbon atoms in R² and the (carbocyclyl)alkyl(ene) moieties-moiety of R¹ is between 4 and 10 and R¹ is not methyl, or

~~R¹ is a first non-aromatic hydrophobic moiety; and~~

~~R² is a second non-aromatic hydrophobic moiety,~~

~~wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2,~~

~~in particular, the plurality of its (d) each drug linker moieties-moiety~~ is represented by the structure of:



or a salt thereof, wherein

R^{a3} is hydrogen, -CH₃, or -CH₂CH₃, wherein the secondary or tertiary amine so defined is optionally protonated as an acid addition salt form;

A_O is absent or is an α-amino acid or a β-amino acid residue;

A' is a substituted or unsubstituted C₂-C₆ alkylene diamine residue

R³⁴ is -CH₂CO₂H or -CH₂CH₂CO₂H;

R² is methyl; and

R¹ is C₁-C₉ alkyl, or

R¹ is (C₃-C₆ carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

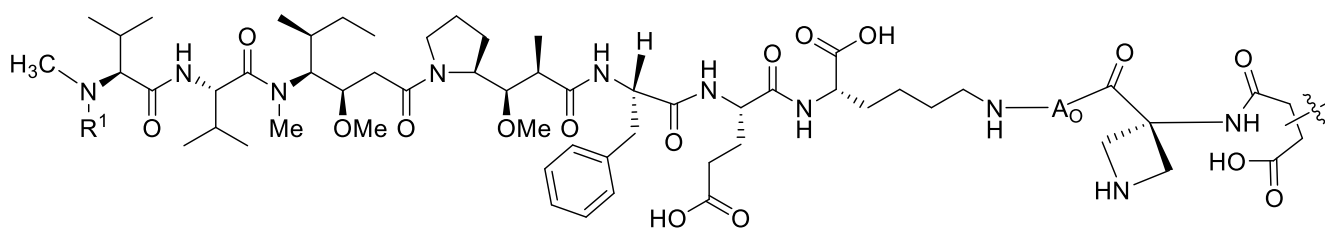
R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group

and R⁴ is C₁-C₆ alkyl,

with the proviso that the total number of carbon atoms in R² and the

(carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10, and R¹ is not methyl, or

(e) each drug linker moiety is represented by the structure of



or a salt thereof, wherein

A_O is absent or is an α-amino acid or a β-amino acid residue; and

R¹ is C₁-C₉ alkyl, or

R¹ is (C₃-C₆ carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group

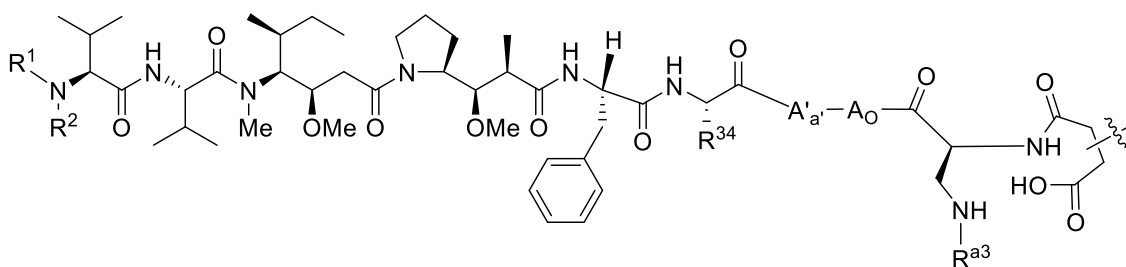
and R⁴ is C₁-C₆ alkyl,

with the proviso that the total number of carbon atoms in R² and the

(carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10, and R¹ is not methyl,

or

(f) ~~wherein a plurality of it~~each drug linker ~~moieties-moiety~~ moiety is represented by the structure of:



or a salt thereof, wherein

R^{a3} is hydrogen, $-CH_3$ or $-CH_2CH_3$, wherein the primary or secondary amine so defined is optionally protonated as an acid addition salt form;

A_0 is absent or is ~~a second subunit of A having the structure of~~ an α -amino acid or a β -amino acid residue;

A' is ~~a second optional Stretcher Unit that is present having the structure of an optionally~~ substituted or unsubstituted C_2 - C_6 alkylene diamine residue, ~~wherein one amino nitrogen atom is covalently attached to A_0 , and the other amino nitrogen atom is covalently attached to the R^{34} -containing amino acid residue, wherein both attachments are through amide functional groups;~~

R^{34} is $-CH_2CO_2H$ or $-CH_2CH_2CO_2H$;

R^2 is methyl; and

R^1 is C_1 - C_9 alkyl, ~~optionally substituted by a C_3 - C_6 carbocyclyl to provide a (carbocyclyl) alkylene of up to 9 total carbon atoms, or~~

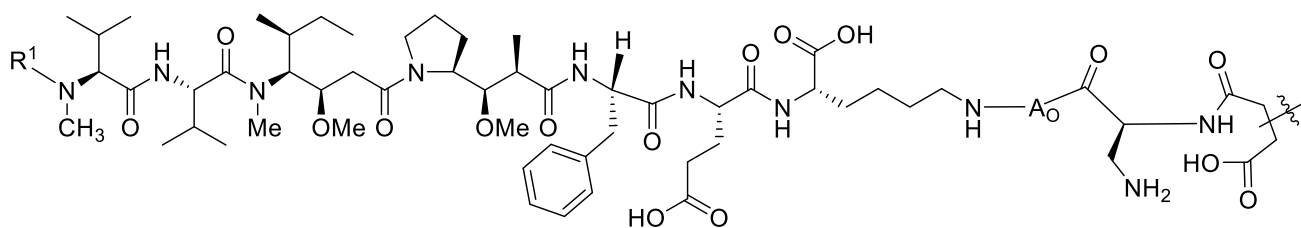
R^1 is $-(C_2-C_6 \text{ alkylene})-X-R^4$, wherein X is an amide or carbamate functional group and R^4 is C_1 - C_6 alkyl,

with the proviso that the total number of carbon atoms in R^2 and the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or

~~R^1 is a first non-aromatic hydrophobic moiety; and
 R^2 is a second non-aromatic hydrophobic moiety;
 wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2,~~

~~wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2,~~

~~in particular the plurality of its (g) each drug linker moieties moiety~~ is represented by the structure of:



or a salt thereof, wherein

A₀ is absent or is an α -amino acid or a β -amino acid residue; and

R¹ is C₁-C₉ alkyl, or

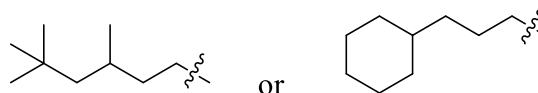
R¹ is (C₃-C₆ carbocyclyl)-alkylene- of up to 9 total carbon atoms, or

R¹ is -(C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,

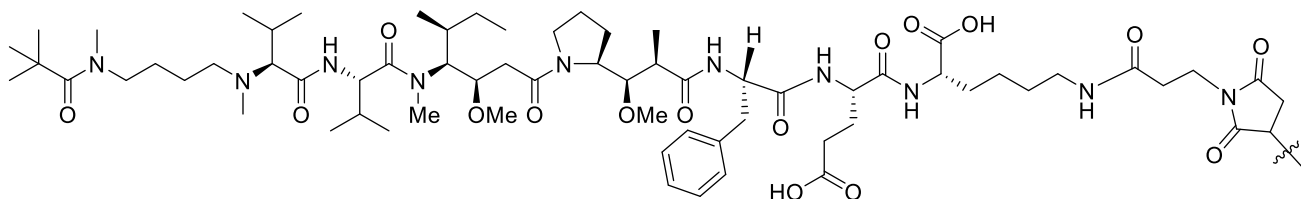
with the proviso that the total number of carbon atoms in R² and the

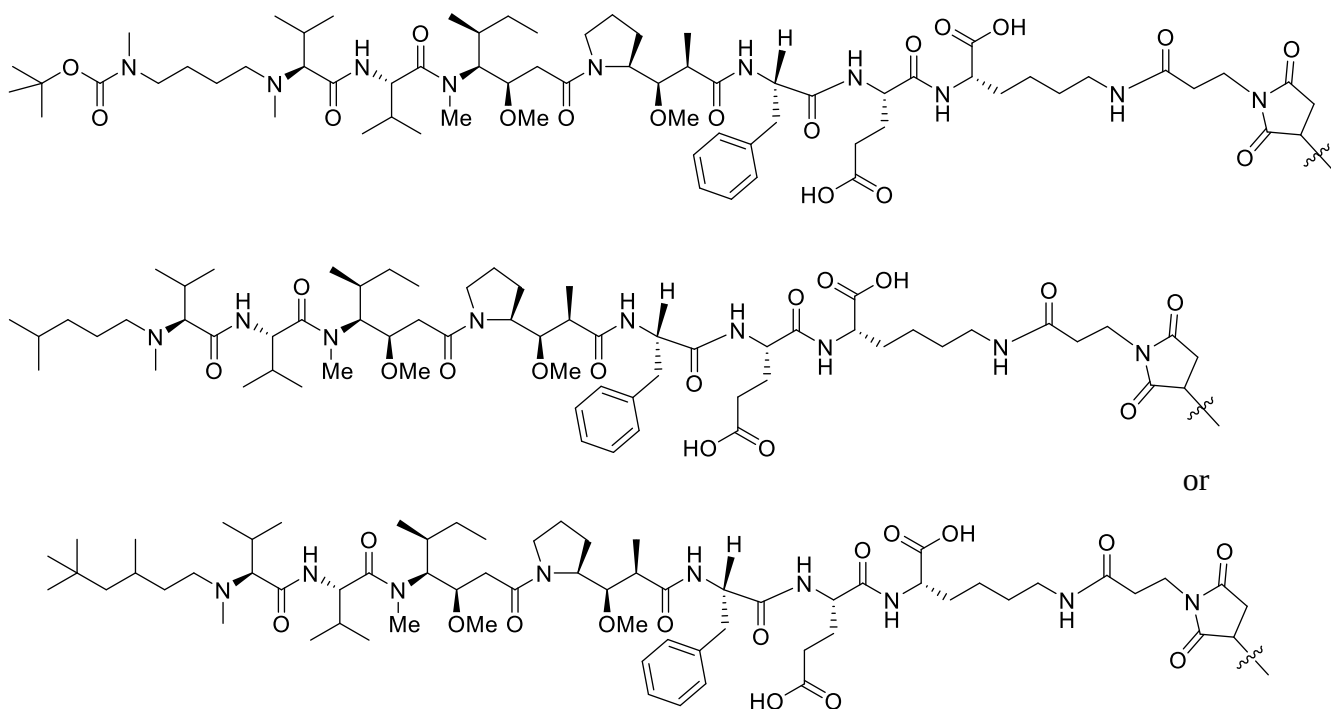
(carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10, and R¹ is not methyl.

209. The Ligand Drug Conjugate ~~composition compound~~ of claim **197**, wherein R¹ is -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₃, CH₂CH₂CH₂C(CH₃)₂, -CH₂CH₂CH₂CH₂N(CH₃)-C(=O)-O-t-Bu, -CH₂CH₂CH₂CH₂N(CH₃)-C(=O)-t-Bu, -CH₂CH₂CH₂N(CH₃)-C(=O)-O-t-Bu, -CH₂CH₂CH₂NH-C(=O)-O-t-Bu, or has the structure of:



2110. The Ligand Drug Conjugate ~~composition compound~~ of claim **121**, wherein a plurality of its each drug linker ~~moieties moiety~~ has the structure of:





5

or a salt thereof.

10

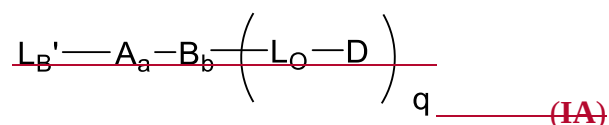
2211. The Ligand Drug Conjugate ~~composition compound~~ of claim ~~12 or 211~~, wherein L is an antibody Ligand Unit of an intact antibody or an antigen-binding fragment thereof, that is capable of selectively binding to a cancer cell antigen, in particular, the antibody the Ligand Unit is of an intact chimeric, humanized or human antibody.

15

2312. The Ligand Drug Conjugate ~~composition compound~~ of claim ~~2211~~, wherein subscript p' ranges from ~~about 2 to about 12~~, or from ~~about 2 to about 10~~, or from ~~about 2 to about 8~~, in particular, subscript p is ~~about 2, about 4 or about 8~~.

20

24.—A Drug Linker compound of Formula **IA**:



25

wherein L_B' is an ligand covalent binding moiety precursor;

A is a first optional Stretcher Unit;

subscript a is 0 or 1 indicating the absence of presence of A, respectively;

B is an optional Branching Unit;

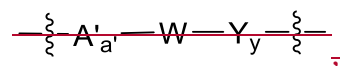
subscript b is 0 or 1, indicating the absence of presence of B, respectively;

~~L_O is an optional secondary linker moiety;~~

~~subscript q is an integer ranging from 1 to 4;~~

~~D is a hydrophobic AF Drug Unit having the structure of any one of claims 1 to 29
conjugated through its C-terminal component's carboxylic acid functional group;~~

~~in particular, L_O is a secondary linker that is present and has the formula of:~~



~~wherein the wavy line adjacent to Y indicates the site of covalent attachment of L_O to
the hydrophobic auristatin Drug Unit and the wavy line adjacent A' to indicates the site of
covalent attachment of L_O to the remainder of the drug linker moiety;~~

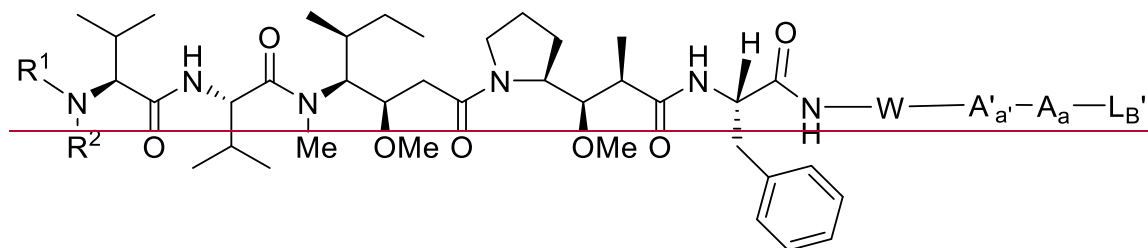
~~A' is a second optional Stretcher Unit, subscript a' is 0 or 1, indicating the absence or
presence of A', respectively;~~

~~W is a peptide Cleavable Unit;~~

~~Y is a peptide Spacer Unit; and~~

~~subscript y is 0 or 1, indicating the absence or presence of Y, respectively.~~

~~25. The Drug Linker compound of claim 24, wherein the compound has the
structure of:~~



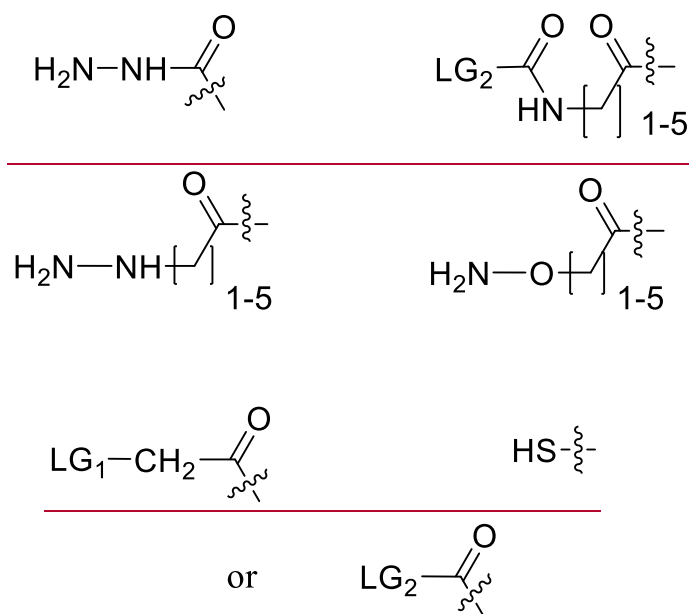
~~or a salt thereof, in particular a pharmaceutically acceptable salt, wherein~~

~~R² is methyl; and~~

~~R¹ is C₃-C₉ alkyl, optionally substituted by a C₃-C₆ carbocyclyl to provide a
(carbocyclyl) alkylene of up to 9 total carbon atoms, or~~

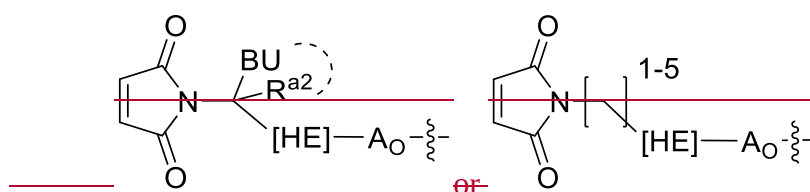
~~R¹ is (C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group
and R⁴ is C₁-C₆ alkyl, with the proviso that the total number of carbon atoms in the
(carbocyclyl)alkyl(ene) moiety of R¹ is between 4 and 10~~

~~26. The Drug Linker compound of claim 25, wherein L_b'-A has or is comprised
of one of the structures of:~~



- 5 ~~— or a salt thereof, wherein~~
~~— LG_1 is a leaving group suitable for nucleophilic displacement by a targeting agent nucleophile;~~
~~— LG_2 is a leaving group suitable for amide bond formation to a targeting agent, or —OH to provide an activateable carboxylic acid suitable for amide bond formation to a targeting agent; and~~
10 ~~— the wavy line indicates the site of covalent attachment to the remainder of the Drug Linker compound structure, or~~

~~wherein L_b , A has the structure of:—~~



- 15 ~~— or a salt thereof, wherein~~

~~the wavy line adjacent to A_O indicates the site of covalent attachments to L_O ; and the other wavy line indicates the site of covalent attachment to a sulfur atom of a Ligand Unit;~~

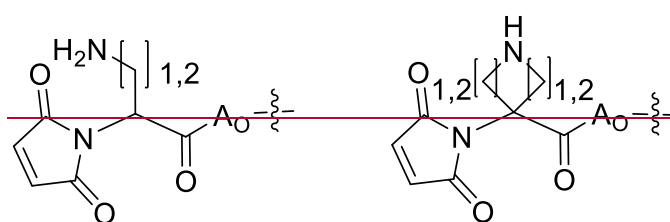
~~A_O is an optional second subunit of A;~~

- 20 ~~[HE] is an optional Hydrolysis Enhancing Unit, which is a component provided by A or a first subunit thereof;~~

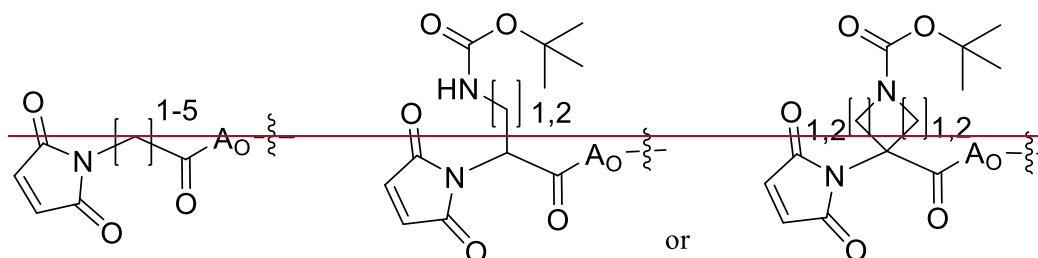
~~BU is a Basic Unit; R^{a2} is an optionally substituted C_4 - C_{12} alkyl group; and the dotted curved line indicates optional cyclization so that in the absence of said cyclization, BU is~~

an acyclic Basic Unit having a primary, secondary or tertiary amine functional group as the basic function group of the acyclic Basic Unit, or in the presence of said cyclization BU is a cyclized Basic Unit in which R^{a2} and BU together with the carbon atom to which both are attached, define an optionally substituted spiro-C₃-C₂₀ heterocycle containing a skeletal basic nitrogen atom of a secondary or tertiary amine functional group as the basic function group of the cyclic Basic Unit,

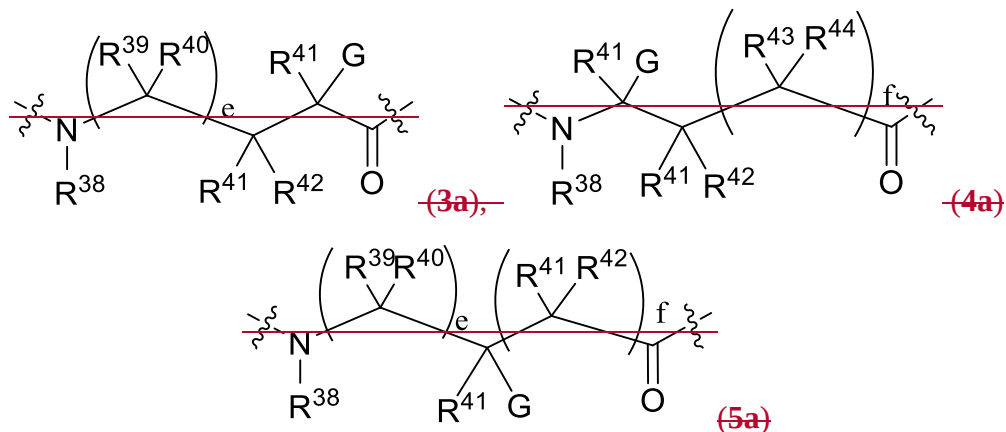
wherein the basic nitrogen atom of the acyclic Basic Unit or cyclic Basic Unit is optionally suitably protected by a nitrogen protecting group, dependent on the degree of substitution of the basic nitrogen atom, or is optionally protonated as an acid addition salt, in particular, L_B'-A has the structure of:



or a salt thereof, in particular as an acid addition salt, or L_B'-A has the structure of:



27. The Drug Linker compound of claim 26, wherein A_O is a second subunit of A that is present and is indicated as A₂, wherein A₂ is an amine-containing acid residue having the structure of formula 3a, formula 4a or formula 5a:



wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to [HE] of the first subunit of A, wherein [HE] is $\text{C}(=\text{O})$ and the wavy line adjacent to the carbonyl carbon atom indicates the site of covalent attachment to L_O , wherein both attachments are through amide functional groups;

subscripts e and f are independently 0 or 1; and

G is hydrogen, OH , OR^{PR} , CO_2H , $\text{CO}_2\text{R}^{\text{PR}}$ or an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, wherein the optional substituent when present is selected from the group consisting of OH , OR^{PR} , CO_2H , and $\text{CO}_2\text{R}^{\text{PR}}$; and wherein R^{PR} is a suitable protecting, or

G is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$ or an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, wherein the optional substituent when present is $\text{N}(\text{R}^{\text{PR}})(\text{R}^{\text{PR}})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is $\text{N}(\text{R}^{45})(\text{R}^{46})$, or an optionally substituted $\text{C}_1\text{-C}_6$ alkyl, wherein the optional substituent when present is $\text{N}(\text{R}^{45})(\text{R}^{46})$, wherein one of R^{45} , R^{46} is hydrogen or R^{PR} , wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl;

R^{38} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl; and

R^{39} - R^{44} are independently selected from the group consisting of hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_6\text{-C}_{20}$ aryl, and optionally substituted $\text{C}_5\text{-C}_{20}$ heteroaryl, or

R^{39} , R^{40} together with the carbon atom to which both are attached define a $\text{C}_3\text{-C}_6$ carbocycle, and R^{41} - R^{44} are as defined herein, or

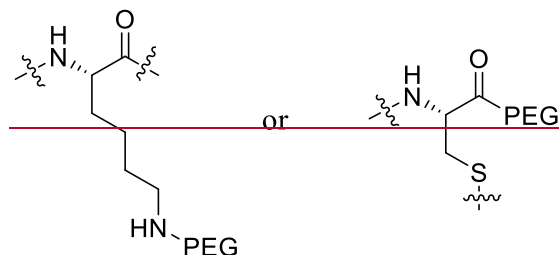
R^{43} , R^{44} together with the carbon atom to which both are attached define a $\text{C}_3\text{-C}_6$ carbocycle, and R^{39} - R^{42} are as defined herein, or

R^{40} and R^{41} , or R^{40} and R^{43} , or R^{41} and R^{43} together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a $\text{C}_5\text{-C}_6$ carbocycle or a $\text{C}_5\text{-C}_6$ heterocycle, and R^{39} , R^{44} and the remainder of R^{40} - R^{43} are as defined herein,

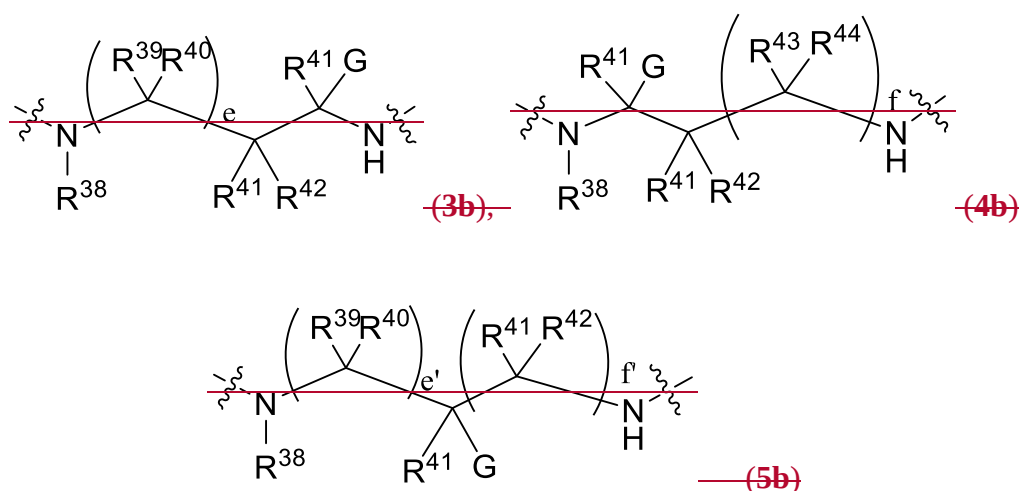
or A_O is an α -amino or β -amino acid residue, wherein its amino nitrogen atom is covalently attached to the remainder of A, and its carboxylic acid carbonyl carbon is covalently attached to A' , wherein both attachments are through amide functional groups,

or A_O is a second subunit of A that is present and is indicated as A_2 wherein A_2 is a β -amino acid residue having the structure of $\text{NHCH}_2\text{CH}_2\text{C}(=\text{O})$ or has the formula of $\text{L}^{\text{P}}(\text{PEG})$, wherein L^{P} is Parallel Connector Unit having the structure of a tri-functional

amine-containing acid residue and PEG is a PEG Unit, in particular, A_2 is $-L^P(PEG)-$ having the structure of:



— wherein the wavy line adjacent to the nitrogen atom indicates the site of covalent attachment to the first subunit of A and the wavy line to the carbonyl carbon atom or the sulfur atom indicates the site of covalent attachment to A' of L_O , wherein A' is preferably an alkylene diamine residue having the structure of formula **3b**, formula **4b** or formula **5b**:



wherein subscript e and f range from 0 to 6;

subscripts e' and f' range from 1 to 6;

the wavy line next to the nitrogen atom of the amine residue to which R^{38} is attached indicates the site of covalent attachment to a first optional Stretcher Unit that is present or to A_O , wherein A_O is an optional second subunit of A that when present is indicated as A_2 ;

the wavy line adjacent to the nitrogen atom of the other amine residue indicates the site of covalent attachment to W ;

wherein both attachments are through amide functional groups;

G is hydrogen, $-OH$, $-OR^{PR}$, $-CO_2H$, $-CO_2R^{PR}$ or an optionally substituted C_1 - C_6 alkyl, wherein the optional substituent when present is selected from the group consisting of $-OH$, $-OR^{PR}$, $-CO_2H$, and $-CO_2R^{PR}$; and wherein R^{PR} is a suitable protecting, or

G is $N(R^{PR})(R^{PR})$ or an optionally substituted C_1 - C_6 alkyl, wherein the optional substituent when present is $N(R^{PR})(R^{PR})$, wherein R^{PR} are independently a protecting group or R^{PR} together form a suitable protecting group, or

G is $N(R^{45})(R^{46})$, or an optionally substituted C_1 - C_6 alkyl, wherein the optional substituent when present is $N(R^{45})(R^{46})$, wherein one of R^{45} , R^{46} is hydrogen or R^{PR} , wherein R^{PR} is a suitable protecting group, and the other is hydrogen or optionally substituted C_1 - C_6 alkyl;

R^{38} is hydrogen or optionally substituted C_1 - C_6 alkyl; and

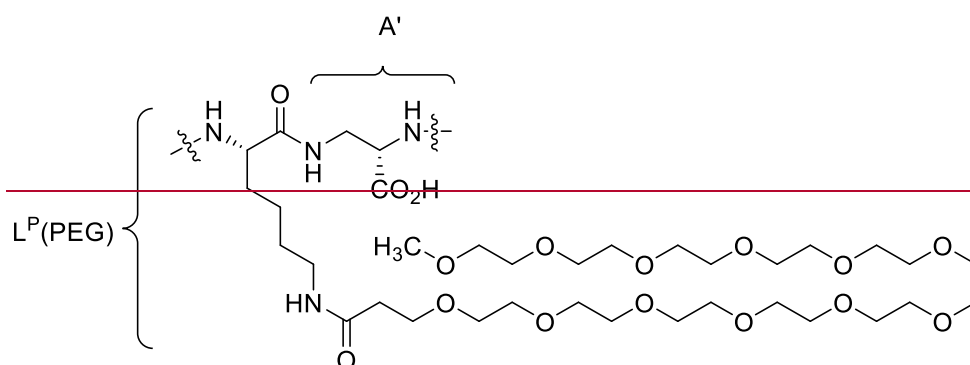
R^{39} - R^{44} are independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_6 - C_{20} aryl, and optionally substituted C_5 - C_{20} heteroaryl, or

R^{39} , R^{40} together with the carbon atom to which both are attached define a C_3 - C_6 carbocyclo, and R^{41} - R^{44} are as defined herein, or

R^{43} , R^{44} together with the carbon atom to which both are attached define a C_3 - C_6 carbocyclo, and R^{39} - R^{42} are as defined herein, or

R^{40} and R^{41} , or R^{40} and R^{43} , or R^{41} and R^{43} together with the carbon atom or heteroatom to which both are attached and the atoms intervening between those carbon atoms and/or heteroatoms define a C_5 - C_6 carbocyclo or a C_5 - C_6 heterocyclo, and R^{39} , R^{44} and the remainder of R^{40} - R^{43} are as defined herein,

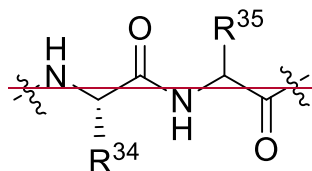
or A' is an optionally substituted diamine residue, wherein one amino nitrogen atom is covalently attached to the remainder of A , and the other amino nitrogen atom is covalently attached to W , wherein both attachments are through amide functional groups, in particular, A_2 - A' has the structure of:



or a salt thereof, wherein the wavy line to the nitrogen atom of $L^P(PEG)$ indicates the site of attachment to the remainder of A and the wavy line to the nitrogen atom of A'

indicates the site of attachment to W, wherein both attachments are through amide functional groups.

28. The Drug Linker compound of any one of claims 24 to 27, wherein W is an amino acid sequence comprised of a dipeptide that provides a recognition site for a protease, wherein the dipeptide has the structure of:



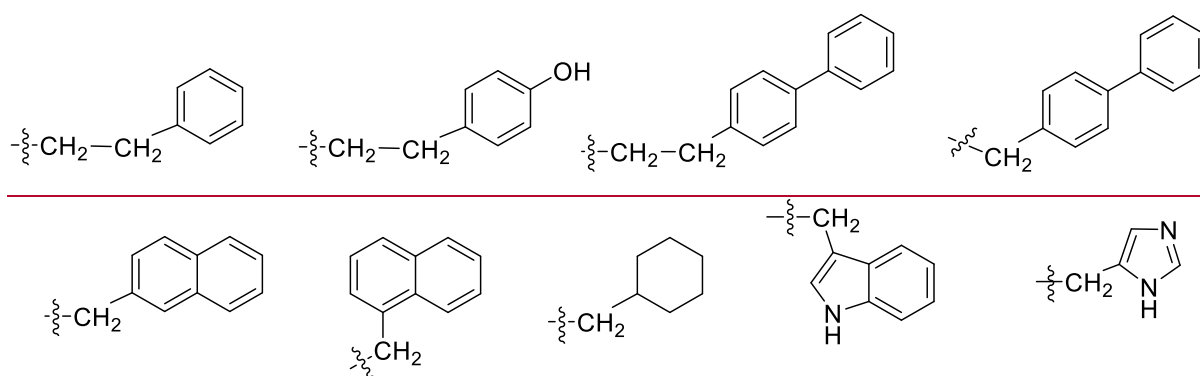
or a salt thereof, wherein

the wavy line at the dipeptide N-terminal indicates the site of covalent attachment as an amide bond to an AF Drug Unit through its C-terminal component's carboxylic acid residue, wherein the amide bond is cleavable by the protease to release the Drug Unit as free drug;

the wavy line at the dipeptide C-terminal indicates the site of covalent attachment to the remainder of the amino acid sequence or to A, or a subunit thereof, as when A₀ is present as A₂;

R³⁴ is hydrogen, or the side chain of a naturally occurring α-amino acid except proline, in particular -CH₃, -C(CH₃)₂-, -CH₂COOH, -CH₂CH₂COOH or -CH₂CH₂CH₂CH₂NH₂-; and

R³⁵ is hydrogen, methyl, isopropyl, sec-butyl, benzyl, p-hydroxy-benzyl, -CH₂OH, -CH(OH)CH₃-, -CH₂CH₂SCH₃-, -CH₂C(=O)NH₂-, -CH₂COOH, -CH₂CH₂C(=O)NH₂-, -CH₂CH₂COOH, -CH₂CH₂CH₂NHC(=NH)NH₂-, -CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂NH-C(=O)CH₃-, -CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂CH₂NHC(=NH)NH₂-, -CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂NH-C(=O)CH₃-, -CH₂CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂NHC(=O)NH₂-, -CH₂CH₂CH₂CH₂NHC(=O)NH₂-, -CH₂CH₂CH(OH)CH₂NH₂-, 2-pyridylmethyl, 4-pyridylmethyl, phenyl or cyclohexyl, or R³⁵ has the structure of one of:



wherein the wavy line indicates the site of covalent attachment to the dipeptide backbone, or

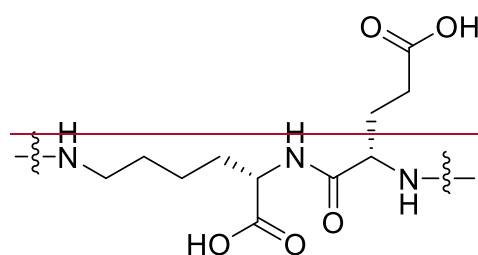
wherein W is a glutamic acid residue, an aspartic acid or a peptide sequence comprised of an N-terminal glutamic acid or aspartic acid residue covalently attached to the hydrophobic AF Drug Unit C-terminal component's carboxylic acid residue through the glutamic acid or aspartic acid α -amino nitrogen atom and to the remainder of the peptide sequence or to A', which is an optional second Stretcher Unit that is present, through the glutamic acid or aspartic acid α -carboxyl, wherein both attachments are through amide bonds;

wherein the amide bond to the C-terminal component is cleavable by a protease to release the Drug Unit as free drug, and

wherein A' is diamine having a carboxylic acid side chain so that the nitrogen atom of one of its amines is covalently attached as an amide bond to the glutamic acid residue, and

the nitrogen atom of the other amine is covalently attached A, or a subunit thereof, as when A₀ is present as A₂;

in particular, A'-W has the structure of:

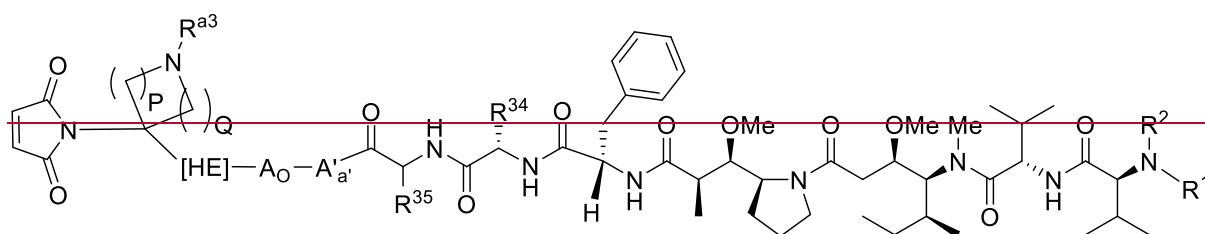


or a salt thereof, wherein

the wavy line adjacent to the glutamic acid α -amino nitrogen atom indicates the site of covalent attachment as an amide bond to the hydrophobic AF Drug Unit through its C-terminal component's carboxylic acid residue, wherein the amide bond is cleavable by the protease to release the Drug Unit as free drug;

and the wavy line adjacent the lysine epsilon amine nitrogen atom indicates the site of covalent attachment to a first optional Stretcher Unit (A) or subunit thereof that is present.

29. The Drug Linker compound of claim 24, wherein the compound has the structure of:



or a salt thereof, wherein HE is an optional Hydrolysis Enhancing Unit;

A₀ is absent or is a second subunit of A;

A' is a second optional Stretcher Unit;

subscript a' is 0 or 1, indicating the absence or presence of A', respectively;

subscript P is 1 or 2;

subscript Q ranges from 1 to 6;

R^{a3} is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₄ alkylene-(C₆-C₁₀ aryl), or R^{PEG1}-O-(CH₂CH₂O)₁₋₃₆-R^{PEG2}, wherein R^{PEG1} is C₁-C₄ alkylene, R^{PEG2} is H or C₁-C₄ alkylene,

wherein the basic nitrogen bonded to R^{a3} is optionally protonated as an acid addition salt or is optionally protected by an acid labile protecting group;

R³⁴ is -CH₃, -C(CH₃)₂-, -CH₂COOH, -CH₂CH₂COOH or -CH₂CH₂CH₂CH₂NH₂; and

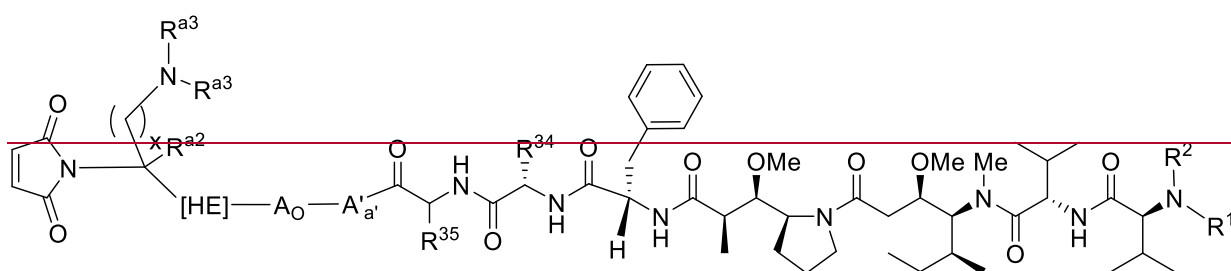
R³⁵ is methyl, isopropyl, -CH₂C(=O)NH₂, -CH₂COOH, -CH₂CH₂C(=O)NH₂, -CH₂CH₂COOH, -CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂NHC(=O)CH₃, -CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂CH₂NHC(=NH)NH₂, -CH₂CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂CH₂NH-C(=O)CH₃, -CH₂CH₂CH₂CH₂NH-C(=O)H, -CH₂CH₂CH₂NHC(=O)NH₂, -CH₂CH₂CH₂CH₂NHC(=O)NH₂ or -CH₂CH₂CH(OH)CH₂NH₂;

R² is methyl; and

R¹ is C₁-C₉ alkyl, optionally substituted by a C₃-C₆ carbocyclyl to provide a (carbocyclyl) alkylene of up to 9 total carbon atoms, or

R¹ is (C₂-C₆ alkylene)-X-R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl;

with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or
 R^1 is a first non-aromatic hydrophobic moiety; and
 R^2 is a second non-aromatic hydrophobic moiety;
 wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2, or
 wherein the compound has the structure of:



or a salt thereof,
 wherein HE is an optional Hydrolysis Enhancing Unit,
 A_O is absent or is a second subunit of A ;
 A' is a second optional Stretcher Unit;
 subscript a' is 0 or 1, indicating the absence or presence of A' , respectively;
 subscript x is 1 or 2;
 R^{a2} is hydrogen or CH_3 or CH_2CH_3 ;
 R^{a3} , at each instance, is independently hydrogen, CH_3 or CH_2CH_3 , or both R^{a3} together with the nitrogen to which they are attached define an azetidiny, pyrrolidiny or piperidiny heterocycl, in which the basic primary, secondary or tertiary amine so defined is optionally protonated as an acid addition salt form, or in which the basic primary or secondary amine is optionally protected by an acid labile protecting group;
 R^{34} is CH_3 , $C(CH_3)_2$, CH_2COOH , CH_2CH_2COOH or $CH_2CH_2CH_2CH_2NH_2$; and
 R^{35} is methyl, isopropyl, $CH_2C(=O)NH_2$, CH_2COOH , $CH_2CH_2C(=O)NH_2$, CH_2CH_2COOH , $CH_2CH_2CH_2NHC(=NH)NH_2$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHC(=O)CH_3$, $CH_2CH_2CH_2NH-C(=O)H$, $CH_2CH_2CH_2CH_2NHC(=NH)NH_2$, $CH_2CH_2CH_2CH_2NH-C(=O)CH_3$, $CH_2CH_2CH_2CH_2NH-C(=O)H$, $CH_2CH_2CH_2NHC(=O)NH_2$, $CH_2CH_2CH_2CH_2NHC(=O)NH_2$ or $CH_2CH_2CH(OH)CH_2NH_2$;

~~R² is methyl; and~~

~~R¹ is C₁-C₉-alkyl, optionally substituted by a C₃-C₆-carbocyclyl to provide a (carbocyclyl)-alkylene of up to 9 total carbon atoms, or~~

~~R¹ is (C₂-C₆ alkylene) X R⁴, wherein X is an amide or carbamate functional group and R⁴ is C₁-C₆ alkyl,~~

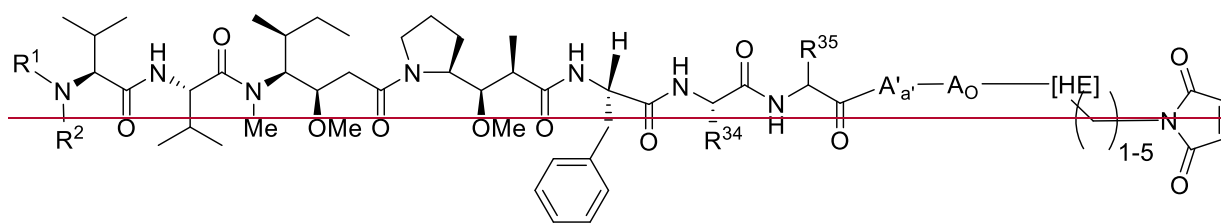
with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or

~~R¹ is a first non-aromatic hydrophobic moiety; and~~

~~R² is a second non-aromatic hydrophobic moiety,~~

wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2, or

~~wherein the compound has the structure of:~~



~~or a salt thereof, wherein~~

~~HE is an optional Hydrolysis Enhancing Unit;~~

 ~~A_0 is absent or is a second subunit of A ;~~

~~A' is a second optional Stretcher Unit;~~

~~subscript a' is 0 or 1, indicating the absence or presence of A';~~

R^{34} is $-CH_3$, $-C(CH_3)_2$, $-CH_2COOH$, $-CH_2CH_2COOH$, or $-CH_2CH_2CH_2CH_2NH_2$; and

R^{35} is methyl, isopropyl, $-CH_2C(=O)NH_2$, $-CH_2COOH$, $-CH_2CH_2C(=O)NH_2$,

$$\begin{array}{c} \text{CH}_2\text{CH}_2\text{COOH}, \text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{-NH})\text{NH}_2, \text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2, \text{CH}_2\text{CH}_2\text{CH}_2\text{NH} \\ \text{C}(\text{-O})\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_2\text{NH C}(\text{-O})\text{H}, \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{-NH})\text{NH}_2, \end{array}$$
$$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2, \text{---CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH-C(=O)CH}_3, \text{---CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH-C(=O)H},$$
$$\begin{array}{l} \text{---CH}_2\text{CH}_2\text{CH}_2\text{NHC(=O)NH}_2, \text{---CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC(=O)NH}_2 \text{---or---} \\ \text{CH}_2\text{CH}_2\text{CH(OH)CH}_2\text{NH}_2; \end{array}$$

~~R² is methyl; and~~

~~R¹ is C₁-C₉-alkyl, optionally substituted by a C₃-C₆-carbocyclyl to provide a (carbocyclyl)-alkylene of up to 9 total carbon atoms, or~~

R^1 is $(C_2-C_6\text{-alkylene})-X-R^4$, wherein X is an amide or carbamate functional group and R^4 is C_1-C_6 alkyl,

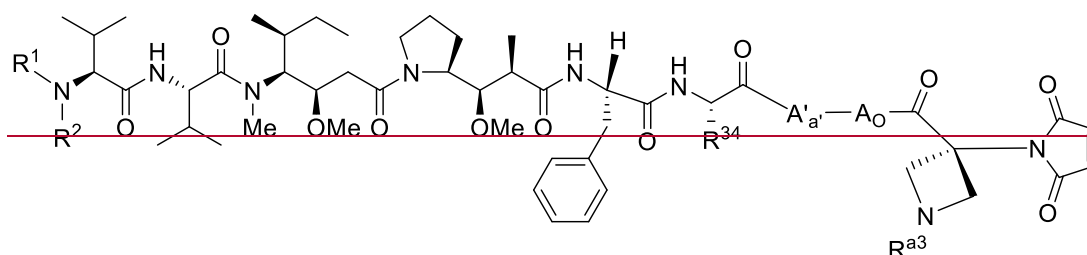
with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or

R^1 is a first non-aromatic hydrophobic moiety; and

R^2 is a second non-aromatic hydrophobic moiety,

wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2,

in particular, the compound has the structure of:



or a salt thereof, wherein

R^{a3} is hydrogen, $-CH_3$ or $-CH_2CH_3$, wherein the secondary or tertiary amine so defined is optionally protonated as an acid addition salt form, or wherein the secondary amine so defined is optionally protected by an acid labile protecting group;

A_O is absent or is a second subunit of A having the structure of an α -amino acid or a β -amino acid residue;

A' is a second optional Stretcher Unit that is present having the structure of an optionally substituted C_2-C_6 alkylene diamine residue, wherein one amino nitrogen atom is covalently attached to A_O , and the other amino nitrogen atom is covalently attached to the R^{34} -containing amino acid residue, wherein both attachments are through amide functional groups;

R^{34} is $-CH_2CO_2H$ or $-CH_2CH_2CO_2H$;

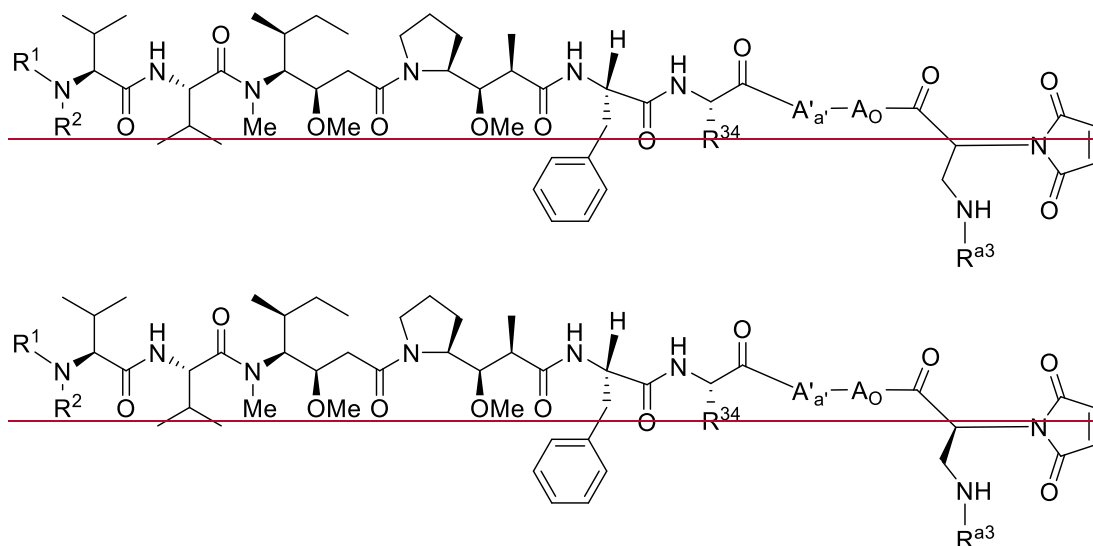
R^2 is methyl; and

R^1 is C_1-C_9 alkyl, optionally substituted by a C_3-C_6 carbocyclyl to provide a (carbocyclyl)-alkylene of up to 9 total carbon atoms, or

R^1 is $(C_2-C_6\text{-alkylene})-X-R^4$, wherein X is an amide or carbamate functional group and R^4 is C_1-C_6 alkyl,

with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or

R^1 is a first non-aromatic hydrophobic moiety; and
 R^2 is a second non-aromatic hydrophobic moiety;
 wherein the first and second hydrophobic moieties provide the hydrophobic AF
 compound characterized by a clogP value of between about 4.4 to about 7.2, or
 in particular the compound has the structure of:



or a salt thereof, wherein

R^{a3} is hydrogen, CH_3 or CH_2CH_3 , wherein the primary or secondary amine so defined
 is optionally protonated as an acid addition salt form or optionally protected by an acid-
 labile protecting group;

A_O is absent or is a second subunit of A having the structure of an α -amino acid or a β -
 amino acid residue;

A' is a second optional Stretcher Unit that is present having the structure of an
 optionally substituted C_2 - C_6 alkylene diamine residue, wherein one amino nitrogen atom is
 covalently attached to A_O , and the other amino nitrogen atom is covalently attached to the
 R^{34} -containing amino acid residue, wherein both attachments are through amide functional
 groups;

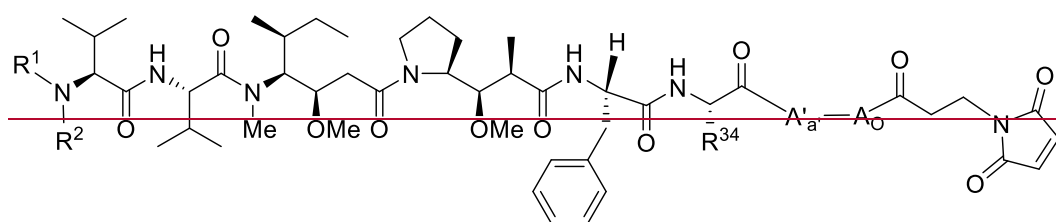
R^{34} is CH_2CO_2H or $CH_2CH_2CO_2H$;

R^2 is methyl; and

R^1 is C_1 - C_9 alkyl, optionally substituted by a C_3 - C_6 carbocyclyl to provide a
 (carbocyclyl) alkylene of up to 9 total carbon atoms, or

R^1 is $(C_2$ - C_6 alkylene)-X- R^4 , wherein X is an amide or carbamate functional group
 and R^4 is C_1 - C_6 alkyl;

with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or
 R^1 is a first non-aromatic hydrophobic moiety; and
 R^2 is a second non-aromatic hydrophobic moiety;
 wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2, or
 in particular, the compound has the structure of:



or a salt thereof, wherein

A_o is absent or is a second subunit of A having the structure of an α -amino acid or a β -amino acid residue;

A' is a second optional Stretcher Unit that is present having the structure of an optionally substituted C_2 - C_6 alkylene diamine residue, wherein one amino nitrogen atom is covalently attached to A_o , and the other amino nitrogen atom is covalently attached to the R^{34} -containing amino acid residue, wherein both attachments are through amide functional groups;

R^{34} is CH_2CO_2H or $CH_2CH_2CO_2H$;

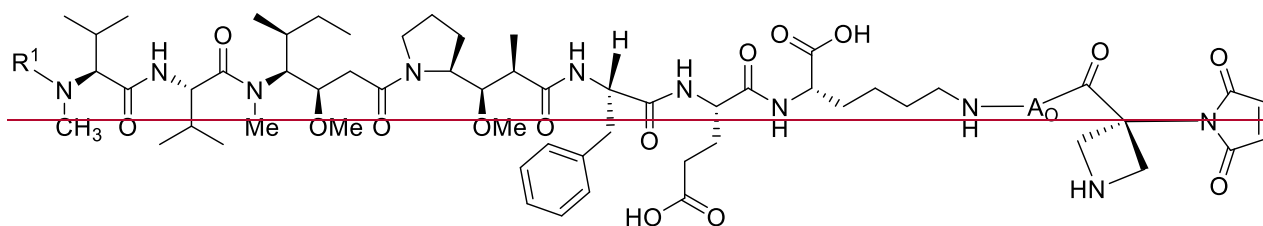
R^2 is methyl; and

R^1 is C_1 - C_9 alkyl, optionally substituted by a C_3 - C_6 carbocyclyl to provide a (carbocyclyl)alkylene of up to 9 total carbon atoms, or

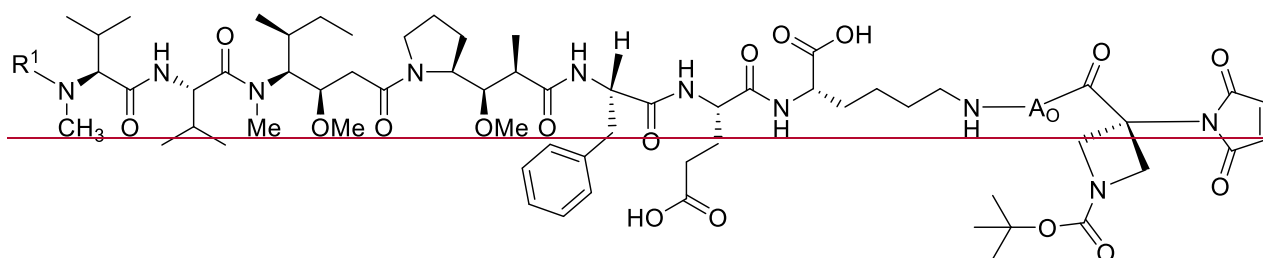
R^1 is $(C_2$ - C_6 alkylene)-X- R^4 , wherein X is an amide or carbamate functional group and R^4 is C_1 - C_6 alkyl,

with the proviso that the total number of carbon atoms in the (carbocyclyl)alkyl(ene) moieties of R^1 is between 4 and 10 and R^1 is not methyl, or
 R^1 is a first non-aromatic hydrophobic moiety; and
 R^2 is a second non-aromatic hydrophobic moiety;
 wherein the first and second hydrophobic moieties provide the hydrophobic AF compound characterized by a clogP value of between about 4.4 to about 7.2.

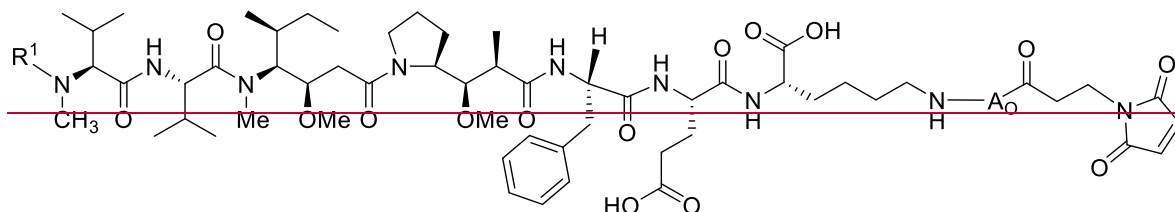
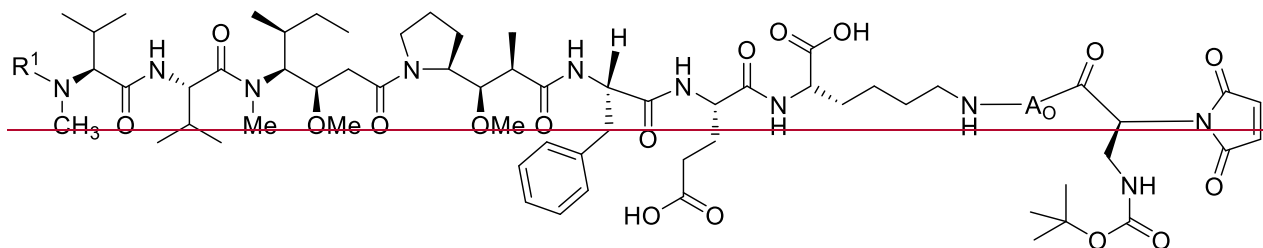
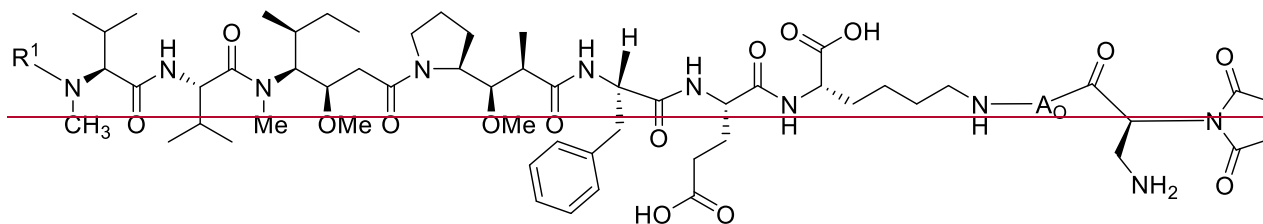
30.—The Drug Linker compound of claim 29, wherein the compound has the structure of:



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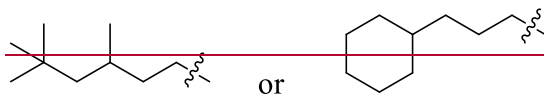
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or a salt thereof, in particular,

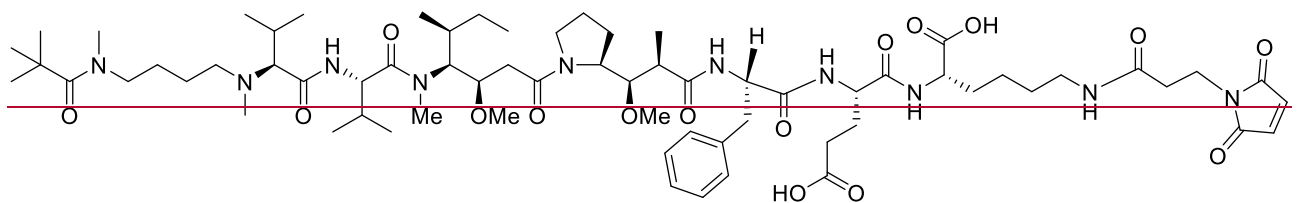
wherein R^1 is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})\text{O}t\text{Bu}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})t\text{Bu}$,

~~CH₂CH₂CH₂N(CH₃)C(=O)O-t-Bu, CH₂CH₂CH₂NH C(=O)O-t-Bu, or has the structure of:~~

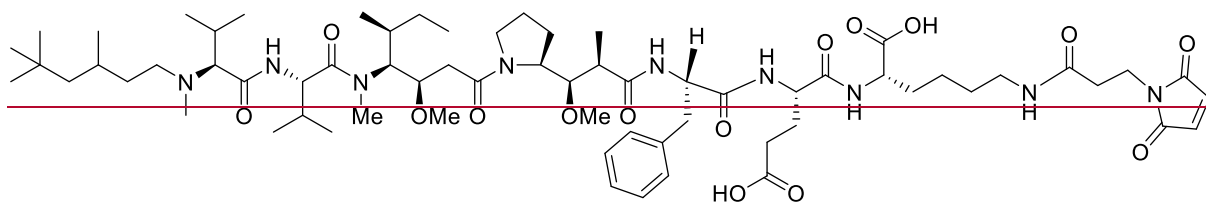
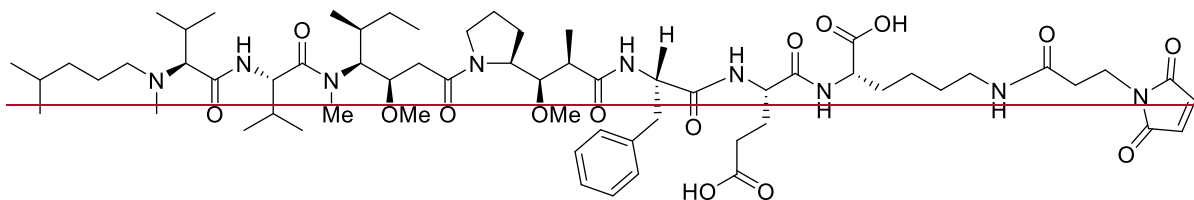
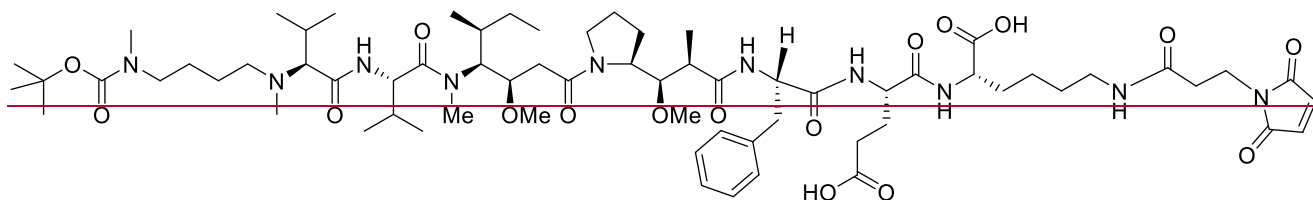


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31. — The Drug Linker compound of claim 30, wherein the compound has the structure of:



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~~or a salt thereof.~~