CLAIMS

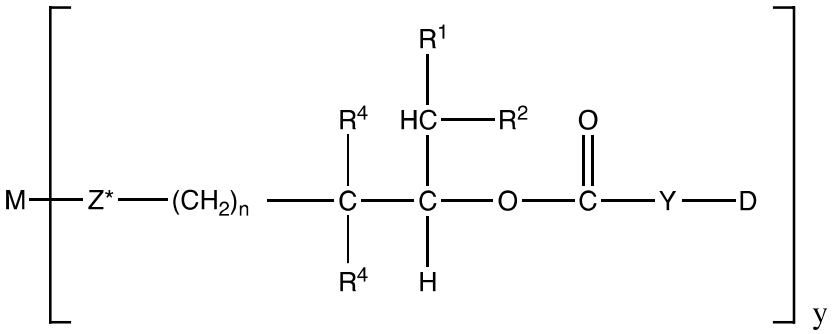
1. A conjugate having the formula

$M\text{-}(Z^*\text{-}L\text{-}D)_y$

wherein M is a macromolecular carrier;
y is a number describing the number of linker-drugs L-D attached to M;
Z* is a connecting group;
L is a releasable linker; and
D is an inhibitor of the DNA damage response.

~~2. The conjugate of Claim 1 wherein D is a PARP inhibitor, ATM inhibitor, or ATR inhibitor.~~

~~3~~2. The conjugate of Claim 1 ~~or 2~~ having the formula



wherein Z* is a connecting group;
n = 0-6;
R^1 and R^2 are each independently H, CN, or SO_2R^5, wherein at least one of R^1 and R^2 is other than H;

wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each R^6 is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each R^4 is independently H or C_1-C_3 alkyl or both R^4 are taken together form a 3-6 member ring; and

Y is either absent or has the formula $N(R^7)CH_2$,

wherein R^7 is optionally substituted C_1-C_4 alkyl or optionally substituted aryl~~; and wherein at least one of R^1 and R^2 is other than H~~.

3. The conjugate of Claim 1 or 2 wherein D is a PARP inhibitor, ATM inhibitor, or ATR inhibitor.

4. The conjugate of Claim ~~3~~2 wherein Y is absent and D is connected ~~to linker L through a carbamate linkage to~~ a primary or secondary amine nitrogen atom of D.

5. The conjugate of any one of Claims 1-4 wherein D is rucaparib, veliparib, niraparib, or berzosertib.

6. The conjugate of Claim~~s 1-3~~ 2 wherein Y has the formula $N(R^7)CH_2$ and D is connected ~~to linker L through an alkyl linkage to~~ a non-basic nitrogen atom of D.

7. The conjugate of Claim 6 wherein D is talazoparib, olaparib, tamiparib, E7016, or CEP-9722.

8. The conjugate of any one of Claims 1-7 wherein M is a PEG of molecular weight between 1,000 and 100,000 Daltons, and y = 1-8.

9. The conjugate of any one of Claims 1-8 wherein M has a hydrodynamic radius between 5 and 50 nm.

10. The conjugate of any one of Claims 1-7 wherein M is an insoluble macromolecular carrier.

11. The conjugate of any one of Claims 1-10 wherein Z* is a carboxamide, carbamate, urea, oxime, thioether, or 1,2,3-triazole.

12. The conjugate of any one of Claims ~~3~~2-10 wherein R^1 and R^2 are selected to provide a half-life for D release between 100-1000 hours at a pH of 7.4 and a temperature of 37 ^oC.

13. The conjugate of claim 2, wherein Z* is a triazole, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, y is 4, and D is talazoparib.

14. The conjugate of claim 2, wherein Z* is a triazole, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, y is 4, and D is olaparib.

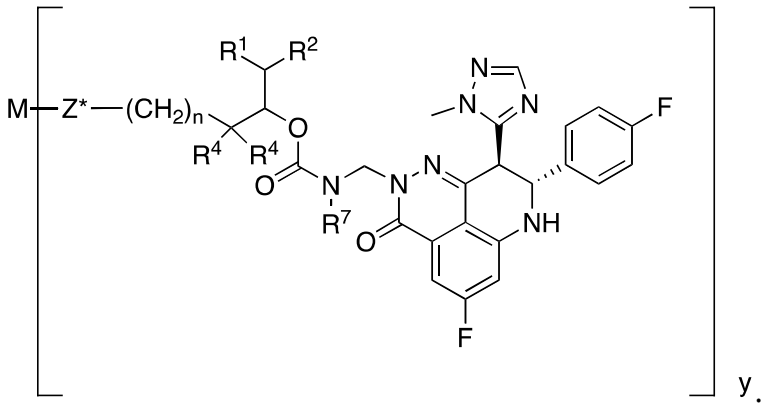
15. The conjugate of claim 13 or 14, wherein M is 40 kDa PEG.

16. The conjugate of claim 2, wherein Z* is a triazole, n is 2, R^1 is $MeSO_2$, R^2 is H, each R^4 is Me, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, y is 1, and D is talazoparib.

17. The conjugate of claim 2, wherein Z* is a triazole, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is absent, R^7 is methyl, y is 1, and D is rucaparib

18. The conjugate of claim 16 or 17, wherein M is 20 kDa PEG.

~~13~~19. The conjugate of Claim 1 having the formula



wherein M is a macromolecular carrier;

n = 0-6;

Z* is a connecting group;

R^1 and R^2 are each independently H, CN, or SO_2R^5, wherein at least one of R^1 and R^2 is other than H,

wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each R^6 is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each R^4 is independently H or C_1-C_3 alkyl or <u>both R^4 are</u> taken together form a 3-6 member ring;

R^7 is optionally substituted C_1-C_3 alkyl or optionally substituted aryl; and

y = 1 to 8~~; and wherein at least one of R^1 and R^2 is other than H~~.

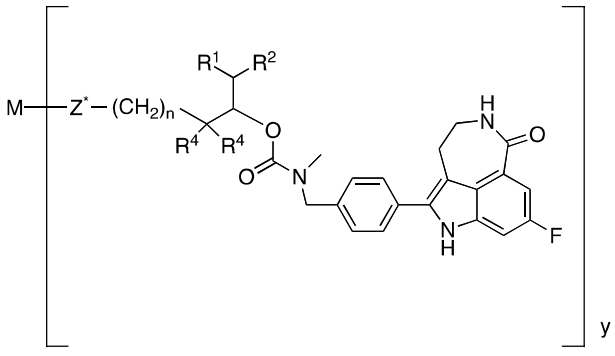
~~14~~<u>20</u>. The conjugate of Claim ~~13~~<u>19</u> wherein M is a 40-kDa 4-armed PEG and y = 4.

~~15~~<u>21</u>. The conjugate of Claim ~~13~~<u>19</u> or ~~14~~<u>20</u> wherein Z* is carboxamide, carbamate, oxime, thioether, or triazole.

<u>22. The conjugate of claim 19, wherein Z* is a triazole, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, R^7 is 2-methoxyethyl, and y is 4.</u>

<u>23. The conjugate of claim 19, wherein Z* is a triazole, n is 2, R^1 is $MeSO_2$, R^2 is H, each R^4 is Me, and R^7 is 2-methoxyethyl, and y is 1.</u>

~~16~~<u>24</u>. The conjugate of Claim 1 having the formula



wherein M is a macromolecular carrier;

n = 0-6;

Z* is a connecting group;

R^1 and R^2 are each independently H, CN, or SO_2R^5, <u>wherein at least one of R^1 and R^2 is other than H,</u>

wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each R^6 is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

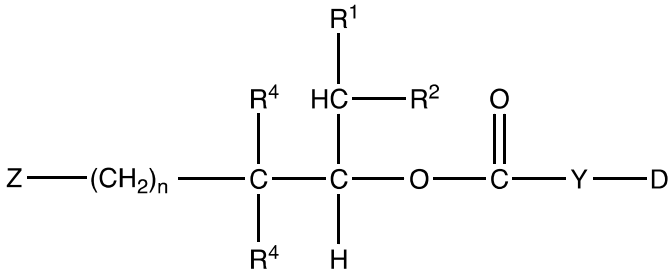
each R^4 is independently H or C_1-C_3 alkyl or both R^4 are taken together form a 3-6 member ring; and

y = 1 to 8~~; and wherein at least one of R^1 and R^2 is other than H~~.

~~17~~25. The conjugate of Claim ~~16~~24 wherein M is a 40-kDa 4-armed PEG and y = 4.

26. The conjugate of any one of Claims 1-25, wherein Z* is a triazole resulting from the cycloaddition of an azide with a cyclooctyne selected from an azadibenzocyclooctyne (DBCO), a bicyclo[6.1.0]non-4-yne (BCN), or 5-hydroxycyclooctyne (5HCO).

~~18~~27. A linker-drug of the formula



wherein Z is a ~~connecting group~~ functional group allowing for conjugation to a macromolecular carrier;

n = 0-6;

R^1 and R^2 are each independently H, CN, or SO_2R^5, wherein at least one of R^1 and R^2 is other than H,

wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or $N(R^6)_2$,

wherein each R^6 is independently optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein $N(R^6)_2$ forms a ring of 4-8 atoms;

each R^4 is independently H or C_1-C_3 alkyl or taken together form a 3-6 member ring;

Y is either absent or has the formula $N(R^7)CH_2$, wherein R^7 is optionally substituted C_1-C_4 alkyl or optionally substituted aryl; and

D is an inhibitor of DNA damage response~~; and wherein at least one of R^1 and R^2 is other than H~~.

28. The linker-drug of claim 27, wherein:

a) Z is azide, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, and D is talazoparib;

b) Z is azide, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, and D is olaparib;

c) Z is azide, n is 4, R^1 is $MeSO_2$, R^2 is H, each R^4 is H, Y is $N(R^7)CH_2$, R^7 is 4-(N,N-diethylcarboxamido)phenyl, and D is talazoparib; or

d) Z is azide, n is 2, R^1 is thiomorpholine-SO_2, R^2 is H, each R^4 is Me, Y is $N(R^7)CH_2$, R^7 is 2-methoxyethyl, and D is talazoparib.

~~19~~29. Use of a conjugate of any one of Claims 1-~~17~~26 for the manufacture of a medicament for treating ~~in the treatment of~~ cancer.

30. A conjugate of any one of claims 1-26 for use in therapy.

~~20~~31. A method of preparing a conjugated inhibitor of DNA damage response, said method comprising the step of contacting a linker-drug of Claim ~~18~~27 or 28 with an activated macromolecular carrier comprising a cognate functional group Z' capable of reacting with functional group Z under conditions such that connecting group Z* is formed, and optionally isolating the conjugate.