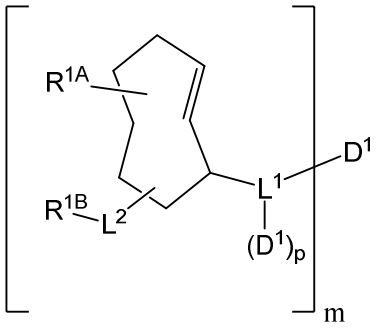
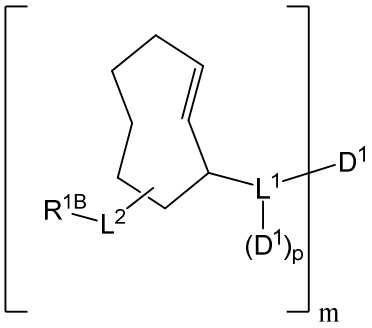
CLAIMS

1. A pharmaceutical combination for use in the treatment or prevention of a disease or disordercomprising one or more of cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration, rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, or pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response, the combination comprising:

(a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof;



(II-A)



(III-A)

wherein

R^{1A}, at each occurrence, is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B}, at each occurrence, is independently selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or C_{1-4}alkyl;

R^{1e}, at each occurrence, is independently $–C_{1-4}$alkylene$–CO_2H$, $–C_{1-4}$alkylene$–CONH_2$, or $–C_{1-4}$alkylene–OH;

R^{1f}, at each occurrence, is independently hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1, at each occurrence, is independently a linker;

L^2, at each occurrence, is independently selected from the group consisting of –C(O)– and C_{1-3}alkylene;

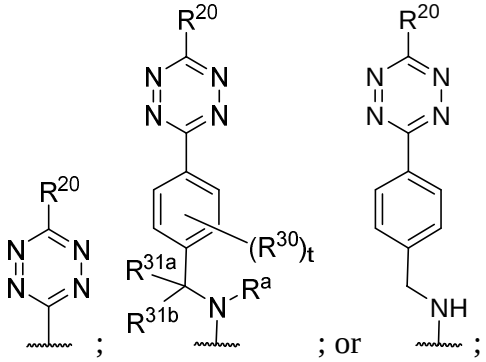
G^1, at each occurrence, is independently an optionally substituted heterocyclyl;

m is 1, 2, or 3

n, at each occurrence, is independently 0, 1, 2, or 3; and

p, at each occurrence, is independently 0, 1, or 2;

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

wherein the tetrazine-containing group is linked or directly bonded to the support;

and

(c) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

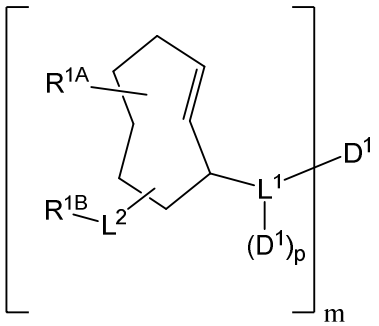
2. The combination of claim 1 for use in enhancing or eliciting an immune response.

3. The combination of claim 1 for use in the treatment or prevention of cancer.

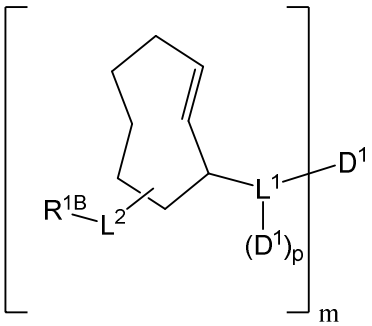
4. The combination of any of claims 1-3, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

5. Use of a pharmaceutical combination in the manufacture of a medicament for the treatment or prevention of a disease or disorder comprising one or more of cancer, infections, tissue injury, stenosis, ischemia, re-vascularization, myocardial infarction, arrhythmias, vascular occlusion, inflammation, autoimmune disorders, transplant rejection, macular degeneration, rheumatoid arthritis, osteoarthritis, peri-prosthetic infections, or pigmented villonodular synovitis; or for use in enhancing or eliciting an immune response, the combination comprising:

(a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt, or composition thereof;



(II-A)



(III-A)

wherein

R^{1A}, at each occurrence, is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B}, at each occurrence, is independently selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–$

$CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1\text{-}6}$alkyl, $–N(R^{1c})–C_{1\text{-}6}$alkylene–$C(O)OC_{1\text{-}6}$alkyl, and $–N(R^{1f})–C_{2\text{-}4}$alkylene–$(N(C_{1\text{-}4}$alkylene–$C(O)OC_{1\text{-}6}$alkyl)–$C_{2\text{-}4}$alkylene$)_n–N(C_{1\text{-}4}$alkylene–$C(O)OC_{1\text{-}6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or $C_{1\text{-}4}$alkyl;

R^{1e}, at each occurrence, is independently $–C_{1\text{-}4}$alkylene–CO_2H, $–C_{1\text{-}4}$alkylene–$CONH_2$, or $–C_{1\text{-}4}$alkylene–OH;

R^{1f}, at each occurrence, is independently hydrogen, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}4}$alkylene–CO_2H;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1, at each occurrence, is independently a linker;

L^2, at each occurrence, is independently selected from the group consisting of –C(O)– and $C_{1\text{-}3}$alkylene;

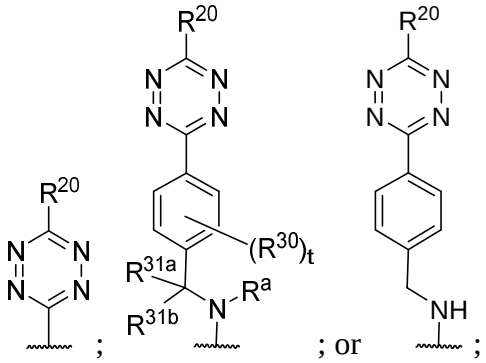
G^1, at each occurrence, is independently an optionally substituted heterocyclyl;

m is 1, 2, or 3

n, at each occurrence, is independently 0, 1, 2, or 3; and

p, at each occurrence, is independently 0, 1, or 2;

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'",

SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R"' at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^{a}, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

wherein the tetrazine-containing group is linked or directly bonded to the support;

and

(c) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

6. The use of claim 5 for enhancing or eliciting an immune response.

7. The use of claim 5 for the treatment or prevention of cancer.

8. The use of any of claims 5-7, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

9. A kit comprising:

a) the compound of formula (II-A) or (III-A), as defined in claim 1, or a pharmaceutically acceptable salt or composition thereof;

b) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof; and

c) instructions for use.

10. A kit comprising:

a) the therapeutic support composition, as defined in claim 1;

b) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof; and

c) instructions for use.

11. A pharmaceutical composition comprising:

a) the compound of formula (II-A) or (III-A), as defined in claim 1, or a pharmaceutically acceptable salt thereof;

b) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt thereof; and

c) a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising:

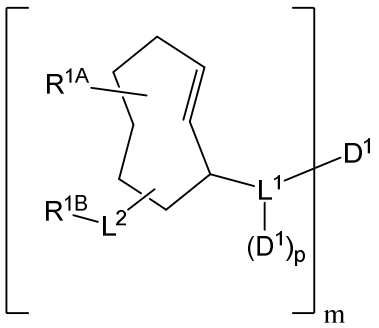
a) the therapeutic support composition, as defined in claim 1;

b) one or more immunomodulatory agents selected from a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt thereof; and

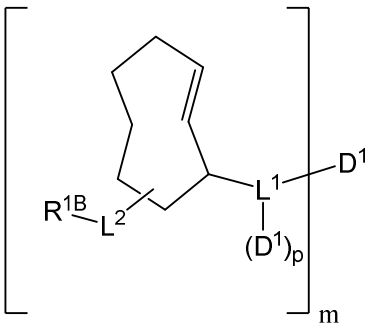
c) a pharmaceutically acceptable carrier.

13. A pharmaceutical combination for use in inhibiting growth of a secondary tumor, or enhancing or eliciting an immune response against a secondary tumor, the combination comprising:

a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof,



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or C_{1-4}alkyl;

R^{1e} is $–C_{1-4}$alkylene$–CO_2H$, $–C_{1-4}$alkylene$–CONH_2$, or $–C_{1-4}$alkylene$–OH$;

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

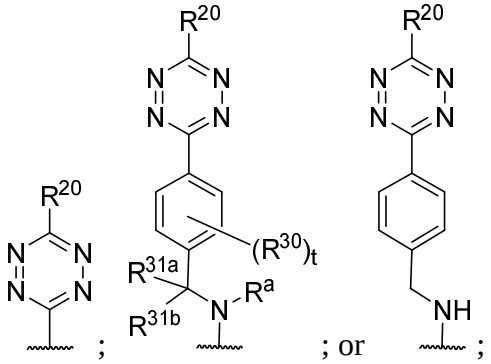
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2; and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

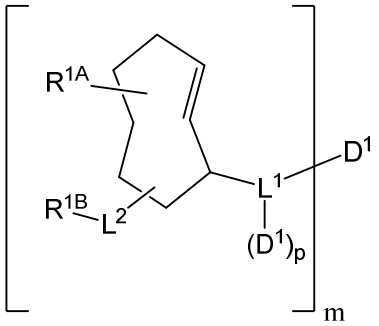
wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R",

NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R"' at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^{a}, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

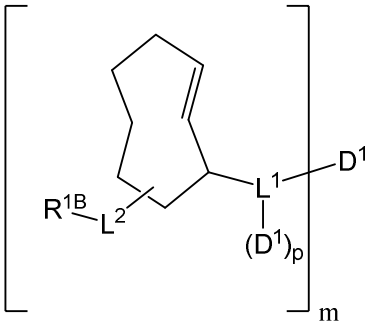
wherein the tetrazine-containing group is linked or directly bonded to the support.

14. Use of a pharmaceutical combination in the manufacture of a medicament for inhibiting growth of a secondary tumor, or enhancing or eliciting an immune response against a secondary tumor, the combination comprising:

a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof,



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or C_{1-4}alkyl;

R^{1e} is $–C_{1-4}$alkylene$–CO_2H$, $–C_{1-4}$alkylene$–CONH_2$, or $–C_{1-4}$alkylene$–OH$;

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene–CO_2H;

D^1, at each occurrence, is independently a payload;

–L^1– is a linker;

–L^2– is selected from the group consisting of –C(O)– and C_{1-3}alkylene;

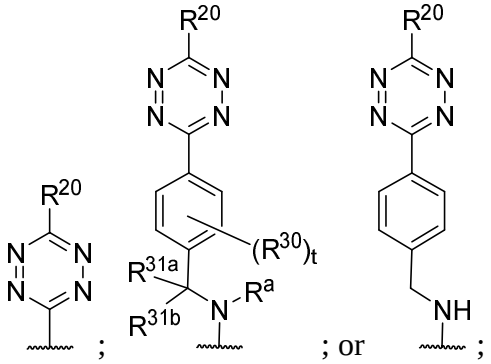
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2; and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



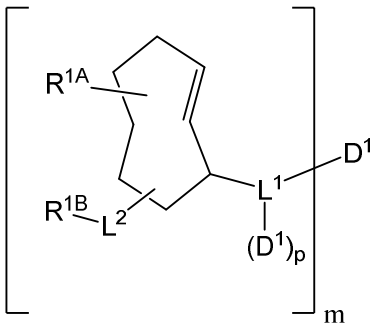
; ; or ;

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

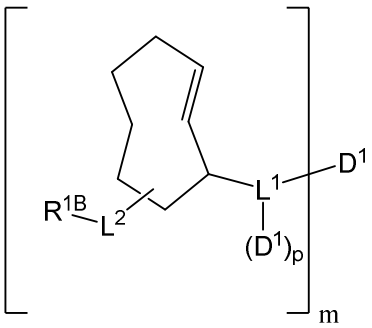
wherein the tetrazine-containing group is linked or directly bonded to the support.

15. A pharmaceutical combination for use in inhibiting tumor metastasis in a subject at risk of tumor metastasis, the combination comprising

a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof;



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or C_{1-4}alkyl;

R^{1e} is $–C_{1-4}$alkylene$–CO_2H$, $–C_{1-4}$alkylene$–CONH_2$, or $–C_{1-4}$alkylene$–OH$;

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

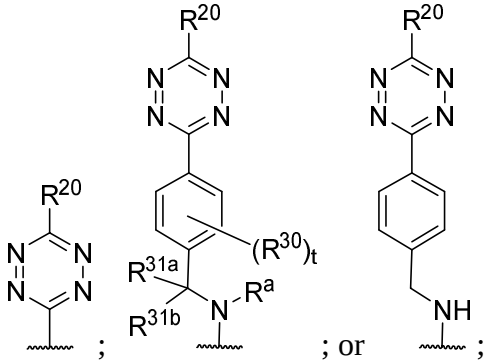
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2;and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

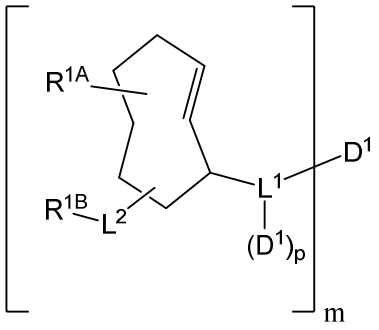
wherein the tetrazine-containing group is linked or directly bonded to the support.

16. The combination of claim 15, further comprising one or more immunomodulatory agents.

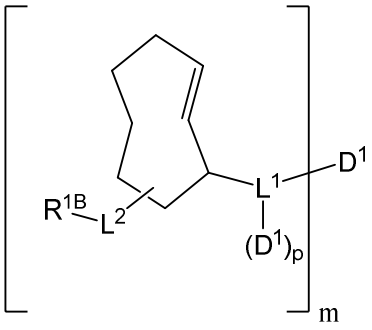
17. The combination of claim 16, wherein the one or more immunomodulatory agents is one or more of an immune checkpoint inhibitor, a toll-like receptor (TLR) agonist, a stimulator of interferon genes (STING) agonist, a cytokine, a cytokine inhibitor, a cytokine receptor agonist, a cytokine receptor antagonist, a chemokine, a chemokine inhibitor, a chemokine receptor agonist, or a chemokine receptor antagonist.

18. Use of a pharmaceutical combination in the manufacture of a medicament for inhibiting tumor metastasis, the combination comprising

a) a compound of formula (II-A) or (III-A), or a pharmaceutically acceptable salt thereof;



(II-A)



(III-A)

wherein

R^{1A} is selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}alkoxy;

R^{1B} is selected from the group consisting of G^1, OH, $–NR^{1c}–C_{1-4}$alkylene$–G^1$, $–NR^{1c}–C_{1-4}$alkylene$–N(R^{1d})_2$, $–N(R^{1c})CHR^{1e}CO_2H$, $–N(R^{1c})–C_{1-6}$alkylene$–CO_2H$, $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–CO_2H)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–CO_2H)_2$, $–N(R^{1c})CHR^{1e}C(O)OC_{1-6}$alkyl, $–N(R^{1c})–C_{1-6}$alkylene$–C(O)OC_{1-6}$alkyl, and $–N(R^{1f})–C_{2-4}$alkylene$–(N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)–C_{2-4}$alkylene$)_n–N(C_{1-4}$alkylene$–C(O)OC_{1-6}$alkyl$)_2$;

R^{1c} and R^{1d}, at each occurrence, are independently hydrogen or C_{1-4}alkyl;

R^{1e} is $–C_{1-4}$alkylene$–CO_2H$, $–C_{1-4}$alkylene$–CONH_2$, or $–C_{1-4}$alkylene$–OH$;

R^{1f} is hydrogen, C_{1-6}alkyl, or C_{1-4}alkylene$–CO_2H$;

D^1, at each occurrence, is independently a payload;

$–L^1–$ is a linker;

$–L^2–$ is selected from the group consisting of $–C(O)–$ and C_{1-3}alkylene;

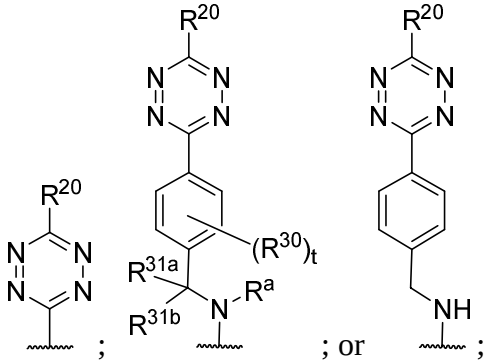
G^1 is an optionally substituted heterocyclyl;

m is 1, 2, or 3

n is 0, 1, 2, or 3; and

p is 0, 1, or 2;and

b) a therapeutic support composition comprising a support and a tetrazine-containing group of formula



; ; or ;

wherein R^{20} is selected from the group consisting of hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, CF_3, CF_2-R', NO_2, OR', SR', C(=O)R', C(=S)R', OC(=O)R'", SC(=O)R'", OC(=S)R'", SC(=S)R'", S(=O)R', $S(=O)_2$R'", $S(=O)_2$NR' R", C(=O)O-R', C(=O)S-R', C(=S)O-R', C(=S)S-R', C(=O)NR'R", C(=S)NR' R", NR'R", NR'C(=O)R", NR'C(=S)R", NR'C(=O)OR", NR'C(=S)OR", NR'C(=O)SR", NR'C(=S)SR", OC(=O)NR'R", SC(=O)NR'R", OC(=S) R'R'", SC(=S)R'R", NR'C(=O)NR"R", and NR'C(=S)NR"R"; R' and R" at each occurrence are independently selected from hydrogen, aryl and alkyl; and R'" at each occurrence is independently selected from aryl and alkyl; R^{30} is halogen, cyano, nitro, hydroxy, alkyl, haloalkyl; alkenyl, alkynyl, alkoxy; halalkoxy; heteroalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl; R^a, R^{31a} and R^{31b} are each independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; and t is 0, 1, 2, 3, or 4;

wherein the tetrazine-containing group is linked or directly bonded to the support.

19. The use of claim 18, wherein the combination further comprises one or more immunomodulatory agents.

20. The use of claim 19, wherein the one or more immunomodulatory agents is one or more of an immune checkpoint inhibitor, a toll-like receptor (TLR) agonist, a stimulator of interferon genes (STING) agonist, a cytokine, a cytokine inhibitor, a cytokine receptor agonist, a cytokine receptor antagonist, a chemokine, a chemokine inhibitor, a chemokine receptor agonist, or a chemokine receptor antagonist.