CLAIMS

1. A bispecific adapter or a pharmaceutically acceptable salt or hydrate thereof comprising a fluorescein, fluorescein isothiocyanate (FITC), or N-hydroxysuccinimide (NHS)-fluorescein conjugated to a radical of a carbonic anhydrase IX (CAIX) ligand via a linker, wherein the linker comprises, consists essentially of, or consists of polyethylene glycol (PEG).

2. The bispecific adapter of claim 1, wherein the CAIX ligand is or comprises 3-((3-(cyclooctylamino)-2,5,6-trifluoro-4-sulfamoylphenyl)thio)propanoic acid (*ortho*-CAL), 3-((2-(cyclooctylamino)-3,5,6-trifluoro-4-sulfamoylphenyl) sulfonyl) propanoic acid (*meta*-CAL), acetazolamide (Aza), or a derivative or analog of any of the foregoing.

3. The bispecific adapter of claim 1, wherein the linker comprises, consists essentially of, or consists of:

PEG_1 to PEG_9;

PEG_3 to PEG_9;

an alkyl; or

$(CH_2)_4$.

4. The bispecific adapter of claim 1, wherein the CAIX ligand is or comprises:

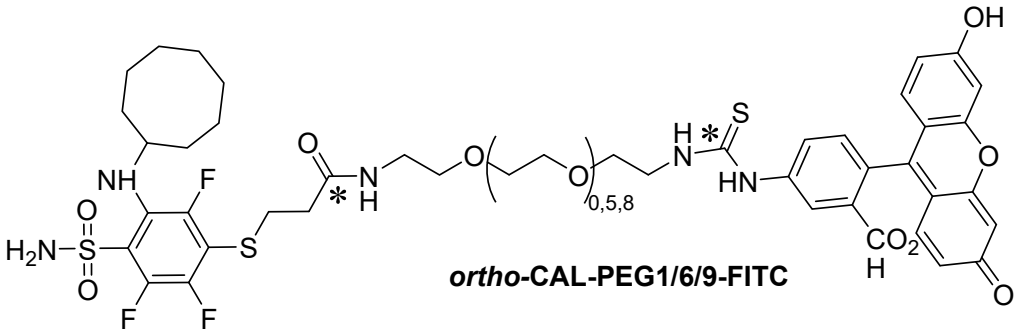
ortho-CAL or a derivative or analog thereof and the linker comprises, consists essentially of, or consists of PEG_1 to PEG_9; or

meta-CAL or a derivative or analog thereof and the linker comprises, consists essentially of, or consists of PEG_3 to PEG_9; or

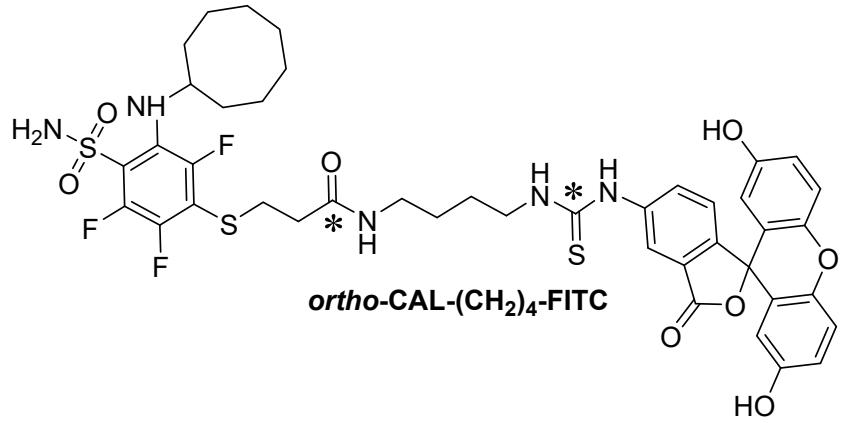
Aza or a derivative or analog thereof.

5. The bispecific adapter of claim 4, wherein the linker comprises, consists essentially of, or consists of PEG_6 or PEG_9.

6. The bispecific adapter of claim 1, comprising a structure of one of the following formulae:

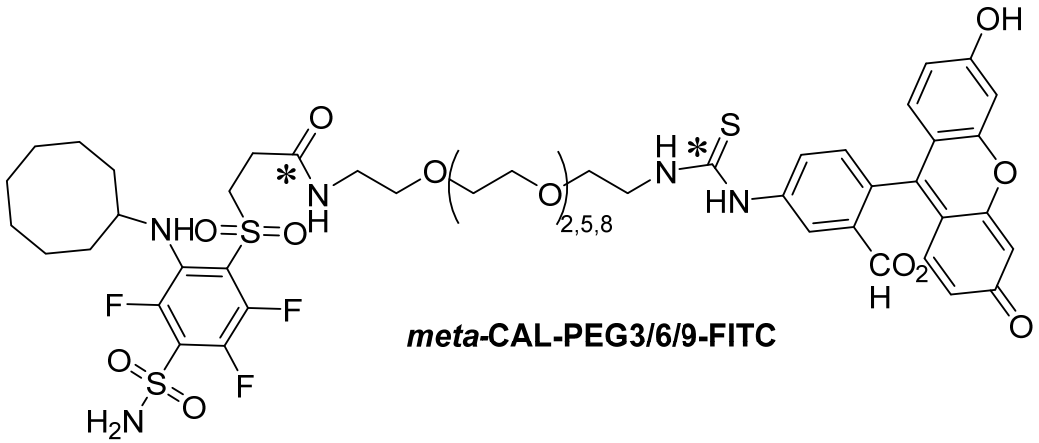


***ortho*-CAL-PEG1/6/9-FITC**



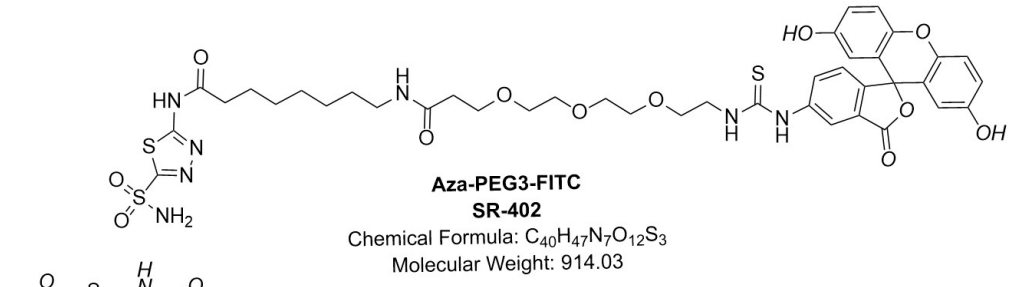
***ortho*-CAL-$(CH_2)_4$-FITC**

,

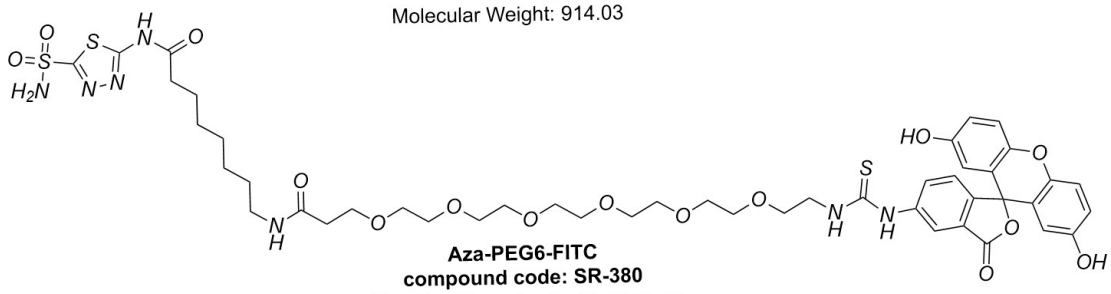


***meta*-CAL-PEG3/6/9-FITC**

,

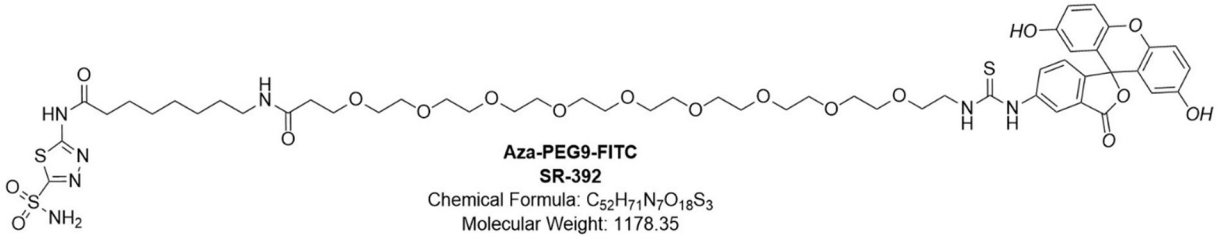


Aza-PEG3-FITC
SR-402
Chemical Formula: $C_{40}H_{47}N_7O_{12}S_3$
Molecular Weight: 914.03



Aza-PEG6-FITC
compound code: SR-380
Chemical Formula: $C_{46}H_{59}N_7O_{15}S_3$
Molecular Weight: 1046.19

or



Aza-PEG9-FITC
SR-392
Chemical Formula: $C_{52}H_{71}N_7O_{18}S_3$
Molecular Weight: 1178.35

,

or a pharmaceutically acceptable salt or hydrate of any of the foregoing.

7. The bispecific adapter of any one of claims 11-6 for use with an anti-fluorescein chimeric antigen receptor (CAR)-T cell in the treatment of cancer and, optionally, a CAIX-expressing cancer.

8. A pharmaceutical composition for the treatment of a CAIX-expressing cancer comprising the bispecific adapter of any one of claims 1-6 and a pharmaceutically acceptable carrier or excipient.

9. A kit comprising:

(i) at least one dosage unit of a bispecific adapter of any one of claims 1-7 or a pharmaceutical composition of claim 8; and

(ii) at least one dosage unit of anti-fluorescein chimeric antigen receptor (CAR)-T cells or a pharmaceutical composition comprising anti-fluorescein CAR-T cells and a pharmaceutically acceptable carrier or excipient;

wherein (i) and (ii) are optionally in separate containers.

10. The kit of claim 9, wherein the CAIX ligand of the bispecific adapter is or comprises:

3-((3-(cyclooctylamino)-2,5,6-trifluoro-4-sulfamoylphenyl)thio)propanoic acid (*ortho*-CAL) or a derivative or analog thereof;

3-((2-(cyclooctylamino)-3,5,6-trifluoro-4-sulfamoylphenyl) sulfonyl) propanoic acid (*meta*-CAL) or a derivative or analog thereof; or

acetazolamide (Aza) or a derivative or analog thereof.

11. Use of:

(i) anti-fluorescein chimeric antigen receptor (CAR)-T cells or a pharmaceutical composition comprising anti-fluorescein CAR-T cells and a pharmaceutically acceptable carrier or excipient in the preparation of a first medicament; and

(ii) a bispecific adapter of any one of claims 1-7 or a pharmaceutical composition of claim 8 in the preparation of a second medicament;

wherein the first and second medicaments are, in combination, for use in the treatment of cancer in a subject.

12. The use of claim 11, wherein the CAR comprises:

a recognition region comprising a single chain fragment variable (scFv) region of an anti-fluorescein antibody;

a co-stimulation domain, which is CD28, CD137 (4-1BB), CD134 (OX40), or CD278 (ICOS); and/or

an activation signaling domain, which is a T cell CD3ζ chain or an Fc receptor γ.

13. The use of claim 11, wherein the fluorescein of the bispecific adapter binds the anti-fluorescein CAR-T cell with affinity upon exposure thereto, and the CAIX ligand of the

bispecific adapter links the bound anti-fluorescein CAR-T cell to a CAIX-expressing cancer cell upon the bispecific adapter binding a receptor on such CAIX-expressing cancer cell with affinity.

14. The use of claim 11, wherein the first medicament of (i) and the second medicament of (ii) are each formulated for administration to the subject simultaneously or sequentially, in either order, by the same or different routes.

15. The use of any one of claims 11-14, wherein the first medicament of (i) and the second medicament of (ii) are each formulated for intravenous administration.

16. The use of any one of claims 11-15, wherein the cancer is a CAIX-expressing cancer and, optionally, ovarian cancer, endometrial cancer, breast cancer, lung cancer, bladder cancer, or clear cell renal cell carcinoma such as, optionally, stage 3-4 clear cell renal cell carcinoma.

17. Use of:

(i) a bispecific adapter of any one of claims 1-7 or a pharmaceutical composition of claim 8 in the preparation of a first medicament for use in combination with the use of

(ii) anti-fluorescein chimeric antigen receptor (CAR-T) cells or a pharmaceutical composition comprising anti-fluorescein CAR-T cells and a pharmaceutically acceptable carrier or excipient to the bispecific adaptor or pharmaceutical composition;

wherein the CAR-T cell are exposed to (i) to enhance activation of the CAR-T cells as compared to CAR-T cells not exposed to (i).

18. The use of claim 17, wherein the anti-fluorescein CAR-T cells are in systemic circulation in a subject when exposed to (i).

19. The use of claim 17, wherein the cancer cells are CAIX-expressing cancer cells.