CLAIMS

1. A method for preparation of a medicament for the treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising the administration of a therapeutically effective quantity of a hexitol derivative selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, and a derivative or analog of diacetyldianhydrogalactitol.

2. The method of claim 1 wherein the malignancy is recurrent glioma.

3. The method of claim 2 wherein the recurrent glioma is glioblastoma multiforme.

4. The method of claim 3 wherein the glioblastoma multiforme is substantially resistant to at least one of temozolomide and bevacizumab.

5. The method of claim 1 wherein the malignancy is a progressive secondary brain tumor.

6. The method of claim 5 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

7. The method of claim 1 wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

8. The method of claim 7 wherein the hexitol derivative is a derivative or analog of dianhydrogalactitol.

9. The method of claim 8 wherein the derivative or analog of dianhydrogalactitol is a derivative of dianhydrogalactitol that is selected from the group consisting of: (i) a derivative of dianhydrogalactitol that has one or both of the hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl; (ii) a derivative of dianhydrogalactitol that has one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl; (iii) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

10. The method of claim 7 wherein the hexitol derivative is dianhydrogalactitol.

11. The method of claim 1 wherein the hexitol derivative is selected from the group consisting of diacetyldianhydrogalactitol and a derivative or analog of diacetyldianhydrogalactitol.

12. The method of claim 11 wherein the hexitol derivative is a derivative or analog of diacetyldianhydrogalactitol.

13. The method of claim 12 wherein the derivative or analog of diacetyldianhydrogalactitol is a derivative of diacetyldianhydrogalactitol that is selected from the group consisting of: (i) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl; (ii) a derivative of diacetyldianhydrogalactitol that has one or both of the hydrogens attached to the epoxide ring replaced with lower alkyl; (iii) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups attached to the same carbons that bear the acetyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

14. The method of claim 11 wherein the hexitol derivative is diacetyldianhydrogalactitol.

15. The method of claim 1 wherein the hexitol derivative is administered in a pharmaceutical composition wherein the pharmaceutical composition comprises at least one excipient, solvent, filler, diluent, buffer, preservative, or additive in addition to the hexitol derivative.

16. A method for preparation of a medicament to improve the efficacy and/or reduce the side effects of the administration of a hexitol derivative for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the hexitol derivative for treatment of the malignancy; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the hexitol derivative for treatment of the malignancy.

17. The method of claim 16 wherein the malignancy is recurrent glioma.

18. The method of claim 17 wherein the recurrent glioma is glioblastoma multiforme.

19. The method of claim 18 wherein the glioblastoma multiforme is substantially resistant to at least one of temozolomide and bevacizumab.

20. The method of claim 16 wherein the malignancy is a progressive secondary brain tumor.

21. The method of claim 20 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

22. The method of claim 16 wherein the factor or parameter is selected from the group consisting of:

(1) dose modification;
(2) route of administration;
(3) schedule of administration;
(4) selection of disease stage;
(5) patient selection;
(6) patient/disease phenotype;
(7) patient/disease genotype;
(8) pre/post-treatment preparation
(9) toxicity management;
(10) pharmacokinetic/pharmacodynamic monitoring;
(11) drug combinations;
(12) chemosensitization;
(13) chemopotentiation;
(14) post-treatment patient management;
(15) alternative medicine/therapeutic support;
(16) bulk drug product improvements;
(17) diluent systems;
(18) solvent systems;
(19) excipients;
(20) dosage forms;
(21) drug delivery systems;
(22) drug conjugate forms;
(23) prodrugs;
(24) multiple drug systems;
(25) biotherapeutic enhancement;
(26) biotherapeutic resistance modulation;
(27) radiation therapy enhancement;
(28) novel mechanisms of action;
(29) selective target cell population therapeutics; and
(30) use with an agent enhancing its activity;

23. The method of claim 22 wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:

(a) continuous i.v. infusion for hours to days;
(b) biweekly administration;
(c) doses greater than 5 mg/m^2/day;
(d) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;
(e) use of caffeine to modulate metabolism;

(f) use of isonazid to modulate metabolism;
(g) selected and intermittent boosting of dosage administration;
(h) administration of single and multiple doses escalating from 5mg/m^2/day via bolus;
(i) oral dosages of below 30 mg/m^2;
(j) oral dosages of above 130 mg/m^2;
(k) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;
(l) dosing at a lower level for an extended period (e.g., 21 days);
(m) dosing at a higher level;
(n) dosing with a nadir/recovery period longer than 21 days;
(o) the use of an alkylating hexitol derivative as a single cytotoxic agent;
(p) immediate release dosing;
(q) slow release dosing;
(r) controlled release dosing;
(s) dosage reduction to control or limit reduction of function of the immune system;
(t) dosage reduction to control or limit myelosuppression;
(u) a dose of 1.5 mg/m^2 (cumulative dose 9 mg/m^2 in a 33-day cycle);
(v) a dose of 3.0 mg/m^2 (cumulative dose 18 mg/m^2 in a 33-day cycle);
(w) a dose of 5.0 mg/m^2 (cumulative dose 30 mg/m^2 in a 33-day cycle);
(x) a dose of 10 mg/m^2 (cumulative dose 60 mg/m^2 in a 33-day cycle);
(y) a dose of 15 mg/m^2 (cumulative dose 90 mg/m^2 in a 33-day cycle);
(z) a dose of 20 mg/m^2 (cumulative dose 120 mg/m^2 in a 33-day cycle);
(aa) a dose of 25 mg/m^2 (cumulative dose 150 mg/m^2 in a 33-day cycle);
(ab) a dose of 30 mg/m^2 (cumulative dose 180 mg/m^2 in a 33-day cycle);
(ac) a dose of 40 mg/m^2 (cumulative dose 240 mg/m^2 in 33-day cycle);
(ad) a dose beginning at 1.5 mg/m^2 and increasing to 3.0 mg/m^2;
(ae) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2;
(af) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2;
(ag) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2;
(ah) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2;
(ai) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2;

(aj) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2; and

(ak) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2, then increasing to 40 mg/m^2.

24. The method of claim 22 wherein the improvement is made by route of administration and the route of administration is at least one route of administration selected from the group consisting of:

(a) topical administration;
(b) oral administration;
(c) slow release oral delivery;
(d) intrathecal administration;
(e) intraarterial administration;
(f) continuous infusion;
(g) intermittent infusion;
(h) intravenous administration, such as intravenous administration for 30 minutes;
(i) administration through a longer infusion;
(j) administration through IV push; and
(k) intraperitoneal administration.

25. The method of claim 22 wherein the improvement is made by schedule of administration and the schedule of administration is at least one schedule of administration selected from the group consisting of:

(a) daily administration;
(b) weekly administration;
(c) weekly administration for three weeks;
(d) biweekly administration;
(e) biweekly administration for three weeks with a 1-2 week rest period;
(f) intermittent boost dose administration; and
(g) daily administration for one week for multiple weeks.

26. The method of claim 22 wherein the improvement is made by selection of disease stage and the selection of disease stage is at least one selection of disease stage selected from the group consisting of:

(a) use for the treatment of recurrent malignant glioma; and
(b) use for the treatment of progressive secondary brain tumor.

27. The method of claim 22 wherein the improvement is made by patient selection and the patient selection is a patient selection carried out by a criterion selected from the group consisting of:

(a) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(b) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(c) selecting patients intolerant of GI toxicities; and

(d) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

28. The method of claim 22 wherein the improvement is made by analysis of patient or disease phenotype and the analysis of patient or disease phenotype is carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular phenotype;

(b) use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of a prostate specific gene, a protein that is a gene product of jun, a protein kinase, desmoglein-3, and a caspase-derived neo-epitope;

(c) surrogate compound dosing; and

(d) low dose pre-testing for enzymatic status.

29. The method of claim 22 wherein the improvement is made by analysis of patient or disease genotype and the analysis of patient or disease genotype is carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(b) use of a gene chip;

(c) use of gene expression analysis;

(d) use of single nucleotide polymorphism (SNP) analysis; and

(e) measurement of the level of a metabolite or a metabolic enzyme.

30. The method of claim 22 wherein the improvement is made by pre/post-treatment preparation and the pre/post-treatment preparation is a method of pre/post treatment preparation selected from the group consisting of:

(a) the use of colchicine or an analog thereof;

(b) the use of a uricosuric;

(c) the use of uricase;

(d) the non-oral use of nicotinamide;

(e) the use of a sustained-release form of nicotinamide;

(f) the use of an inhibitor of poly-ADP ribose polymerase;

(g) the use of caffeine;

(h) the use of leucovorin rescue;

(i) infection control; and

(j) the use of an anti-hypertensive agent.

31. The method of claim 22 wherein the improvement is made by toxicity management and the toxicity management is a method of toxicity management selected from the group consisting of:

(a) the use of colchicine or an analog thereof;
(b) the use of a uricosuric;
(c) the use of uricase;
(d) the non-oral use of nicotinamide;
(e) the use of a sustained-release form of nicotinamide;
(f) the use of an inhibitor of poly-ADP ribose polymerase;
(g) the use of caffeine;
(h) the use of leucovorin rescue;
(i) the use of sustained-release allopurinol;
(j) the non-oral use of allopurinol;
(k) the use of bone marrow transplants;
(l) the use of a blood cell stimulant;
(m) the use of blood or platelet infusions;
(n) the administration of an agent selected from the group consisting of filgrastim (Neupogen®), G-CSF, and GM-CSF;
(o) the application of a pain management technique;
(p) the administration of an anti-inflammatory agent;
(q) the administration of fluids;
(r) the administration of a corticosteroid;
(s) the administration of an insulin control medication;
(t) the administration of an antipyretic;
(u) the administration of an anti-nausea treatment;
(v) the administration of an anti-diarrheal treatment;
(w) the administration of N-acetylcysteine;
(x) the administration of an antihistamine; and
(y) the administration of agents for reduction of gastric toxicity.

32. The method of claim 22 wherein the improvement is made by pharmacokinetic/pharmacodynamic monitoring and the pharmacokinetic/pharmacodynamic monitoring is a method selected from the group consisting of:

(a) multiple determinations of blood plasma levels; and
(b) multiple determinations of at least one metabolite in blood or urine.

33. The method of claim 22 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:

(c) use with thymidylate synthetase inhibitors;
(d) use with signal transduction inhibitors;
(e) use with cisplatin or platinum analogs;
(f) use with alkylating agents;
(g) use with anti-tubulin agents;
(h) use with antimetabolites;

(i) use with berberine;
(j) use with apigenin;
(k) use with colchicine or an analog thereof;
(l) use with genistein;
(m) use with etoposide;
(n) use with cytarabine;
(o) use with camptothecins;
(p) use with vinca alkaloids;
(q) use with topoisomerase inhibitors;
(r) use with 5-fluorouracil;
(s) use with curcumin;
(t) use with NF-κB inhibitors;
(u) use with rosmarinic acid;
(v) use with mitoguazone;
(w) use with meisoindigo;
(x) use with imatinib;
(y) use with dasatinib;
(z) use with nilotinib;
(aa) use with epigenetic modulators;
(ab) use with transcription factor inhibitors;
(ac) use with taxol;
(ad) use with homoharringtonine;
(ae) use with pyridoxal;
(af) use with spirogermanium;
(ag) use with caffeine;
(ah) use with nicotinamide;
(ai) use with methylglyoxalbisguanylhydrazone;
(aj) use with Rho kinase inhibitors;
(ak) use with 1,2,4-benzotriazine oxides;
(al) use with an alkylglycerol;
(am) use with an inhibitor of a Mer, Ax1, or Tyro-3 receptor kinase;
(an) use with an inhibitor of ATR kinase;
(ao) use with a modulator of Fms kinase, Kit kinase, MAP4K4 kinase, TrkA kinase, or TrkB kinase;
(ap) use with endoxifen;
(aq) use with a mTOR inhibitor;
(ar) use with an inhibitor of Mnk1a kinase, Mkn1b kinase, Mnk2a kinase, or Mnk2b kinase;
(as) use with a modulator of pyruvate kinase M2;
(at) use with a modulator of phosphoinositide 3-kinases;
(au) use with a cysteine protease inhibitor;
(av) use with phenformin;
(aw) use with Sindbis virus-based vectors;
(ax) use with peptidomimetics that act as mimetics of Smac and inhibit IAPs to promote apoptosis;
(ay) use with a Raf kinase inhibitor;

(az) use with a nuclear transport modulator;
(ba) use with an acid ceramidase inhibitor and a choline kinase inhibitor;
(bb) use with tyrosine kinase inhibitors;
(bc) use with anti-CS1 antibodies;
(bd) use with inhibitors of protein kinase CK2;
(be) use with anti-guanylyl cyclase C (GCC) antibodies;
(bf) use with histone deacetylase inhibitors;
(bg) use with cannabinoids;
(bh) use with glucagon-like peptide-1 (GLP-1) receptor agonists;
(bi) use with inhibitors of Bcl-2 or Bcl-xL;
(bj) use with Stat3 pathway inhibitors;
(bk) use with inhibitors of polo-like kinase 1 (Plk1);
(bl) use with GBPAR1 activators;
(bm) use with modulators of serine-threonine protein kinase and poly(ADP-ribose) polymerase (PARP) activity;
(bn) use with taxanes;
(bo) use with inhibitors of dihydrofolate reductase;
(bp) use with inhibitors of aromatase;
(bq) use with benzimidazole-based anti-neoplastic agents;
(br) use with an O6-methylguanine-DNA-methyltransferase (MGMT) inhibitor;
(bs) use with CCR9 inhibitors;
(bt) use with acid sphingomyelinase inhibitors;
(bu) use with peptidomimetic macrocycles;
(bv) use with cholanic acid amides;
(bw) use with substituted oxazaphosphorines;
(bx) use with anti-TWEAK receptor antibodies;
(by) use with an ErbB3 binding protein;
(bz) use with a glutathione S-transferase-activated anti-neoplastic compound;
(ca) use with substituted phosphorodiamidates;
(cb) use with inhibitors of MEKK protein kinase;
(cd) use with COX-2 inhibitors;
(ce) use with cimetidine and a cysteine derivative;
(cf) use with anti-IL-6 receptor antibody;
(cg) use with an antioxidant;
(ch) use with an isoxazole inhibitor of tubulin polymerization;
(ci) use with PARP inhibitors;
(cj) use with Aurora protein kinase inhibitors;
(ck) use with peptides binding to prostate-specific membrane antigen;
(cl) use with CD19 binding agents;
(cm) use with benzodiazepines;
(cn) use with Toll-like receptor (TLR) agonists;
(co) use with bridged bicyclic sulfamides;
(cp) use with inhibitors of epidermal growth factor receptor kinase;

(cq) use with a ribonuclease of the T2 family having actin-binding activity;

(cr) use with myrsinoic acid A or an analog thereof;

(cs) use with inhibitors of a cyclin-dependent kinase;

(ct) use with inhibitors of the interaction between p53 and MDM2;

(cu) use with inhibitors of the receptor tyrosine kinase MET;

(cv) use with largazole or largazole analogs;

(cw) use with inhibitors of AKT protein kinase;

(cx) use with 2′-fluoro-5-methyl-β-L-arabinofuranosyluridine or L-deoxythymidine;

(cy) use with HSP90 modulators;

(cz) use with inhibitors of JAK kinases;

(da) use with inhibitors of PDK1 protein kinase;

(db) use with PDE4 inhibitors;

(de) use with inhibitors of proto-oncogene c-Met tyrosine kinase;

(df) use with inhibitors of indoleamine 2,3-dioxygenase;

(dg) use with agents that inhibit expression of ATDC (TRIM29);

(dh) use with proteomimetic inhibitors of the interaction of nuclear receptor with coactivator peptides;

(di) use with antagonists of XIAP family proteins;

(dj) use with tumor-targeted superantigens;

(dk) use with inhibitors of Pim kinases;

(dl) use with inhibitors of CHK1 or CHK2 kinases;

(dm) use with inhibitors of angiopoietin-like 4 protein;

(dn) use with Smo antagonists;

(do) use with nicotinic acetylcholine receptor antagonists;

(dp) use with farnesyl protein transferase inhibitors;

(dq) use with adenosine A3 receptor antagonists;

(dr) use with a cancer vaccine;

(ds) use with a JAK2 inhibitor; and

(dt) use with a Src inhibitor.

34. The method of claim 22 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:

(i) use with ACE inhibitors;

(ii) use with adenosine kinase inhibitors;

(iii) use with adrenal cortex antagonists;

(iv) use with AKT pathway inhibitors;

(v) use with angiogenesis inhibitors;

(vi) use with angiostatic steroids;

(vii) use with anti-androgens;

(viii) use with anti-estrogens;

(ix) use with anti-hypercalcemia agents;

(x) use with apoptosis inhibitors;

(xi) use with ATI receptor antagonists;

(xii) use with aurora kinase inhibitors;
(xiii) use with aromatase inhibitors;
(xiv) use with bisphosphonates;
(xv) use with Bruton's tyrosine kinase inhibitors;
(xvi) use with calcineurin inhibitors;
(xvii) use with CaM kinase II inhibitors;
(xviii) use with CD45 tyrosine phosphatase inhibitors;
(xix) use with CDC25 phosphatase inhibitors;
(xx) use with CHK kinase inhibitors;
(xxi) use with compounds targeting decreasing a protein or lipid kinase activity;
(xxii) use with compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase;
(xxiii) use with compounds which induce cell differentiation processes;
(xxiv) use with cRAF kinase inhibitors;
(xxv) use with cyclin dependent kinase inhibitors;
(xxvi) use with cysteine protease inhibitors;
(xxvii) use with DNA intercalators;
(xxviii) use with DNA strand breakers;
(xxix) use with E3 ligase inhibitors;
(xxx) use with EDG binders;
(xxxi) use with endocrine hormones;
(xxxii) use with farnesyltransferase inhibitors;
(xxxiii) use with Flk-1 kinase inhibitors;
(xxxiv) use Flt-3 inhibitors;
(xxxv) use with gonadorelin agonists;
(xxxvi) heparanase inhibitors;
(xxxvii) use with histone deacetylase (HDAC) inhibitors;
(xxxviii) use with HSP90 inhibitors;
(xxxix) use with IκBα inhibitors;
(xl) use with insulin receptor tyrosine kinase inhibitors;
(xli) use with c-Jun N-terminal kinase inhibitors;
(xlii) use with microtubule binding agents;
(xliii) use with mitogen-activated protein (MAP) kinase inhibitors;
(xliv) use with MDM2 inhibitors;
(xlv) use with MEK inhibitors;
(xlvi) use with methionine aminopeptidase inhibitors;
(xlvii) use with MMP inhibitors;
(xlviii) use with NGFR tyrosine kinase inhibitors;
(xlix) use with p38 MAP kinase inhibitors;
(l) use with p56 tyrosine kinase inhibitors;
(li) use with PDGFR tyrosine kinase inhibitors;
(lii) use with phosphatidylinositol 3-kinase inhibitors;
(liii) use with phosphatase inhibitors;
(liv) use with platinum agents;

(lv) use with protein phosphatase inhibitors;
(lvi) use with PKC inhibitors;
(lvii) use with PKC delta kinase inhibitors;
(lviii) use with polyamine synthesis inhibitors;
(lix) use with proteasome inhibitors;
(lx) use with PTP1B inhibitors;
(lxi) use with protein tyrosine kinase inhibitors;
(lxii) use with SRC family tyrosine kinase inhibitors;
(lxiii) use with Syk tyrosine kinase inhibitors;
(lxiv) use with Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitors;
(lxv) use with inhibitors of Ras oncogenic isoforms;
(lxvi) use with retinoids;
(lxvii) use with ribonucleotide reductase inhibitors;
(lxviii) use with RNA polymerase II elongation inhibitors;
(lxix) use with S-adenosylmethionine decarboxylase inhibitors;
(lxx) use with serine/threonine kinase inhibitors;
(lxxi) use with compounds which target, decrease, or inhibit the activity or function of serine/threonine mTOR kinase;
(lxxii) use with somatostatin receptor antagonists;
(lxxiii) use with telomerase inhibitors;
(lxxiv) use with topoisomerase inhibitors;
(lxxv) use with VEGFR tyrosine kinase inhibitors; and
(lxxvi) use with RANKL inhibitors.

35. The method of claim 22 wherein the improvement is made by chemosensitization and the chemosensitization comprises the use of a hexitol derivative as a chemosensitizer in combination with an agent selected from the group consisting of:
(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin or platinum analogs;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) colchicine or an analog of colchicine;
(m) genistein;
(n) etoposide;
(o) cytarabine;
(p) camptothecin;
(q) vinca alkaloids;
(r) 5-fluorouracil;

(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid; and
(v) mitoguazone.

36. The method of claim 22 wherein the improvement is made by chemopotentiation and the chemopotentiation comprises the use of a hexitol derivative as a chemopotentiator in combination with an agent selected from the group consisting of:

(a) fraudulent nucleosides;
(b) fraudulent nucleotides;
(c) thymidylate synthetase inhibitors;
(d) signal transduction inhibitors;
(e) cisplatin or platinum analogs;
(f) alkylating agents;
(g) anti-tubulin agents;
(h) antimetabolites;
(i) berberine;
(j) apigenin;
(k) colchicine or analogs of colchicine;
(l) genistein;
(m) etoposide;
(n) cytarabine;
(o) camptothecins;
(p) vinca alkaloids;
(q) topoisomerase inhibitors;
(r) 5-fluorouracil;
(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid;
(v) mitoguazone; and
(w) a biotherapeutic.

37. The method of claim 22 wherein the improvement is made by post-treatment management and the post-treatment management is a method selected from the group consisting of:

(a) a therapy associated with pain management;
(b) nutritional support;
(c) administration of an anti-emetic;
(d) an anti-nausea therapy;
(e) administration of an anti-inflammatory agent;
(f) administration of an anti-pyretic agent; and
(g) administration of an immune stimulant.

38. The method of claim 22 wherein the improvement is made by alternative medicine/post-treatment support and the alternative medicine/post-treatment support is administration of a herbal medication created either synthetically or through extraction.

(a) hypnosis;
(b) acupuncture;
(c) meditation;
(d) a herbal medication created either synthetically or through extraction; and
(e) applied kinesiology.

39. The method of claim 38 wherein the herbal medication created either synthetically or through extraction is selected from the group consisting of:
(a) a NF-κB inhibitor;
(b) a natural anti-inflammatory;
(c) an immunostimulant;
(d) an antimicrobial; and
(e) a flavonoid, isoflavone, or flavone.

40. The method of claim 39 wherein the herbal medication created either synthetically or through extraction is a NF-κB inhibitor, and the NF-κB inhibitor is selected from the group consisting of parthenolide, curcumin, and rosmarinic acid.

41. The method of claim 39 wherein the herbal medication created either synthetically or through extraction is a natural anti-inflammatory, and the natural anti-inflammatory is selected from the group consisting of rhein and parthenolide.

42. The method of claim 39 wherein the herbal medication created either synthetically or through extraction is an immunostimulant, and the immunostimulant is a product found in or isolated from Echinacea.

43. The method of claim 39 wherein the herbal medication created either synthetically or through extraction is an anti-microbial, and the anti-microbial is berberine.

44. The method of claim 39 wherein the herbal medication created either synthetically or through extraction is a flavonoid, isoflavone, or flavone, and the flavonoid or flavone is selected from the group consisting of apigenenin, genistein, genistin, 6″-O-malonylgenistin, 6″-O-acetylgenistin, daidzein, daidzin, 6″-O-malonyldaidzin, 6″-O-acetylgenistin, glycitein, glycitin, 6″-O-malonylglycitin, and 6-O-acetylglycitin.

45. The method of claim 22 wherein the improvement is made by a bulk drug product improvement and the bulk drug product improvement is a bulk drug product improvement selected from the group consisting of:
(a) salt formation;
(b) preparation as a homogeneous crystal structure;
(c) preparation as a pure isomer;
(d) increased purity;
(e) preparation with lower residual solvent content; and
(f) preparation with lower residual heavy metal content.

46. The method of claim 22 wherein the improvement is made by use of a diluent and the diluent is a diluent selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) dimethylformamide (DMF)
(e) dimethylacetamide (DMA);
(f) ethanol;
(g) benzyl alcohol;
(h) dextrose-containing water for injection;
(i) Cremophor;
(j) cyclodextrin; and
(k) PEG.

47. The method of claim 22 wherein the improvement is made by use of a solvent system and the solvent system is a solvent system selected from the group consisting of:

(a) an emulsion;
(b) DMSO;
(c) NMF;
(d) DMF;
(e) DMA;
(f) ethanol;
(g) benzyl alcohol;
(h) dextrose-containing water for injection;
(i) Cremophor;
(j) PEG; and
(k) salt systems.

48. The method of claim 22 wherein the improvement is made by use of an excipient and the excipient is an excipient selected from the group consisting of:

(a) mannitol;
(b) albumin;
(c) EDTA;
(d) sodium bisulfite;
(e) benzyl alcohol;
(f) carbonate buffers;
(g) phosphate buffers;
(h) PEG;
(i) vitamin A;
(j) vitamin D;
(k) vitamin E;
(l) esterase inhibitors;
(m) cytochrome P450 inhibitors;
(n) multi-drug resistance (MDR) inhibitors;
(o) organic resins;
(p) detergents;

(q) perillyl alcohol or an analog thereof; and

49. The method of claim 22 wherein the improvement is made by use of a dosage form and the dosage form is a dosage form selected from the group consisting of:

(a) tablets;
(b) capsules;
(c) topical gels;
(d) topical creams;
(e) patches;
(f) suppositories;
(g) lyophilized dosage fills;
(h) immediate-release formulations;
(i) slow-release formulations;
(j) controlled-release formulations; and
(k) liquid in capsules.

50. The method of claim 22 wherein the improvement is made by use of a drug delivery system and the drug delivery system is a drug delivery system selected from the group consisting of:

(a) oral dosage forms;
(b) nanocrystals;
(c) nanoparticles;
(d) cosolvents;
(e) slurries;
(f) syrups;
(g) bioerodible polymers;
(h) liposomes;
(i) slow-release injectable gels;
(j) microspheres; and
(k) targeting compositions with epidermal growth factor receptor-binding peptides.

51. The method of claim 22 wherein the improvement is made by use of a drug conjugate form and the drug conjugate form is a drug conjugate form selected from the group consisting of:

(a) a polymer system;
(b) polylactides;
(c) polyglycolides;
(d) amino acids;
(e) peptides;
(f) multivalent linkers;
(g) immunoglobulins;
(h) cyclodextrin polymers;
(i) modified transferrin;
(j) hydrophobic or hydrophobic-hydrophilic polymers;
(k) conjugates with a phosphonoformic acid partial ester;

(l) conjugates with a cell-binding agent incorporating a charged cross-linker; and

(m) conjugates with β-glucuronides through a linker.

52. The method of claim 22 wherein the improvement is made by use of a prodrug system and the prodrug system is a prodrug system selected from the group consisting of:

(a) the use of enzyme sensitive esters;
(b) the use of dimers;
(c) the use of Schiff bases;
(d) the use of pyridoxal complexes;
(e) the use of caffeine complexes;
(f) the use of nitric oxide-releasing prodrugs;
(g) the use of prodrugs with fibroblast activation protein α-cleavable oligopeptides;
(h) the use of prodrugs that are products of reaction with an acetylating or carbamylating agent;
(i) the use of prodrugs that are hexanoate conjugates;
(j) the use of prodrugs that are polymer-agent conjugates; and
(k) the use of prodrugs that are subject to redox activation.

53. The method of claim 22 wherein wherein the improvement is made by use of a multiple drug system and the multiple drug system is a multiple drug system selected from the group consisting of:

(a) inhibitors of multi-drug resistance;
(b) specific drug resistance inhibitors;
(c) specific inhibitors of selective enzymes;
(d) signal transduction inhibitors;
(e) meisoindigo;
(f) imatinib;
(g) hydroxyurea;
(h) dasatinib;
(i) capecitabine;
(j) nilotinib;
(k) repair inhibition agents; and
(l) topoisomerase inhibitors with non-overlapping side effects.

54. The method of claim 22 wherein the improvement is made by biotherapeutic enhancement and the biotherapeutic enhancement is be performed by use in combination as sensitizers/potentiators with a therapeutic agent or technique that is a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;

(f) gene therapies;
(g) ribozymes; and
(h) RNA interference.

55. The method of claim 22 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a malignancy resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;
(f) gene therapies;
(g) ribozymes; and
(h) RNA interference.

56. The method of claim 22 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a malignancy associated with a mutation in or dysregulation of the *AHI1* gene also resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;
(f) gene therapies;
(g) ribozymes; and
(h) RNA interference.

57. The method of claim 22 wherein the improvement is made by radiation therapy enhancement and the radiation therapy enhancement is a radiation therapy enhancement agent or technique selected from the group consisting of:

(a) use with hypoxic cell sensitizers;
(b) use with radiation sensitizers/protectors;
(c) use with photosensitizers;
(d) use with radiation repair inhibitors;
(e) use with thiol depleting agents;
(f) use with vaso-targeted agents;
(g) use with DNA repair inhibitors;
(h) use with radioactive seeds;
(i) use with radionuclides;
(j) use with radiolabeled antibodies; and
(k) use with brachytherapy.

58. The method of claim 22 wherein the improvement is by use of a novel mechanism of action and the novel mechanism of action is a novel mechanism of action that is a therapeutic interaction with a target or mechanism selected from the group consisting of:

(a) inhibitors of poly-ADP ribose polymerase;
(b) agents that affect vasculature;
(c) agents that promote vasodilation;
(d) oncogenic targeted agents;
(e) signal transduction inhibitors;
(f) agents inducing EGFR inhibition;
(g) agents inducing Protein Kinase C inhibition;
(h) agents inducing Phospholipase C downregulation;
(i) agents including jun downregulation;
(j) agents modulating expression of histone genes;
(k) agents modulating expression of VEGF;
(l) agents modulating expression of ornithine decarboxylase;
(m) agents modulating expression of jun D;
(n) agents modulating expression of v-jun;
(o) agents modulating expression of GPCRs;
(p) agents modulating expression of protein kinase A;
(q) agents modulating expression of protein kinases other than protein kinase A;
(r) agents modulating expression of telomerase;
(s) agents modulating expression of prostate specific genes; and
(t) agents modulating expression of histone deacetylase.

59. The method of claim 22 wherein the improvement is made by use of selective target cell population therapeutics and the use of selective target cell population therapeutics is a use selected from the group consisting of:

(a) use against radiation sensitive cells;
(b) use against radiation resistant cells; and
(c) use against energy depleted cells.

60. The method of claim 22 wherein the improvement is made by use with an agent to enhance the activity of the hexitol derivative and the agent to enhance the activity of the hexitol derivative is selected from the group consisting of:

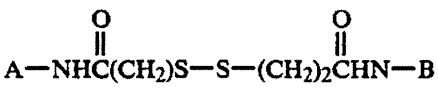
(a) nicotinamide;
(b) caffeine;
(c) tetandrine; and
(d) berberine.

61. The method of claim 22 wherein the improvement is made by use with an agent to counteract myelosuppression and the agent to counteract myelosuppression is a dithiocarbamate.

62. The method of claim 22 wherein the improvement is made by use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier

and the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:

(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

A-NH$(CH_2)_2$S-S-B (cleavable linkage)

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

A-NH=CH$(CH_2)_3$CH=NH-B (non-cleavable linkage)

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

63. The method of claim 22 wherein the method to improve the efficacy and/or reduce the side effects of the administration of an alkylating hexitol derivative exerts a cytotoxic effect against cancer stem cells.

64. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a hexitol derivative for the treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a modified hexitol derivative or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative, wherein the modified hexitol derivative or the derivative, analog or prodrug of the modified hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor as compared with an unmodified hexitol derivative;

(b) a composition comprising:

(i) a therapeutically effective quantity of a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, drug delivery system, agent for counteracting myelosuppression, or agent for increasing the ability of the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative to pass through the blood-brain barrier, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor as compared with an unmodified hexitol derivative;

(c) a therapeutically effective quantity of a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative that is incorporated into a dosage form, wherein a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor as compared with an unmodified hexitol derivative; and

(d) a therapeutically effective quantity of a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative that is subjected to a bulk drug product improvement, wherein the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative subject to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor as compared with an unmodified alkylating hexitol derivative.

65. The pharmaceutical composition of claim 64 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of recurrent glioma.

66. The composition of claim 65 wherein the recurrent glioma is glioblastoma multiforme.

67. The composition of claim 66 wherein the glioblastoma multiforme is resistant to substantially resistant to at least one of temozolomide and bevacizumab.

68. The pharmaceutical composition of claim 64 wherein the malignancy is a progressive secondary brain tumor.

69. The pharmaceutical composition of claim 68 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

70. The pharmaceutical composition of claim 64 wherein the composition comprises a drug combination comprising:

(i) a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative; and

(ii) an additional therapeutic agent selected from the group consisting of:

(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin or platinum analogs;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) amonafide;
(m) vinca alkaloids;
(n) 5-fluorouracil;
(o) curcumin;
(p) NF-κB inhibitors;
(q) rosmarinic acid;
(r) mitoguazone; and
(s) tetrandrine.

71. The pharmaceutical composition of claim 64 wherein the composition comprises:

(a) a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative; and

(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;

(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) colchicine or an analog of colchicine;
(xiii) genistein;
(xiv) etoposide;
(xv) cytarabine;
(xvi) camptothecin;
(xvii) vinca alkaloids;
(xviii) 5-fluorouracil;
(xix) curcumin;
(xx) NF-κB inhibitors;
(xxi) rosmarinic acid; and
(xxii) mitoguazone;

wherein the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative acts as a chemosensitizer.

72. The pharmaceutical composition of claim 64 wherein the composition comprises:

(a) a hexitol derivative, a modified hexitol derivative, or a derivative, analog, or prodrug of a hexitol derivative or a modified hexitol derivative; and

(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) colchicine or an analog of colchicine;
(xiii) genistein;
(xiv) etoposide;
(xv) cytarabine;
(xvi) camptothecin;
(xvii) vinca alkaloids;
(xviii) 5-fluorouracil;
(xix) curcumin;
(xx) NF-κB inhibitors;
(xxi) rosmarinic acid;
(xxii) mitoguazone; and

(xxiii) tetandrine;

wherein the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative acts as a chemopotentiator.

73. The pharmaceutical composition of claim 64 wherein the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(i) salt formation;
(ii) preparation as a homogeneous crystal structure;
(iii) preparation as a pure isomer;
(iv) increased purity;
(v) preparation with lower residual solvent content; and
(vi) preparation with lower residual heavy metal content.

74. The pharmaceutical composition of claim 64 wherein the composition comprises the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative and a diluent, wherein the diluent is selected from the group consisting of:

(i) an emulsion;
(ii) dimethylsulfoxide (DMSO);
(iii) N-methylformamide (NMF)
(iv) dimethylformamide (DMF)
(v) dimethylacetamide (DMA);
(vi) ethanol;
(vii) benzyl alcohol;
(viii) dextrose-containing water for injection;
(ix) Cremophor;
(x) cyclodextrins; and
(xi) PEG.

75. The pharmaceutical composition of claim 64 wherein the composition comprises the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative and a solvent system, wherein the solvent system is selected from the group consisting of:

(i) an emulsion;
(ii) DMSO;
(iii) NMF;
(iv) DMF;
(v) DMA;
(vi) ethanol;
(vii) benzyl alcohol;
(viii) dextrose-containing water for injection;
(ix) Cremophor;
(x) PEG; and
(xi) salt systems.

76. The pharmaceutical composition of claim 64 wherein the composition comprises the hexitol derivative, the modified hexitol derivative, or the derivative, analog, or prodrug of the hexitol derivative or the modified hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(i) mannitol;
(ii) albumin;
(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) carbonate buffers;
(vii) phosphate buffers;
(viii) PEG;
(ix) vitamin A;
(x) vitamin D;
(xi) vitamin E;
(xii) esterase inhibitors;
(xiii) cytochrome P450 inhibitors;
(xiv) multi-drug resistance (MDR) inhibitors;
(xv) organic resins;
(xvi) detergents;
(xvii) perillyl alcohol or an analog thereof; and
(xviii) activators of channel-forming receptors.

77. The pharmaceutical composition of claim 64 wherein the hexitol derivative, modified hexitol derivative, or derivative, analog, or prodrug of the hexitol derivative or alkylating hexitol derivative is incorporated into a dosage form selected from the group consisting of:

(i) tablets;
(ii) capsules;
(iii) topical gels;
(iv) topical creams;
(v) patches;
(vi) suppositories;
(vii) lyophilized dosage fills;
(viii) immediate-release formulations;
(ix) slow-release formulations;
(x) controlled-release formulations; and
(xi) liquid in capsules.

78. The pharmaceutical composition of claim 64 wherein the composition comprises:

(a) the hexitol derivative, modified hexitol derivative, or derivative, analog, or prodrug of the hexitol derivative or modified alkylating hexitol derivative; and

(b) a drug delivery system, wherein the drug delivery system is selected from the group consisting of:

(i) oral dosage forms;
(ii) nanocrystals;
(iii) nanoparticles;
(iv) cosolvents;
(v) slurries;
(vi) syrups;
(vii) bioerodible polymers;
(viii) liposomes;
(ix) slow-release injectable gels;
(x) microspheres; and
(xi) targeting compositions with epidermal growth factor receptor-binding peptides.

79. The pharmaceutical composition of claim 64 wherein the composition comprises a hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of a hexitol derivative or modified hexitol derivative which is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;
(ii) polylactides;
(iii) polyglycolides;
(iv) amino acids;
(v) peptides;
(vi) multivalent linkers;
(vii) immunoglobulins;
(viii) cyclodextrin polymers;
(ix) modified transferrin;
(x) hydrophobic or hydrophobic-hydrophilic polymers;
(xi) conjugates with a phosphonoformic acid partial ester;
(xii) conjugates with a cell-binding agent incorporating a charged cross-linker; and
(xiii) conjugates with β-glucuronides through a linker.

80. The pharmaceutical composition of claim 64 wherein the composition comprises a hexitol derivative, modified hexitol derivative, or derivative or analog of a hexitol derivative or modified hexitol derivative that is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:

(i) enzyme sensitive esters;
(ii) dimers;
(iii) Schiff bases;
(iv) pyridoxal complexes;
(v) caffeine complexes;
(vi) nitric oxide-releasing prodrugs;
(vii) prodrugs with fibroblast activation protein α-cleavable oligopeptides
(viii) products of reaction with an acylating or carbamylating agent;
(ix) hexanoate conjugates;

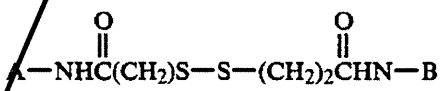
(x) polymer-agent conjugates; and
(xi) prodrugs that are subject to redox activation.

81. The pharmaceutical composition of claim 64 wherein the therapeutic agent is the hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of the hexitol derivative or modified alkylating hexitol derivative and the composition further comprises at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:
(i) an inhibitor of multi-drug resistance;
(ii) a specific drug resistance inhibitor;
(iii) a specific inhibitor of a selective enzyme;
(iv) a signal transduction inhibitor;
(v) an inhibitor of a repair enzyme; and
(vi) a topoisomerase inhibitor with non-overlapping side effects.

82. The pharmaceutical composition of claim 64 wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, and a derivative or analog of diacetyldianhydrogalactitol.

83. The pharmaceutical composition of claim 64 wherein the therapeutic agent is the hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of the hexitol derivative or modified alkylating hexitol derivative and the composition further comprises an agent for counteracting myelosuppression, wherein the agent that counteracts myelosuppression is a dithiocarbamate.

84. The pharmaceutical composition of claim 64 wherein the therapeutic agent is the hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of the hexitol derivative or modified alkylating hexitol derivative and the composition further comprises an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:
(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

A-NH(CH$_2$)$_2$S-S-B (cleavable linkage)

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

A-NH=CH(CH_2)$_3$CH=NH-B (non-cleavable linkage)

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

85. The pharmaceutical composition of claim 64 wherein the alkylating hexitol derivative is dianhydrogalactitol.

86. The pharmaceutical composition of claim 64 wherein the alkylating hexitol derivative is a derivative or analog of dianhydrogalactitol.

87. The pharmaceutical composition of claim 86 wherein the derivative or analog of dianhydrogalactitol is a derivative of dianhydrogalactitol that is selected from the group consisting of: (i) a derivative of dianhydrogalactitol that has one or both of the hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl; (ii) a derivative of dianhydrogalactitol that has one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl; (iii) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

88. The pharmaceutical composition of claim 64 wherein the alkylating hexitol derivative is diacetyldianhydrogalactitol.

89. The pharmaceutical composition of claim 64 wherein the alkylating hexitol derivative is a derivative or analog of diacetyldianhydrogalactitol.

90. The pharmaceutical composition of claim 89 wherein the derivative or analog of diacetyldianhydrogalactitol is a derivative of diacetyldianhydrogalactitol that is selected from the group consisting of: (i) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl; (ii) a derivative of diacetyldianhydrogalactitol that has one or both of the hydrogens attached to the epoxide ring replaced with lower alkyl; (iii) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups attached to the same carbons that bear the acetyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

91. The pharmaceutical composition of claim 64 wherein the pharmaceutical composition is formulated to exert a cytotoxic effect against cancer stem cells.

92. A kit, comprising, separately packaged, comprising two or more different doses of a hexitol derivative for treatment of a malignancy.

93. The kit of claim 92 wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol.

94. The kit of claim 93 wherein the hexitol derivative is dianhydrogalactitol.

95. The kit of claim 94 wherein the two or more different doses are:
(a) 1.5 mg/m^2 and 3.0 mg/m^2;
(b) 1.5 mg/m^2, 3.0 mg/m^2, and 5.0 mg/m^2;
(c) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, and 10 mg/m^2;
(d) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, and 15 mg/m^2;
(e) 10 mg/m^2; (iv) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, and 20 mg/m^2;
(f) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, and 25 mg/m^2;
(g) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, and 30 mg/m^2; and
(h) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, and 40 mg/m^2.

96. The kit of claim 92 wherein the hexitol derivative is in the form of a pharmaceutical composition.

97. The kit of claim 92 wherein the doses are assembled into a blister pack.

98. The kit of claim 92 wherein the kit further comprises instructions for use.

Claims

1. A method for preparation of a medicament for the treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising the step of preparing a medicament for administration to a patient suffering from recurrent glioma or progressive secondary brain tumor, the medicament comprising a therapeutically effective quantity of a hexitol derivative selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol.

2. The method of claim 1 wherein the malignancy is recurrent glioma.

3. The method of claim 2 wherein the recurrent glioma is glioblastoma multiforme.

4. The method of claim 3 wherein the glioblastoma multiforme is substantially resistant to at least one of temozolomide and bevacizumab.

5. The method of claim 4 wherein the glioblastoma is substantially resistant to bevacizumab.

6. The method of claim 1 wherein the malignancy is a progressive secondary brain tumor.

7. The method of claim 6 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

8. The method of claim 1 wherein the hexitol derivative is dianhydrogalactitol.

9. The method of claim 1 wherein the hexitol derivative is diacetyldianhydrogalactitol.

10. The method of claim 1 wherein the hexitol derivative is administered in a pharmaceutical composition wherein the pharmaceutical composition comprises at least one excipient, solvent, filler, diluent, buffer, preservative, or additive in addition to the hexitol derivative, wherein the medicament comprises the pharmaceutical composition.

11. A method for preparation of a medicament to improve the efficacy and/or reduce the side effects of the administration of a hexitol derivative for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the hexitol derivative for treatment of the malignancy; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the hexitol derivative for treatment of the

malignancy and preparing the medicament according to the modified factor or parameter, wherein the hexitol derivative for use in preparation of the medicament is selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol.

12. The method of claim 11 wherein the malignancy is recurrent glioma.

13. The method of claim 12 wherein the recurrent glioma is glioblastoma multiforme.

14. The method of claim 13 wherein the glioblastoma multiforme is substantially resistant to at least one of temozolomide and bevacizumab.

15. The method of claim 14 wherein the glioblastoma multiforme is substantially resistant to bevacizumab.

16. The method of claim 11 wherein the malignancy is a progressive secondary brain tumor.

17. The method of claim 16 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

18. The method of claim 11 wherein the factor or parameter for preparing the medicament is selected from the group consisting of:

(1) dose modification;
(2) route of administration;
(3) schedule of administration;
(4) selection of disease stage;
(5) patient selection;
(6) patient/disease phenotype;
(7) patient/disease genotype;
(8) pre/post-treatment preparation
(9) drug combinations;
(10) chemosensitization;
(11) chemopotentiation;
(12) drug delivery systems;
(13) drug conjugate forms;
(14) prodrugs;
(15) multiple drug systems;
(16) biotherapeutic enhancement;
(17) biotherapeutic resistance modulation;
(18) radiation therapy enhancement;
(19) novel mechanisms of action;
(20) selective target cell population therapeutics; and
(21) use with an agent enhancing its activity.

19. The method of claim 18 wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:

(a) continuous i.v. infusion for hours to days;
(b) biweekly administration;
(c) doses greater than 5 mg/m^2/day;
(d) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;
(e) use of caffeine to modulate metabolism;
(f) use of isonazid to modulate metabolism;
(g) selected and intermittent boosting of dosage administration;
(h) administration of single and multiple doses escalating from 5mg/m^2/day via bolus;
(i) oral dosages of below 30 mg/m^2;
(j) oral dosages of above 130 mg/m^2;
(k) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;
(l) dosing at a lower level for an extended period (e.g., 21 days);
(m) dosing at a higher level;
(n) dosing with a nadir/recovery period longer than 21 days;
(o) the use of an alkylating hexitol derivative as a single cytotoxic agent;
(p) immediate release dosing;
(q) slow release dosing;
(r) controlled release dosing;
(s) dosage reduction to control or limit reduction of function of the immune system;
(t) dosage reduction to control or limit myelosuppression;
(u) a dose of 1.5 mg/m^2 (cumulative dose 9 mg/m^2 in a 33-day cycle);
(v) a dose of 3.0 mg/m^2 (cumulative dose 18 mg/m^2 in a 33-day cycle);
(w) a dose of 5.0 mg/m^2 (cumulative dose 30 mg/m^2 in a 33-day cycle);
(x) a dose of 10 mg/m^2 (cumulative dose 60 mg/m^2 in a 33-day cycle);
(y) a dose of 15 mg/m^2 (cumulative dose 90 mg/m^2 in a 33-day cycle);
(z) a dose of 20 mg/m^2 (cumulative dose 120 mg/m^2 in a 33-day cycle);
(aa) a dose of 25 mg/m^2 (cumulative dose 150 mg/m^2 in a 33-day cycle);
(ab) a dose of 30 mg/m^2 (cumulative dose 180 mg/m^2 in a 33-day cycle);
(ac) a dose of 40 mg/m^2 (cumulative dose 240 mg/m^2 in 33-day cycle);
(ad) a dose beginning at 1.5 mg/m^2 and increasing to 3.0 mg/m^2;

(ae) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2;

(af) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2;

(ag) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2;

(ah) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2;

(ai) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2;

(aj) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2; and

(ak) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2, then increasing to 40 mg/m^2.

20. The method of claim 19 wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:

(a) a dose beginning at 1.5 mg/m^2 and increasing to 3.0 mg/m^2;

(b) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2;

(c) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2;

(d) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2;

(e) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2;

(f) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2;

(g) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2; and

(h) a dose beginning at 1.5 mg/m^2, increasing to 3.0 mg/m^2, then increasing to 5.0 mg/m^2, then increasing to 10 mg/m^2, then increasing to 15 mg/m^2, then increasing to 20 mg/m^2, then increasing to 25 mg/m^2, then increasing to 30 mg/m^2, then increasing to 40 mg/m^2.

21. The method of claim 18 wherein the improvement is made by route of administration and the route of administration is at least one route of administration selected from the group consisting of:

(a) topical administration;

(b) oral administration;
(c) slow release oral delivery;
(d) intrathecal administration;
(e) intraarterial administration;
(f) continuous infusion;
(g) intermittent infusion;
(h) intravenous administration, such as intravenous administration for 30 minutes;
(i) administration through a longer infusion;
(j) administration through IV push; and
(k) intraperitoneal administration.

22. The method of claim 18 wherein the improvement is made by schedule of administration and the schedule of administration is at least one schedule of administration selected from the group consisting of:
(a) daily administration;
(b) weekly administration;
(c) weekly administration for three weeks;
(d) biweekly administration;
(e) biweekly administration for three weeks with a 1-2 week rest period;
(f) intermittent boost dose administration; and
(g) daily administration for one week for multiple weeks.

23. The method of claim 18 wherein the improvement is made by selection of disease stage and the selection of disease stage is use for the treatment of progressive secondary brain tumor.

24. The method of claim 18 wherein the improvement is made by patient selection and the patient selection is a patient selection carried out by a criterion selected from the group consisting of:
(a) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;
(b) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;
(c) selecting patients intolerant of GI toxicities; and
(d) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

25. The method of claim 18 wherein the improvement is made by analysis of patient or disease phenotype and the analysis of patient or disease phenotype is carried out by use of a method for measurement of a marker selected from the group consisting of desmoglein-3 and a caspase-derived neo-epitope.

26. The method of claim 18 wherein the improvement is made by analysis of patient or disease genotype and the analysis of patient or disease genotype is carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(b) use of a gene chip;

(c) use of gene expression analysis;

(d) use of single nucleotide polymorphism (SNP) analysis; and

(e) measurement of the level of a metabolite or a metabolic enzyme.

27. The method of claim 18 wherein the improvement is made by pre/post-treatment preparation and the pre/post-treatment preparation is a method of pre/post treatment preparation selected from the group consisting of:

(a) the use of colchicine or an analog thereof;

(b) the use of a uricosuric;

(c) the use of uricase;

(d) the non-oral use of nicotinamide;

(e) the use of a sustained-release form of nicotinamide;

(f) the use of an inhibitor of poly-ADP ribose polymerase;

(g) the use of caffeine;

(h) the use of leucovorin rescue;

(i) infection control; and

(j) the use of an anti-hypertensive agent.

28. The method of claim 18 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:

(a) use with thymidylate synthetase inhibitors;

(b) use with signal transduction inhibitors;

(c) use with cisplatin or platinum analogs;

(d) use with alkylating agents;

(e) use with anti-tubulin agents;

(f) use with antimetabolites;

(g) use with berberine;

(h) use with apigenin;

(i) use with colchicine or an analog thereof;

(j) use with genistein;

(k) use with etoposide;

(l) use with cytarabine;

(m) use with camptothecins;

(n) use with vinca alkaloids;

(p) use with 5-fluorouracil;

(q) use with curcumin;

(r) use with NF-κB inhibitors;

(s) use with rosmarinic acid;

(t) use with mitoguazone;

(u) use with meisoindigo;

(v) use with imatinib;
(w) use with dasatinib;
(x) use with nilotinib;
(y) use with epigenetic modulators;
(z) use with transcription factor inhibitors;
(aa) use with taxol;
(ab) use with homoharringtonine;
(ac) use with pyridoxal;
(ad) use with spirogermanium;
(ae) use with caffeine;
(af) use with nicotinamide;
(ag) use with methylglyoxalbisguanylhydrazone;
(ah) use with Rho kinase inhibitors;
(ai) use with 1,2,4-benzotriazine oxides;
(aj) use with an alkylglycerol;
(ak) use with an inhibitor of a Mer, Ax1, or Tyro-3 receptor kinase;
(al) use with an inhibitor of ATR kinase;
(am) use with a modulator of Fms kinase, Kit kinase, MAP4K4 kinase, TrkA kinase, or TrkB kinase;
(an) use with endoxifen;
(ao) use with a mTOR inhibitor;
(ap) use with an inhibitor of Mnk1a kinase, Mkn1b kinase, Mnk2a kinase, or Mnk2b kinase;
(aq) use with a modulator of pyruvate kinase M2;
(ar) use with a modulator of phosphoinositide 3-kinases;
(as) use with a cysteine protease inhibitor;
(at) use with phenformin;
(au) use with Sindbis virus-based vectors;
(av) use with peptidomimetics that act as mimetics of Smac and inhibit IAPs to promote apoptosis;
(aw) use with a Raf kinase inhibitor;
(ax) use with a nuclear transport modulator;
(ay) use with an acid ceramidase inhibitor and a choline kinase inhibitor;
(az) use with tyrosine kinase inhibitors;
(ba) use with anti-CS1 antibodies;
(bb) use with inhibitors of protein kinase CK2;
(bc) use with anti-guanylyl cyclase C (GCC) antibodies;
(bd) use with histone deacetylase inhibitors;
(be) use with cannabinoids;
(bf) use with glucagon-like peptide-1 (GLP-1) receptor agonists;
(bg) use with inhibitors of Bcl-2 or Bcl-xL;
(bh) use with Stat3 pathway inhibitors;
(bi) use with inhibitors of polo-like kinase 1 (Plk1);
(bj) use with GBPAR1 activators;
(bk) use with modulators of serine-threonine protein kinase and poly(ADP-ribose) polymerase (PARP) activity;
(bl) use with taxanes;

(bm) use with inhibitors of dihydrofolate reductase;
(bn) use with inhibitors of aromatase;
(bo) use with benzimidazole-based anti-neoplastic agents;
(bp) use with an O6-methylguanine-DNA-methyltransferase (MGMT) inhibitor;
(bq) use with CCR9 inhibitors;
(br) use with acid sphingomyelinase inhibitors;
(bs) use with peptidomimetic macrocycles;
(bt) use with cholanic acid amides;
(bu) use with substituted oxazaphosphorines;
(bv) use with anti-TWEAK receptor antibodies;
(bw) use with an ErbB3 binding protein;
(bx) use with a glutathione S-transferase-activated anti-neoplastic compound;
(by) use with substituted phosphorodiamidates;
(bz) use with inhibitors of MEKK protein kinase;
(ca) use with COX-2 inhibitors;
(cb) use with cimetidine and a cysteine derivative;
(cc) use with anti-IL-6 receptor antibody;
(cd) use with an antioxidant;
(ce) use with an isoxazole inhibitor of tubulin polymerization;
(cf) use with PARP inhibitors;
(cg) use with Aurora protein kinase inhibitors;
(ch) use with peptides binding to prostate-specific membrane antigen;
(ci) use with CD19 binding agents;
(cj) use with benzodiazepines;
(ck) use with Toll-like receptor (TLR) agonists;
(cl) use with bridged bicyclic sulfamides;
(cm) use with inhibitors of epidermal growth factor receptor kinase;
(cn) use with a ribonuclease of the T2 family having actin-binding activity;
(co) use with myrsinoic acid A or an analog thereof;
(cp) use with inhibitors of a cyclin-dependent kinase;
(cq) use with inhibitors of the interaction between p53 and MDM2;
(cr) use with inhibitors of the receptor tyrosine kinase MET;
(cs) use with largazole or largazole analogs;
(ct) use with inhibitors of AKT protein kinase;
(cu) use with 2′-fluoro-5-methyl-β-L-arabinofuranosyluridine or L-deoxythymidine;
(cv) use with HSP90 modulators;
(cw) use with inhibitors of JAK kinases;
(cx) use with inhibitors of PDK1 protein kinase;
(cy) use with PDE4 inhibitors;
(cz) use with inhibitors of proto-oncogene c-Met tyrosine kinase;
(da) use with inhibitors of indoleamine 2,3-dioxygenase;
(db) use with agents that inhibit expression of ATDC (TRIM29);

(dc) use with proteomimetic inhibitors of the interaction of nuclear receptor with coactivator peptides;
(dd) use with antagonists of XIAP family proteins;
(de) use with tumor-targeted superantigens;
(df) use with inhibitors of Pim kinases;
(dg) use with inhibitors of CHK1 or CHK2 kinases;
(dh) use with inhibitors of angiopoietin-like 4 protein;
(di) use with Smo antagonists;
(dj) use with nicotinic acetylcholine receptor antagonists;
(dk) use with farnesyl protein transferase inhibitors;
(dl) use with adenosine A3 receptor antagonists;
(dm) use with a cancer vaccine;
(dn) use with a JAK2 inhibitor; and
(do) use with a Src inhibitor.

29. The method of claim 28 wherein the drug combination is selected from the group consisting of:
(a) use with meisoindigo;
(b) use with imatinib;
(c) use with dasatinib;
(d) use with nilotinib;
(e) use with epigenetic modulators;
(f) use with transcription factor inhibitors;
(g) use with taxol;
(h) use with homoharringtonine;
(i) use with pyridoxal;
(j) use with spirogermanium;
(k) use with caffeine;
(l) use with nicotinamide;
(m) use with methylglyoxalbisguanylhydrazone;
(n) use with Rho kinase inhibitors;
(o) use with 1,2,4-benzotriazine oxides;
(p) use with an alkylglycerol;
(q) use with an inhibitor of a Mer, Ax1, or Tyro-3 receptor kinase;
(r) use with an inhibitor of ATR kinase;
(s) use with a modulator of Fms kinase, Kit kinase, MAP4K4 kinase, TrkA kinase, or TrkB kinase;
(t) use with endoxifen;
(u) use with a mTOR inhibitor;
(v) use with an inhibitor of Mnk1a kinase, Mkn1b kinase, Mnk2a kinase, or Mnk2b kinase;
(w) use with a modulator of pyruvate kinase M2;
(x) use with a modulator of phosphoinositide 3-kinases;
(y) use with a cysteine protease inhibitor;
(z) use with phenformin;
(aa) use with Sindbis virus-based vectors;
(ab) use with peptidomimetics that act as mimetics of Smac and inhibit IAPs to promote apoptosis;

(ac) use with a Raf kinase inhibitor;
(ad) use with a nuclear transport modulator;
(ae) use with an acid ceramidase inhibitor and a choline kinase inhibitor;
(af) use with anti-CS1 antibodies;
(ag) use with inhibitors of protein kinase CK2;
(ah) use with anti-guanylyl cyclase C (GCC) antibodies;
(ai) use with histone deacetylase inhibitors;
(aj) use with cannabinoids;
(ak) use with glucagon-like peptide-1 (GLP-1) receptor agonists;
(al) use with inhibitors of Bcl-2 or Bcl-xL;
(am) use with Stat3 pathway inhibitors;
(an) use with inhibitors of polo-like kinase 1 (Plk1);
(ao) use with GBPAR1 activators;
(ap) use with modulators of serine-threonine protein kinase and poly(ADP-ribose) polymerase (PARP) activity;
(aq) use with taxanes;
(ar) use with inhibitors of dihydrofolate reductase;
(as) use with inhibitors of aromatase;
(at) use with benzimidazole-based anti-neoplastic agents;
(au) use with an O6-methylguanine-DNA-methyltransferase (MGMT) inhibitor;
(av) use with CCR9 inhibitors;
(aw) use with acid sphingomyelinase inhibitors;
(ax) use with peptidomimetic macrocycles;
(ay) use with cholanic acid amides;
(az) use with substituted oxazaphosphorines;
(ba) use with anti-TWEAK receptor antibodies;
(bb) use with an ErbB3 binding protein;
(bc) use with a glutathione S-transferase-activated anti-neoplastic compound;
(bd) use with substituted phosphorodiamidates;
(be) use with inhibitors of MEKK protein kinase;
(bf) use with COX-2 inhibitors;
(bg) use with cimetidine and a cysteine derivative;
(bh) use with anti-IL-6 receptor antibody;
(bi) use with an antioxidant;
(bj) use with an isoxazole inhibitor of tubulin polymerization;
(bk) use with Aurora protein kinase inhibitors;
(bl) use with peptides binding to prostate-specific membrane antigen;
(bm) use with CD19 binding agents;
(bn) use with benzodiazepines;
(bo) use with Toll-like receptor (TLR) agonists;
(bp) use with bridged bicyclic sulfamides;
(bq) use with inhibitors of epidermal growth factor receptor kinase;
(br) use with a ribonuclease of the T2 family having actin-binding activity;

(bs) use with myrsinoic acid A or an analog thereof;
(bt) use with inhibitors of a cyclin-dependent kinase;
(bu) use with inhibitors of the interaction between p53 and MDM2;
(bv) use with inhibitors of the receptor tyrosine kinase MET;
(bw) use with largazole or largazole analogs;
(bx) use with inhibitors of AKT protein kinase;
(by) use with 2′-fluoro-5-methyl-β-L-arabinofuranosyluridine or L-deoxythymidine;
(bz) use with HSP90 modulators;
(ca) use with inhibitors of JAK kinases;
(cb) use with inhibitors of PDK1 protein kinase;
(cc) use with PDE4 inhibitors;
(cd) use with inhibitors of proto-oncogene c-Met tyrosine kinase;
(ce) use with inhibitors of indoleamine 2,3-dioxygenase;
(cf) use with agents that inhibit expression of ATDC (TRIM29);
(cg) use with proteomimetic inhibitors of the interaction of nuclear receptor with coactivator peptides;
(ch) use with antagonists of XIAP family proteins;
(ci) use with tumor-targeted superantigens;
(cj) use with inhibitors of Pim kinases;
(ck) use with inhibitors of CHK1 or CHK2 kinases;
(cl) use with inhibitors of angiopoietin-like 4 protein;
(cm) use with Smo antagonists;
(cn) use with nicotinic acetylcholine receptor antagonists;
(co) use with farnesyl protein transferase inhibitors;
(cp) use with adenosine A3 receptor antagonists;
(cq) use with a JAK2 inhibitor; and
(cr) use with a Src inhibitor.

30. The method of claim 18 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:
(a) use with ACE inhibitors;
(b) use with adenosine kinase inhibitors;
(c) use with adrenal cortex antagonists;
(d) use with AKT pathway inhibitors;
(e) use with angiogenesis inhibitors;
(f) use with angiostatic steroids;
(g) use with anti-androgens;
(h) use with anti-estrogens;
(i) use with anti-hypercalcemia agents;
(j) use with apoptosis inhibitors;
(k) use with ATI receptor antagonists;
(l) use with aurora kinase inhibitors;
(m) use with aromatase inhibitors;
(n) use with bisphosphonates;
(o) use with Bruton’s tyrosine kinase inhibitors;
(p) use with calcineurin inhibitors;

(q) use with CaM kinase II inhibitors;
(r) use with CD45 tyrosine phosphatase inhibitors;
(s) use with CDC25 phosphatase inhibitors;
(t) use with CHK kinase inhibitors;
(u) use with compounds targeting/decreasing a protein or lipid kinase activity;
(v) use with compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase;
(w) use with compounds which induce cell differentiation processes;
(x) use with cRAF kinase inhibitors;
(y) use with cyclin dependent kinase inhibitors;
(z) use with cysteine protease inhibitors;
(aa) use with DNA intercalators;
(ab) use with DNA strand breakers;
(ac) use with E3 ligase inhibitors;
(ad) use with EDG binders;
(ae) use with endocrine hormones;
(af) use with farnesyltransferase inhibitors;
(ag) use with Flk-1 kinase inhibitors;
(ah) use with Flt-3 inhibitors;
(ai) use with gonadorelin agonists;
(aj) use with heparanase inhibitors;
(ak) use with histone deacetylase (HDAC) inhibitors;
(al) use with IκBα inhibitors;
(am) use with insulin receptor tyrosine kinase inhibitors;
(an) use with c-Jun N-terminal kinase inhibitors;
(ao) use with microtubule binding agents;
(ap) use with mitogen-activated protein (MAP) kinase inhibitors;
(aq) use with MDM2 inhibitors;
(ar) use with MEK inhibitors;
(as) use with methionine aminopeptidase inhibitors;
(at) use with MMP inhibitors;
(au) use with NGFR tyrosine kinase inhibitors;
(av) use with p38 MAP kinase inhibitors;
(aw) use with p56 tyrosine kinase inhibitors;
(ax) use with PDGFR tyrosine kinase inhibitors;
(ay) use with phosphatidylinositol 3-kinase inhibitors;
(az) use with phosphatase inhibitors;
(ba) use with protein phosphatase inhibitors;
(bb) use with PKC inhibitors;
(bc) use with PKC delta kinase inhibitors;
(bd) use with polyamine synthesis inhibitors;
(be) use with proteasome inhibitors;
(bf) use with PTP1B inhibitors;
(bg) use with protein tyrosine kinase inhibitors;
(bh) use with SRC family tyrosine kinase inhibitors;
(bi) use with Syk tyrosine kinase inhibitors;

(bj) use with Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitors;
(bk) use with inhibitors of Ras oncogenic isoforms;
(bl) use with retinoids;
(bm) use with ribonucleotide reductase inhibitors;
(bn) use with RNA polymerase II elongation inhibitors;
(bo) use with S-adenosylmethionine decarboxylase inhibitors;
(bp) use with serine/threonine kinase inhibitors;
(bq) use with compounds which target, decrease, or inhibit the activity or function of serine/threonine mTOR kinase;
(br) use with somatostatin receptor antagonists;
(bs) use with telomerase inhibitors;
(bu) use with VEGFR tyrosine kinase inhibitors; and
(bt) use with RANKL inhibitors.

31. The method of claim 18 wherein the improvement is made by chemosensitization and the chemosensitization comprises the use of a hexitol derivative as a chemosensitizer in combination with an agent selected from the group consisting of:
(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin or platinum analogs;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) colchicine or an analog of colchicine;
(m) genistein;
(n) etoposide;
(o) cytarabine;
(p) camptothecin;
(q) vinca alkaloids;
(r) 5-fluorouracil;
(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid; and
(v) mitoguazone.

32. The method of claim 18 wherein the improvement is made by chemopotentiation and the chemopotentiation comprises the use of a hexitol derivative as a chemopotentiator in combination with an agent selected from the group consisting of:
(a) fraudulent nucleosides;
(b) fraudulent nucleotides;
(c) thymidylate synthetase inhibitors;
(d) signal transduction inhibitors;
(e) cisplatin or platinum analogs;

(f) alkylating agents;
(g) anti-tubulin agents;
(h) antimetabolites;
(i) berberine;
(j) apigenin;
(k) colchicine or analogs of colchicine;
(l) genistein;
(m) etoposide;
(n) cytarabine;
(o) camptothecins;
(p) vinca alkaloids;
(q) topoisomerase inhibitors;
(r) 5-fluorouracil;
(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid;
(v) mitoguazone; and
(w) a biotherapeutic.

33. The method of claim 18 wherein the improvement is made by use of a drug delivery system and the drug delivery system is a drug delivery system selected from the group consisting of:

(a) oral dosage forms;
(b) nanocrystals;
(c) nanoparticles;
(d) cosolvents;
(e) slurries;
(f) syrups;
(g) bioerodible polymers;
(h) liposomes;
(i) slow-release injectable gels;
(j) microspheres; and
(k) targeting compositions with epidermal growth factor receptor-binding peptides.

34. The method of claim 18 wherein the improvement is made by use of a drug conjugate form and the drug conjugate form is a drug conjugate form selected from the group consisting of:

(a) a polymer system;
(b) polylactides;
(c) polyglycolides;
(d) amino acids;
(e) peptides;
(f) multivalent linkers;
(g) immunoglobulins;
(h) cyclodextrin polymers;
(i) modified transferrin;
(j) hydrophobic or hydrophobic-hydrophilic polymers;

(k) conjugates with a phosphonoformic acid partial ester;

(l) conjugates with a cell-binding agent incorporating a charged cross-linker; and

(m) conjugates with β-glucuronides through a linker.

35. The method of claim 18 wherein the improvement is made by use of a prodrug system and the prodrug system is a prodrug system selected from the group consisting of:

(a) the use of enzyme sensitive esters;

(b) the use of dimers;

(c) the use of Schiff bases;

(d) the use of pyridoxal complexes;

(e) the use of caffeine complexes;

(f) the use of nitric oxide-releasing prodrugs;

(g) the use of prodrugs with fibroblast activation protein α-cleavable oligopeptides;

(h) the use of prodrugs that are products of reaction with an acetylating or carbamylating agent;

(i) the use of prodrugs that are hexanoate conjugates;

(j) the use of prodrugs that are polymer-agent conjugates; and

(k) the use of prodrugs that are subject to redox activation.

36. The method of claim 18 wherein the improvement is made by use of a multiple drug system and the multiple drug system is a multiple drug system selected from the group consisting of:

(a) inhibitors of multi-drug resistance;

(b) specific drug resistance inhibitors;

(c) specific inhibitors of selective enzymes;

(d) signal transduction inhibitors;

(e) meisoindigo;

(f) imatinib;

(g) hydroxyurea;

(h) dasatinib;

(i) capecitabine;

(j) nilotinib;

(k) repair inhibition agents; and

(l) topoisomerase inhibitors with non-overlapping side effects.

37. The method of claim 18 wherein the improvement is made by biotherapeutic enhancement and the biotherapeutic enhancement is be performed by use in combination as sensitizers/potentiators with a therapeutic agent or technique that is a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;

(b) cytokines;

(c) lymphokines;

(d) therapeutic antibodies;

(e) antisense therapies;

(f) gene therapies;

(g) ribozymes; and
(h) RNA interference.

38. The method of claim 18 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a malignancy resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;
(f) gene therapies;
(g) ribozymes; and
(h) RNA interference.

39. The method of claim 18 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a malignancy associated with a mutation in or dysregulation of the *AHI1* gene also resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;
(f) gene therapies;
(g) ribozymes; and
(h) RNA interference.

40. The method of claim 18 wherein the improvement is made by radiation therapy enhancement and the radiation therapy enhancement is a radiation therapy enhancement agent or technique selected from the group consisting of:

(a) use with hypoxic cell sensitizers;
(b) use with radiation sensitizers/protectors;
(c) use with photosensitizers;
(d) use with radiation repair inhibitors;
(e) use with thiol depleting agents;
(f) use with vaso-targeted agents;
(g) use with DNA repair inhibitors;
(h) use with radioactive seeds;
(i) use with radionuclides;
(j) use with radiolabeled antibodies; and
(k) use with brachytherapy.

41. The method of claim 18 wherein the improvement is by use of a novel mechanism of action and the novel mechanism of action is a novel mechanism of action that is a therapeutic interaction with a target or mechanism selected from the group consisting of:

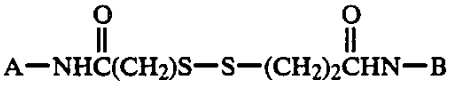
(a) inhibitors of poly-ADP ribose polymerase;
(b) agents that affect vasculature;
(c) agents that promote vasodilation;
(d) oncogenic targeted agents;
(e) signal transduction inhibitors;
(f) agents inducing EGFR inhibition;
(g) agents inducing Protein Kinase C inhibition;
(h) agents inducing Phospholipase C downregulation;
(i) agents including jun downregulation;
(j) agents modulating expression of histone genes;
(k) agents modulating expression of VEGF;
(l) agents modulating expression of ornithine decarboxylase;
(m) agents modulating expression of jun D;
(n) agents modulating expression of v-jun;
(o) agents modulating expression of GPCRs;
(p) agents modulating expression of protein kinase A;
(q) agents modulating expression of protein kinases other than protein kinase A;
(r) agents modulating expression of telomerase;
(s) agents modulating expression of prostate specific genes; and
(t) agents modulating expression of histone deacetylase.

42. The method of claim 18 wherein the improvement is made by use of selective target cell population therapeutics and the use of selective target cell population therapeutics is a use selected from the group consisting of:
(a) use against radiation sensitive cells;
(b) use against radiation resistant cells; and
(c) use against energy depleted cells.

43. The method of claim 18 wherein the improvement is made by use with an agent to enhance the activity of the hexitol derivative and the agent to enhance the activity of the hexitol derivative is selected from the group consisting of:
(a) nicotinamide;
(b) caffeine;
(c) tetandrine; and
(d) berberine.

44. The method of claim 18 wherein the improvement is made by use with an agent to counteract myelosuppression and the agent to counteract myelosuppression is a dithiocarbamate.

45. The method of claim 18 wherein the improvement is made by use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier and the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:
(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)
wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

$$A\text{-}NH(CH_2)_2S\text{-}S\text{-}B \text{ (cleavable linkage)}$$

(D-III(a)),
wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

$$A\text{-}NH{=}CH(CH_2)_3CH{=}NH\text{-}B \text{ (non-cleavable linkage)}$$

(D-III(b)),
wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

46. The method of claim 18 wherein the method to improve the efficacy and/or reduce the side effects of the administration of an alkylating hexitol derivative exerts a cytotoxic effect against cancer stem cells.

47. A pharmaceutical composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a hexitol derivative for the treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor comprising an alternative selected from the group consisting of a composition comprising:

(a) a therapeutically effective quantity of a hexitol derivative or a prodrug of a hexitol derivative; and

(b) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, drug delivery system, drug conjugate form, additional therapeutic agent that is part of a multiple drug system, agent for counteracting myelosuppression, or agent for increasing the ability of the hexitol derivative or the prodrug of the hexitol derivative to pass through the blood-brain barrier, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy selected from the group consisting of recurrent glioma and progressive secondary brain tumor;

wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol and wherein the prodrug of the hexitol derivative is selected from the group consisting of a prodrug of dianhydrogalactitol and a prodrug of diacetyldianhydrogalactitol.

48. The pharmaceutical composition of claim 47 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of recurrent glioma.

49. The pharmaceutical composition of claim 48 wherein the recurrent glioma is glioblastoma multiforme.

50. The pharmaceutical composition of claim 49 wherein the glioblastoma multiforme is substantially resistant to at least one of temozolomide and bevacizumab.

51. The pharmaceutical composition of claim 50 wherein the glioblastoma multiforme is substantially resistant to bevacizumab.

52. The pharmaceutical composition of claim 47 wherein the malignancy is a progressive secondary brain tumor.

53. The pharmaceutical composition of claim 52 wherein the progressive secondary brain tumor is a brain tumor that is a metastasis of a malignancy selected from the group consisting of adenocarcinoma of the breast, small-cell lung carcinoma, and melanoma.

54. The pharmaceutical composition of claim 47 wherein the composition comprises a drug combination comprising:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) cisplatin or platinum analogs;

(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone; and
(xix) tetrandrine.

55. The pharmaceutical composition of claim 47 wherein the composition comprises:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) colchicine or an analog of colchicine;
(xiii) genistein;
(xiv) etoposide;
(xv) cytarabine;
(xvi) camptothecin;
(xvii) vinca alkaloids;
(xviii) 5-fluorouracil;
(xix) curcumin;
(xx) NF-κB inhibitors;
(xxi) rosmarinic acid; and
(xxii) mitoguazone;

wherein the dianhydrogalactitol, diacetyldianhydrogalactitol, prodrug of dianhydrogalactitol, or prodrug of diacetyldianhydrogalactitol acts as a chemosensitizer.

56. The pharmaceutical composition of claim 47 wherein the composition comprises:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) colchicine or an analog of colchicine;
(xiii) genistein;
(xiv) etoposide;
(xv) cytarabine;
(xvi) camptothecin;
(xvii) vinca alkaloids;
(xviii) 5-fluorouracil;
(xix) curcumin;
(xx) NF-κB inhibitors;
(xxi) rosmarinic acid; and
(xxii) mitoguazone;

wherein the dianhydrogalactitol, diacetyldianhydrogalactitol, prodrug of dianhydrogalactitol, or prodrug of diacetyldianhydrogalactitol acts as a chemopotentiator.

57. The pharmaceutical composition of claim 47 wherein the composition comprises:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) a drug delivery system, wherein the drug delivery system is selected from the group consisting of:

(i) oral dosage forms;
(ii) nanocrystals;
(iii) nanoparticles;
(iv) cosolvents;
(v) slurries;
(vi) syrups;
(vii) bioerodible polymers;
(viii) liposomes;
(ix) slow-release injectable gels;
(x) microspheres; and

(xi) targeting compositions with epidermal growth factor receptor-binding peptides.

58. The pharmaceutical composition of claim 47 wherein the composition comprises a hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol which is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;
(ii) polylactides;
(iii) polyglycolides;
(iv) amino acids;
(v) peptides;
(vi) multivalent linkers;
(vii) immunoglobulins;
(viii) cyclodextrin polymers;
(ix) modified transferrin;
(x) hydrophobic or hydrophobic-hydrophilic polymers;
(xi) conjugates with a phosphonoformic acid partial ester;
(xii) conjugates with a cell-binding agent incorporating a charged cross-linker; and
(xiii) conjugates with β-glucuronides through a linker.

59. The pharmaceutical composition of claim 47 comprising a hexitol derivative selected from the group consisting of a prodrug of dianhydrogalactitol and a prodrug of diacetyldianhydrogalactitol wherein the prodrug is selected from the group consisting of:

(i) enzyme sensitive esters;
(ii) dimers;
(iii) Schiff bases;
(iv) pyridoxal complexes;
(v) caffeine complexes;
(vi) nitric oxide-releasing prodrugs;
(vii) prodrugs with fibroblast activation protein α-cleavable oligopeptides;
(viii) products of reaction with an acylating or carbamylating agent;
(ix) hexanoate conjugates;
(x) polymer-agent conjugates; and
(xi) prodrugs that are subject to redox activation.

60. The pharmaceutical composition of claim 47 comprising:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(i) an inhibitor of multi-drug resistance;

(ii) a specific drug resistance inhibitor;
(iii) a specific inhibitor of a selective enzyme;
(iv) a signal transduction inhibitor;
(v) an inhibitor of a repair enzyme; and
(vi) a topoisomerase inhibitor with non-overlapping side effects.

61. The pharmaceutical composition of claim 47 comprising:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

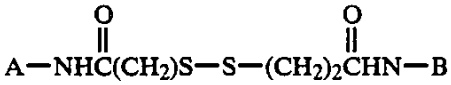
(b) an agent for counteracting myelosuppression, wherein the agent that counteracts myelosuppression is a dithiocarbamate.

62. The pharmaceutical composition of claim 47 comprising:

(a) a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol; and

(b) an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:

(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

$$A\text{-}NH(CH_2)_2S\text{-}S\text{-}B \text{ (cleavable linkage)}$$

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

$$A\text{-}NH{=}CH(CH_2)_3CH{=}NH\text{-}B \text{ (non-cleavable linkage)}$$

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

63. A kit, comprising, separately packaged, comprising two or more different doses of a hexitol derivative for treatment of a malignancy, wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of dianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol.

64. The kit of claim 63 wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol.

65. The kit of claim 64 wherein the hexitol derivative is dianhydrogalactitol.

66. The kit of claim 65 wherein the two or more different doses are:

(a) 1.5 mg/m^2 and 3.0 mg/m^2;

(b) 1.5 mg/m^2, 3.0 mg/m^2, and 5.0 mg/m^2;

(c) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, and 10 mg/m^2;

(d) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, and 15 mg/m^2;

(e) 10 mg/m^2; (iv) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, and 20 mg/m^2;

(f) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, and 25 mg/m^2;

(g) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, and 30 mg/m^2; and

(h) 1.5 mg/m^2, 3.0 mg/m^2, 5.0 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, and 40 mg/m^2.

67. The kit of claim 63 wherein the hexitol derivative is in the form of a pharmaceutical composition.

68. The kit of claim 63 wherein the doses are assembled into a blister pack.

69. The kit of claim 63 wherein the kit further comprises instructions for use.