

CLAIMS

1. A peptide ligand specific for EphA2, or a pharmaceutically acceptable salt or modified derivative thereof, the peptide ligand comprising a polypeptide comprising three cysteine residues, separated by two loop sequences, and a non-aromatic molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that two polypeptide loops are formed on the molecular scaffold, wherein the peptide ligand is a peptide ligand which comprises an amino acid selected from:

(β -Ala)-Sar₁₀-A(HArg)DC(HyP)LVNPLCLHP(D-Asp)W(HArg)C (SEQ ID NO: 2);

ACMNDWWCAMGWKCA (SEQ ID NO: 3);

ACVPDRRCAYMNVCA (SEQ ID NO: 4);

ACVVDGRCAYMNVCA (SEQ ID NO: 5);

ACVDSRCAYMNVCA (SEQ ID NO: 6);

ACVPDSRCAYMNVCA (SEQ ID NO: 7);

ACYVGKECAIRNVCA (SEQ ID NO: 8);

ACYVGKECAYMNVCA (SEQ ID NO: 9);

ARDCPLVNPLCLHPGWTC (SEQ ID NO: 10);

A(HArg)DCPLVNPLCLHPGWTC (SEQ ID NO: 11);

CPLVNPLCLHPGWTCCLHG (SEQ ID NO: 12);

CPLVNPLCLHPGWTCCL(D-His)G (SEQ ID NO: 13);

CPLVNPLCLHPGWSCRQ (SEQ ID NO: 14);

CPLVNPLCLHPGWSC(HArg)GQ (SEQ ID NO: 15);

ACVPDRRCAYMNVCA (SEQ ID NO: 16);

DLRCGGDPRCAYMNVCA (SEQ ID NO: 17);

SRPCVIDSRCAYMNVCA (SEQ ID NO: 18);

ESRCSPDARCAVMNVCA (SEQ ID NO: 19);

HSGCRPDPRCAYMNVCA (SEQ ID NO: 20);

GSGCKPDSRCAYMNVCA (SEQ ID NO: 21);

ETVCLPDSRCAYMNVCA (SEQ ID NO: 22);

GQVCIVDARCAVMNVCA (SEQ ID NO: 23);

ACVPDRRCAFENVCDH (SEQ ID NO: 24);

ACVPDRRCAFMNVCEDR (SEQ ID NO: 25);

ACVPDRRCAFQDVCDHE (SEQ ID NO: 26);

ACVPDRRCAFRDVCLTG (SEQ ID NO: 27);

ACQPSNHCAFMYNYCA (SEQ ID NO: 28);

ACSPTPACAVQNLCA (SEQ ID NO: 29);

ACTSCWAYPDSFCA (SEQ ID NO: 30);

ACTKPTGFCAYPDTICA (SEQ ID NO: 31);
ACRGEWGYCAYPDTICA (SEQ ID NO: 32);
ACRNWGMYCAYPDTICA (SEQ ID NO: 33);
ACPDWGKYCAYPDTICA (SEQ ID NO: 34);
ACRVYGPYCAYPDTICA (SEQ ID NO: 35);
ACSSCWAYPDSVCA (SEQ ID NO: 36);
ACQSCWAYPDITYCA (SEQ ID NO: 37);
ACGFMGLEPCETFCA (SEQ ID NO: 38);
ACGFMGLVPCEVHCA (SEQ ID NO: 39);
ACGFMGLEPCCEMVCA (SEQ ID NO: 40);
ACGFMGLEPCVITYCA (SEQ ID NO: 41);
ACGFMGLEPCELVCA (SEQ ID NO: 42);
ACGFMGLVPCNVFCA (SEQ ID NO: 43);
ACGFMGLEPCELFCA (SEQ ID NO: 44);
ACGFMGLEPCELCMPK (SEQ ID NO: 45);
ACGFMGLEPCELYCA (SEQ ID NO: 46);
ACGFMGLEPCELYCAHT (SEQ ID NO: 47);
ACGFMGLEPCEMYCA (SEQ ID NO: 48);
ACGFMGLVPCELYCADN (SEQ ID NO: 49);
ACPLVNPLCLTSGWKCA (SEQ ID NO: 50);
ACPMVNPLCLHPGWICA (SEQ ID NO: 51);
ACPLVNPLCLHPGWICA (SEQ ID NO: 52);
ACPLVNPLCLHPGWRCA (SEQ ID NO: 53);
ACPLVNPLCNLPGWTCA (SEQ ID NO: 54);
ACPLVNPLCLVPGWSCA (SEQ ID NO: 55);
ACPLVNPLCLLDGWTCA (SEQ ID NO: 56);
ACPLVNPLCLMPGWGCA (SEQ ID NO: 57);
ACPLVNPLCMIGNWTCA (SEQ ID NO: 58);
ACPLVNPLCLMTGWSCA (SEQ ID NO: 59);
ACPLVNPLCMMGGWKCA (SEQ ID NO: 60);
ACPLVNPLCLYGSWKCA (SEQ ID NO: 61);
ACPLVNPLCLHPGWTCA (SEQ ID NO: 62);
ARDCPLVNPLCLHPGWTCA (SEQ ID NO: 63);
RPACPLVNPLCLHPGWTCA (SEQ ID NO: 64);
RPPCPLVNPLCLHPGWTCA (SEQ ID NO: 65);
KHSCPLVNPLCLHPGWTCA (SEQ ID NO: 66);
ACPLVNPLCLHPGWTCLHG (SEQ ID NO: 67);

ACPLVNPLCLHPGWTCL(D-His)G (SEQ ID NO: 68);
 ACPLVNPLCLHPG(2Nal)TCLHG (SEQ ID NO: 69);
 RHDCPLVNPLCLLPGWTC (SEQ ID NO: 70);
 TPRCPLVNPLCLMPGWTC (SEQ ID NO: 71);
 ACPLVNPLCLAPGWTC (SEQ ID NO: 72);
 ACPLVNPLCLAPGWTCRS (SEQ ID NO: 73);
 ACPLVNPLCLEPGWTC (SEQ ID NO: 74);
 ACPLVNPLCLEPGWTCAR (SEQ ID NO: 75);
 ACPLVNPLCLHPGWSCA (SEQ ID NO: 76);
 ACPLVNPLCLHPGWSCRQ (SEQ ID NO: 77);
 ACPLVNPLCLHPGWSC(HArg)GQ (SEQ ID NO: 78);
 ACPLVNPLCLHPG(2Nal)SCRQ (SEQ ID NO: 79);
 ACPLVNPLCLTPGWTCNT (SEQ ID NO: 80);
 ACPMVNPLCLHPGWKCA (SEQ ID NO: 81);
 ACPMVNPLCLTPGWICA (SEQ ID NO: 82);
 ACPMVNPLCLHPGWTC (SEQ ID NO: 83);
 H(D-Asp)VT-C(Aib)(1Nal)G(Aib)F(1Nal)CP(tBuGly)N(HArg)P(D-Asp)C (SEQ ID NO: 84);
 A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)W(HArg)C (SEQ ID NO: 85);
 A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)WTC (SEQ ID NO: 86);
 A(HArg)DC(HyP)LVNPLCLHP(D-Ala)WTC (SEQ ID NO: 87);
 A(HArg)DCPLVNPLCLHP(D-Ala)WTC (SEQ ID NO: 88);
 ARDC(HyP)LVNPLCLHPGWTC (SEQ ID NO: 89);
 ARDCPLVNPLCL(D-3,3-DPA)PGWTC (SEQ ID NO: 90);
 ARDCPLVNPLCLHPGWTC (SEQ ID NO: 91);
 A(HArg)DCPLVNPLCLHP(D-Cya)WTC (SEQ ID NO: 92);
 A(D-Arg)DC(HyP)LVNPLCL(D-3,3-DPA)P(D-Asp)W(HArg)C (SEQ ID NO: 93); and
 CPLVNPLCLHPGWTC (SEQ ID NO: 97);

wherein HyP is hydroxyproline, HArg is homoarginine, Sar is sarcosine, HArg is homoarginine, D-Asp is D-aspartic acid, 2Nal is 2-naphthylalanine, 1Nal is 1-naphthylalanine, Aib is 2-aminoisobutyric acid, tBuGly is *tert*-leucine, hSerMe is homoserine(methyl), D-Ala is D-alanine, D-3,3-DPA is 3,3-diphenyl-D-alanine, D-Cya is D-cysteic acid, D-Arg is D-arginine, HPhe is homophenylalanine, and D-His is D-histidine.

2. The peptide ligand as defined in claim 1, wherein the molecular scaffold is selected from 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA).

3. The peptide ligand as defined in claim 1 or claim 2, wherein the molecular scaffold is selected from 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA) and the peptide ligand is

(β -Ala)-Sar₁₀-A(HArg)D-C_iPLVNPLC_{ii}LHPGWTC_{iii} ((β -Ala)-Sar₁₀-(SEQ ID NO: 11)) (BCY6014; Compound 67);

wherein Sar is sarcosine, HArg is homoarginine and HyP is hydroxyproline.

4. The peptide ligand as defined in any one of claims 1 to 3, wherein said peptide ligand is selected from:

ACMNDWWCAMGWKCA-Sar6-K(FI) ((SEQ ID NO: 3)-Sar6-K(FI));

ACVPDRRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 4)-Sar6-K(FI));

ACVVDGRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 5)-Sar6-K(FI));

ACVDSRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 6)-Sar6-K(FI));

ACVPDSRCAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 7)-Sar6-K(FI));

ACYVGKECAIRNVCA-Sar6-K(FI) ((SEQ ID NO: 8)-Sar6-K(FI));

ACYVGKECAYMNVCA-Sar6-K(FI) ((SEQ ID NO: 9)-Sar6-K(FI));

FI-G-Sar5-ACYVGKECAYMNVCA (FI-G-Sar5-(SEQ ID NO: 9));

FI-(β -Ala)-Sar10-ARDCPLVNPLCLHPGWTC (FI-(β -Ala)-Sar10-(SEQ ID NO: 10));

FI-(β -Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTC (FI-(β -Ala)-Sar10-(SEQ ID NO: 11));

Ac-CPLVNPLCLHPGWTCCLHG-Sar6-(D-K[FI]) (Ac-(SEQ ID NO: 12)-Sar6-(D-K[FI]));

Ac-CPLVNPLCLHPGWTCCL(D-His)G-Sar6-(D-K[FI]) (Ac-SEQ ID NO: 13)-Sar6-(D-K[FI]));

Ac-CPLVNPLCLHPGWSCRGQ-Sar6-(D-K[FI]) (Ac-(SEQ ID NO: 14)-Sar6-(D-K[FI]));

Ac-CPLVNPLCLHPGWSC(HArg)GQ-Sar6-(D-K[FI]) (Ac-(SEQ ID NO: 15)-Sar6-(D-K[FI]));

ACMNDWWCAMGWKCA (SEQ ID NO: 3);

ACVPDRRCAYMNVCA (SEQ ID NO: 4);

(β -Ala)-Sar10-ACVPDRRCAYMNVCA ((β -Ala)-Sar10-(SEQ ID NO: 16));

DLRCGGDPRCAYMNVCA (SEQ ID NO: 17);

SRPCVIDSRCAYMNVCA (SEQ ID NO: 18);

ESRCSPDARCAVMNVCA (SEQ ID NO: 19);

HSGCRPDPRCAVMNVCA (SEQ ID NO: 20);

GSGCKPDSRCAYMNVCA (SEQ ID NO: 21);

ETVCLPDSRCAYMNVCA (SEQ ID NO: 22);

GQVCIVDARCAVMNVCA (SEQ ID NO: 23);

ACVPDRRCAFENVVCVDH (SEQ ID NO: 24);

ACVPDRRCAFMNVCEDR (SEQ ID NO: 25);
ACVPDRRCAFQDVCDHE (SEQ ID NO: 26);
ACVPDRRCAFRDVCLTG (SEQ ID NO: 27);
ACYVGKECAYMNVCA (SEQ ID NO: 9);
ACQPSNHCAFMNYCA (SEQ ID NO: 28);
ACSPTPACAVQNLCA (SEQ ID NO: 29);
ACTSCWAYPDSFCA (SEQ ID NO: 30);
ACTKPTGFCAYPDTICA (SEQ ID NO: 31);
ACRGEWGYCAYPDTICA (SEQ ID NO: 32);
ACRNWGMYCAYPDTICA (SEQ ID NO: 33);
ACPDWGKYCAYPDTICA (SEQ ID NO: 34);
ACRVYGPYCAYPDTICA (SEQ ID NO: 35);
ACSSCWAYPDSVCA (SEQ ID NO: 36);
ACQSCWAYPDTYCA (SEQ ID NO: 37);
ACGFMGLEPCETFCA (SEQ ID NO: 38);
ACGFMGLVPCEVHCA (SEQ ID NO: 39);
ACGFMGLEPCCEMVCA (SEQ ID NO: 40);
ACGFMGLEPCVTYCA (SEQ ID NO: 41);
ACGFMGLEPCELVCA (SEQ ID NO: 42);
ACGFMGLVPCNVFCA (SEQ ID NO: 43);
ACGFMGLEPCELFCA (SEQ ID NO: 44);
ACGFMGLEPCELCMPK (SEQ ID NO: 45);
ACGFMGLEPCELYCA (SEQ ID NO: 46);
ACGFMGLEPCELYCAHT (SEQ ID NO: 47);
ACGFMGLEPCEMYCA (SEQ ID NO: 48);
ACGFMGLVPCELYCADN (SEQ ID NO: 49);
ACPLVNPLCLTSGWKCA (SEQ ID NO: 50);
ACPMVNPLCLHPGWICA (SEQ ID NO: 51);
ACPLVNPLCLHPGWICA (SEQ ID NO: 52);
ACPLVNPLCLHPGWICA (SEQ ID NO: 53);
ACPLVNPLCNLPGWTCA (SEQ ID NO: 54);
ACPLVNPLCLVPGWSCA (SEQ ID NO: 55);
ACPLVNPLCLLDGWTCA (SEQ ID NO: 56);
ACPLVNPLCLMPGWGCA (SEQ ID NO: 57);
ACPLVNPLCMIGNWTCA (SEQ ID NO: 58);
ACPLVNPLCLMTGWSCA (SEQ ID NO: 59);
ACPLVNPLCMMGGWKCA (SEQ ID NO: 60);

ACPLVNPLCLYGSWKCA (SEQ ID NO: 61);
 ACPLVNPLCLHPGWTCA (SEQ ID NO: 62);
 ARDCPLVNPLCLHPGWTCA (SEQ ID NO: 63);
 ((β -Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTC ((β -Ala)-Sar10-(SEQ ID NO: 11);
 Ac-ARDCPLVNPLCLHPGWTCA-Sar6-(D-K) (Ac-(SEQ ID NO: 63)-Sar6-(D-K));
 Ac-A(HArg)DCPLVNPLCLHPGWTCA- Sar6-(D-K) (Ac-(SEQ ID NO: 11)-A-Sar6-(D-K));
 RPACPLVNPLCLHPGWTCA (SEQ ID NO: 64);
 RPPCPLVNPLCLHPGWTCA (SEQ ID NO: 65);
 KHSCPLVNPLCLHPGWTCA (SEQ ID NO: 66);
 ACPLVNPLCLHPGWTCLHG (SEQ ID NO: 67);
 Ac-CPLVNPLCLHPGWTCLHG (Ac-(SEQ ID NO: 12));
 ((β -Ala)-Sar10-ACPLVNPLCLHPGWTCLHG ((β -Ala)-Sar10-(SEQ ID NO: 67));
 ((β -Ala)-Sar10-ACPLVNPLCLHPGWTCL(D-His)G ((β -Ala)-Sar10-(SEQ ID NO: 68));
 Ac-CPLVNPLCLHPGWTCLHG-Sar6-(D-K) (Ac-(SEQ ID NO: 12)-Sar6-(D-K));
 Ac-CPLVNPLCLHPGWTCL(D-His)G-Sar6-(D-K) (Ac-(SEQ ID NO: 13)- Sar6-(D-K));
 ACPLVNPLCLHPG(2NaI)TCLHG (SEQ ID NO: 69);
 RHDCPLVNPLCLLPGWTC (SEQ ID NO: 70);
 TPRCPLVNPLCLMPGWTC (SEQ ID NO: 71);
 ACPLVNPLCLAPGWTC (SEQ ID NO: 72);
 ACPLVNPLCLAPGWTCRS (SEQ ID NO: 73);
 ACPLVNPLCLEPGWTC (SEQ ID NO: 74);
 ACPLVNPLCLEPGWTCAR (SEQ ID NO: 75);
 ACPLVNPLCLHPGWSCA (SEQ ID NO: 76);
 ACPLVNPLCLHPGWSCRQ (SEQ ID NO: 77);
 Ac-CPLVNPLCLHPGWSCRQ (Ac-(SEQ ID NO: 14));
 ((β -Ala)-Sar10-ACPLVNPLCLHPGWSCRQ ((β -Ala)-Sar10-(SEQ ID NO: 77);
 ((β -Ala)-Sar10-ACPLVNPLCLHPGWSC(HArg)GQ ((β -Ala)-Sar10-(SEQ ID NO: 78));
 Ac-CPLVNPLCLHPGWSCRQ-Sar6-(D-K) (Ac-(SEQ ID NO: 14)-Sar6-(D-K));
 Ac-CPLVNPLCLHPGWSC(HArg)GQ-Sar6-(D-K) (Ac-(SEQ ID NO: 15) -Sar6-(D-K));
 ACPLVNPLCLHPG(2NaI)SCRQ (SEQ ID NO: 79);
 ACPLVNPLCLTPGWTCTNT (SEQ ID NO: 80);
 ACPMVNPLCLHPGWKCA (SEQ ID NO: 81);
 ACPMVNPLCLTPGWICA (SEQ ID NO: 82);
 ACPMVNPLCLHPGWTC (SEQ ID NO: 83);
 ((β -Ala)-Sar10-H(D-Asp)VT-C(Aib)(1NaI)G(Aib)F(1NaI)CP(tBuGly)N(HArg)P(D-Asp)C
 ((β -Ala)-Sar10-(SEQ ID NO: 84));

((β-Ala)-Sar10-A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)W(HArg)C ((β-Ala)-Sar10-(SEQ ID NO: 85));
 ((β-Ala)-Sar10-A(HArg)DC(HyP)(Hse(Me))VNPLCLHP(D-Asp)WTC ((β-Ala)-Sar10-(SEQ ID NO: 86));
 ((β-Ala)-Sar10-A(HArg)DC(HyP)LVNPLCLHP(D-Ala)WTC ((β-Ala)-Sar10-(SEQ ID NO: 87));
 ((β-Ala)-Sar10-A(HArg)DCPLVNPLCLHP(D-Ala)WTC ((β-Ala)-Sar10-(SEQ ID NO: 88));
 ((β-Ala)-Sar10-ARDC(HyP)LVNPLCLHPGWTC ((β-Ala)-Sar10-(SEQ ID NO: 89));
 ((β-Ala)-Sar10-ARDCPLVNPLCL(D-3,3-DPA)PGWTC ((β-Ala)-Sar10-(SEQ ID NO: 90));
 ((β-Ala)-Sar10-ARDCPLVNPLCLHPGWTCCLH ((β-Ala)-Sar10-(SEQ ID NO: 91))
 Ac-(SEQ ID NO: 12)-Sar6-(D-K[Ac]);
 ((β-AlaSO₃H)-Sar4-(Cya)-Sar4-(Cya)-A(HArg)DCPLVNPLCLHP(D-Cya)WTC ((β-AlaSO₃H)-Sar4-(Cya)-Sar4-(Cya)-(SEQ ID NO: 92));
 ((β-Ala)-Sar10-ARDCPLVNPLCLHPGWTC ((β-Ala)-Sar10-(SEQ ID NO: 10));
 A(HArg)DCPLVNPLCLHPGWTC (SEQ ID NO: 11);
 ((β-Ala)-Sar5-(SEQ ID NO: 11);
 ((β-AlaSO₃H)-Sar10-(SEQ ID NO: 11);
 ((β-Ala)-Sar10-A(D-Arg)DC(HyP)LVNPLCL(D-3,3-DPA)P(D-Asp)W(HArg)C ((β-Ala)-Sar10-(SEQ ID NO: 93)); and
 ((β-AlaSO₃H)-Sar5-(SEQ ID NO: 11);

or a pharmaceutically acceptable salt thereof.

5. The peptide ligand as defined in any one of claims 1 to 3, wherein said peptide ligand is ((β-Ala)-Sar10-A(HArg)DCPLVNPLCLHPGWTC ((β-Ala)-Sar10-(SEQ ID NO: 11) or a pharmaceutically acceptable salt thereof.
6. The peptide ligand as defined in any one of claims 1 to 5, wherein the pharmaceutically acceptable salt is selected from a free acid or a sodium, potassium, calcium, ammonium salt.
7. The peptide ligand as defined in any one of claims 1 to 6, wherein the EphA2 is human EphA2.
8. A drug conjugate comprising a peptide ligand as defined in any one of claims 1 to 7, conjugated to one or more effector and/or functional groups.

9. The drug conjugate as defined in claim 8, wherein said functional group is a cytotoxic agent selected from DM1 or monomethyl auristatin E (MMAE).

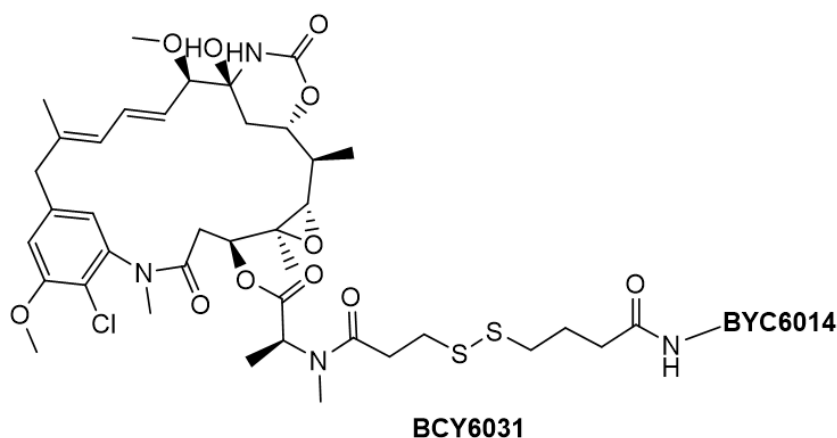
10. The drug conjugate as defined in claim 9, which additionally comprises a linker between said peptide ligand and said cytotoxic agent.

11. The drug conjugate as defined in claim 10, wherein said cytotoxic agent is MMAE and the linker is selected from: -Val-Cit-, -Trp-Cit-, -Val-Lys-, -D-Trp-Cit-, -Ala-Ala-Asn-, D-Ala-Phe-Lys- or -Glu-Pro-Cit-Gly-hPhe-Tyr-Leu- (SEQ ID NO: 98).

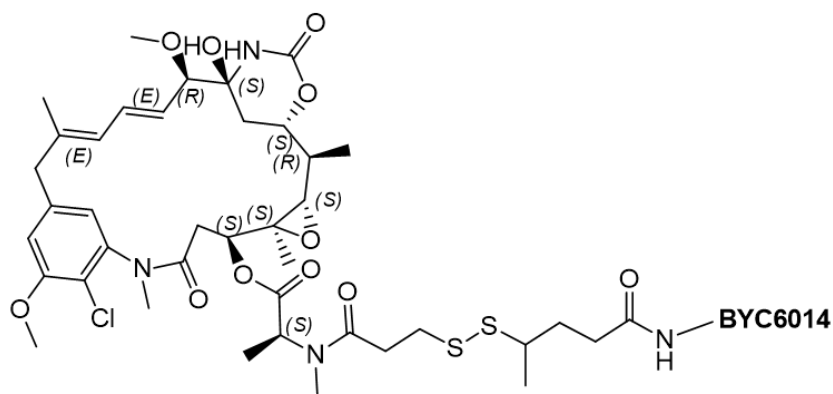
12. The drug conjugate as defined in claim 11, wherein said cytotoxic agent is MMAE and the linker is -Val-Cit-.

13. The drug conjugate as defined in claim 10, wherein said cytotoxic agent is DM1 and the linker is selected from: -S-S-, -SS(SO₃H)-, -SS-(Me)-, -(Me)-SS-(Me)-, -SS-(Me₂)- or -SS-(Me)-SO₃H-.

14. The drug conjugate as defined in any one of claims 8 to 13, which is selected from any one of BCY6031:



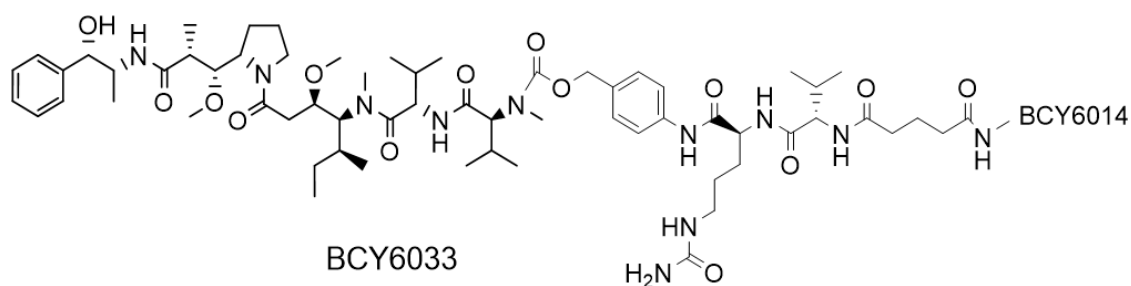
and BCY6032:



BCY6032

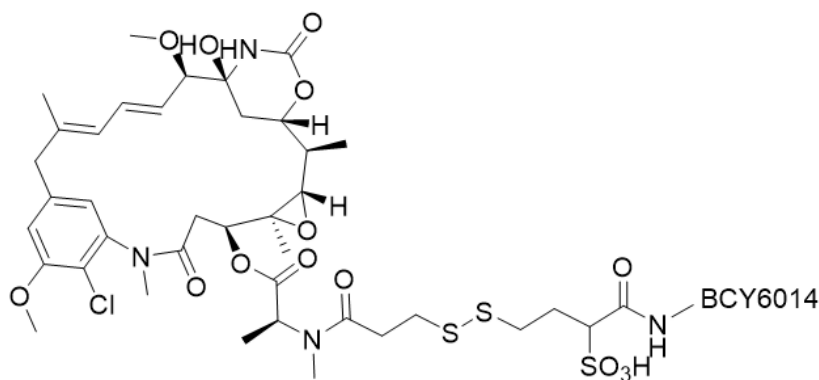
the Bicycle drug conjugates (BDCs) listed in Tables 11 or 13; or

BCY6033:



BCY6033

and BCY6082:



BCY6082

wherein BCY6014 is $(\beta\text{-Ala})\text{-Sar}_{10}\text{-A(HArg)D-C}_i\text{PLVNPLC}_{ii}\text{LHPGWTC}_{iii}$ ($(\beta\text{-Ala})\text{-Sar}_{10}\text{-(SEQ ID NO: 11)}$).

15. The drug conjugate as defined in claim 14, which is selected from any one of: BCY6031, BCY6033, and BCY6082.

16. A pharmaceutical composition which comprises the peptide ligand of any one of claims 1 to 7 or the drug conjugate of any one of claims 8 to 15, in combination with one or more pharmaceutically acceptable excipients.
17. The drug conjugate as defined in any one of claims 8 to 15, for use in suppressing or treating a disease or disorder characterised by overexpression of EphA2 in diseased tissue.
18. The drug conjugate as defined in any one of claims 8 to 15, for use in suppressing or treating cancer.
19. The drug conjugate for use as defined in claim 18, wherein the cancer is selected from: prostate cancer, lung cancer (such as non-small cell lung carcinomas (NSCLC)), breast cancer (such as triple negative breast cancer), gastric cancer, ovarian cancer, oesophageal cancer, multiple myeloma and fibrosarcoma.
20. Use of a drug conjugate as defined in any one of claims 8 to 15 in the manufacture of a medicament for suppressing or treating cancer in a patient in need thereof, wherein said patient is identified as having an increased copy number variation (CNV) of EphA2.