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(54) Title: RNAI AGENTS FOR INHIBITING EXPRESSION OF HIF-2 ALPHA (*EPAS1*), COMPOSITIONS THEREOF, AND METHODS OF USE

(57) Abstract: The present disclosure relates to RNAi agents, for example, double stranded RNAi agents, able to inhibit HIF-2 alpha (*EPAS1*) gene expression. Also disclosed are pharmaceutical compositions that include HIF-2 alpha RNAi agents and methods of use thereof. The HIF-2 alpha RNAi agents disclosed herein may be linked or conjugated to targeting ligands (such as compounds that have affinity for integrins, including alpha-v-beta-3 and alpha-v-beta-5 integrins) and pharmacokinetic (PK) enhancers, to facilitate the delivery to cells and tissues, including to clear cell renal cell carcinoma (ccRCC) cells and tumors. Delivery of compositions comprising the HIF-2 alpha RNAi agents *in vivo* provides for inhibition of HIF-2 alpha gene expression. The HIF-2 alpha RNAi agents can be used in methods of treatment of various diseases and disorders, including ccRCC.

RNAi Agents for Inhibiting Expression of HIF-2 alpha (*EPAS1*), Compositions Thereof, and Methods of Use

SEQUENCE LISTING

[0001] This application contains a Sequence Listing which has been submitted in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy is named 30663_SEQ_LISTING.txt and is 227 kb in size.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Application Serial Nos. 62/790,360, filed January 9, 2019; 62/827,564, filed April 1, 2019; and 62/839,381, filed April 26, 2019; all of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

[0003] The present disclosure relates to RNA interference (RNAi) agents, for example, double stranded RNAi agents, for inhibition of HIF-2 alpha (*EPAS1*) gene expression, compositions that include HIF-2 alpha RNAi agents, and methods of use thereof.

BACKGROUND

[0004] Hypoxia-inducible factor-2 alpha (referred to as HIF-2 alpha, HIF2-alpha, Hif2alpha, or Hif2α), which is also known as endothelial PAS domain-containing protein 1 (EPAS1), is a hypoxia-inducible transcription factor that responds to decreases in available oxygen (hypoxia). HIF-2 alpha is encoded by the *EPAS1* gene (alternatively referred to herein as the "HIF-2 alpha gene"), and its expression is known to be upregulated under low oxygen conditions.

[0005] In certain human populations residing in high altitudes (such as Tibetans), it has been discovered that a high proportion of the population has evolved to carry certain allele variants of the HIF-2 alpha gene that serve to improve oxygen transport in the body in low oxygen environments. In more typical altitude environments, however, over-expression of wild-type *EPAS1* has been associated with increased hypertension and stroke, and with symptoms similar to mountain sickness due to excess production of red blood cells. Mutations

in this gene have also been associated with erythrocytosis familial type 4 and pulmonary hypertension.

[0006] Notably, while HIF-2 alpha is broadly expressed in a variety of tissues in humans, HIF-2 alpha protein has been identified as being required for expression of, or to enhance the expression of, various genes involved in an assortment of diseases, including tumor progression. For example, HIF-2 alpha is thought to play a role in the progression of uveal melanomas by promoting the autocrine loop VEGF-pVEGFR2/KDR, and by enhancing the expression of LDHA, thus conferring a growth advantage.

[0007] EPAS1 has also been shown to be associated with, or upregulate the expression of, other factors, including: cMyc (which favors cell proliferation, transformation, neoplasia and tumorigenesis, and which is highly expressed in most cancers); Interleukin 8 (a pro-inflammatory mediator, for example, in gingivitis and psoriasis); SP-1 (a transcription factor involved in IL-8 regulation and a coactivator of cMyc); LDH5 (which is linked with tumor necrosis and increased tumor size); and LANA (Latency Associated Nuclear Antigen, which is associated with Kaposi's sarcoma-associated Herpesvirus). In addition, HIF (hypoxia induced factor) activity in general may play a role in angiogenesis required for cancer tumor growth. For example, HIF-2 alpha is believed to be involved in several other diseases, including renal cancer, clear cell renal cell carcinoma (and metastases of this and other cancers), melanoma, inflammation, chronic inflammation, neovascular diseases, rheumatoid arthritis, uveal melanoma, chondrosarcoma, and multiple myeloma. Mutations in *EPAS1* gene have also been correlated to early onset of neuroendocrine tumors such as paragangliomas, somatostatinomas and/or pheochromocytomas. The mutations are commonly somatic missense mutations located in the primary hydroxylation site of HIF-2α. These mutations are believed to disrupt the protein hydroxylation/degradation mechanism and lead to protein stabilization and pseudohypoxic signaling. In addition, neuroendocrine tumors release erythropoietin (EPO) into circulating blood, and lead to polycythemia.

[0008] More specifically, HIF-2 alpha has been linked to tumor progression and metastasis in clear cell renal cell carcinoma (ccRCC). It is believed that a high proportion of ccRCC tumors express a mutant form of the Von Hippel-Landau protein that is incapable of degrading HIF-2 alpha, which leads to accumulation of HIF-2 alpha and activation of HIF-2 alpha-regulated genes that promote tumor growth and metastasis.

[0009] There continues to be a need for viable therapeutic treatments to treat various diseases, including carcinomas such as ccRCC. Similarly, there continues to be a need for therapeutic drug products that are capable of inhibiting the expression and/or reducing the

production of HIF-2 alpha. As just one example, a substantial reduction of HIF-2 alpha expression in ccRCC cells may be able to inhibit the undesired growth or otherwise slow the progression of these cancer cells.

[0010] One known method of inhibiting gene expression is through RNA interference (RNAi), by administering oligonucleotide-based drug products that are capable of inhibiting or silencing gene expression (*for example*, RNAi agents). However, great challenges remain in both identifying potent and stable oligonucleotide sequences capable of silencing gene expression *in vivo*, as well as determining therapeutically viable methods to safely and selectively deliver the therapeutic to the desired cells or tissues. Oligonucleotide-based drug products tend to readily and rapidly be degraded or filtered through the body when administered *in vivo* due to, among other things, their relatively small size and inherent organic properties, which often prevent them from reaching the intended target cells and/or tissues. Various attempts have been proposed to try to overcome this limitation including, for example, by encapsulation in liposomes, by iontophoresis, by incorporation into other vehicles such as hydrogels, cyclodextrins, biodegradable nanocapsules, bioadhesive microspheres, proteinaceous vectors, or Dynamic Polyconjugates™ (DPCs) (*see*, for example WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, each of which is incorporated herein by reference). Alternatively, conjugation of the oligonucleotides to targeting ligands, such as compounds having affinity to cell surface molecules, cell receptor ligands, haptens, antibodies, monoclonal antibodies, antibody fragments, or antibody mimics with affinity to cell surface molecules, have seen some recent success in delivering oligonucleotide-based therapeutics to hepatocytes in the liver. To date, however, efforts to target oligonucleotide-based drug products to extrahepatic cells have largely failed either due to a lack of efficacy, toxicities, or a combination of both.

[0011] Despite certain advances in the field, there continues to exist a need for improved delivery mechanisms to facilitate the delivery of therapeutics, including oligonucleotides and oligonucleotide-based drug products, *in vivo*. Further, there remains a need for potent and selective inhibitors of HIF-2 alpha.

SUMMARY

[0012] Disclosed herein are RNA interference (RNAi) agents (also herein termed RNAi agent, RNAi trigger, or trigger), for example, double-stranded RNAi agents, that are able to selectively and efficiently inhibit the expression of a HIF-2 alpha (*EPAS1*) gene. Further

disclosed herein are compositions that include an RNAi agent for inhibiting expression of HIF-2 alpha, wherein the HIF-2 alpha RNAi agent is linked to at least one targeting ligand that has affinity for a cell receptor present on a targeted cell, and, optionally, to at least one pharmacokinetic (PK) enhancer. The HIF-2 alpha RNAi agents disclosed herein can selectively and efficiently decrease or inhibit expression of a HIF-2 alpha (*EPAS1*) gene in a subject, for example, a human or animal subject.

[0013] In general, the present disclosure features HIF-2 alpha gene-specific RNAi agents, compositions that include HIF-2 alpha RNAi agents, and methods for inhibiting expression of a HIF-2 alpha (*EPAS1)* gene *in vivo* and/or *in vitro* using the HIF-2 alpha RNAi agents and compositions that include HIF-2 alpha RNAi agents described herein.

[0014] The described HIF-2 alpha RNAi agents can be used in methods for therapeutic treatment (including prophylactic and preventative treatment) of conditions and diseases that can be mediated at least in part by the reduction in HIF-2 alpha expression, including, for example, carcinomas such as clear cell renal cell carcinoma (ccRCC). The HIF-2 alpha RNAi agents disclosed herein can selectively reduce HIF-2 alpha gene expression in cells in a subject. The methods disclosed herein include the administration of one or more HIF-2 alpha RNAi agents to a subject, *for example*, a human or animal subject, using any suitable methods known in the art, such as intravenous infusion, intravenous injection, or subcutaneous injection.

[0015] In one aspect, the disclosure features RNAi agents for inhibiting expression of the human HIF-2 alpha (*EPAS1*) gene, wherein the RNAi agent includes a sense strand and an antisense strand. The HIF-2 alpha RNAi agents can further be linked or conjugated to one or more targeting ligands and/or one or more PK enhancers.

[0016] Also described herein are pharmaceutical compositions that include an RNAi agent capable of inhibiting the expression of a HIF-2 alpha (*EPAS1*) gene, wherein the composition further includes at least one pharmaceutically acceptable excipient. The pharmaceutical compositions described herein that include one or more of the disclosed HIF-2 alpha RNAi agents are able to selectively and efficiently decrease or inhibit expression of a HIF-2 alpha gene *in vivo*. The compositions that include one or more HIF-2 alpha RNAi agents can be administered to a subject, such as a human or animal subject, for the treatment (including prophylactic treatment or inhibition) of conditions and diseases that can be mediated at least in part by a reduction in HIF-2 alpha expression, including, for example, carcinomas such as ccRCC.

[0017] One aspect described herein is an RNAi agent for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene, comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3;

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand; and

(iii) one or more targeting ligands.

[0018] In another aspect described is an RNAi agent capable of inhibiting expression of a HIF-2 alpha (*EPAS1*) gene comprising:

(i) an antisense strand that is between 18 and 49 nucleotides in length that is at least partially complementary to a HIF-2 alpha (*EPAS1*) gene (SEQ ID NO:1);

(ii) a sense strand that is at least partially complementary to the antisense strand;

(iii) a targeting ligand linked to the sense strand; and

(iv) a PK enhancer linked to the sense strand.

[0019] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UUUCAUGAAAUCGUUACGUUG (SEQ ID NO: 827). In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UUUCAUGAAAUCGUUACGUUG (SEQ ID NO: 827), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UUUCAUGAAAUCGUUACGUUG (SEQ ID NO: 827), wherein SEQ ID NO: 827 is located at positions 1-21 (5′ → 3′) of the antisense strand.

[0020] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide

sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 7A through 7G showing all internucleoside linkages). In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0021] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0022] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO: 113), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO: 113), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and

uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0023] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACAUAGUACAUAGAGAAUGUG (SEQ ID NO: 883). In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACAUAGUACAUAGAGAAUGUG (SEQ ID NO: 883), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACAUAGUACAUAGAGAAUGUG (SEQ ID NO: 883), wherein SEQ ID NO: 883 is located at positions 1-21 (5′ → 3′) of the antisense strand.

[0024] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902). In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902), wherein SEQ ID NO: 902 is located at positions 1-21 (5′ → 3′) of the antisense strand.

[0025] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:761),

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (NH2-C6) is as defined in Table 7, and s represents a phosphorothioate linkage. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:761), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0026] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO:90), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) (Z)$_3$-(TriAlk14)s(invAb)scacauucuCfUfAfugu^{Z}ac^{Z}ua^{Z}ug^{Z}us(invAb)(C6-S)-X (SEQ ID NO:806), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (TriAlk14), (C6-S), and (invAb) are as defined in Table 7, and s represents a phosphorothioate linkage. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO:90), and a sense strand that consists

of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) $(Z)_3$-(TriAlk14)s(invAb)scacauucuCfUfAfugu^{Z}ac^{Z}ua^{Z}ug^{Z}us(invAb)(C6-S)-X (SEQ ID NO:806), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0027] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO:113), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) $(Z)_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcau^{Z}ac^{Z}ua^{Z}ac^{Z}as(invAb)(C6-S)-X (SEQ ID NO:810), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (TriAlk14), (C6-S), and (invAb), as defined in Table 7, and s represents a phosphorothioate linkage. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO:113), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) $(Z)_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcau^{Z}ac^{Z}ua^{Z}ac^{Z}as(invAb)(C6-S)-X (SEQ ID NO:810), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0028] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) selected from the group consisting of: Y-(NH-

C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:740), Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X (SEQ ID NO:756), Y-(NH-C6)scsaacg^{Z}uaa^{Z}CfGfAfu^{Z}uuc^{Z}augaasa(invAb)(6-S)-X (SEQ ID NO:757), and Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X (SEQ ID NO:762), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^{Z}, a^{Z}, g^{Z}, and c^{Z} represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (NH2-C6), (invAb), and (6-S) are as defined in Table 7, and s represents a phosphorothioate linkage. In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) selected from the group consisting of: Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:740), Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X (SEQ ID NO:756), Y-(NH-C6)scsaacg^{Z}uaa^{Z}CfGfAfu^{Z}uuc^{Z}augaasa(invAb)(6-S)-X (SEQ ID NO:757), and Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X (SEQ ID NO:762), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0029] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UUUCAUGAAAUCGUUACGUUG (SEQ ID NO:827);

ACAUAGUACAUAGAGAAUGUG (SEQ ID NO:883); or

UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902);

wherein the HIF-2 alpha RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

[0030] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UUUCAUGAAAUCGUUACGUUG (SEQ ID NO:827);

ACAUAGUACAUAGAGAAUGUG (SEQ ID NO:883); or

UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902);

wherein the HIF-2 alpha RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound having affinity for an integrin receptor.

[0031] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UUUCAUGAAAUCGUUACGUUG (SEQ ID NO:827);

ACAUAGUACAUAGAGAAUGUG (SEQ ID NO:883); or

UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902);

wherein the HIF-2 alpha RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound having affinity for an integrin receptor; and wherein the respective antisense strand sequence is located at positions 1-21 of the antisense strand.

[0032] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequence (5′ → 3′) pairs:

UUUCAUGAAAUCGUUACGUUG (SEQ ID NO:827) and

CAACGUAACGAUUUCAUGAAA (SEQ ID NO: 428);

ACAUAGUACAUAGAGAAUGUG (SEQ ID NO:883) and

CACAUUCUCUAUGUACUAUGU (SEQ ID NO: 485); or

UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902) and

ACACAACUGUCCAUACUAACA (SEQ ID NO: 507);

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

[0033] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′) pairs:

UUUCAUGAAAUCGUUACGUUG (SEQ ID NO:827) and

CAACGUAACGAUUUCAUGAAA (SEQ ID NO: 428);

ACAUAGUACAUAGAGAAUGUG (SEQ ID NO:883) and

CACAUUCUCUAUGUACUAUGU (SEQ ID NO: 485); or

UGUUAGUAUGGACAGUUGUGU (SEQ ID NO: 902) and

ACACAACUGUCCAUACUAACA (SEQ ID NO: 507);

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0034] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30);

asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90); or

usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO: 113);

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage; and wherein the HIF-2 alpha RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides of the sense strand are modified nucleotides.

[0035] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30);

asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90); or

usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO: 113);

wherein the HIF-2 alpha RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides of the sense strand are modified nucleotides; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0036] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises modified nucleotide sequences that differs by 0 or 1 nucleotides from one of the following nucleotide sequence pairs (5′ → 3′):

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:761);

asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90) and

$(Z)_3$-(TriAlk14)s(invAb)scacauucuCfUfAfugu^{Z}ac^{Z}ua^{Z}ug^{Z}us(invAb)(C6-S)-X (SEQ ID NO: 806);

usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO:113) and

$(Z)_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcau^{Z}ac^{Z}ua^{Z}ac^{Z}as(invAb)(C6-S)-X (SEQ ID NO: 328);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:810) and

Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:740);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X (SEQ ID NO:756);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacg^{Z}uaa^{Z}CfGfAfu^{Z}uuc^{Z}augaasa(invAb)(6-S)-X (SEQ ID NO:757);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X (SEQ ID NO:762); wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^{Z}, a^{Z}, g^{Z}, and c^{Z} represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (TriAlk14), (NH2-C6), (C6-S), (6-S), and (invAb), as defined in Table 7, and s represents a phosphorothioate linkage.

[0037] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises one of the following nucleotide sequence pairs (5′ → 3′):

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:761);

asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg (SEQ ID NO: 90) and

(*Z*)$_3$-(TriAlk14)s(invAb)scacauucuCfUfAfugu^{Z}ac^{Z}ua^{Z}ug^{Z}us(invAb)(C6-S)-X (SEQ ID NO:806);

usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu (SEQ ID NO:113) and

(*Z*)$_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcau^{Z}ac^{Z}ua^{Z}ac^{Z}as(invAb)(C6-S)-X (SEQ ID NO:810);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X (SEQ ID NO:740);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X (SEQ ID NO:756);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacg^{Z}uaa^{Z}CfGfAfu^{Z}uuc^{Z}augaasa(invAb)(6-S)-X (SEQ ID NO:757);

usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO:30) and

Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X (SEQ ID NO:762);

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); u^{Z}, a^{Z}, g^{Z}, and c^{Z} represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for

example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), (TriAlk14), (NH2-C6), (C6-S), (6-S), and (invAb), as defined in Table 7, and s represents a phosphorothioate linkage; and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0038] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UUUCAUGAAAUCGUUACGU (SEQ ID NO: 5);

UGUUAGUAUGGACAGUUGU (SEQ ID NO: 10); and

ACAUAGUACAUAGAGAAUG (SEQ ID NO: 13).

[0039] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UUUCAUGAAAUCGUUACGU (SEQ ID NO: 5);

UGUUAGUAUGGACAGUUGU (SEQ ID NO: 10); and

ACAUAGUACAUAGAGAAUG (SEQ ID NO: 13).

wherein all or substantially all of the nucleotides are modified nucleotides.

[0040] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UUUCAUGAAAUCGUUACGU (SEQ ID NO: 5);

UGUUAGUAUGGACAGUUGU (SEQ ID NO: 10); and

ACAUAGUACAUAGAGAAUG (SEQ ID NO: 13);

wherein all or substantially all of the nucleotides are modified nucleotides, and wherein SEQ ID NO:5, SEQ ID NO: 10 and SEQ ID NO: 13, respectively, is located at nucleotide positions 1-19 (5′ → 3′) of the antisense strand.

[0041] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by 0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5′ → 3′):

UUUCAUGAAAUCGUUACGU (SEQ ID NO:5) and ACGUAACGAUUUCAUGAAA (SEQ ID NO: 17);

UGUUAGUAUGGACAGUUGU (SEQ ID NO:10); and ACAACUGUCCAUACUAACA (SEQ ID NO: 22); or

ACAUAGUACAUAGAGAAUG (SEQ ID NO:13) and CAUUCUCUAUGUACUAUGU (SEQ ID NO:25).

[0042] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by 0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5′ → 3′):

UUUCAUGAAAUCGUUACGU (SEQ ID NO:5) and ACGUAACGAUUUCAUGAAA (SEQ ID NO: 17);

UGUUAGUAUGGACAGUUGU (SEQ ID NO:10); and ACAACUGUCCAUACUAACA (SEQ ID NO: 22); or

ACAUAGUACAUAGAGAAUG (SEQ ID NO:13) and CAUUCUCUAUGUACUAUGU (SEQ ID NO:25); and

wherein all or substantially all of the nucleotides are modified nucleotides.

[0043] In some embodiments, the compositions described herein comprising one or more HIF-2 alpha RNAi agents are packaged in a kit, container, pack, dispenser, pre-filled syringes, or vials. In some embodiments, the compositions described herein are administered parenterally, e.g., by intravenous injection, intravenous infusion, or subcutaneous injection.

[0044] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0045] Other objects, features, aspects, and advantages of the invention will be apparent from the following detailed description, accompanying figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. Schematic diagram of a HIF-2 alpha RNAi agent (shown as the double-helix) linked to a tridentate targeting group that includes three Structure 2-avb3 targeting ligands, a

C18-diacid PK enhancer, and four internal Structure 2-abv3 targeting ligands linked shown linked to internal nucleotides on the HIF-2 alpha RNAi agent. Chemical structures for the targeting ligands, targeting group, and PK enhancer are shown.

FIG. 2. Schematic diagram of a HIF-2 alpha RNAi agent (shown as the double-helix) shown linked to a PK enhancer on one end, and a tridentate scaffold suitable for forming a tridentate targeting group that includes three targeting ligands on the other end. The HIF-2 alpha RNA agent diagram further shows certain possible sites for linking targeting ligands (represented as "TL" in Figure 2) to the HIF-2 alpha RNAi agent, including showing four targeting ligands linked to internal nucleotides.

FIG. 3A to 3D. Chemical structure representation of HIF-2 alpha RNAi agent AD06299, in a free acid form, showing "TL" at the 2' position of nucleotides 2, 4, 6, and 8 (3'→ 5') of the sense strand starting from the first nucleotide that forms a base pair with the antisense strand (starting on Fig. 3D and continuing to Fig. 3C). "TL" represents the site of conjugation of a targeting ligand on these internal nucleotides.

FIG. 4A to 4B. Images showing the tumor size from tumor-bearing mice on day 36 according to the study described in Example 16 herein. Figure 4A shows the tumor size from the vehicle control group (D5W), with the left kidney being the contralateral kidney and the right kidney (larger) the tumor kidney. Figure 4B shows the tumor size from the mice administered with HIF-2 alpha RNAi agent, with the left kidney being the contralateral kidney and the right kidney being the tumor kidney.

FIG. 5A to 5B. Images showing immunohistochemistry (IHC) staining of HIF-2 alpha protein from the tumor-bearing mice dosed according to Example 16 herein. Figure 5A shows the vehicle control group (D5W), with darkened spots showing the presence of HIF-2 alpha protein. Figure 5B shows the treatment group mice administered with HIF-2 alpha RNAi agent.

FIG. 6. Bar graph reflecting the tumor size of animals dosed according to Example 19 herein. Animals were categorized based on tumor size measurements on day 34.

FIG. 7A. to 7G. Schematic showing nucleotides, internucleoside linkages, and sense strand modifications of AD05971, AD06153, AD06157, AD05930, AD05966, AD05967 and AD05972 as synthesized on solid support, wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; aAlk, cAlk, gAlk,

and uAlk represent 2′-O-propargyl adenosine, cytidine, guanosine, and uridine, respectively, o represents a phosponate linkage, and s represents a phosphorothioate linkage, and invAb, 6-SS-6, C6-SS-C6, NH2-C6, and TriAlk14 are all as defined in Table 7. Further modifications to the RNAi agents of Figure 7 may be effected following cleavage from the solid support, such as addition of targeting ligands and PK Enhancers.

DETAILED DESCRIPTION

RNAi Agents

[0046] Described herein are RNAi agents for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene (referred to herein as HIF-2 alpha or HIF2α RNAi agents, or HIF-2 alpha or HIF2α RNAi triggers). A HIF-2 alpha RNAi agent described herein includes a sense strand (also referred to as a passenger strand), and an antisense strand (also referred to as a guide strand). The sense strand and the antisense strand can be partially, substantially, or fully complementary to each other. The length of the RNAi agent sense and antisense strands described herein each can be 16 to 49 nucleotides in length. In some embodiments, the sense and antisense strands are independently 17 to 26 nucleotides in length. The sense and antisense strands can be either the same length or different lengths. In some embodiments, the sense and antisense strands are independently 21 to 26 nucleotides in length. In some embodiments, the sense and antisense strands are independently 21 to 24 nucleotides in length. In some embodiments, both the sense strand and the antisense strand are 21 nucleotides in length. In some embodiments, the sense and/or antisense strands are independently 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. The RNAi agents described herein, upon delivery to a cell expressing HIF-2 alpha, inhibit the expression of one or more HIF-2 alpha (*EPAS1)* genes *in vivo* or *in vitro*.

[0047] One aspect described herein is an RNAi agent for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene, comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3;

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand; and

(iii) one or more targeting ligands.

[0048] In another aspect described is an RNAi agent capable of inhibiting expression of a HIF-2 alpha (*EPAS1*) gene comprising:

(i) an antisense strand that is between 18 and 49 nucleotides in length that is at least partially complementary to a HIF-2 alpha (*EPAS1*) gene (SEQ ID NO:1);

(ii) a sense strand that is at least partially complementary to the antisense strand;

(iii) a targeting ligand linked to the sense strand; and

(iv) a PK enhancer linked to the sense strand.

[0049] An antisense strand of a HIF-2 alpha RNAi agent described herein includes at least 16 consecutive nucleotides that have at least 85% complementarity to a core stretch sequence (also referred to herein as a "core stretch" or "core sequence") of the same number of nucleotides in a HIF-2 alpha mRNA and to a core stretch of the same number of nucleotides in the corresponding sense strand. In some embodiments, this antisense strand core stretch is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, this antisense strand core stretch is 19 nucleotides in length. In some embodiments, this antisense strand core stretch is 17 nucleotides in length.

[0050] A sense strand of the HIF-2 alpha RNAi agents described herein includes at least 16 consecutive nucleotides that have at least 85% identity to a core stretch of the same number of nucleotides in a HIF-2 alpha mRNA. In some embodiments, this sense strand core stretch is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, this sense strand core stretch is 17 nucleotides in length. In some embodiments, this sense strand core stretch is 19 nucleotides in length.

[0051] In some embodiments, the HIF-2 alpha RNAi agents disclosed herein target a portion of a HIF-2 alpha gene having the sequence of any of the sequences disclosed in Table 1.

[0052] Examples of HIF-2 alpha RNAi agent antisense strands that can be included in the HIF-2 alpha RNAi agents disclosed herein are provided in Table 3. Examples of HIF-2 alpha RNAi agent antisense strands that can be included in the HIF-2 alpha RNAi agents disclosed herein are provided in Tables 4, 4.1, 4.2, and 4.3. Examples of HIF-2 alpha RNAi agent duplexes are provided in Table 5. Examples of 19-nucleotide core stretch sequences that consist of or are included in the sense strands and antisense strands of HIF-2 alpha RNAi agents disclosed herein, are provided in Table 2.

[0053] In some embodiments, described herein are compositions that include one or more HIF-2 alpha RNAi agents that have the duplex structures disclosed in Table 5.

[0054] In a further aspect, the HIF-2 alpha RNAi agents disclosed herein can be delivered to target cells or tissues by covalently linking or conjugating the RNAi agent to one or more targeting ligands (for example, a ligand that includes a compound having affinity for one or more cell receptors located on a cell that expresses HIF-2 alpha). In some embodiments, a suitable targeting ligand includes or consists of a compound having affinity for one or more integrins (alternatively referred to as "integrin receptors").

[0055] The HIF-2 alpha RNAi agents can be delivered to cells, including but not limited to carcinoma cells such as (ccRCC) cells, using any oligonucleotide delivery technology known in the art. Nucleic acid delivery methods include, but are not limited to, by linking or conjugating to a targeting ligand, by encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres, proteinaceous vectors, or Dynamic Polyconjugates™ (DPCs).

[0056] In some embodiments, a HIF-2 alpha RNAi agent is linked to a targeting ligand comprising a compound that has affinity for one or more integrins (hereinafter referred to as an "integrin targeting ligand"). In some embodiments, a suitable targeting ligand for use with the HIF-2 alpha RNAi agents disclosed herein has affinity for integrin alpha-v-beta 3, integrin alpha-v-beta-5, or both of these integrins. Targeting ligands can be present individually (just one targeting compound present), or two or more targeting ligands may be linked via a branch point or scaffold, together forming a targeting group, and the branch point or scaffold of the targeting group is then singularly linked to the RNAi agent. Targeting groups may include two targeting ligands (referred to as "bidentate"), three targeting ligands ("tridentate"), four targeting ligands ("tetradentate"), or more than four targeting ligands. In some embodiments, a HIF-2 alpha RNAi agent is linked to two or more targeting ligands. In some embodiments, a HIF-2 alpha RNAi agent is linked to two to ten targeting ligands. In some embodiments, a HIF-2 alpha RNAi agent is liked to seven targeting ligands. In some embodiments, a HIF-2 alpha RNAi agent is liked to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more than 10 targeting ligands.

[0057] In some embodiments, when HIF-2 alpha RNAi agents are conjugated to targeting ligands that include compounds having affinity for integrin alpha-v-beta 3 and/or integrin alpha-v-beta-5, the RNAi agents are selectively internalized by ccRCC cells, either through receptor-mediated endocytosis or by other means. Examples of targeting ligands and targeting groups that have affinity for integrin alpha-v-beta 3 and/or integrin alpha-v-beta-5 that are useful for delivering HIF-2 alpha RNAi agents are disclosed, for example, in PCT Patent Publication No. WO 2019/210200, which is incorporated by reference herein in its entirety.

[0058] A targeting ligand can be linked to the 3′ or 5′ end of a sense strand, the 3′ or 5′ end of an antisense strand, and/or internally to one or more individual nucleotides of the sense strand and/or the antisense strand of a HIF-2 alpha RNAi agent. In some embodiments, a targeting ligand or targeting group is linked to the 3′ or 5′ end of the sense strand. In some embodiments, a targeting ligand or targeting group is linked to the 5′ end of the sense strand. In some embodiments, a targeting ligand or targeting group is linked internally to a nucleotide of the sense strand and/or the antisense strand of the RNAi agent. In some embodiments, a targeting ligand or targeting group is linked to the 5' terminal end of the sense strand, and one or more targeting ligands are linked to one or more internal nucleotides of the sense strand. In some embodiments, a targeting ligand or targeting group is linked to the RNAi agent via a linker.

[0059] A targeting ligand or a targeting group, with or without a linker, can be linked to the 5′ or 3′ end of any of the sense and/or antisense strands disclosed in Tables 2, 3, or 4, 4.1, 4.2, or 4.3. A linker, with or without a targeting ligand or targeting group, can be attached to the 5′ or 3′ end of any of the sense and/or antisense strands disclosed in Tables 2, 3, or 4, 4.1, 4.2, or 4.3.

[0060] In a further aspect, the HIF-2 alpha RNAi agents disclosed herein can be linked or conjugated to one or more pharmacokinetic/pharmacodynamic (PK) enhancers. As used herein, a PK enhancer (also referred to as a "pharmacokinetic (PK) modifier") is a compound that, when linked to an oligonucleotide-based drug product or other therapeutic, may increase systemic circulation time of the therapeutic *in vivo* (increased half-life or plasma residence time) versus the free form of the therapeutic by limiting renal excretion without impeding delivery of the therapeutic to the targeted cells or tissues, or that otherwise provides a pharmacodynamic improvement over the therapeutic without a PK enhancer. Exemplary PK enhancers suitable for use with HIF-2 alpha RNAi agents are disclosed herein are disclosed. The person of ordinary skill in the art, in view of the selected therapeutic, would be able to readily design relevant *in vivo* and/or *in vitro* studies to identify additional suitable PK enhancers. For example, studies may be readily designed comparing the therapeutic both with and without the PK enhancer that quantify the amount of drug product remaining in systemic circulation of the subject at various time intervals, or that evaluate the effect or potency or duration of effect of the therapeutic at relevant time points. Such is within the knowledge of the person of ordinary skill in the art.

[0061] In another aspect, the disclosure features methods for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene, wherein the methods include administering to a subject or to a cell

of a subject an amount of a HIF-2 alpha RNAi agent capable of inhibiting the expression of a HIF-2 alpha gene, wherein the HIF-2 alpha RNAi agent comprises a sense strand and an antisense strand, and wherein the antisense strand includes the sequence of any one of the antisense strand nucleotide sequences in Table 2 or Table 3. In some embodiments, disclosed herein are methods of inhibiting expression of a HIF-2 alpha gene, wherein the methods include administering to a subject or to a cell an amount of a HIF-2 alpha RNAi agent capable of inhibiting the expression of a HIF-2 alpha gene, wherein the HIF-2 alpha RNAi agent comprises a sense strand and an antisense strand, and wherein the sense strand includes the sequence of any one of the sense strand nucleotide sequences in Tables 2, 4, 4.1, 4.2, or 4.3. Also described herein are compositions for use in such methods.

[0062] Methods for delivering HIF-2 alpha RNAi agents to cells that express integrins (also referred to herein as "integrin receptors") in a subject, such as a mammal, *in vivo*, are also disclosed herein. In some embodiments, the delivery of the HIF-2 alpha RNAi agents to the desired cells is facilitated by linking the HIF-2 RNAi agent to one or more targeting ligands and/or one or more PK enhancers. Compositions for use in such methods are also described.

[0063] In a further aspect, the disclosure features methods of treatment (including preventative or prophylactic treatment) of diseases, conditions, or symptoms that can be mediated at least in part by a reduction in HIF-2 alpha expression, including ccRCC, wherein the methods include administering to a subject in need thereof a HIF-2 alpha RNAi agent having an antisense strand that includes the sequence of any of the sequences in Tables 2 or 3. In some embodiments, described herein are methods of treatment (including preventative treatment) of diseases, symptoms, or conditions that can be mediated at least in part by a reduction in HIF-2 alpha expression, including ccRCC, wherein the methods include administering to a subject in need thereof a HIF-2 alpha RNAi agent having a sense strand comprising the sequence of any of the sequences in Tables 2, 4, 4.1, 4.2, or 4.3. Also described herein are compositions for use in such methods.

[0064] Also described are methods of treating a human subject having a pathological state (such as a condition or disease), or being at risk of developing a pathological state, that is mediated at least in part by HIF-2 alpha gene expression, the methods comprising the step of administering to the subject a therapeutically effective amount of a HIF-2 alpha RNAi agent and/or HIF-2 alpha RNAi agent-containing composition. The method of treating a subject with a HIF-2 alpha RNAi agent and/or HIF-2 alpha RNAi agent-containing composition can optionally be combined with one or more steps of administering one or more additional (for example, a second, third, etc.) therapeutics or treatments. An additional therapeutic can be

another HIF-2 alpha RNAi agent (for example, a HIF-2 alpha RNAi agent that targets a different sequence within the HIF-2 alpha gene). An additional therapeutic can also be a small molecule drug, antibody, antibody fragment, and/or aptamer.

[0065] In a further aspect, described herein are pharmaceutical compositions that include one or more described HIF-2 alpha RNAi agent(s), optionally combined with one or more additional (second, third, etc.) therapeutics. In some embodiments, the pharmaceutical compositions that include one or more described HIF-2 alpha RNAi agent(s), optionally combined with one or more additional (for example second, third, etc.) therapeutics, can be formulated in a pharmaceutically acceptable carrier or diluent. In some embodiments, these compositions can be administered to a subject, such as a mammal. In some embodiments, the mammal is a human. In some embodiments, the optional one or more additional therapeutics is a drug product indicated for the treatment of cancer, such as one or more carcinomas. The HIF-2 alpha RNAi agent and additional therapeutic(s) can be administered in a single composition or they can be administered separately. In some embodiments, the one or more additional therapeutics is administered separately in separate dosage forms from the RNAi agent (*for example*, the HIF-2 alpha RNAi agent is administered by intravenous infusion or injection, while the additional therapeutic involved in the method of treatment dosing regimen is administered orally). In some embodiments, the described HIF-2 alpha RNAi agent(s) are administered to a subject in need thereof via intravenous infusion or injection, and the one or more optional additional therapeutics are also administered by intravenous infusion, injection, or orally, and together the administration provides for a treatment regimen for diseases and conditions that can be mediated by HIF-2 alpha gene expression, such as ccRCC. In some embodiments, the HIF-2 alpha RNAi agent and one or more additional therapeutics are combined into a single dosage form (for example, a "cocktail" formulated into a single composition for intravenous infusion or injection). The HIF-2 alpha RNAi agents, with or without the one or more additional therapeutics, can be combined with one or more excipients to form pharmaceutical compositions.

[0066] In some embodiments, disclosed herein are methods for inhibiting expression of a HIF-2 alpha gene in a cell or a subject, wherein the methods include administering to the cell or subject a HIF-2 alpha RNAi agent having a sense strand comprising the sequence of any of the sequences in Tables 4, 4.1, 4.2, or 4.3, and an antisense strand comprising the sequence of any of the sequences in Table 3.

[0067] In some embodiments, compositions for delivering a HIF-2 alpha RNAi agent to a ccRCC cell, *in vivo*, are described, the compositions comprising: a HIF-2 alpha RNAi agent

linked or conjugated to one or more targeting ligands. In some embodiments, the targeting ligand includes a compound having affinity for integrin alpha-v-beta-3 and/or integrin alpha-v-beta-5. In some embodiments, the HIF-2 alpha RNAi agent linked or conjugated to one or more targeting ligands is further linked or conjugated to one or more PK enhancers.

[0068] In some embodiments, disclosed herein are compositions for delivering a HIF-2 alpha RNAi agent to a ccRCC cell *in vivo*, the composition including a HIF-2 alpha RNAi agent conjugated or linked to one or more targeting ligands and/or targeting groups. In some embodiments, the targeting ligands and/or targeting groups comprise compounds having affinity to one or more integrins. In some embodiments, compositions for delivering a HIF-2 alpha RNAi agent to a ccRCC cell *in vivo* are described, the composition including a HIF-2 alpha RNAi agent linked to an alpha-v-beta-3 and/or alpha-v-beta-5 integrin targeting ligand.

[0069] In some embodiments, disclosed herein are methods for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene in a cell, wherein the methods include administering to the cell a HIF-2 alpha RNAi agent that includes an antisense strand that is at least partially complementary to the portion of the HIF-2 alpha mRNA having the sequence in Table 1. In some embodiments, disclosed herein are methods of inhibiting expression of a HIF-2 alpha gene in a cell, wherein the methods include administering to a cell a HIF-2 alpha RNAi agent that includes an antisense strand comprising the sequence of any of the sequences in Tables 2 or 3, and a sense strand that comprises any of the sequences in Table 2 or Table 4, 4.1, 4.2, or 4.3, that is at least partially complementary to the antisense strand. In some embodiments, disclosed herein are methods of inhibiting expression of a HIF-2 alpha gene in a cell, wherein the methods include administering a HIF-2 alpha RNAi agent that includes a sense strand that comprises any of the sequences in Table 2 or Table 4, 4.1, 4.2, or 4.3, and an antisense strand that includes the sequence of any of the sequences in Tables 2 or 3 that is at least partially complementary to the sense strand.

[0070] In some embodiments, disclosed herein are compositions for inhibiting expression of a HIF-2 alpha gene in a cell, wherein the methods include administering a composition that comprises a HIF-2 alpha RNAi agent having the duplex structure of a duplex set forth in Table 5.

[0071] The HIF-2 alpha RNAi agents disclosed herein are designed to target specific positions on a HIF-2 alpha (*EPAS1*) gene (SEQ ID NO:1). As defined herein, an antisense strand sequence is designed to target a HIF-2 alpha gene at a given position on the gene when the 5′ terminal nucleobase of the antisense strand is aligned with a position that is 19 nucleotides downstream (towards the 3′ end) from the position on the gene when base pairing

to the gene. For example, as illustrated in Tables 1 and 2 herein, an antisense strand sequence designed to target a HIF-2 alpha gene at position 5033 requires that when base pairing to the gene, the 5′ terminal nucleobase of the antisense strand is aligned with position 5051 of the HIF-2 alpha (*EPAS1*) gene.

[0072] As provided herein, a HIF-2 alpha RNAi agent does not require that the nucleobase at position 1 (5′ → 3′) of the antisense strand be complementary to the gene, provided that there is at least 85% complementarity (for example, at least 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% complementarity) of the antisense strand and the gene across a core stretch sequence of at least 16 consecutive nucleotides. For example, for a HIF-2 alpha RNAi agent disclosed herein that is designed to target position 5033 of a HIF-2 alpha gene, the 5′ terminal nucleobase of the antisense strand of the of the HIF-2 alpha RNAi agent must be aligned with position 5051 of the gene; however, the 5′ terminal nucleobase of the antisense strand may be, but is not required to be, complementary to position 5051 of a HIF-2 alpha gene, provided that there is at least 85% complementarity (for example, at least 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% complementarity) of the antisense strand and the gene across a core stretch sequence of at least 16 consecutive nucleotides. As shown by, among other things, examples disclosed herein, the specific site of binding of the gene by the antisense strand of the HIF-2 alpha RNAi agent (for example, whether the HIF-2 alpha RNAi agent is designed to target a HIF-2 alpha (*EPAS1*) gene at position 5033 or at some other position) is important to the level of inhibition achieved by the HIF-2 alpha RNAi agent.

[0073] The described HIF-2 alpha RNAi agents can mediate RNA interference to inhibit the expression of one or more genes necessary for production of HIF-2 alpha protein. HIF-2 alpha RNAi agents can also be used to treat or prevent various diseases, disorders, or conditions, including ccRCC. Furthermore, compositions for delivery of HIF-2 alpha RNAi agents to ccRCC cells *in vivo* are described.

[0074] The pharmaceutical compositions including one or more HIF-2 alpha RNAi agents can be administered in a number of ways depending upon whether local or systemic treatment is desired. Administration can be, but is not limited to, intravenous, intraarterial, subcutaneous, intraperitoneal, subdermal (for example, via an implanted device), and intraparenchymal administration. In some embodiments, the pharmaceutical compositions described herein are administered by intravenous infusion or injection.

[0075] In some embodiments, the compositions described herein comprising one or more HIF-2 alpha RNAi agents are packaged in a kit, container, pack, dispenser, pre-filled syringes,

infusion bag, or vials. In some embodiments, the compositions described herein are administered parenterally.

[0076] Each HIF-2 alpha RNAi agent comprises a sense strand and an antisense strand. The sense strand and the antisense strand each can be 16 to 30 nucleotides in length. The sense and antisense strands can be either the same length or they can be different lengths. In some embodiments, the sense and antisense strands are each independently 17 to 27 nucleotides in length. In some embodiments, the sense and antisense strands are each independently 17-21 nucleotides in length. In some embodiments, both the sense and antisense strands are each 21-26 nucleotides in length. In some embodiments, the sense and antisense strands are each 21-24 nucleotides in length. In some embodiments, the sense strand is about 19 nucleotides in length while the antisense strand is about 21 nucleotides in length. In some embodiments, the sense strand is about 21 nucleotides in length while the antisense strand is about 23 nucleotides in length. In some embodiments, a sense strand is 23 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, both the sense and antisense strands are each 21 nucleotides in length. In some embodiments, the RNAi agent sense and antisense strands are each independently 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 nucleotides in length. In some embodiments, a double-stranded RNAi agent has a duplex length of about 16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleotides.

[0077] In some embodiments, the region of perfect, substantial, or partial complementarity between the sense strand and the antisense strand is 16-26 (for example, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides in length and occurs at or near the 5′ end of the antisense strand (for example, this region may be separated from the 5′ end of the antisense strand by 0, 1, 2, 3, or 4 nucleotides that are not perfectly, substantially, or partially complementary).

[0078] The sense strand and antisense strand each contain a core stretch (also referred to herein as a "core sequence" or a "core stretch sequence") that is 16 to 23 nucleotides in length. An antisense strand core stretch is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a nucleotide sequence (sometimes referred to, *for example*, as a target sequence) present in the HIF-2 alpha (*EPAS1*) mRNA target. A sense strand core stretch sequence is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a core stretch sequence in the antisense strand, and thus the sense strand core stretch sequence is typically perfectly identical or at least about 85% identical to a nucleotide sequence (target sequence) present in the HIF-2 alpha mRNA target. A sense strand core stretch sequence can be the same length as a corresponding antisense core sequence or it can be a different length. In some embodiments, the antisense strand core stretch sequence is 16, 17, 18,

19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, the sense strand core stretch sequence is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length.

[0079] Examples of nucleotide sequences used in forming HIF-2 alpha RNAi agents are provided in Tables 2, 3, and 4 (as well as 4.1, 4.2, and 4.3). Examples of RNAi agent duplexes, that include the sense strand and antisense strand sequences in Tables 2, 3, and 4, are shown in Table 5.

[0080] The HIF-2 alpha RNAi agent sense and antisense strands anneal to form a duplex. A sense strand and an antisense strand of a HIF-2 alpha RNAi agent can be partially, substantially, or fully complementary to each other. Within the complementary duplex region, the sense strand core stretch sequence is at least 85% complementary or 100% complementary to the antisense core stretch sequence. In some embodiments, the sense strand core stretch sequence contains a sequence of at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 nucleotides that is at least 85% or 100% complementary to a corresponding 16, 17, 18, 19, 20, 21, 22, or 23 nucleotide sequence of the antisense strand core stretch sequence (for example, the sense and antisense core stretch sequences of a HIF-2 alpha RNAi agent may have a region of at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 nucleotides that is at least 85% base paired or 100% base paired.)

[0081] In some embodiments, the antisense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, the sense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2 or Table 4, 4.1, 4.2, or 4.3.

[0082] The sense strand and/or the antisense strand can optionally and independently contain an additional 1, 2, 3, 4, 5, or 6 nucleotides (extension) at the 3′ end, the 5′ end, or both the 3′ and 5′ ends of the core stretch sequences. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sequence in the HIF-2 alpha mRNA. The sense strand additional nucleotides, if present, may or may not be identical to the corresponding sequence in the HIF-2 alpha mRNA. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sense strand's additional nucleotides, if present.

[0083] As used herein, an extension comprises 1, 2, 3, 4, 5, or 6 nucleotides at the 5' and/or 3' end of the sense strand core stretch sequence and/or antisense strand core stretch sequence. The extension nucleotides on a sense strand may or may not be complementary to nucleotides,

either core stretch sequence nucleotides or extension nucleotides, in the corresponding antisense strand. Conversely, the extension nucleotides on an antisense strand may or may not be complementary to nucleotides, either core stretch nucleotides or extension nucleotides, in the corresponding sense strand. In some embodiments, both the sense strand and the antisense strand of an RNAi agent contain 3′ and 5′ extensions. In some embodiments, one or more of the 3′ extension nucleotides of one strand base pairs with one or more 5′ extension nucleotides of the other strand. In other embodiments, one or more of 3′ extension nucleotides of one strand do not base pair with one or more 5′ extension nucleotides of the other strand. In some embodiments, a HIF-2 alpha RNAi agent has an antisense strand having a 3′ extension and a sense strand having a 5′ extension. In some embodiments, the extension nucleotide(s) are unpaired and form an overhang. As used herein, an "overhang" refers to a stretch of one or more unpaired nucleotides located at a terminal end of either the sense strand or the antisense strand that does not form part of the hybridized or duplexed portion of an RNAi agent disclosed herein.

[0084] In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In other embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, or 3 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprise nucleotides that are complementary to the corresponding HIF-2 alpha mRNA sequence. In some embodiments, one or more of the antisense strand extension nucleotides comprise nucleotides that are not complementary to the corresponding HIF-2 alpha mRNA sequence.

[0085] In some embodiments, the 5' and/or 3′ end of the antisense strand can include abasic residues (Ab), which can also be referred to as an "abasic site" or "abasic nucleotide." An abasic residue (Ab) is a nucleotide or nucleoside that lacks a nucleobase at the 1′ position of the sugar moiety. (*See, for example,* U.S. Patent No. 5,998,203, which is incorporated by reference herein). In some embodiments, an abasic residue can be placed internally in a nucleotide sequence. In some embodiments, Ab or AbAb can be added to the 3′ end of the antisense strand. In some embodiments, the 5′ end of the sense strand can include one or more additional abasic residues (for example, (Ab) or (AbAb)). In some embodiments, UUAb, UAb, or Ab are added to the 3′ end of the sense strand. In some embodiments, an abasic (deoxyribose) residue can be replaced with a ribitol (abasic ribose) residue.

[0086] In some embodiments, the sense strand or the antisense strand may include a "terminal cap," which as used herein is a non-nucleotide compound or other moiety that can

be incorporated at one or more termini of a strand of an RNAi agent disclosed herein, and can provide the RNAi agent, in some instances, with certain beneficial properties, such as, for example, protection against exonuclease degradation. In some embodiments, inverted abasic residues (invAb) are added as terminal caps (*see* Table 7). (See, for example, F. Czauderna, Nucleic Acids Res., 2003, 31(11), 2705-16). Terminal caps are generally known in the art, and include, for example, inverted abasic residues as well as carbon chains such as a terminal C_3H_7 (propyl), C_6H_{13} (hexyl), or $C_{12}H_{25}$ (dodecyl) group. In some embodiments, a terminal cap is present at either the 5′ terminal end, the 3′ terminal end, or both the 5′ and 3′ terminal ends of the sense strand. In some embodiments, the 3′ end of the sense strand may include additional abasic residues or inverted abasic terminal caps.

[0087] In some embodiments, one or more inverted abasic residues (invAb) are added to the 3′ end of the sense strand. In some embodiments, one or more inverted abasic residues (invAb) are added to the 5′ end of the sense strand. In some embodiments, one or more inverted abasic residues or inverted abasic sites are inserted between the targeting ligand and the nucleotide sequence of the sense strand of the RNAi agent. In some embodiments, the inclusion of one or more inverted abasic residues or inverted abasic sites at or near the terminal end or terminal ends of the sense strand of an RNAi agent allows for enhanced activity or other desired properties of an RNAi agent.

[0088] In some embodiments, one or more inverted abasic residues (invAb) are added to the 5′ end of the sense strand. In some embodiments, one or more inverted abasic residues can be inserted between the targeting ligand and the nucleotide sequence of the sense strand of the RNAi agent. In some embodiments, the inclusion of one or more inverted abasic residues at or near the terminal end or terminal ends of the sense strand of an RNAi agent may allow for enhanced activity or other desired properties of an RNAi agent. In some embodiments, an inverted abasic (deoxyribose) residue can be replaced with an inverted ribitol (abasic ribose) residue.

[0089] In some embodiments, the 3′ end of the antisense strand core stretch sequence, or the 3′ end of the antisense strand sequence, may include an inverted abasic residue (invAb (see Table 7)).

[0090] In some embodiments, a HIF-2 alpha RNAi agent comprises a sense strand having a 3′ extension of 1, 2, 3, 4, or 5 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprises adenosine, uracil, or thymidine nucleotides, AT dinucleotide, or nucleotides that correspond to or are the identical to nucleotides in the HIF-2 alpha mRNA sequence. In some embodiments, the 3′ sense strand extension includes or

consists of one of the following sequences, but is not limited to: T, UT, TT, UU, UUT, TTT, or TTTT (each listed 5′ to 3′).

[0091] In some embodiments, a HIF-2 alpha RNAi agent comprises a sense strand having a 5′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprise nucleotides that correspond to or are identical to nucleotides in the HIF-2 alpha mRNA sequence. In some embodiments, the sense strand 5′ extension is one of the following sequences, but is not limited to: CA, AUAGGC, AUAGG, AUAG, AUA, A, AA, AC, GCA, GGCA, GGC, UAUCA, UAUC, UCA, UAU, U, UU (each listed 5′ to 3′). A sense strand can have a 3′ extension and/or a 5' extension.

[0092] Examples of sequences used in forming HIF-2 alpha RNAi agents are provided in Tables 2, 3, and 4, 4.1, 4.2, and 4.3. In some embodiments, a HIF-2 alpha RNAi agent antisense strand includes a sequence of any of the sequences in Tables 2 or 3. In certain embodiments, a HIF-2 alpha RNAi agent antisense strand comprises or consists of any one of the modified sequences in Table 3. In some embodiments, a HIF-2 alpha RNAi agent antisense strand includes the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 2-15, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, or 2-21, of any of the sequences in Tables 2 or 3. In some embodiments, a HIF-2 alpha RNAi agent sense strand includes the sequence of any of the sequences in Tables 2 or 4. In some embodiments, a HIF-2 alpha RNAi agent sense strand includes the sequence of nucleotides (from 5′ end → 3′ end) 1-18, 1-19, 1-20, 1-21, 2-19, 2-20, 2-21, 3-20, 3-21, or 4-21 of any of the sequences in Tables 2 or 4. In certain embodiments, a HIF-2 alpha RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 4, 4.1, 4.2, or 4.3.

[0093] In some embodiments, the sense and antisense strands of the RNAi agents described herein contain the same number of nucleotides. In some embodiments, the sense and antisense strands of the RNAi agents described herein contain different numbers of nucleotides. In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a blunt end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a blunt end. In some embodiments, both ends of an RNAi agent form blunt ends. In some embodiments, neither end of an RNAi agent is blunt-ended. As used herein a "blunt end" refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands are complementary (form a complementary base-pair).

[0094] In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a frayed end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a frayed end. In some embodiments, both ends of an RNAi

agent form a frayed end. In some embodiments, neither end of an RNAi agent is a frayed end. As used herein a frayed end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands from a pair (do not form an overhang) but are not complementary (form a non-complementary pair). In some embodiments, one or more unpaired nucleotides at the end of one strand of a double stranded RNAi agent form an overhang. The unpaired nucleotides may be on the sense strand or the antisense strand, creating either 3' or 5' overhangs. In some embodiments, the RNAi agent contains: a blunt end and a frayed end, a blunt end and 5′ overhang end, a blunt end and a 3′ overhang end, a frayed end and a 5′ overhang end, a frayed end and a 3′ overhang end, two 5′ overhang ends, two 3′ overhang ends, a 5′ overhang end and a 3′ overhang end, two frayed ends, or two blunt ends. Typically, when present, overhangs are located at the 3' terminal ends of the sense strand, the antisense strand, or both the sense strand and the antisense strand.

[0095] Modified nucleotides, when used in various polynucleotide or oligonucleotide constructs, can preserve activity of the compound in cells while at the same time increasing the serum stability of these compounds, and can also minimize the possibility of activating interferon activity in humans upon administering of the polynucleotide or oligonucleotide construct.

[0096] In some embodiments, a HIF-2 alpha RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid. In some embodiments, a HIF-2 alpha RNAi agent is prepared as a sodium salt. Such forms that are well known in the art are within the scope of the inventions disclosed herein.

Definitions

[0097] As used herein, the terms "oligonucleotide" and "polynucleotide" mean a polymer of linked nucleosides each of which can be independently modified or unmodified.

[0098] As used herein, an "RNAi agent" (also referred to as an "RNAi trigger") means a composition that contains an RNA or RNA-like (for example, chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting (for example, degrades or inhibits under appropriate conditions) translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. As used herein, RNAi agents may operate through the RNA interference mechanism (for example, by inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). While it is believed that RNAi agents, as that term is used herein, operate primarily through the RNA

interference mechanism, the disclosed RNAi agents are not bound by or limited to any particular pathway or mechanism of action. RNAi agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: short (or small) interfering RNAs (siRNAs), double stranded RNAs (dsRNA), micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the RNAi agents described herein is at least partially complementary to the mRNA being targeted (HIF-2 alpha mRNA). RNAi agents can include one or more modified nucleotides and/or one or more non-phosphodiester linkages.

[0099] As used herein, the terms "silence," "reduce," "inhibit," "down-regulate," or "knockdown" when referring to expression of a given gene, mean that the expression of the gene, as measured by the level of RNA transcribed from the gene or the level of polypeptide, protein, or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is treated with the RNAi agents described herein as compared to a second cell, group of cells, tissue, organ, or subject that has not or have not been so treated.

[0100] As used herein, the terms "sequence" and "nucleotide sequence" mean a succession or order of nucleobases or nucleotides, described with a succession of letters using standard nomenclature.

[0101] As used herein, a "base," "nucleotide base," or "nucleobase," is a heterocyclic pyrimidine or purine compound that is a component of a nucleotide, and includes the primary purine bases adenine and guanine, and the primary pyrimidine bases cytosine, thymine, and uracil. A nucleobase may further be modified to include, without limitation, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. (See, for example, Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008). The synthesis of such modified nucleobases (including phosphoramidite compounds that include modified nucleobases) is known in the art.

[0102] As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleobase or nucleotide sequence (for example, RNAi agent sense strand or targeted mRNA) in relation to a second nucleobase or nucleotide sequence (for example, RNAi agent antisense strand or a single-stranded antisense oligonucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize (form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions in vitro)) and form a duplex or double helical structure under certain standard conditions with an oligonucleotide or polynucleotide including the second nucleotide

sequence. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification. For example, a and Af, as defined herein, are complementary to U (or T) and identical to A for the purposes of determining identity or complementarity.

[0103] As used herein, "perfectly complementary" or "fully complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, all (100%) of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0104] As used herein, "partially complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 70%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0105] As used herein, "substantially complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 85%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0106] As used herein, the terms "complementary," "fully complementary," "partially complementary," and "substantially complementary" are used with respect to the nucleobase or nucleotide matching between the sense strand and the antisense strand of an RNAi agent, or between the antisense strand of an RNAi agent and a sequence of a HIF-2 alpha (*EPAS1*) mRNA.

[0107] As used herein, the term "substantially identical" or "substantial identity," as applied to a nucleic acid sequence means the nucleotide sequence (or a portion of a nucleotide sequence) has at least about 85% sequence identity or more, for example, at least 90%, at least 95%, or at least 99% identity, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the same type of nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the

window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompass nucleotide sequences substantially identical to those disclosed herein.

[0108] As used herein, the terms "treat," "treatment," and the like, mean the methods or steps taken to provide relief from or alleviation of the number, severity, and/or frequency of one or more symptoms of a disease in a subject. As used herein, "treat" and "treatment" may include the preventative treatment, management, prophylactic treatment, and/or inhibition or reduction of the number, severity, and/or frequency of one or more symptoms of a disease in a subject.

[0109] As used herein, the phrase "introducing into a cell," when referring to an RNAi agent, means functionally delivering the RNAi agent into a cell. The phrase "functional delivery," means delivering the RNAi agent to the cell in a manner that enables the RNAi agent to have the expected biological activity, for example, sequence-specific inhibition of gene expression.

[0110] As used herein, the term "isomers" refers to compounds that have identical molecular formulae, but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images are termed "enantiomers," or sometimes optical isomers. A carbon atom bonded to four non-identical substituents is termed a "chiral center."

[0111] As used herein, unless specifically identified in a structure as having a particular conformation, for each structure in which asymmetric centers are present and thus give rise to enantiomers, diastereomers, or other stereoisomeric configurations, each structure disclosed herein is intended to represent all such possible isomers, including their optically pure and racemic forms. For example, the structures disclosed herein are intended to cover mixtures of diastereomers as well as single stereoisomers.

[0112] As used in a claim herein, the phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. When used in a claim herein, the phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention.

[0113] The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (for example, N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which

the compound or composition is placed. Accordingly, as used herein, the structures disclosed herein envisage that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover the disclosed compounds and compositions regardless of their state of protonation based on the environment (such as pH), as would be readily understood by the person of ordinary skill in the art.

[0114] As used herein, the term "linked" or "conjugated" when referring to the connection between two compounds or molecules means that two molecules are joined by a covalent bond or are associated via noncovalent bonds (for example, hydrogen bonds or ionic bonds). In some examples, where the term "linked" or "conjugated" refers to the association between two molecules via noncovalent bonds, the association between the two different molecules has a K_D of less than 1×10^{-4} M (for example, less than 1×10^{-5} M, less than 1×10^{-6} M, or less than 1×10^{-7} M) in physiologically acceptable buffer (for example, buffered saline). Unless stated, the terms "linked" and "conjugated" as used herein may refer to the connection between a first compound and a second compound either with or without any intervening atoms or groups of atoms.

[0115] As used herein, a linking group is one or more atoms that connects one molecule or portion of a molecule to another to second molecule or second portion of a molecule. Similarly, as used in the art, the term scaffold is sometimes used interchangeably with a linking group. Linking groups may comprise any number of atoms or functional groups. In some embodiments, linking groups may not facilitate any biological or pharmaceutical response, and merely serve to link two biologically active molecules.

[0116] Unless stated otherwise, use of the symbol  as used herein means that any group or groups may be linked thereto that is in accordance with the scope of the inventions described herein.

[0117] As used herein, the term "including" is used to herein mean, and is used interchangeably with, the phrase "including but not limited to." The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless the context clearly indicates otherwise.

[0118] As used in a claim herein, the phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. When used in a claim herein, the phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention.

Modified Nucleotides

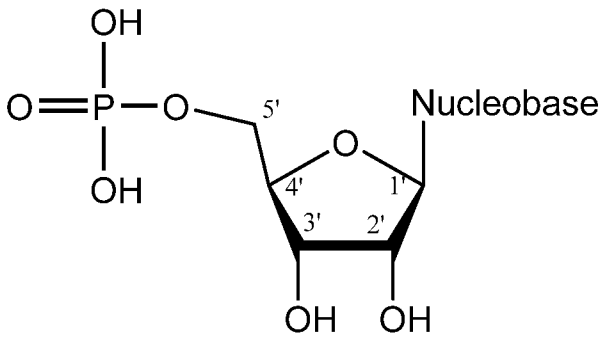
[0119] In some embodiments, a HIF-2 alpha RNAi agent contains one or more modified nucleotides. As used herein, a "modified nucleotide" is a nucleotide other than a ribonucleotide (2′-hydroxyl nucleotide). In some embodiments, at least 50% (for example, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100%) of the nucleotides are modified nucleotides. As used herein, modified nucleotides can include, but are not limited to, deoxyribonucleotides, nucleotide mimics, abasic nucleotides, 2′-modified nucleotides, inverted nucleotides, modified nucleobase-comprising nucleotides, bridged nucleotides, peptide nucleic acids (PNAs), 2′,3′-seco nucleotide mimics (unlocked nucleobase analogues), locked nucleotides, 3′-O-methoxy (2′ internucleoside linked) nucleotides, 2'-F-Arabino nucleotides, 5'-Me, 2'-fluoro nucleotide, morpholino nucleotides, vinyl phosphonate deoxyribonucleotides, vinyl phosphonate containing nucleotides, and cyclopropyl phosphonate containing nucleotides. 2′-modified nucleotides (i.e., a nucleotide with a group other than a hydroxyl group at the 2′ position of the five-membered sugar ring) include, but are not limited to, 2′-O-methyl nucleotides, 2′-fluoro nucleotides (also referred to herein as 2′-deoxy-2′-fluoro nucleotides), 2′-deoxy nucleotides, 2′-methoxyethyl (2′-O-2-methoxylethyl) nucleotides (also referred to as 2′-MOE), 2′-amino nucleotides, and 2′-alkyl nucleotides. It is not necessary for all positions in a given compound to be uniformly modified. Conversely, more than one modification can be incorporated in a single HIF-2 alpha RNAi agent or even in a single nucleotide thereof. The HIF-2 alpha RNAi agent sense strands and antisense strands can be synthesized and/or modified by methods known in the art. Modification at one nucleotide is independent of modification at another nucleotide.

[0120] Modified nucleobases include synthetic and natural nucleobases, such as 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, (for example, 2-aminopropyladenine, 5-propynyluracil, or 5-propynylcytosine), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, inosine, xanthine, hypoxanthine, 2-aminoadenine, 6-alkyl (for example, 6-methyl, 6-ethyl, 6-isopropyl, or 6-n-butyl) derivatives of adenine and guanine, 2-alkyl (for example, 2-methyl, 2-ethyl, 2-isopropyl, or 2-n-butyl) and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, cytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-sulfhydryl, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (for example, 5-bromo), 5-trifluoromethyl, and other 5-substituted uracils and cytosines, 7-methylguanine and 7-

methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

[0121] In some embodiments, all or substantially all of the nucleotides of an RNAi agent are modified nucleotides. As used herein, an RNAi agent wherein substantially all of the nucleotides present are modified nucleotides is an RNAi agent having four or fewer (0, 1, 2, 3, or 4) nucleotides in both the sense strand and the antisense strand being ribonucleotides (unmodified). As used herein, a sense strand wherein substantially all of the nucleotides present are modified nucleotides is a sense strand having two or fewer (0, 1, or 2) nucleotides in the sense strand being unmodified ribonucleotides. As used herein, an antisense sense strand wherein substantially all of the nucleotides present are modified nucleotides is an antisense strand having two or fewer (0, 1, or 2) nucleotides in the sense strand being unmodified ribonucleotides. In some embodiments, one or more nucleotides of an RNAi agent is an unmodified ribonucleotide.

[0122] As mentioned elsewhere herein, in some embodiments, the HIF-2 alpha RNAi agents disclosed herein can be linked to one or more targeting ligands and/or one or more PK enhancers on internal nucleotides of the sense strand or antisense strand of the RNAi agent to facilitate the delivery of the HIF-2 alpha RNAi agent *in vivo*. In some embodiments, the targeting ligands or PK enhancers are linked or conjugated to one or more internal nucleotides of the sense strand of the HIF-2 alpha RNAi agent. For example, a targeting ligand may be linked to an individual nucleotide at the 2' position of the ribose ring, the 3' position of the ribose ring, the 1' position of the ribose ring or to the nucleobase of the nucleotide, the 4' position of the ribose ring, the 5' position of the nucleotide, or to the oxygen atom on the ribose ring. The following depicts a hypothetical ribose nucleotide, with the carbons numbered:



[0123] In some embodiments, to facilitate the linkage of one or more targeting ligands to internal nucleotides, 2'-O-propargyl modified nucleotides are incorporated to the nucleotide sequence (*See, for example*, Table 7 and Tables 4, 4.1, 4.2, and 4.3). The 2'-O-propargyl modified nucleotides, after synthesis of the respective strand, can be linked or conjugated to

targeting ligands, targeting groups, and/or PK enhancers at the 2' position using standard coupling techniques as known in the art.

[0124] In some embodiments, a HIF-2 alpha RNAi agents disclosed herein may be synthesized to have at least one 2'-O-propargyl modified nucleotide in the sense strand to facilitate the linkage to a targeting ligand or targeting group. In some embodiments, the sense strand of an RNAi agent is synthesized to include at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, or more than 10 2'-O-propargyl modified nucleotides, in order to facilitate the linkage to at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, or more than 10 targeting ligands and/or targeting groups, respectively, to internal nucleotides. In some embodiments, the HIF-2 alpha RNAi agents disclosed herein may be synthesized with one 2'-O-propargyl modified nucleotide in the sense strand. In some embodiments, the HIF-2 alpha RNAi agent disclosed herein may be synthesized with two 2'-O-propargyl modified nucleotides in the sense strand. In some embodiments, the HIF-2 alpha RNAi agent disclosed herein may be synthesized with three 2'-O-propargyl modified nucleotides in the sense strand. In some embodiments, the HIF-2 alpha RNAi agent disclosed herein may be synthesized with four 2'-O-propargyl modified nucleotides in the sense strand. In some embodiments, the HIF-2 alpha RNAi agent disclosed herein may be synthesized with five 2'-O-propargyl modified nucleotides in the sense strand. In some embodiments, the HIF-2 alpha RNAi agent disclosed herein may be synthesized with more than five 2'-O-propargyl modified nucleotides in the sense strand.

Modified Internucleoside Linkages

[0125] In some embodiments, one or more nucleotides of a HIF-2 alpha RNAi agent are linked by non-standard linkages or backbones (for example, modified internucleoside linkages or modified backbones). Modified internucleoside linkages or backbones include, but are not limited to, phosphorothioate groups (represented herein as a lower case "s"), chiral phosphorothioates, thiophosphates, phosphorodithioates, phosphotriesters, aminoalkyl-phosphotriesters, alkyl phosphonates (for example, methyl phosphonates or 3′-alkylene phosphonates), chiral phosphonates, phosphinates, phosphoramidates (for example, 3′-amino phosphoramidate, aminoalkylphosphoramidates, or thionophosphoramidates), thionoalkyl-phosphonates, thionoalkylphosphotriesters, morpholino linkages, boranophosphates having normal 3′-5′ linkages, 2′-5′ linked analogs of boranophosphates, or boranophosphates having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3′-5′ to 5′-3′ or 2′-5′ to 5′-2′. In some embodiments, a modified internucleoside linkage or backbone lacks a

phosphorus atom. Modified internucleoside linkages lacking a phosphorus atom include, but are not limited to, short chain alkyl or cycloalkyl inter-sugar linkages, mixed heteroatom and alkyl or cycloalkyl inter-sugar linkages, or one or more short chain heteroatomic or heterocyclic inter-sugar linkages. In some embodiments, modified internucleoside backbones include, but are not limited to, siloxane backbones, sulfide backbones, sulfoxide backbones, sulfone backbones, formacetyl and thioformacetyl backbones, methylene formacetyl and thioformacetyl backbones, alkene-containing backbones, sulfamate backbones, methyleneimino and methylenehydrazino backbones, sulfonate and sulfonamide backbones, amide backbones, and other backbones having mixed N, O, S, and CH_2 components.

[0126] In some embodiments, a sense strand of a HIF-2 alpha RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, an antisense strand of a HIF-2 alpha RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages. In some embodiments, a sense strand of a HIF-2 alpha RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, an antisense strand of a HIF-2 alpha RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, or 4 phosphorothioate linkages.

[0127] In some embodiments, a HIF-2 alpha RNAi agent sense strand contains at least two phosphorothioate internucleoside linkages. In some embodiments, the at least two phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 3' end of the sense strand. In some embodiments, one phosphorothioate internucleoside linkage is at the 5’ end of the sense strand, and another phosphorothioate linkage is at the 3’ end of the sense strand. In some embodiments, two phosphorothioate internucleoside linkage are located at the 5’ end of the sense strand, and another phosphorothioate linkage is at the 3’ end of the sense strand. In some embodiments, the sense strand does not include any phosphorothioate internucleoside linkages between the nucleotides, but contains one, two, or three phosphorothioate linkages between the terminal nucleotides on both the 5’ and 3’ ends and the optionally present inverted abasic residue terminal caps. In some embodiments, the targeting ligand is linked to the sense strand via a phosphorothioate linkage.

[0128] In some embodiments, a HIF-2 alpha RNAi agent antisense strand contains four phosphorothioate internucleoside linkages. In some embodiments, the four phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 5' end of the antisense strand and between the nucleotides at positions 19-21, 20-22, 21-23, 22-24, 23-25, or 24-26 from the 5' end. In some embodiments, three phosphorothioate internucleoside linkages

are located between positions 1-4 from the 5' end of the antisense strand, and a fourth phosphorothioate internucleoside linkage is located between positions 20-21 from the 5' end of the antisense strand. In some embodiments, a HIF-2 alpha RNAi agent contains at least three or four phosphorothioate internucleoside linkages in the antisense strand.

[0129] In some embodiments, a HIF-2 alpha RNAi agent contains one or more modified nucleotides and one or more modified internucleoside linkages. In some embodiments, a 2′-modified nucleoside is combined with modified internucleoside linkage.

HIF-2 alpha RNAi Agents

[0130] In some embodiments, the HIF-2 alpha RNAi agents disclosed herein target a HIF-2 alpha gene at or near the positions of the HIF-2 alpha gene sequence shown in Table 1. In some embodiments, the antisense strand of a HIF-2 alpha RNAi agent disclosed herein includes a core stretch sequence that is fully, substantially, or at least partially complementary to a target HIF-2 alpha 19-mer sequence disclosed in Table 1.

Table 1. HIF-2 alpha 19-mer mRNA Target Sequences (taken from *homo sapiens* endothelial PAS domain protein 1 (EPAS1 or HIF-2 alpha) transcript, GenBank NM_001430.4 (SEQ ID NO:1))

SEQ ID No.	HIF-2 alpha 19-mer Target Sequences (5′ → 3′)	Corresponding Positions on SEQ ID NO: 1
2	ACGUAACGAUUUCAUGAAC	5033-5051
3	ACAACUGUCCAUACUAACA	3442-3460
4	CAUUCUCUAUGUACUAUGU	4135-4153

[0131] In some embodiments, a HIF-2 alpha RNAi agent includes an antisense strand wherein position 19 of the antisense strand (5′→3′) is capable of forming a base pair with position 1 of a 19-mer target sequence disclosed in Table 1. In some embodiments, a HIF-2 alpha RNAi agent includes an antisense strand wherein position 1 of the antisense strand (5′→3′) is capable of forming a base pair with position 19 of the 19-mer target sequence disclosed in Table 1.

[0132] In some embodiments, a HIF-2 alpha RNAi agent includes an antisense strand wherein position 2 of the antisense strand (5′ → 3′) is capable of forming a base pair with position 18 of the 19-mer target sequence disclosed in Table 1. In some embodiments, a HIF-2 alpha RNAi agent includes an antisense strand wherein positions 2 through 18 of the antisense

strand (5′ → 3′) are capable of forming base pairs with each of the respective complementary bases located at positions 18 through 2 of the 19-mer target sequence disclosed in Table 1.

[0133] For the RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) can be perfectly complementary to the HIF-2 alpha gene, or can be non-complementary to the HIF-2 alpha gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) is a U, A, or dT. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) forms an A:U or U:A base pair with the sense strand.

[0134] In some embodiments, a HIF-2 alpha RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, a HIF-2 alpha RNAi sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 1-18, or 2-18 of any of the sense strand sequences in Table 2 or Table 4, 4.1, 4.2, or 4.3.

[0135] In some embodiments, a HIF-2 alpha RNAi agent is comprised of (i) an antisense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3, and (ii) a sense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 1-17 or 1-18 of any of the sense strand sequences in Table 2 or Table 4, 4.1, 4.2, or 4.3.

[0136] In some embodiments, the HIF-2 alpha RNAi agents include core 19-mer nucleotide sequences shown in the following Table 2.

Table 2. HIF-2 alpha RNAi Agent Antisense Strand and Sense Strand Core Stretch Base Sequences (N=any nucleobase)

SEQ ID No.	Antisense Strand Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID No.	Sense Strand Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions on SEQ ID NO: 1
5	UUUCAUGAAAUCGUUACGU	17	ACGUAACGAUUUCAUGAAA	5033-5051
6	GUUCAUGAAAUCGUUACGU	18	ACGUAACGAUUUCAUGAAC	5033-5051
7	AUUCAUGAAAUCGUUACGU	19	ACGUAACGAUUUCAUGAAU	5033-5051
8	NUUCAUGAAAUCGUUACGU	20	ACGUAACGAUUUCAUGAAN	5033-5051
9	NUUCAUGAAAUCGUUACGN	21	NCGUAACGAUUUCAUGAAN	5033-5051
10	UGUUAGUAUGGACAGUUGU	22	ACAACUGUCCAUACUAACA	3442-3460
11	NGUUAGUAUGGACAGUUGU	23	ACAACUGUCCAUACUAACN	3442-3460
12	NGUUAGUAUGGACAGUUGN	24	NCAACUGUCCAUACUAACN	3442-3460
13	ACAUAGUACAUAGAGAAUG	25	CAUUCUCUAUGUACUAUGU	4135-4153
14	UCAUAGUACAUAGAGAAUG	26	CAUUCUCUAUGUACUAUGA	4135-4153
15	NCAUAGUACAUAGAGAAUG	27	CAUUCUCUAUGUACUAUGN	4135-4153
16	NCAUAGUACAUAGAGAAUN	28	NAUUCUCUAUGUACUAUGN	4135-4153

[0137] The HIF-2 alpha RNAi agent sense strands and antisense strands that comprise or consist of the sequences in Table 2 can be modified nucleotides or unmodified nucleotides. In some embodiments, the HIF-2 alpha RNAi agents having the sense and antisense strand sequences that comprise or consist of the sequences in Table 2 are all or substantially all modified nucleotides.

[0138] In some embodiments, the antisense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2. In some embodiments, the sense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2.

[0139] As used herein, each N listed in a sequence disclosed in Table 2 may be independently selected from any and all nucleobases (including those found on both modified and unmodified nucleotides). In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is not complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is the same as the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is different from the N nucleotide at the corresponding position on the other strand.

[0140] Certain modified HIF-2 alpha RNAi agent antisense strands, as well as their underlying unmodified nucleobase sequences, are provided in Table 3. Certain modified HIF-2 alpha RNAi agent sense strands, as well as their underlying unmodified nucleobase sequences, are provided in Table 4 (as well as reflected in 4.1, 4.2, and 4.3). In forming HIF-2 alpha RNAi agents, each of the nucleotides in each of the underlying base sequences listed in Tables 3 and 4, as well as in Table 2, above, can be a modified nucleotide.

[0141] The HIF-2 alpha RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2 or Table 4, 4.1, 4.2, or 4.3, can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

[0142] In some embodiments, a HIF-2 alpha RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3.

[0143] In some embodiments, a HIF-2 alpha RNAi agent comprises or consists of a duplex having the nucleobase sequences of the sense strand and the antisense strand of any of the sequences in Table 2, Table 3 or Table 4, 4.1, 4.2, or 4.3.

[0144] Examples of antisense strands containing modified nucleotides are provided in Table 3. Examples of sense strands containing modified nucleotides are provided in Table 4.

[0145] As used in Tables 3 and 4 and 4.1, 4.2, and 4.3, the following notations are used to indicate modified nucleotides, targeting groups, and linking groups:

A	=	adenosine-3′-phosphate;
C	=	cytidine-3′-phosphate;
G	=	guanosine-3′-phosphate;
U	=	uridine-3′-phosphate
I	=	inosine-3′-phosphate
a	=	2′-O-methyladenosine-3′-phosphate
as	=	2′-O-methyladenosine-3′-phosphorothioate
c	=	2′-O-methylcytidine-3′-phosphate
cs	=	2′-O-methylcytidine-3′-phosphorothioate
g	=	2′-O-methylguanosine-3′-phosphate
gs	=	2′-O-methylguanosine-3′-phosphorothioate
t	=	2′-O-methyl-5-methyluridine-3′-phosphate
ts	=	2′-O-methyl-5-methyluridine-3′-phosphorothioate
u	=	2′-O-methyluridine-3′-phosphate
us	=	2′-O-methyluridine-3′-phosphorothioate
i	=	2′-O-methylinosine-3′-phosphate
is	=	2′-O-methylinosine-3′-phosphorothioate
Af	=	2′-fluoroadenosine-3′-phosphate
Afs	=	2′-fluoroadenosine-3′-phosporothioate
Cf	=	2′-fluorocytidine-3′-phosphate
Cfs	=	2′-fluorocytidine-3′-phosphorothioate
Gf	=	2′-fluoroguanosine-3′-phosphate
Gfs	=	2′-fluoroguanosine-3′-phosphorothioate
Tf	=	2′-fluoro-5′-methyluridine-3′-phosphate
Tfs	=	2′-fluoro-5′-methyluridine-3′-phosphorothioate
Uf	=	2′-fluorouridine-3′-phosphate
Ufs	=	2′-fluorouridine-3′-phosphorothioate

dA	=	2′-deoxyadenosine-3′-phosphate
dAs	=	2′-deoxyadenosine-3′-phosphorothioate
dC	=	2′-deoxycytidine-3′-phosphate
dCs	=	2′-deoxycytidine-3′-phosphorothioate
dG	=	2′-deoxyguanosine-3′-phosphate
dGs	=	2′-deoxyguanosine-3′-phosphorothioate
dT	=	2′-deoxythymidine-3′-phosphate
dTs	=	2′-deoxythymidine-3′-phosphorothioate
dU	=	2′-deoxyuridine-3′-phosphate
dUs	=	2′-deoxyuridine-3′-phosphorothioate
AUNA	=	2′,3′-seco-adenosine-3′-phosphate
AUNAS	=	2′,3′-seco-adenosine-3′-phosphorothioate
CUNA	=	2′,3′-seco-cytidine-3′-phosphate
CUNAS	=	2′,3′-seco-cytidine-3′-phosphorothioate
GUNA	=	2′,3′-seco-guanosine-3′-phosphate
GUNAS	=	2′,3′-seco-guanosine-3′-phosphorothioate
UUNA	=	2′,3′-seco-uridine-3′-phosphate
UUNAS	=	2′,3′-seco-uridine-3′-phosphorothioate
aAlk	=	2′-O-propargyladenosine-3′-phosphate, see Table 7
aAlks	=	2′-O-propargyladenosine-3′-phosphorothioate, see Table 7
cAlk	=	2′-O-propargylcytidine-3′-phosphate, see Table 7
cAlks	=	2′-O-propargylcytidine-3′-phosphorothioate, see Table 7
gAlk	=	2′-O-propargylguanosine-3′-phosphate, see Table 7
gAlks	=	2′-O-propargylguanosine-3′-phosphorothioate, see Table 7
tAlk	=	2′-O-propargyl-5-methyluridine-3′-phosphate, see Table 7
tAlks	=	2′-O-propargyl-5-methyluridine-3′-phosphorothioate, see Table 7
uAlk	=	2′-O-propargyluridine-3′-phosphate, see Table 7
uAlks	=	2′-O-propargyluridine-3′-phosphorothioate, see Table 7
a_2N	=	see Table 7
a_2Ns	=	see Table 7
(invAb)	=	inverted abasic deoxyribonucleotide, see Table 7
(invAb)s	=	inverted abasic deoxyribonucleotide-5′-phosphorothioate, see Table 7
s	=	phosphorothioate linkage
(C6-SS-Alk)	=	see Table 7
(C6-SS-C6)	=	see Table 7
(C3-SS-C3)	=	see Table 7
(6-SS-6)	=	see Table 7

(NH2-C6) = see Table 7
(C6-NH2) = see Table 7
(TriAlk#) = see Table 7
(TriAlk#)s = see Table 7

[0146] As the person of ordinary skill in the art would readily understand, unless otherwise indicated by the sequence (such as, for example, by a phosphorothioate linkage "s"), when present in an oligonucleotide, the nucleotide monomers are mutually linked by 5'-3'-phosphodiester bonds. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides. Further, the person of ordinary skill in the art would readily understand that the terminal nucleotide at the 3' end of a given oligonucleotide sequence would typically have a hydroxyl (-OH) group at the respective 3' position of the given monomer instead of a phosphate moiety *ex vivo*. Additionally, for the embodiments disclosed herein, when viewing the respective strand 5' → 3', the inverted abasics are inserted such that the 3' position of the deoxyribose is linked at the 3' end of the preceding monomer on the respective strand. Moreover, as the person of ordinary skill would readily understand and appreciate, while the phosphorothioate chemical structures depicted herein typically show the anion on the sulfur atom, the inventions disclosed herein encompass all phosphorothioate tautomers (for example, where the sulfur atom has a double-bond and the anion is on an oxygen atom). Unless expressly indicated otherwise herein, such understandings of the person of ordinary skill in the art are used when describing the HIF-2 alpha RNAi agents and compositions of HIF-2 alpha RNAi agents disclosed herein.

[0147] Certain specific examples of linking groups used with the HIF-2 alpha RNAi agents disclosed herein are provided below in Table 7. Certain examples of targeting ligands and/or targeting groups, and PK enhancers, that can be linked or conjugated to the HIF-2 alpha RNAi agents disclosed herein, are also disclosed herein. For example, certain example PK enhancing compounds are provided below in Table 6. Further, in some embodiments, the PK enhancer can be positioned at the 3' terminal end of the sense strand of a HIF-2 alpha RNAi agent.

[0148] Linking groups include but are not limited to the following, for which their chemical structures are provided below in Table 7: (NH2-C6), (C6-NH2), (C6-SS-C6), (6-

SS-6), (TriAlk1), (TriAlk1)s, (TriAlk2), (TriAlk2)s, (TriAlk3), (TriAlk3)s, (TriAlk4), (TriAlk4)s, (TriAlk5), (TriAlk5)s, (TriAlk6), (TriAlk6)s, (TriAlk7), (TriAlk7)s, (TriAlk8), (TriAlk8)s, (TriAlk9), (TriAlk9)s, (TriAlk10), (TriAlk10)s, (TriAlk11), (TriAlk11)s, (TriAlk12), (TriAlk12)s, (TriAlk13), (TriAlk13)s, (TriAlk14), or (TriAlk14)s. Each sense strand and/or antisense strand can have any targeting ligands or targeting groups, linking groups, and/or PK enhancers listed herein, as well as other targeting ligand/groups, other linking groups, and/or other PK enhancers, conjugated to the 5′ and/or 3′ end of the sequence.

Table 3. HIF-2 alpha RNAi Agent Antisense Strand Sequences

Antisense Strand ID:	Modified Antisense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM03465-AS	usUfsuCfaUfgAfaAfucgUfuAfcGfususg	29	UUUCAUGAAAUCGUUACGUUG	827
AM05815-AS	usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg	30	UUUCAUGAAAUCGUUACGUUG	827
AM06491-AS	usGfsusCfaAfaGfaUfaCfuAfuGfuCfcAfsg	31	UGUCAAAGAUACUAUGUCCAG	828
AM06493-AS	usUfscsUfcGfgagucUfaGfcGfcAfuGfsg	32	UUCUCGGAGUCUAGCGCAUGG	829
AM06495-AS	usUfsusGfcGfagcauCfcGfgUfaCfuGfsg	33	UUUGCGAGCAUCCGGUACUGG	830
AM06497-AS	usUfsusGfcGfaGfgGfuUfgUfaGfaUfgAfsc	34	UUUGCGAGGGUUGUAGAUGAC	831
AM06499-AS	usCfsgsAfaGfuUfcUfgAfuUfcCfcGfaAfsg	35	UCGAAGUUCUGAUUCCCGAAG	832
AM06501-AS	usUfsusCfaGfggcuaUfuGfgGfcGfuGfsg	36	UUUCAGGGCUAUUGGGCGUGG	833
AM06503-AS	usGfsasAfaUfcCfgUfcUfgGfgUfaCfuGfsc	37	UGAAAUCCGUCUGGGUACUGC	834
AM06505-AS	usAfsusGfcUfuUfgCfuUfcCfgGfcAfusCf	38	UAUGCUUUGCUUCCGGCAUC	835
AM06525-AS	usGfscsUfuGfuccggCfaUfcAfaAfgGfsg	39	UGCUUGUCCGGCAUCAAAGGG	836
AM06527-AS	usUfsusGfcGfcucagUfgGfcUfuGfuCfsc	40	UUUGCGCUCAGUGGCUUGUCC	837
AM06529-AS	usUfsgsAfcGfaCfaGfgCfuGfuAfgUfcCfsu	41	UUGACGACAGGCUGUAGUCCU	838
AM06531-AS	usAfsgsUfcUfgCfcAfgGfuAfaGfuCfcsg	42	UAGUCUGCCAGGUAAGUCCG	839
AM06533-AS	usUfsasCfgUfuGfgAfgUfuGfaCfcCfuUfsc	43	UUACGUUGGAGUUGACCCUUC	840
AM06535-AS	usAfsusAfcGfuUfgGfaGfuUfgAfcCfcUfsg	44	UAUACGUUGGAGUUGACCCUG	841
AM06537-AS	usAfscsAfuAfcGfuUfgGfaGfuUfgAfcCfsc	45	UACAUACGUUGGAGUUGACCC	842
AM06539-AS	usGfsasUfaAfcCfaCfaUfaCfgUfuGfgAfsg	46	UGAUAACCACAUACGUUGGAG	843
AM06551-AS	usGfsgsAfuUfgUfcAfcAfcCfuAfuGfgsc	47	UGGAUUGUCACACCUAUGGC	844
AM06553-AS	usUfscsGfgAfuUfgUfcAfcAfcCfuAfuGfsg	48	UUCGGAUUGUCACACCUAUGG	845
AM06555-AS	usAfscsAfaCfgUfgCfcAfuCfaGfaCfcsc	49	UACAACGUGCCAUCAGACCC	846

Antisense Strand ID:	Modified Antisense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM06557-AS	usAfsusCfcGfaGfuCfaCfaUfaGfcUfcAfsg	50	UAUCCGAGUCACAUAGCUCAG	847
AM06559-AS	usGfsgsUfgUfcGfuCfcCfuCfuUfaCfcsc	51	UGGUGUCGUCCCUCUUACCC	848
AM06561-AS	usUfsusAfcGfuUfgAfcAfgGfuAfgGfsg	52	UUUACGUUGACAGGUAGGG	849
AM06563-AS	usUfsusAfcGfuUfgAfcAfgGfuAfgGfgusu	53	UUUACGUUGACAGGUAGGGUU	850
AM06565-AS	usCfsgsUfuAfcGfuUfgAfcAfgGfuAfgGfsg	54	UCGUUACGUUGACAGGUAGGG	851
AM06567-AS	usCfsgsUfuAfcGfuUfgAfcAfgGfuAfgsg	55	UCGUUACGUUGACAGGUAGG	852
AM06569-AS	usAfsasAfuCfgUfuAfcGfuUfgAfcAfgGfsu	56	UAAAUCGUUACGUUGACAGGU	853
AM06878-AS	usUfscsGfuUfuUfcAfgAfgCfaAfaCfuGfsc	57	UUCGUUUUCAGAGCAAACUGC	854
AM06880-AS	asGfsusUfgUfuGfuAfgAfcUfuUfcAfcCfsu	58	AGUUGUUGUAGACUUUCACCU	855
AM06882-AS	usCfsgsUfuAfuCfcAfaAfgAfuGfuGfuCfsc	59	UCGUUAUCCAAAGAUGUGUCC	856
AM06884-AS	asUfscsAfcUfuCfaAfuCfuUfcAfgGfuCfsg	60	AUCACUUCAAUCUUCAGGUCG	857
AM06886-AS	usUfsusAfgCfuGfgAfaGfuCfuUfcCfcGfsu	61	UUUAGCUGGAAGUCUUCCCGU	858
AM06888-AS	asGfsasUfaCfuAfuGfuCfcUfgUfuAfgCfsu	62	AGAUACUAUGUCCUGUUAGCU	859
AM06890-AS	usUfscsAfcCfuCfaCfaGfuCfaUfaUfcUfsg	63	UUCACCUCACAGUCAUAUCUG	860
AM06892-AS	usGfsusAfaAfaCfaAfuUfgUfgUfaCfuCfsc	64	UGUAAAACAAUUGUGUACUCC	861
AM06894-AS	usCfsasCfaUfaCfgUfuGfgAfgUfuGfaCfsc	65	UCACAUACGUUGGAGUUGACC	862
AM06896-AS	asCfscsAfcAfuAfcGfuUfgGfaGfuUfgAfsc	66	ACCACAUACGUUGGAGUUGAC	863
AM06898-AS	usAfsusUfgUfcAfcAfcCfuAfuGfgCfaUfsc	67	UAUUGUCACACCUAUGGCAUC	864
AM06900-AS	asAfsasCfcAfuCfuCfaUfgGfuAfgUfuCfsc	68	AAACCAUCUCAUGGUAGUUCC	865
AM06902-AS	usCfsusAfaAfcCfaUfcUfcAfuGfgUfaGfsc	69	UCUAAACCAUCUCAUGGUAGC	866
AM06904-AS	asGfsusUfcCfaUfgUfaAfuUfgGfuAfuCfsg	70	AGUUCCAUGUAAUUGGUAUCG	867
AM06906-AS	asUfscsGfuUfaCfgUfuGfaCfaGfgUfaGfsg	71	AUCGUUACGUUGACAGGUAGG	868
AM06982-AS	usUfsusCfaUfgAfaAfuCfgUfuAfcGfusUfsg	72	UUUCAUGAAAUCGUUACGUUG	827

Antisense Strand ID:	Modified Antisense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM06985-AS	usUfsusCfsasUfgAfaAfuCfgUfuAfscsGfsusUfsg	73	UUUCAUGAAAUCGUUACGUUG	827
AM07140-AS	usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsc	74	UUUCAUGAAAUCGUUACGUUC	869
AM07143-AS	usUfsusCfaUfgAfaAfuCfgUfuAfcGfuCfsc	75	UUUCAUGAAAUCGUUACGUCC	870
AM07144-AS	usUfsusCfaUfG$_{UNA}$AfaAfuCfgUfuAfcGfuCfsc	76	UUUCAUGAAAUCGUUACGUCC	870
AM07511-AS	usUfsuCfaUfgAfaAfuCfgUfuAfcGfuUfsg	77	UUUCAUGAAAUCGUUACGUUG	827
AM07531-AS	asAfsgsGfcUfuUfcAfgGfuAfcAfaGfuUfsg	78	AAGGCUUUCAGGUACAAGUUG	871
AM07533-AS	usUfsusAfgCfuCfcAfcCfuGfuGfuAfaGfsu	79	UUUAGCUCCACCUGUGUAAGU	872
AM07535-AS	asAfsgsUfcAfaAfgAfuAfcUfaUfgUfcCfsu	80	AAGUCAAAGAUACUAUGUCCU	873
AM07537-AS	asGfsusUfaCfuCfuUfcUfcAfgAfcAfcAfsg	81	AGUUACUCUUCUCAGACACAG	874
AM07539-AS	usUfsusAfgCfuUfgGfuGfaAfuAfgGfaAfsg	82	UUUAGCUUGGUGAAUAGGAAG	875
AM07541-AS	asUfscsUfuGfuAfaAfuAfgUfgUfgCfuGfsg	83	AUCUUGUAAAUAGUGUGCUGG	876
AM07543-AS	usUfsgsUfaCfuUfuAfaAfuAfgGfgGfsc	84	UUGUACUUUAAAUAGGGGC	877
AM07545-AS	asGfsgsUfaAfaAfcAfaUfuGfuGfuAfcUfsc	85	AGGUAAAACAAUUGUGUACUC	878
AM07547-AS	asCfsusUfgUfuAfgUfaUfgGfaCfaGfuUfsg	86	ACUUGUUAGUAUGGACAGUUG	879
AM07549-AS	usCfsasAfcUfuUfcAfcAfgAfuAfaCfcAfsc	87	UCAACUUUCACAGAUAACCAC	880
AM07551-AS	usCfscsAfuUfuCfcGfuUfuCfuAfaGfuUfsc	88	UCCAUUUCCGUUUCUAAGUUC	881
AM07553-AS	asAfsusGfaCfuccacUfgCfuCfgGfaUfsc	89	AAUGACUCCCACUGCUCGGAUC	882
AM07555-AS	asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsg	90	ACAUAGUACAUAGAGAAUGUG	883
AM07557-AS	usCfsusAfcCfuacauGfuCfaCfuGfaCfsc	91	UCUACCUACAUGUCACUGACC	884
AM07559-AS	usCfsasAfuGfuGfcUfuUfgUfgUfgUfsc	92	UCAAUGUGCUUUGUGUGUGUC	885
AM07561-AS	usUfsgsGfcAfaUfaAfgUfcUfaUfcCfgGfsu	93	UUGGCAAUAAGUCUAUCCGGU	886
AM07563-AS	asGfsgsAfaUfuUfcUfcAfuAfgAfaCfuUfsc	94	AGGAAUUUCUCAUAGAACUUC	887
AM07565-AS	asGfscsAfuUfuAfcAfcGfuCfaGfuAfaCfsc	95	AGCAUUUACACGUCAGUAACC	888

Antisense Strand ID:	Modified Antisense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07567-AS	asCfsgsUfuCfaUfgAfaAfuCfgUfuAfcGfsu	96	ACGUUCAUGAAAUCGUUACGU	889
AM07569-AS	usAfsasCfgUfuCfaUfgAfaAfuCfgUfuAfsc	97	UAACGUUCAUGAAAUCGUUAC	890
AM07571-AS	asUfsasAfcGfuUfcAfuGfaAfaUfcGfuUfsc	98	AUAACGUUCAUGAAAUCGUUC	891
AM07573-AS	usUfscsCfuUfaUfaAfaGfuUfaAfgCfuCfsc	99	UUCCUUAUAAAGUUAAGCUCC	892
AM07603-AS	usUfsusCfaUfgAfaAfucgUfuAfcGfuUfsg	102	UUUCAUGAAAUCGUUACGUUG	893
AM07723-AS	asCfsasUfaGfuAfcAfuAfgAfgAfaUfgUfsc	103	ACAUAGUACAUAGAGAAUGUC	894
AM07725-AS	asCfsasUfaGfuAfcAfuAfgAfgAfaUfgCfsg	104	ACAUAGUACAUAGAGAAUGCG	827
AM07727-AS	asCfsasUfaGfuAfcAfuAfgAfgAfaUfgGfsg	105	ACAUAGUACAUAGAGAAUGGG	894
AM07729-AS	asCfsasUfaGfuAfcAfuAfgAfgAfaUfgCfsc	106	ACAUAGUACAUAGAGAAUGCC	895
AM07733-AS	usGfsasAfuCfuccucAfuGfgUfcGfcusu	107	UGAAUCUCCUCAUGGUCGCUU	896
AM07735-AS	usGfsasAfuUfcAfuAfgGfcUfgAfgCfgusu	108	UGAAUUCAUAGGCUGAGCGUU	897
AM07737-AS	usCfsasCfuUfacuacCfuGfaCfcCfuUfsg	109	UCACUUACUACCUGACCCUUG	898
AM07739-AS	usGfscsUfuGfaacagGfgAfuUfcAfgUfsc	110	UGCUUGAACAGGGAUUCAGUC	899
AM07741-AS	asGfsasUfgUfuugucAfuGfgCfaCfuGfsa	111	AGAUGUUUGUCAUGGCACUGA	900
AM07743-AS	usCfscsAfcAfucaaaUfgUfgAfgGfuGfsc	112	UCCACAUCAAAUGUGAGGUGC	901
AM07745-AS	usGfsusUfaGfuAfuGfgAfcAfgUfuGfuGfsu	113	UGUUAGUAUGGACAGUUGUGU	902
AM07747-AS	usGfsasAfgUfcAfaAfgAfuAfcUfaUfgCfsc	114	UGAAGUCAAAGAUACUAUGCC	903
AM07891-AS	usGfsusUfaGfuauggAfcAfgUfuGfuGfsc	115	UGUUAGUAUGGACAGUUGUGC	904
AM07893-AS	usGfsusUfaGfuauggAfcAfgUfuGfuGfsg	116	UGUUAGUAUGGACAGUUGUGG	905
AM07895-AS	usGfsusUfaGfuauggAfcAfgUfuGfuCfsc	117	UGUUAGUAUGGACAGUUGUCC	906
AM08400-AS	usUfsusCfaUfgAfaAfuCfgUfuAfcGfuusg	118	UUUCAUGAAAUCGUUACGUUG	907

Table 4. HIF-2 alpha RNAi Agent Sense Strand Sequences

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM05339-SS	(NH2-C6)uAuascguaaCfGfAfuuuCfaugaaa(invdT)(C6-SS-C6)(C12)	119	UAUACGUAACGAUUUCAUGAAAT	909
AM05814-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)	120	CAACGUAACGAUUUCAUGAAA	910
AM05816-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)	121	CAACGUAACGAUUUCAUGAAA	910
AM06490-SS	(NH2-C6)scsuggacauAfGfUfaucuuugacas(invAb)(C6-SS-C6)	122	CUGGACAUAGUAUCUUUGACA	911
AM06492-SS	(NH2-C6)scscaugcgcUfAfGfacuccgagaas(invAb)(C6-SS-C6)	123	CCAUGCGCUAGACUCCGAGAA	912
AM06494-SS	(NH2-C6)scscaguaccGfGfAfugcucgcaaas(invAb)(C6-SS-C6)	124	CCAGUACCGGAUGCUCGCAAA	913
AM06496-SS	(NH2-C6)sgsucaucuaCfAfAfcccucgcaaas(invAb)(C6-SS-C6)	125	GUCAUCUACAACCCUCGCAAA	914
AM06498-SS	(NH2-C6)scsuucgggaAfUfCfagaacuucgas(invAb)(C6-SS-C6)	126	CUUCGGGAAUCAGAACUUCGA	915
AM06500-SS	(NH2-C6)scscacgcccAfAfUfagcccugaaas(invAb)(C6-SS-C6)	127	CCACGCCCAAUAGCCCUGAAA	916
AM06502-SS	(NH2-C6)sgscaguaccCfAfGfacggauuucas(invAb)(C6-SS-C6)	128	GCAGUACCCAGACGGAUUUCA	917
AM06504-SS	(NH2-C6)sgsaugccgGfAfAfgcaaagcauas(invAb)(C6-SS-C6)	129	GAUGCCGGAAGCAAAGCAUA	918
AM06524-SS	(NH2-C6)scsccuuugaUfGfCfcggacaagcas(invAb)(C6-SS-C6)	130	CCCUUUGAUGCCGGACAAGCA	919
AM06526-SS	(NH2-C6)sgsgacaagcCfAfCfugagcgcaaas(invAb)(C6-SS-C6)	131	GGACAAGCCACUGAGCGCAAA	920
AM06528-SS	(NH2-C6)sasggacuacAfGfCfcugucgucaas(invAb)(C6-SS-C6)	132	AGGACUACAGCCUGUCGUCAA	921
AM06530-SS	(NH2-C6)scsggacuuAfCfCfuggcagacuas(invAb)(C6-SS-C6)	133	CGGACUUACCUGGCAGACUA	922
AM06532-SS	(NH2-C6)sgsaagggucAfAfCfuccaacguaas(invAb)(C6-SS-C6)	134	GAAGGGUCAACUCCAACGUAA	923
AM06534-SS	(NH2-C6)scsagggucaAfCfUfccaacguauas(invAb)(C6-SS-C6)	135	CAGGGUCAACUCCAACGUAUA	924
AM06536-SS	(NH2-C6)sgsggucaacUfCfCfaacguauguas(invAb)(C6-SS-C6)	136	GGGUCAACUCCAACGUAUGUA	925
AM06538-SS	(NH2-C6)scsuccaacgUfAfUfgugguuaucas(invAb)(C6-SS-C6)	137	CUCCAACGUAUGUGGUUAUCA	926
AM06550-SS	(NH2-C6)sgsccauagGfUfGfugacaauccas(invAb)(C6-SS-C6)	138	GCCAUAGGUGUGACAAUCCA	927

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM06552-SS	(NH2-C6)scscauagguGfUfGfacaauccgaas(invAb)(C6-SS-C6)	139	CCAUAGGUGUGACAAUCCGAA	928
AM06554-SS	(NH2-C6)sgsggucugAfUfGfgcacguuguas(invAb)(C6-SS-C6)	140	GGGUCUGAUGGCACGUUGUA	929
AM06556-SS	(NH2-C6)scsugagcuaUfGfUfgacucggauas(invAb)(C6-SS-C6)	141	CUGAGCUAUGUGACUCGGAUA	930
AM06558-SS	(NH2-C6)sgsgguaagAfGfGfgacgacaccas(invAb)(C6-SS-C6)	142	GGGUAAGAGGGACGACACCA	931
AM06560-SS	(NH2-C6)scsccuacCfUfGfucaacguaaas(invAb)(C6-SS-C6)	143	CCCUACCUGUCAACGUAAA	932
AM06562-SS	(NH2-C6)s(invAb)scccuacCfUfGfucaacguaaas(invAb)(C6-SS-C6)	144	CCCUACCUGUCAACGUAAA	932
AM06564-SS	(NH2-C6)scsccuaccuGfUfCfaacguaacgas(invAb)(C6-SS-C6)	145	CCCUACCUGUCAACGUAACGA	933
AM06566-SS	(NH2-C6)scscuaccuGfUfCfaacguaacgas(invAb)(C6-SS-C6)	146	CCUACCUGUCAACGUAACGA	934
AM06568-SS	(NH2-C6)sasccugucaAfCfGfuaacgauuuas(invAb)(C6-SS-C6)	147	ACCUGUCAACGUAACGAUUUA	935
AM06877-SS	(NH2-C6)s(invAb)sgcaguuugCfUfCfugaaaacgaas(invAb)(C6-SS-C6)	148	GCAGUUUGCUCUGAAAACGAA	936
AM06879-SS	(NH2-C6)s(invAb)saggugaaaGfUfCfuacaacaacus(invAb)(C6-SS-C6)	149	AGGUGAAAGUCUACAACAACU	937
AM06881-SS	(NH2-C6)s(invAb)sggacacauCfUfUfuggauaacgas(invAb)(C6-SS-C6)	150	GGACACAUCUUUGGAUAACGA	938
AM06883-SS	(NH2-C6)s(invAb)scgaccugaAfGfAfuugaagugaus(invAb)(C6-SS-C6)	151	CGACCUGAAGAUUGAAGUGAU	939
AM06885-SS	(NH2-C6)s(invAb)sacgggaagAfCfUfuccagcuaaas(invAb)(C6-SS-C6)	152	ACGGGAAGACUUCCAGCUAAA	940
AM06887-SS	(NH2-C6)s(invAb)sagcuaacaGfGfAfcauaguaucus(invAb)(C6-SS-C6)	153	AGCUAACAGGACAUAGUAUCU	941
AM06889-SS	(NH2-C6)s(invAb)scagauaugAfCfUfgugaggugaas(invAb)(C6-SS-C6)	154	CAGAUAUGACUGUGAGGUGAA	942
AM06891-SS	(NH2-C6)s(invAb)sggaguacaCfAfAfuuguuuuacas(invAb)(C6-SS-C6)	155	GGAGUACACAAUUGUUUUACA	943
AM06893-SS	(NH2-C6)s(invAb)sggucaacuCfCfAfacguaugugas(invAb)(C6-SS-C6)	156	GGUCAACUCCAACGUAUGUGA	944
AM06895-SS	(NH2-C6)s(invAb)sgucaacucCfAfAfcguauguggus(invAb)(C6-SS-C6)	157	GUCAACUCCAACGUAUGUGGU	945
AM06897-SS	(NH2-C6)s(invAb)sgaugccauAfGfGfugugacaauas(invAb)(C6-SS-C6)	158	GAUGCCAUAGGUGUGACAAUA	946

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AM06899-SS	(NH2-C6)s(invAb)sggaacuacCfAfUfgagaugguuus(invAb)(C6-SS-C6)	159	GGAACUACCAUGAGAUGGUUU	947
AM06901-SS	(NH2-C6)s(invAb)sgcuaccauGfAfGfaugguuuagas(invAb)(C6-SS-C6)	160	GCUACCAUGAGAUGGUUUAGA	948
AM06903-SS	(NH2-C6)s(invAb)scgauaccaAfUfUfacauggaacus(invAb)(C6-SS-C6)	161	CGAUACCAAUUACAUGGAACU	949
AM06905-SS	(NH2-C6)s(invAb)sccuaccugUfCfAfacguaacgaus(invAb)(C6-SS-C6)	162	CCUACCUGUCAACGUAACGAU	950
AM06981-SS	(NH2-C6)scsasascsguaaCfGfAfuuucausgsasasas(invAb)(C6-SS-C6)	163	CAACGUAACGAUUUCAUGAAA	910
AM06983-SS	(NH2-C6)scsaascgsuasaCfsGfAfsuusucsausgasaas(invAb)(C6-SS-C6)	164	CAACGUAACGAUUUCAUGAAA	910
AM06984-SS	(NH2-C6)scsasacguaaCfGfAfuuucaugasasas(invAb)(C6-SS-C6)	165	CAACGUAACGAUUUCAUGAAA	910
AM06986-SS	(NH2-C6)scasacsgusaasCfGfsAfusuuscasugsaasas(invAb)(C6-SS-C6)	166	CAACGUAACGAUUUCAUGAAA	910
AM07071-SS	(NH2-C6)csaacguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)	167	CAACGUAACGAUUUCAUGAAA	910
AM07138-SS	(NH2-C6)s(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	168	CAACGUAACGAUUUCAUGAAA	910
AM07139-SS	(NH2-C6)s(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	169	GAACGUAACGAUUUCAUGAAA	951
AM07141-SS	(NH2-C6)s(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	170	GAACGUAACGAUUUCAUGAAA	952
AM07142-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	171	GGACGUAACGAUUUCAUGAAA	953
AM07145-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)(C6-SS-C6)	172	GGACGUAACGAUUUCAUIAAA	954
AM07146-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)(C6-SS-C6)	173	GGACGUAACGAUUUCAUGAAA	953
AM07224-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	174	CAACGUAACGAUUUCAUGAAA	910
AM07225-SS	(NH2-C6)s(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)(6-SS-6)	175	CAACGUAACGAUUUCAUGAAA	910
AM07226-SS	(NH2-C6)s(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)(6-SS-6)	176	GAACGUAACGAUUUCAUGAAA	951
AM07227-SS	(NH2-C6)s(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)(6-SS-6)	177	GAACGUAACGAUUUCAUGAAA	952
AM07228-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)(6-SS-6)	178	GGACGUAACGAUUUCAUGAAA	953

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AM07229-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)(6-SS-6)	179	GGACGUAACGAUUUCAUIAAA	954
AM07230-SS	(NH2-C6)s(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)(6-SS-6)	180	GGACGUAACGAUUUCAUGAAA	953
AM07231-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C3-SS-C3)	181	CAACGUAACGAUUUCAUGAAA	910
AM07268-SS	(NH2-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)(C6-SS-C6)	182	CAACGUAACGAUUUCAUGAAA	910
AM07269-SS	(NH2-C6)scsaascgsuasaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	183	CAACGUAACGAUUUCAUGAAA	910
AM07270-SS	(NH2-C6)scsaacguaaCfGfAfuuucausgsasasas(invAb)(C6-SS-C6)	184	CAACGUAACGAUUUCAUGAAA	910
AM07271-SS	(NH2-C6)scsasascsgsuaaCfGfAfuuucaugaaas(invAb)(C6-SS-C6)	185	CAACGUAACGAUUUCAUGAAA	910
AM07272-SS	(NH2-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)(C6-SS-C6)	186	CAACGUAACGAUUUCAUGAAA	910
AM07273-SS	(NH2-C6)scsaacgusaasCfGfsAfusuucaugaaas(invAb)(C6-SS-C6)	187	CAACGUAACGAUUUCAUGAAA	910
AM07274-SS	(NH2-C6)scsaascgsuaaCfGfAfuuucausgasaas(invAb)(C6-SS-C6)	188	CAACGUAACGAUUUCAUGAAA	910
AM07275-SS	(NH2-C6)scsasascguaaCfGfAfuuucaugasasas(invAb)(C6-SS-C6)	189	CAACGUAACGAUUUCAUGAAA	910
AM07301-SS	(NH2-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)	190	CAACGUAACGAUUUCAUGAAA	910
AM07302-SS	(NH2-C6)scsaascgsuasaCfGfAfuuucaugaaas(invAb)	191	CAACGUAACGAUUUCAUGAAA	910
AM07303-SS	(NH2-C6)scsaacguaaCfGfAfuuucausgsasasas(invAb)	192	CAACGUAACGAUUUCAUGAAA	910
AM07304-SS	(NH2-C6)scsasascsgsuaaCfGfAfuuucaugaaas(invAb)	193	CAACGUAACGAUUUCAUGAAA	910
AM07305-SS	(NH2-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)	194	CAACGUAACGAUUUCAUGAAA	910
AM07306-SS	(NH2-C6)scsaacgusaasCfGfsAfusuucaugaaas(invAb)	195	CAACGUAACGAUUUCAUGAAA	910
AM07307-SS	(NH2-C6)scsaascgsuaaCfGfAfuuucausgasaas(invAb)	196	CAACGUAACGAUUUCAUGAAA	910
AM07308-SS	(NH2-C6)scsasascguaaCfGfAfuuucaugasasas(invAb)	197	CAACGUAACGAUUUCAUGAAA	910
AM07403-SS	(TriAlk1)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	198	CAACGUAACGAUUUCAUGAAA	910

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AM07404-SS	(TriAlk2)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	199	CAACGUAACGAUUUCAUGAAA	910
AM07405-SS	(TriAlk3)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	200	CAACGUAACGAUUUCAUGAAA	910
AM07406-SS	(TriAlk6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	201	CAACGUAACGAUUUCAUGAAA	910
AM07407-SS	(TriAlk4)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	202	CAACGUAACGAUUUCAUGAAA	910
AM07408-SS	(TriAlk5)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	203	CAACGUAACGAUUUCAUGAAA	910
AM07493-SS	(NH2-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)(6-SS-6)	204	CAACGUAACGAUUUCAUGAAA	910
AM07528-SS	(NH2-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)(6-SS-6)	205	CAACGUAACGAUUUCAUGAAA	910
AM07530-SS	(NH2-C6)s(invAb)scaacuuguAfCfCfugaaaiccuus(invAb)(C6-SS-C6)(invAb)	206	CAACUUGUACCUGAAAICCUU	955
AM07532-SS	(NH2-C6)s(invAb)sacuuacacAfGfGfuggagcuaaas(invAb)(C6-SS-C6)(invAb)	207	ACUUACACAGGUGGAGCUAAA	956
AM07534-SS	(NH2-C6)s(invAb)saggacauaGfUfAfucuuugacuus(invAb)(C6-SS-C6)(invAb)	208	AGGACAUAGUAUCUUUGACUU	957
AM07536-SS	(NH2-C6)s(invAb)scugugucuGfAfGfaagaguaacus(invAb)(C6-SS-C6)(invAb)	209	CUGUGUCUGAGAAGAGUAACU	958
AM07538-SS	(NH2-C6)s(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)(C6-SS-C6)(invAb)	210	CUUCCUAUUCACCAAGCUAAA	959
AM07540-SS	(NH2-C6)s(invAb)sccagcacaCfUfAfuuuacaagaus(invAb)(C6-SS-C6)(invAb)	211	CCAGCACACUAUUUACAAGAU	960
AM07542-SS	(NH2-C6)s(invAb)sgccccuauUfUfUfuaaaguacaas(invAb)(C6-SS-C6)(invAb)	212	GCCCCUAUUUUUAAAGUACAA	961
AM07544-SS	(NH2-C6)s(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)(C6-SS-C6)(invAb)	213	GAGUACACAAUUGUUUUACCU	962
AM07546-SS	(NH2-C6)s(invAb)scaacugucCfAfUfacuaacaagus(invAb)(C6-SS-C6)(invAb)	214	CAACUGUCCAUACUAACAAGU	963
AM07548-SS	(NH2-C6)s(invAb)sgugguuauCfUfGfugaaaguugas(invAb)(C6-SS-C6)(invAb)	215	GUGGUUAUCUGUGAAAGUUGA	964
AM07550-SS	(NH2-C6)s(invAb)sgaacuuagAfAfAfcggaaauggas(invAb)(C6-SS-C6)(invAb)	216	GAACUUAGAAACGGAAAUGGA	965
AM07552-SS	(NH2-C6)s(invAb)sgauccgagCfAfGfuggagucauus(invAb)(C6-SS-C6)(invAb)	217	GAUCCGAGCAGUGGAGUCAUU	966
AM07554-SS	(NH2-C6)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(C6-SS-C6)(invAb)	218	CACAUUCUCUAUGUACUAUGU	967

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AM07556-SS	(NH2-C6)s(invAb)sggucagugAfCfAfuguagguagas(invAb)(C6-SS-C6)(invAb)	219	GGUCAGUGACAUGUAGGUAGA	968
AM07558-SS	(NH2-C6)s(invAb)sgacacacaCfAfAfagcacauugas(invAb)(C6-SS-C6)(invAb)	220	GACACACACAAAGCACACAUUGA	969
AM07560-SS	(NH2-C6)s(invAb)saccggauaGfAfCfuuauuiccaas(invAb)(C6-SS-C6)(invAb)	221	ACCGGAUAGACUUAUUiCCAA	970
AM07562-SS	(NH2-C6)s(invAb)sgaaguucuAfUfGfagaaauuccus(invAb)(C6-SS-C6)(invAb)	222	GAAGUUCUAUGAGAAAUUCCU	971
AM07564-SS	(NH2-C6)s(invAb)sgguuacugAfCfGfuguaaaugcus(invAb)(C6-SS-C6)(invAb)	223	GGUUACUGACGUGUAAAUGCU	972
AM07566-SS	(NH2-C6)s(invAb)sacguaacgAfUfUfucaugaacgus(invAb)(C6-SS-C6)(invAb)	224	ACGUAACGAUUUCAUGAACGU	973
AM07568-SS	(NH2-C6)s(invAb)sguaacgauUfUfCfaugaacguuas(invAb)(C6-SS-C6)(invAb)	225	GUAACGAUUUCAUGAACGUUA	974
AM07570-SS	(NH2-C6)s(invAb)sgaacgauuUfCfAfugaacguuaus(invAb)(C6-SS-C6)(invAb)	226	GAACGAUUUCAUGAACGUUAU	975
AM07572-SS	(NH2-C6)s(invAb)sggagcuuaAfCfUfuuauaaggaas(invAb)(C6-SS-C6)(invAb)	227	GGAGCUUAACUUUAUAAGGAA	976
AM07619-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(C6-SS-C6)(invAb)	228	CAACGUAACGAUUUCAUGAAA	910
AM07621-SS	(C6-SS-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(C6-SS-C6)(invAb)	229	CAACGUAACGAUUUCAUGAAA	910
AM07705-SS	(TriAlk7)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	230	CAACGUAACGAUUUCAUGAAA	910
AM07706-SS	(TriAlk8)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	231	CAACGUAACGAUUUCAUGAAA	910
AM07707-SS	(TriAlk10)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	232	CAACGUAACGAUUUCAUGAAA	910
AM07708-SS	(TriAlk11)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	233	CAACGUAACGAUUUCAUGAAA	910
AM07709-SS	(TriAlk12)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	234	CAACGUAACGAUUUCAUGAAA	910
AM07710-SS	(NH2-C6)scsaacguaaCfGfAfuuucaAlkugaasa(invAb)(6-SS-6)	235	CAACGUAACGAUUUCAUGAAA	910
AM07711-SS	(NH2-C6)scsaacguaAlkaCfGfAfuuucaugaasa(invAb)(6-SS-6)	236	CAACGUAACGAUUUCAUGAAA	910
AM07712-SS	(NH2-C6)scsaacguaAlkaCfGfAfuuucaAlkugaasa(invAb)(6-SS-6)	237	CAACGUAACGAUUUCAUGAAA	910
AM07713-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(C6-NH2)	238	CAACGUAACGAUUUCAUGAAA	910

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AM07721-SS	(NH2-C6)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(6-SS-6)	239	CACAUUCUCUAUGUACUAUGU	967
AM07722-SS	(NH2-C6)s(invAb)sgacauucuCfUfAfuguacuaugus(invAb)(6-SS-6)	240	GACAUUCUCUAUGUACUAUGU	977
AM07724-SS	(NH2-C6)s(invAb)scgcauucuCfUfAfuguacuaugus(invAb)(6-SS-6)	241	CGCAUUCUCUAUGUACUAUGU	978
AM07726-SS	(NH2-C6)s(invAb)scccauucuCfUfAfuguacuaugus(invAb)(6-SS-6)	242	CCCAUUCUCUAUGUACUAUGU	979
AM07728-SS	(NH2-C6)s(invAb)sggcauucuCfUfAfuguacuaugus(invAb)(6-SS-6)	243	GGCAUUCUCUAUGUACUAUGU	980
AM07730-SS	(NH2-C6)s(invAb)scaca_2NuucuCfUfAfuguacuaugus(invAb)(6-SS-6)	244	CACAUUCUCUAUGUACUAUGU	981
AM07731-SS	(NH2-C6)s(invAb)sccca_2NuucuCfUfAfuguacuaugus(invAb)(6-SS-6)	245	CCCAUUCUCUAUGUACUAUGU	982
AM07732-SS	(NH2-C6)s(invAb)sgcgaccAfUfGfaggagauucauus(invAb)(6-SS-6)	246	GCGACCAUGAGGAGAUUCAUU	983
AM07734-SS	(NH2-C6)s(invAb)scgcucaGfCfCfuaugaauucauus(invAb)(6-SS-6)	247	CGCUCAGCCUAUGAAUUCAUU	984
AM07736-SS	(NH2-C6)s(invAb)scaagggucAfGfGfuaguaagugas(invAb)(6-SS-6)	248	CAAGGGUCAGGUAGUAAGUGA	985
AM07738-SS	(NH2-C6)s(invAb)sgacugaauCfCfCfuguucaagcas(invAb)(6-SS-6)	249	GACUGAAUCCCUGUUCAAGCA	986
AM07740-SS	(NH2-C6)s(invAb)sucagugccAfUfGfacaaacaucus(invAb)(6-SS-6)	250	UCAGUGCCAUGACAAACAUCU	987
AM07742-SS	(NH2-C6)s(invAb)sgcaccucaCfAfUfuugauguggas(invAb)(6-SS-6)	251	GCACCUCACAUUUGAUGUGGA	988
AM07744-SS	(NH2-C6)s(invAb)sacacaacuGfUfCfcauacuaacas(invAb)(6-SS-6)	252	ACACAACUGUCCAUACUAACA	989
AM07746-SS	(NH2-C6)s(invAb)sggcauaguAfUfCfuuugacuucas(invAb)(6-SS-6)	253	GGCAUAGUAUCUUUGACUUCA	990
AM07776-SS	(NH2-C6)s(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)(6-SS-6)	254	GAGUACACAAUUGUUUUACCU	962
AM07777-SS	(NH2-C6)s(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)(6-SS-6)	255	CUUCCUAUUCACCAAGCUAAA	959
AM07778-SS	(NH2-C6)s(invAb)sggucagugAfCfAfuguagguagas(invAb)(6-SS-6)	256	GGUCAGUGACAUGUAGGUAGA	968
AM07801-SS	(TriAlk13)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	257	CAACGUAACGAUUUCAUGAAA	910
AM07813-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(6-SS-6)	258	CAACGUAACGAUUUCAUGAAA	910

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AM07814-SS	(C6-SS-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(6-SS-6)	259	CAACGUAACGAUUUCAUGAAA	910
AM07817-SS	(NH2-C6)scsaAlkaAlkcguAlkaAlkaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)(6-SS-6)	260	CAACGUAACGAUUUCAUGAAA	910
AM07818-SS	(C6-SS-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	261	CAACGUAACGAUUUCAUGAAA	910
AM07822-SS	(NH2-C6)scsaacguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(6-SS-6)	262	CAACGUAACGAUUUCAUGAAA	910
AM07823-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaAlkugaaAlksa(invAb)(6-SS-6)	263	CAACGUAACGAUUUCAUGAAA	910
AM07824-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaugaaAlksa(invAb)(6-SS-6)	264	CAACGUAACGAUUUCAUGAAA	910
AM07825-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaAlkugaasa(invAb)(6-SS-6)	265	CAACGUAACGAUUUCAUGAAA	910
AM07826-SS	(NH2-C6)scsaaAlkcguaAlkaCfGfAfuuucaugaasa(invAb)(6-SS-6)	266	CAACGUAACGAUUUCAUGAAA	910
AM07827-SS	(NH2-C6)scsaacguaaCfGfAfuuucaAlkugaaAlksa(invAb)(6-SS-6)	267	CAACGUAACGAUUUCAUGAAA	910
AM07828-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaugaaAlksa(invAb)(6-SS-6)	268	CAACGUAACGAUUUCAUGAAA	910
AM07829-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaAlkugaasa(invAb)(6-SS-6)	269	CAACGUAACGAUUUCAUGAAA	910
AM07830-SS	(NH2-C6)scsaacguaAlkaCfGfAfuuucaugaaAlksa(invAb)(6-SS-6)	270	CAACGUAACGAUUUCAUGAAA	910
AM07831-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaaAlksa(invAb)(6-SS-6)	271	CAACGUAACGAUUUCAUGAAA	910
AM07832-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	272	CAACGUAACGAUUUCAUGAAA	910
AM07833-SS	(NH2-C6)scsaAlkaAlkcguaaCfGfAfuuucaugaAlkaAlksa(invAb)(6-SS-6)	273	CAACGUAACGAUUUCAUGAAA	910
AM07834-SS	(NH2-C6)scsaacAlkguaaAlkCfGfAfuuuAlkcaugAlkaasa(invAb)(6-SS-6)	274	CAACGUAACGAUUUCAUGAAA	910
AM07835-SS	(NH2-C6)scsaacgAlkuaaAlkCfGfAfuAlkuucAlkaugaasa(invAb)(6-SS-6)	275	CAACGUAACGAUUUCAUGAAA	910
AM07836-SS	(NH2-C6)scsaacguaAlkaAlkCfGfAfuAlkuAlkucaugaasa(invAb)(6-SS-6)	276	CAACGUAACGAUUUCAUGAAA	910
AM07837-SS	(NH2-C6)scsaAlkacAlkguAlkaaAlkCfGfAfuuucaugaasa(invAb)(6-SS-6)	277	CAACGUAACGAUUUCAUGAAA	910
AM07838-SS	(NH2-C6)scsaAlkaAlkcAlkgAlkuaaCfGfAfuuucaugaasa(invAb)(6-SS-6)	278	CAACGUAACGAUUUCAUGAAA	910

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07839-SS	(NH2-C6)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(6-SS-6)	279	CAACGUAACGAUUUCAUGAAA	910
AM07840-SS	(NH2-C6)scsaacguaaCfGfAfuuucauAlkgAlkaAlksa(invAb)(6-SS-6)	280	CAACGUAACGAUUUCAUGAAA	910
AM07890-SS	(NH2-C6)s(invAb)sgcacaacuGfUfCfcauacuaacas(invAb)(6-SS-6)	281	GCACAACUGUCCAUACUAACA	991
AM07892-SS	(NH2-C6)s(invAb)sccacaacuGfUfCfcauacuaacas(invAb)(6-SS-6)	282	CCACAACUGUCCAUACUAACA	992
AM07894-SS	(NH2-C6)s(invAb)sggacaacuGfUfCfcauacuaacas(invAb)(6-SS-6)	283	GGACAACUGUCCAUACUAACA	993
AM08018-SS	(NH2-C6)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)(6-SS-6)	284	CAACGUAACGAUUUCAUGAAA	910
AM08019-SS	(NH2-C6)scsaacAlkguaaAlkCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(6-SS-6)	285	CAACGUAACGAUUUCAUGAAA	910
AM08020-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugAlkaasa(invAb)(6-SS-6)	286	CAACGUAACGAUUUCAUGAAA	910
AM08021-SS	(NH2-C6)scsaacguaaCfGfAfuuucaAlkuAlkgAlkaAlkasa(invAb)(6-SS-6)	287	CAACGUAACGAUUUCAUGAAA	910
AM08022-SS	(NH2-C6)scsaacguaaCfGfAfuuucAlkaAlkuAlkgAlkaasa(invAb)(6-SS-6)	288	CAACGUAACGAUUUCAUGAAA	910
AM08023-SS	(NH2-C6)scsaacguaaCfGfAfuuuAlkcAlkaAlkuAlkgaasa(invAb)(6-SS-6)	289	CAACGUAACGAUUUCAUGAAA	910
AM08024-SS	(NH2-C6)scsaacguaaCfGfAfuuAlkuAlkcAlkaAlkugaasa(invAb)(6-SS-6)	290	CAACGUAACGAUUUCAUGAAA	910
AM08025-SS	(NH2-C6)scsaacguaaCfGfAfuAlkuAlkuAlkcAlkaugaasa(invAb)(6-SS-6)	291	CAACGUAACGAUUUCAUGAAA	910
AM08026-SS	(NH2-C6)scsaacguaaCfGfAfuAlkuuAlkcaAlkugAlkaaAlksa(invAb)(6-SS-6)	292	CAACGUAACGAUUUCAUGAAA	910
AM08027-SS	(NH2-C6)scsaacguaaCfGfAfuuucaAlkugAlkaaAlksa(invAb)(6-SS-6)	293	CAACGUAACGAUUUCAUGAAA	910
AM08028-SS	(NH2-C6)scsaacguaaCfGfAfuuuAlkcaugAlkaaAlksa(invAb)(6-SS-6)	294	CAACGUAACGAUUUCAUGAAA	910
AM08029-SS	(NH2-C6)scsaacguaaCfGfAfuuuAlkcaAlkugaaAlksa(invAb)(6-SS-6)	295	CAACGUAACGAUUUCAUGAAA	910
AM08030-SS	(NH2-C6)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaasa(invAb)(6-SS-6)	296	CAACGUAACGAUUUCAUGAAA	910
AM08031-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugAlkaAlkaAlksa(invAb)(6-SS-6)	297	CAACGUAACGAUUUCAUGAAA	910
AM08032-SS	(NH2-C6)scsaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)(C6-SS-C6)dT	298	CAACGUAACGAUUUCAUGAAAT	994

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08033-SS	(NH2-C6)scsaacguaaCfGfAfuuucauAlkgAlkaaAlksa(invAb)(6-SS-6)	299	CAACGUAACGAUUUCAUGAAA	910
AM08034-SS	(NH2-C6)scsaacguaaCfGfAfuuucauAlkgAlkaAlkasa(invAb)(6-SS-6)	300	CAACGUAACGAUUUCAUGAAA	910
AM08035-SS	(NH2-C6)scsaacguaaAlkCfGfAfuuuAlkcaugAlkaasa(invAb)(6-SS-6)	301	CAACGUAACGAUUUCAUGAAA	910
AM08036-SS	(NH2-C6)scsaacAlkguaaCfGfAfuuuAlkcaugAlkaasa(invAb)(6-SS-6)	302	CAACGUAACGAUUUCAUGAAA	910
AM08037-SS	(NH2-C6)scsaacAlkguaaAlkCfGfAfuuucaugAlkaasa(invAb)(6-SS-6)	303	CAACGUAACGAUUUCAUGAAA	910
AM08038-SS	(NH2-C6)scsaacAlkguaaAlkCfGfAfuuuAlkcaugaasa(invAb)(6-SS-6)	304	CAACGUAACGAUUUCAUGAAA	910
AM08092-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)dT	305	CAACGUAACGAUUUCAUGAAAT	994
AM08093-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaaAlksa(invAb)(C6-SS-C6)dT	306	CAACGUAACGAUUUCAUGAAAT	994
AM08108-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)(C6-SS-C6)dT	307	CAACGUAACGAUUUCAUGAAAT	994
AM08109-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)(C6-SS-C6)dT	308	CAACGUAACGAUUUCAUGAAAT	994
AM08110-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugaAlkaAlksa(invAb)(C6-SS-C6)dT	309	CAACGUAACGAUUUCAUGAAAT	994
AM08111-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaaAlksa(invAb)(C6-SS-C6)dT	310	CAACGUAACGAUUUCAUGAAAT	994
AM08112-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkasa(invAb)(C6-SS-C6)dT	311	CAACGUAACGAUUUCAUGAAAT	994
AM08113-SS	(TriAlk14)scsaacguaaCfGfAfuuucaugaAlkaAlksa(invAb)(C6-SS-C6)dT	312	CAACGUAACGAUUUCAUGAAAT	994
AM08114-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaasa(invAb)(C6-SS-C6)dT	313	CAACGUAACGAUUUCAUGAAAT	994
AM08115-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaAlkasa(invAb)(C6-SS-C6)dT	314	CAACGUAACGAUUUCAUGAAAT	994
AM08116-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugaAlkasa(invAb)(C6-SS-C6)dT	315	CAACGUAACGAUUUCAUGAAAT	994
AM08117-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaaAlksa(invAb)(C6-SS-C6)dT	316	CAACGUAACGAUUUCAUGAAAT	994
AM08118-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaugAlkaasa(invAb)(C6-SS-C6)dT	317	CAACGUAACGAUUUCAUGAAAT	994
AM08119-SS	(C6-SS-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-NH2)	318	CAACGUAACGAUUUCAUGAAA	910

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08120-SS	(C6-SS-C6)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(C6-NH2)	319	CAACGUAACGAUUUCAUGAAA	910
AM08121-SS	(C6-SS-C6)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)(C6-NH2)	320	CAACGUAACGAUUUCAUGAAA	910
AM08122-SS	(C6-SS-C6)scsaAlkacAlkguAlkaaAlkCfGfAfuuucaugaasa(invAb)(C6-NH2)	321	CAACGUAACGAUUUCAUGAAA	910
AM08123-SS	(C6-SS-C6)scsaAlkaAlkcgAlkuAlkaaCfGfAfuuucaugaasa(invAb)(C6-NH2)	322	CAACGUAACGAUUUCAUGAAA	910
AM08124-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(C6-SS-C6)dT	323	CACAUUCUCUAUGUACUAUGUT	995
AM08125-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguAlkacAlkuaAlkugAlkus(invAb)(C6-SS-C6)dT	324	CACAUUCUCUAUGUACUAUGUT	995
AM08126-SS	(TriAlk14)s(invAb)scaAlkcaAlkuuAlkcuAlkCfUfAfuguacuaugus(invAb)(C6-SS-C6)dT	325	CACAUUCUCUAUGUACUAUGUT	995
AM08127-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguacAlkuAlkauAlkgAlkus(invAb)(C6-SS-C6)dT	326	CACAUUCUCUAUGUACUAUGUT	995
AM08128-SS	(TriAlk14)s(invAb)sacacaacuGfUfCfcauacuaacas(invAb)(C6-SS-C6)dT	327	ACACAACUGUCCAUACUAACAT	996
AM08129-SS	(TriAlk14)s(invAb)sacacaacuGfUfCfcauAlkacAlkuaAlkacAlkas(invAb)(C6-SS-C6)dT	328	ACACAACUGUCCAUACUAACAT	996
AM08130-SS	(TriAlk14)s(invAb)sacAlkacAlkaaAlkcuAlkGfUfCfcauacuaacas(invAb)(C6-SS-C6)dT	329	ACACAACUGUCCAUACUAACAT	996
AM08131-SS	(TriAlk14)s(invAb)sacacaacuGfUfCfcauacAlkuAlkaaAlkcAlkas(invAb)(C6-SS-C6)dT	330	ACACAACUGUCCAUACUAACAT	996
AM08132-SS	(TriAlk14)scsaacguaaCfGfAfuuucaugAlkaaAlksa(invAb)(C6-SS-C6)dT	331	CAACGUAACGAUUUCAUGAAAT	994
AM08133-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugAlkaasa(invAb)(C6-SS-C6)dT	332	CAACGUAACGAUUUCAUGAAAT	994
AM08134-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugaasa(invAb)(C6-SS-C6)dT	333	CAACGUAACGAUUUCAUGAAAT	994
AM08135-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaugaaAlksa(invAb)(C6-SS-C6)dT	334	CAACGUAACGAUUUCAUGAAAT	994
AM08233-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(Om-C18-DA)	335	CAACGUAACGAUUUCAUGAAA	910
AM08234-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(Dap-C18-DA)	336	CAACGUAACGAUUUCAUGAAA	910
AM08372-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(Lys-C18-DA)	337	CAACGUAACGAUUUCAUGAAA	910
AM08394-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)s(Lys-C18-DA)	338	CAACGUAACGAUUUCAUGAAA	910

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08395-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(C6-SS-C6)dT	339	CAACGUAACGAUUUCAUGAAAT	994
AM08396-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(Lys-C18-DA)	340	CAACGUAACGAUUUCAUGAAA	910
AM08397-SS	(TriAlk14)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(C6-SS-C6)dT	341	CAACGUAACGAUUUCAUGAAAT	994
AM08398-SS	(TriAlk14)s(invAb)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(C6-SS-C6)dT	342	CAACGUAACGAUUUCAUGAAAT	994
AM08399-SS	(TriAlk14)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(Lys-C18-DA)	343	CAACGUAACGAUUUCAUGAAA	910
AM10042-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)dT	344	CAACGUAACGAUUUCAUGAAAT	994

[0149] As shown in Table 4, above, many of the example HIF-2 alpha nucleotide sequences are shown to further include reactive linking groups at 5' terminal end, the 3' terminal end, or both the 5' and the 3' terminal ends of the nucleotide sequence of the sense strand. For example, several HIF-2 alpha nucleotide sequences shown in Table 4 above have an (NH2-C6) linking group or a (TriAlk) linking group at the 5' end of the nucleotide sequence. Similarly, several of the HIF-2 alpha nucleotide sequences shown in Table 4 above have a (C6-SS-C6) or (6-SS-6) linking group at the 3' end of the nucleotide sequence. Such reactive linking groups are positioned to facilitate the linking of targeting ligands, targeting groups, and/or PK enhancers to the HIF-2 alpha RNAi agents disclosed herein. Linking or conjugation reactions are well known in the art and provide for formation of covalent linkages between two molecules or reactants. Suitable conjugation reactions for use in the scope of the inventions herein include, but are not limited to, amide coupling reaction, Michael addition reaction, hydrazone formation reaction and click chemistry cycloaddition reaction.

[0150] In some embodiments, targeting ligands can be synthesized as a tetrafluorophenyl (TFP) ester, which can be displaced by a reactive amino group (for example, NH2-C6) to attach the targeting ligand to the HIF-2 alpha RNAi agents disclosed herein. In some embodiments, targeting ligands are synthesized as azides, which can be conjugated to a propargyl or DBCO group, for example, via click chemistry cycloaddition reaction.

[0151] Additionally, several of the nucleotide sequences were synthesized with a dT nucleotide at the 3' terminal end of the sense strand, followed by (3' → 5') a linker (*for example*, C6-SS-C6), which can in some embodiments be used after cleavage from the resin to facilitate the linkage to additional components, such as, for example, a PK enhancer or one or more targeting ligands. Synthesis in this manner involves dT attached to the resin, followed by the coupling of the linker and the remaining nucleotides of the sense strand. As described herein, upon conjugation of the desired PK enhancer (or targeting ligand(s)) the terminal dT is cleaved off the molecule. Table 4.1 below shows the nucleotide sequences identified in Table 4, above, but without the inclusion of the 3' terminal dT nucleotide.

[0152] Futher, Table 4.2 below, shows the nucleotide sequences identified in Table 4, above, but without the terminal linking groups present.

Table 4.1. HIF-2 alpha RNAi Agent Sense Strand Sequences Shown Without 3' Terminal dT

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08032-SS	(NH2-C6)scsaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)(C6-SS-C6)	345	CAACGUAACGAUUUCAUGAAA	428
AM08092-SS	(NH2-C6)scsaaAlkcguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)	346	CAACGUAACGAUUUCAUGAAA	428
AM08093-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaaAlksa(invAb)(C6-SS-C6)	347	CAACGUAACGAUUUCAUGAAA	428
AM08108-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)(C6-SS-C6)	348	CAACGUAACGAUUUCAUGAAA	428
AM08109-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)(C6-SS-C6)	349	CAACGUAACGAUUUCAUGAAA	428
AM08110-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugaAlkaAlksa(invAb)(C6-SS-C6)	350	CAACGUAACGAUUUCAUGAAA	428
AM08111-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaaAlksa(invAb)(C6-SS-C6)	351	CAACGUAACGAUUUCAUGAAA	428
AM08112-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaAlkasa(invAb)(C6-SS-C6)	352	CAACGUAACGAUUUCAUGAAA	428
AM08113-SS	(TriAlk14)scsaacguaaCfGfAfuuucaugaAlkaAlksa(invAb)(C6-SS-C6)	353	CAACGUAACGAUUUCAUGAAA	428
AM08114-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkuAlkgaasa(invAb)(C6-SS-C6)	354	CAACGUAACGAUUUCAUGAAA	428
AM08115-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaAlkasa(invAb)(C6-SS-C6)	355	CAACGUAACGAUUUCAUGAAA	428
AM08116-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugaAlkasa(invAb)(C6-SS-C6)	356	CAACGUAACGAUUUCAUGAAA	428
AM08117-SS	(TriAlk14)scsaacguaaCfGfAfuuucauAlkgaaAlksa(invAb)(C6-SS-C6)	357	CAACGUAACGAUUUCAUGAAA	428
AM08118-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaugAlkaasa(invAb)(C6-SS-C6)	358	CAACGUAACGAUUUCAUGAAA	428
AM08124-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(C6-SS-C6)	359	CACAUUCUCUAUGUACUAUGU	485
AM08125-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguAlkacAlkuaAlkugAlkus(invAb)(C6-SS-C6)	360	CACAUUCUCUAUGUACUAUGU	485
AM08126-SS	(TriAlk14)s(invAb)scaAlkcaAlkuuAlkcuAlkCfUfAfuguacuaugus(invAb)(C6-SS-C6)	361	CACAUUCUCUAUGUACUAUGU	485
AM08127-SS	(TriAlk14)s(invAb)scacauucuCfUfAfuguacAlkuAlkauAlkgAlkus(invAb)(C6-SS-C6)	362	CACAUUCUCUAUGUACUAUGU	485
AM08128-SS	(TriAlk14)s(invAb)sacacaacuGfUfCfcauacuaacas(invAb)(C6-SS-C6)	363	ACACAACUGUCCAUACUAACA	507

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08129-SS	(TriAlk14)s(invAb)sacacaacuGfUfCfcauAlkacAlkuaAlkacAlkas(invAb)(C6-SS-C6)	364	ACACAACUGUCCAUACUAACA	507
AM08130-SS	(TriAlk14)s(invAb)sacAlkacAlkaaAlkcuAlkGfUfCfcauacuaacas(invAb)(C6-SS-C6)	365	ACACAACUGUCCAUACUAACA	507
AM08131-SS	(TriAlk14)s(invAb)sacacaacnGfUfCfcauacAlkuAlkaaAlkcAlkas(invAb)(C6-SS-C6)	366	ACACAACUGUCCAUACUAACA	507
AM08132-SS	(TriAlk14)scsaacguaaCfGfAfuuucaugAlkaaAlksa(invAb)(C6-SS-C6)	367	CAACGUAACGAUUUCAUGAAA	428
AM08133-SS	(TriAlk14)scsaacguaaCfGfAfuuucaAlkugAlkaasa(invAb)(C6-SS-C6)	368	CAACGUAACGAUUUCAUGAAA	428
AM08134-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugaasa(invAb)(C6-SS-C6)	369	CAACGUAACGAUUUCAUGAAA	428
AM08135-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaugaaAlksa(invAb)(C6-SS-C6)	370	CAACGUAACGAUUUCAUGAAA	428
AM08395-SS	(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)(C6-SS-C6)	371	CAACGUAACGAUUUCAUGAAA	428
AM08397-SS	(TriAlk14)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(C6-SS-C6)	372	CAACGUAACGAUUUCAUGAAA	428
AM08398-SS	(TriAlk14)s(invAb)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s(C6-SS-C6)	373	CAACGUAACGAUUUCAUGAAA	428
AM10024-SS	(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-SS-C6)	374	CAACGUAACGAUUUCAUGAAA	428

Table 4.2. HIF-2 alpha RNAi Agent Sense Strand Sequences Shown Without Terminal Linking Groups

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM05339-SS	uAuascguaaCfGfAfuuuCfaugaaa(invdT)	375	UAUACGUAACGAUUUCAUGAAAT	909
AM05814-SS	scsaacguaaCfGfAfuuucaugaasa(invAb)	376	CAACGUAACGAUUUCAUGAAA	910
AM05816-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	377	CAACGUAACGAUUUCAUGAAA	910
AM06490-SS	csuggacauAfGfUfaucuuugacas(invAb)	378	CUGGACAUAGUAUCUUUGACA	911
AM06492-SS	cscaugcgcUfAfGfacuccgagaas(invAb)	379	CCAUGCGCUAGACUCCGAGAA	912
AM06494-SS	cscaguaccGfGfAfugcucgcaaas(invAb)	380	CCAGUACCGGAUGCUCGCAAA	913
AM06496-SS	gsucaucuaCfAfAfcccucgcaaas(invAb)	381	GUCAUCUACAACCCUCGCAAA	914
AM06498-SS	csuucgggaAfUfCfagaacuucgas(invAb)	382	CUUCGGGAAUCAGAACUUCGA	915
AM06500-SS	cscacgcccAfAfUfagcccugaaas(invAb)	383	CCACGCCCAAUAGCCCUGAAA	916
AM06502-SS	gscaguaccCfAfGfacggauuucas(invAb)	384	GCAGUACCCAGACGGAUUUCA	917
AM06504-SS	gsaugccgGfAfAfgcaaagcauas(invAb)	385	GAUGCCGGAAGCAAAGCAUA	918
AM06524-SS	csccuuugaUfGfCfcggacaagcas(invAb)	386	CCCUUUGAUGCCGGACAAGCA	919
AM06526-SS	gsgacaagcCfAfCfugagcgcaaas(invAb)	387	GGACAAGCCACUGAGCGCAAA	920
AM06528-SS	asggacuacAfGfCfcugucgucaas(invAb)	388	AGGACUACAGCCUGUCGUCAA	921
AM06530-SS	csggacuuAfCfCfuggcagacuas(invAb)	389	CGGACUUACCUGGCAGACUA	922
AM06532-SS	gsaagggucAfAfCfuccaacguaas(invAb)	390	GAAGGGUCAACUCCAACGUAA	923
AM06534-SS	csagggucaAfCfUfccaacguauas(invAb)	391	CAGGGUCAACUCCAACGUAUA	924
AM06536-SS	gsggucaacUfCfCfaacguauguas(invAb)	392	GGGUCAACUCCAACGUAUGUA	925
AM06538-SS	csuccaacgUfAfUfgugguuaucas(invAb)	393	CUCCAACGUAUGUGGUUAUCA	926

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM06550-SS	gsccauagGfUfGfugacaauccas(invAb)	394	GCCAUAGGUGUGACAAUCCA	927
AM06552-SS	cscauagguGfUfGfacaauccgaas(invAb)	395	CCAUAGGUGUGACAAUCCGAA	928
AM06554-SS	gsggucugAfUfGfgcacgugugas(invAb)	396	GGGUCUGAUGGCACGUUGUA	929
AM06556-SS	csugagcuaUfGfUfgacucggauas(invAb)	397	CUGAGCUAUGUGACUCGGAUA	930
AM06558-SS	gsgguaagAfGfGfgacgacaccas(invAb)	398	GGGUAAGAGGGACGACACCA	931
AM06560-SS	csccuacCfUfGfucaacguaaas(invAb)	399	CCCUACCUGUCAACGUAAA	932
AM06562-SS	(invAb)scccuacCfUfGfucaacguaaas(invAb)	400	CCCUACCUGUCAACGUAAA	932
AM06564-SS	csccuaccuGfUfCfaacguaacgas(invAb)	401	CCCUACCUGUCAACGUAACGA	933
AM06566-SS	cscuaccuGfUfCfaacguaacgas(invAb)	402	CCUACCUGUCAACGUAACGA	934
AM06568-SS	asccugucaAfCfGfuaacgauuuas(invAb)	403	ACCUGUCAACGUAACGAUUUA	935
AM06877-SS	(invAb)sgcagunuugCfUfCfugaaaacgaas(invAb)	404	GCAGUUUGCUCUGAAAACGAA	936
AM06879-SS	(invAb)saggugaaaGfUfCfuacaacaacus(invAb)	405	AGGUGAAAGUCUACAACAACU	937
AM06881-SS	(invAb)sggacacauCfUfUfuggauaacgas(invAb)	406	GGACACAUCUUUGGAUAACGA	938
AM06883-SS	(invAb)scgaccugaAfGfAfuugaagugaus(invAb)	407	CGACCUGAAGAUUGAAGUGAU	939
AM06885-SS	(invAb)sacgggaagAfCfUfuccagcuaaas(invAb)	408	ACGGGAAGACUUCCAGCUAAA	940
AM06887-SS	(invAb)sagcuaacaGfGfAfcauaguaucus(invAb)	409	AGCUAACAGGACAUAGUAUCU	941
AM06889-SS	(invAb)scagauaugAfCfUfgugaggugaas(invAb)	410	CAGAUAUGACUGUGAGGUGAA	942
AM06891-SS	(invAb)sggaguacaCfAfAfuugunuuacas(invAb)	411	GGAGUACACAAUUGUUUUACA	943
AM06893-SS	(invAb)sggucaacuCfCfAfacguaugugas(invAb)	412	GGUCAACUCCAACGUAUGUGA	944
AM06895-SS	(invAb)sgucaacucCfAfAfcguauguggus(invAb)	413	GUCAACUCCAACGUAUGUGGU	945

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM06897-SS	(invAb)sgaugccauAfGfGfugugacaauas(invAb)	414	GAUGCCAUAGGUGUGACAAUA	946
AM06899-SS	(invAb)sggaacuacCfAfUfgagaugguuus(invAb)	415	GGAACUACCAUGAGAUGGUUU	947
AM06901-SS	(invAb)sgcuaccauGfAfGfaugguuuagas(invAb)	416	GCUACCAUGAGAUGGUUUAGA	948
AM06903-SS	(invAb)scgauaccaAfUfUfacauggaacus(invAb)	417	CGAUACCAAUUACAUGGAACU	949
AM06905-SS	(invAb)sccuaccugUfCfAfacguaacgaus(invAb)	418	CCUACCUGUCAACGUAACGAU	950
AM06981-SS	csasascsguaaCfGfAfuuucausgsasasas(invAb)	419	CAACGUAACGAUUUCAUGAAA	910
AM06983-SS	csaascgsuasaCfsGfAfsuusucsausgasaas(invAb)	420	CAACGUAACGAUUUCAUGAAA	910
AM06984-SS	csasacguaaCfGfAfuuucaugasasas(invAb)	421	CAACGUAACGAUUUCAUGAAA	910
AM06986-SS	casacsgusaasCfGfsAfusuuscasugsaasas(invAb)	422	CAACGUAACGAUUUCAUGAAA	910
AM07071-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	423	CAACGUAACGAUUUCAUGAAA	910
AM07138-SS	(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)	424	CAACGUAACGAUUUCAUGAAA	910
AM07139-SS	(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)	425	GAACGUAACGAUUUCAUGAAA	951
AM07141-SS	(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)	426	GAACGUAACGAUUUCAUGAAA	952
AM07142-SS	(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)	427	GGACGUAACGAUUUCAUGAAA	953
AM07145-SS	(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)	428	GGACGUAACGAUUUCAUIAAA	954
AM07146-SS	(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)	429	GGACGUAACGAUUUCAUGAAA	953
AM07224-SS	csaacguaaCfGfAfuuucaugaaasa(invAb)(6-SS-6)	430	CAACGUAACGAUUUCAUGAAA	910
AM07225-SS	(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)	431	CAACGUAACGAUUUCAUGAAA	910
AM07226-SS	(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)	432	GAACGUAACGAUUUCAUGAAA	951
AM07227-SS	(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)	433	GAACGUAACGAUUUCAUGAAA	952

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07228-SS	(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)	434	GGACGUAACGAUUUCAUGAAA	953
AM07229-SS	(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)	435	GGACGUAACGAUUUCAUIAAA	954
AM07230-SS	(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)	436	GGACGUAACGAUUUCAUGAAA	953
AM07231-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	437	CAACGUAACGAUUUCAUGAAA	910
AM07268-SS	csaacguaaCfGfAfuusucsausgasaas(invAb)	438	CAACGUAACGAUUUCAUGAAA	910
AM07269-SS	csaascgsuasaCfGfAfuuucaugaaas(invAb)	439	CAACGUAACGAUUUCAUGAAA	910
AM07270-SS	csaacguaaCfGfAfuuucausgsasasas(invAb)	440	CAACGUAACGAUUUCAUGAAA	910
AM07271-SS	csasascsgsuaaCfGfAfuuucaugaaas(invAb)	441	CAACGUAACGAUUUCAUGAAA	910
AM07272-SS	csaacguasaCfsGfAfsuusucaugaaas(invAb)	442	CAACGUAACGAUUUCAUGAAA	910
AM07273-SS	csaacgusaasCfGfsAfusuucaugaaas(invAb)	443	CAACGUAACGAUUUCAUGAAA	910
AM07274-SS	csaascguaaCfGfAfuuucausgasaas(invAb)	444	CAACGUAACGAUUUCAUGAAA	910
AM07275-SS	csasascguaaCfGfAfuuucaugasasas(invAb)	445	CAACGUAACGAUUUCAUGAAA	910
AM07301-SS	csaacguaaCfGfAfuusucsausgasaas(invAb)	446	CAACGUAACGAUUUCAUGAAA	910
AM07302-SS	csaascgsuasaCfGfAfuuucaugaaas(invAb)	447	CAACGUAACGAUUUCAUGAAA	910
AM07303-SS	csaacguaaCfGfAfuuucausgsasasas(invAb)	448	CAACGUAACGAUUUCAUGAAA	910
AM07304-SS	csasascsgsuaaCfGfAfuuucaugaaas(invAb)	449	CAACGUAACGAUUUCAUGAAA	910
AM07305-SS	csaacguasaCfsGfAfsuusucaugaaas(invAb)	450	CAACGUAACGAUUUCAUGAAA	910
AM07306-SS	csaacgusaasCfGfsAfusuucaugaaas(invAb)	451	CAACGUAACGAUUUCAUGAAA	910
AM07307-SS	csaascguaaCfGfAfuuucausgasaas(invAb)	452	CAACGUAACGAUUUCAUGAAA	910
AM07308-SS	csasascguaaCfGfAfuuucaugasasas(invAb)	453	CAACGUAACGAUUUCAUGAAA	910

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07403-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	454	CAACGUAACGAUUUCAUGAAA	910
AM07404-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	455	CAACGUAACGAUUUCAUGAAA	910
AM07405-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	456	CAACGUAACGAUUUCAUGAAA	910
AM07406-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	457	CAACGUAACGAUUUCAUGAAA	910
AM07407-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	458	CAACGUAACGAUUUCAUGAAA	910
AM07408-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	459	CAACGUAACGAUUUCAUGAAA	910
AM07493-SS	csaacguasaCfsGfAfsuusucaugaaas(invAb)	460	CAACGUAACGAUUUCAUGAAA	910
AM07528-SS	csaacguaaCfGfAfuusucsausgasaas(invAb)	461	CAACGUAACGAUUUCAUGAAA	910
AM07530-SS	(invAb)scaacuuguAfCfCfugaaaiccuus(invAb)(invAb)	462	CAACUUGUACCUGAAAICCUU	955
AM07532-SS	(invAb)sacuuacacAfGfGfuggagcuaaas(invAb)(invAb)	463	ACUUACACAGGUGGAGCUAAA	956
AM07534-SS	(invAb)saggacauaGfUfAfucuuugacuus(invAb)(invAb)	464	AGGACAUAGUAUCUUUGACUU	957
AM07536-SS	(invAb)scugugucuGfAfGfaagaguaacus(invAb)(invAb)	465	CUGUGUCUGAGAAGAGUAACU	958
AM07538-SS	(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)(invAb)	466	CUUCCUAUUCACCAAGCUAAA	959
AM07540-SS	(invAb)sccagcacaCfUfAfuuuacaagaus(invAb)(invAb)	467	CCAGCACACUAUUUACAAGAU	960
AM07542-SS	(invAb)sgccccuauUfUfUfuaaaguacaas(invAb)(invAb)	468	GCCCCUAUUUUUAAAGUACAA	961
AM07544-SS	(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)(invAb)	469	GAGUACACAAUUGUUUUACCU	962
AM07546-SS	(invAb)scaacugucCfAfUfacuaacaagus(invAb)(invAb)	470	CAACUGUCCAUACUAACAAGU	963
AM07548-SS	(invAb)sgugguuauCfUfGfugaaaguugas(invAb)(invAb)	471	GUGGUUAUCUGUGAAAGUUGA	964
AM07550-SS	(invAb)sgaacuuagAfAfAfcggaaauggas(invAb)(invAb)	472	GAACUUAGAAACGGAAAUGGA	965
AM07552-SS	(invAb)sgauccgagCfAfGfuggagucauus(invAb)(invAb)	473	GAUCCGAGCAGUGGAGUCAUU	966

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07554-SS	(invAb)scacauucuCfUfAfuguacuaugus(invAb)(invAb)	474	CACAUUCUCUAUGUACUAUGU	967
AM07556-SS	(invAb)sggucagugAfCfAfuguagguagas(invAb)(invAb)	475	GGUCAGUGACAUGUAGGUAGA	968
AM07558-SS	(invAb)sgacacacaCfAfAfagcacauugas(invAb)(invAb)	476	GACACACACAAAGCACACAUUGA	969
AM07560-SS	(invAb)saccggauaGfAfCfuuauuiccaas(invAb)(invAb)	477	ACCGGAUAGACUUAUUICCAA	970
AM07562-SS	(invAb)sgaaguucuAfUfGfagaaauuccus(invAb)(invAb)	478	GAAGUUCUAUGAGAAAUUCCU	971
AM07564-SS	(invAb)sgguuacugAfCfGfuguaaaugcus(invAb)(invAb)	479	GGUUACUGACGUGUAAAUGCU	972
AM07566-SS	(invAb)sacguaacgAfUfUfucaugaacgus(invAb)(invAb)	480	ACGUAACGAUUUCAUGAACGU	973
AM07568-SS	(invAb)sguaacgauUfUfCfaugaacguuas(invAb)(invAb)	481	GUAACGAUUUCAUGAACGUUA	974
AM07570-SS	(invAb)sgaacgauuUfCfAfugaacguuaus(invAb)(invAb)	482	GAACGAUUUCAUGAACGUUAU	975
AM07572-SS	(invAb)sggagcuuaAfCfUfuuauaaggaas(invAb)(invAb)	483	GGAGCUUAACUUUAUAAGGAA	976
AM07619-SS	csaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(invAb)	484	CAACGUAACGAUUUCAUGAAA	1016
AM07621-SS	scsaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)(invAb)	485	CAACGUAACGAUUUCAUGAAA	1016
AM07705-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	486	CAACGUAACGAUUUCAUGAAA	910
AM07706-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	487	CAACGUAACGAUUUCAUGAAA	910
AM07707-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	488	CAACGUAACGAUUUCAUGAAA	910
AM07708-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	489	CAACGUAACGAUUUCAUGAAA	910
AM07709-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	490	CAACGUAACGAUUUCAUGAAA	910
AM07710-SS	csaacguaaCfGfAfuuucaAlkugaasa(invAb)	491	CAACGUAACGAUUUCAUGAAA	1017
AM07711-SS	csaacguaAlkaCfGfAfuuucaugaasa(invAb)	492	CAACGUAACGAUUUCAUGAAA	1018
AM07712-SS	csaacguaAlkaCfGfAfuuucaAlkugaasa(invAb)	493	CAACGUAACGAUUUCAUGAAA	1019

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07713-SS	csaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)	494	CAACGUAACGAUUUCAUGAAA	1016
AM07721-SS	(invAb)scacauucuCfUfAfuguacuaugus(invAb)	495	CACAUUCUCUAUGUACUAUGU	967
AM07722-SS	(invAb)sgacauucuCfUfAfuguacuaugus(invAb)	496	GACAUUCUCUAUGUACUAUGU	977
AM07724-SS	(invAb)scgcauucuCfUfAfuguacuaugus(invAb)	497	CGCAUUCUCUAUGUACUAUGU	978
AM07726-SS	(invAb)scccauucuCfUfAfuguacuaugus(invAb)	498	CCCAUUCUCUAUGUACUAUGU	979
AM07728-SS	(invAb)sggcauucuCfUfAfuguacuaugus(invAb)	499	GGCAUUCUCUAUGUACUAUGU	980
AM07730-SS	(invAb)scaca_2NuucuCfUfAfuguacuaugus(invAb)	500	CACAUUCUCUAUGUACUAUGU	981
AM07731-SS	(invAb)sccca_2NuucuCfUfAfuguacuaugus(invAb)	501	CCCAUUCUCUAUGUACUAUGU	982
AM07732-SS	(invAb)sgcgaccAfUfGfaggagauucauus(invAb)	502	GCGACCAUGAGGAGAUUCAUU	983
AM07734-SS	(invAb)scgcucaGfCfCfuaugaauucauus(invAb)	503	CGCUCAGCCUAUGAAUUCAUU	984
AM07736-SS	(invAb)scaagggucAfGfGfuaguaagugas(invAb)	504	CAAGGGUCAGGUAGUAAGUGA	985
AM07738-SS	(invAb)sgacugaauCfCfCfuguucaagcas(invAb)	505	GACUGAAUCCCUGUUCAAGCA	986
AM07740-SS	(invAb)sucagugccAfUfGfacaaacaucus(invAb)	506	UCAGUGCCAUGACAAACAUCU	987
AM07742-SS	(invAb)sgcaccucaCfAfUfuugauguggas(invAb)	507	GCACCUCACAUUUGAUGUGGA	988
AM07744-SS	(invAb)sacacaacuGfUfCfcauacuaacas(invAb)	508	ACACAACUGUCCAUACUAACA	989
AM07746-SS	(invAb)sggcauaguAfUfCfuuugacuucas(invAb)	509	GGCAUAGUAUCUUUGACUUCA	990
AM07776-SS	(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)	510	GAGUACACAAUUGUUUUACCU	962
AM07777-SS	(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)	511	CUUCCUAUUCACCAAGCUAAA	959
AM07778-SS	(invAb)sggucagugAfCfAfuguagguagas(invAb)	512	GGUCAGUGACAUGUAGGUAGA	968
AM07801-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	513	CAACGUAACGAUUUCAUGAAA	910

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07813-SS	csaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)	514	CAACGUAACGAUUUCAUGAAA	1016
AM07814-SS	csaaAlkcguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)	515	CAACGUAACGAUUUCAUGAAA	1016
AM07817-SS	csaAlkaAlkcguAlkaAlkaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)	516	CAACGUAACGAUUUCAUGAAA	1020
AM07818-SS	scsaacguaaCfGfAfuuucaugaasa(invAb)	517	CAACGUAACGAUUUCAUGAAA	910
AM07822-SS	csaacguaAlkaCfGfAfuuucaAlkugaaAlksa(invAb)	518	CAACGUAACGAUUUCAUGAAA	1021
AM07823-SS	csaaAlkcguaaCfGfAfuuucaAlkugaaAlksa(invAb)	519	CAACGUAACGAUUUCAUGAAA	1022
AM07824-SS	csaaAlkcguaAlkaCfGfAfuuucaugaaAlksa(invAb)	520	CAACGUAACGAUUUCAUGAAA	1023
AM07825-SS	csaaAlkcguaAlkaCfGfAfuuucaAlkugaaasa(invAb)	521	CAACGUAACGAUUUCAUGAAA	1024
AM07826-SS	csaaAlkcguaAlkaCfGfAfuuucaugaasa(invAb)	522	CAACGUAACGAUUUCAUGAAA	1025
AM07827-SS	csaacguaaCfGfAfuuucaAlkugaaAlksa(invAb)	523	CAACGUAACGAUUUCAUGAAA	1006
AM07828-SS	csaaAlkcguaaCfGfAfuuucaugaaAlksa(invAb)	524	CAACGUAACGAUUUCAUGAAA	1026
AM07829-SS	csaaAlkcguaaCfGfAfuuucaAlkugaasa(invAb)	525	CAACGUAACGAUUUCAUGAAA	1027
AM07830-SS	csaacguaAlkaCfGfAfuuucaugaaAlksa(invAb)	526	CAACGUAACGAUUUCAUGAAA	1028
AM07831-SS	csaacguaaCfGfAfuuucaugaaAlksa(invAb)	527	CAACGUAACGAUUUCAUGAAA	999
AM07832-SS	csaaAlkcguaaCfGfAfuuucaugaasa(invAb)	528	CAACGUAACGAUUUCAUGAAA	998
AM07833-SS	csaAlkaAlkcguaaCfGfAfuuucaugaAlkaAlksa(invAb)	529	CAACGUAACGAUUUCAUGAAA	1029
AM07834-SS	csaacAlkguaaAlkCfGfAfuuuAlkcaugAlkaasa(invAb)	530	CAACGUAACGAUUUCAUGAAA	1030
AM07835-SS	csaacgAlkuaaAlkCfGfAfuAlkuucAlkaugaasa(invAb)	531	CAACGUAACGAUUUCAUGAAA	1031
AM07836-SS	csaacguaAlkaAlkCfGfAfuAlkuAlkucaugaasa(invAb)	532	CAACGUAACGAUUUCAUGAAA	1032
AM07837-SS	csaAlkacAlkguAlkaaAlkCfGfAfuuucaugaasa(invAb)	533	CAACGUAACGAUUUCAUGAAA	1033

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM07838-SS	csaAlkaAlkcAlkgAlkuaaCfGfAfuuucaugaasa(invAb)	534	CAACGUAACGAUUUCAUGAAA	1034
AM07839-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	535	CAACGUAACGAUUUCAUGAAA	1015
AM07840-SS	csaacguaaCfGfAfuuucauAlkgAlkaAlkaAlksa(invAb)	536	CAACGUAACGAUUUCAUGAAA	1035
AM07890-SS	(invAb)sgcacaacuGfUfCfcauacuaacas(invAb)	537	GCACAACUGUCCAUACUAACA	991
AM07892-SS	(invAb)sccacaacuGfUfCfcauacuaacas(invAb)	538	CCACAACUGUCCAUACUAACA	992
AM07894-SS	(invAb)sggacaacuGfUfCfcauacuaacas(invAb)	539	GGACAACUGUCCAUACUAACA	993
AM08018-SS	csaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)	540	CAACGUAACGAUUUCAUGAAA	1000
AM08019-SS	csaacAlkguaaAlkCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	541	CAACGUAACGAUUUCAUGAAA	1036
AM08020-SS	csaacguaaCfGfAfuuucaugAlkaasa(invAb)	542	CAACGUAACGAUUUCAUGAAA	999
AM08021-SS	csaacguaaCfGfAfuuucaAlkuAlkgAlkaAlkasa(invAb)	543	CAACGUAACGAUUUCAUGAAA	1000
AM08022-SS	csaacguaaCfGfAfuuucAlkaAlkuAlkgAlkaasa(invAb)	544	CAACGUAACGAUUUCAUGAAA	1037
AM08023-SS	csaacguaaCfGfAfuuuAlkcAlkaAlkuAlkgaasa(invAb)	545	CAACGUAACGAUUUCAUGAAA	1038
AM08024-SS	csaacguaaCfGfAfuuAlkuAlkcAlkaAlkugaasa(invAb)	546	CAACGUAACGAUUUCAUGAAA	1039
AM08025-SS	csaacguaaCfGfAfuAlkuAlkuAlkcAlkaugaasa(invAb)	547	CAACGUAACGAUUUCAUGAAA	1040
AM08026-SS	csaacguaaCfGfAfuAlkuuAlkcaAlkugAlkaaAlksa(invAb)	548	CAACGUAACGAUUUCAUGAAA	1041
AM08027-SS	csaacguaaCfGfAfuuucaAlkugAlkaaAlksa(invAb)	549	CAACGUAACGAUUUCAUGAAA	1001
AM08028-SS	csaacguaaCfGfAfuuuAlkcaugAlkaaAlksa(invAb)	550	CAACGUAACGAUUUCAUGAAA	1042
AM08029-SS	csaacguaaCfGfAfuuuAlkcaAlkugaaAlksa(invAb)	551	CAACGUAACGAUUUCAUGAAA	1043
AM08030-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaasa(invAb)	552	CAACGUAACGAUUUCAUGAAA	1043
AM08031-SS	csaacguaaCfGfAfuuucaugAlkaAlkaAlksa(invAb)	553	CAACGUAACGAUUUCAUGAAA	1044

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08032-SS	csaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)	554	CAACGUAACGAUUUCAUGAAA	997
AM08033-SS	csaacguaaCfGfAfuuucauAlkgAlkaaAlksa(invAb)	555	CAACGUAACGAUUUCAUGAAA	997
AM08034-SS	csaacguaaCfGfAfuuucauAlkgAlkaAlkasa(invAb)	556	CAACGUAACGAUUUCAUGAAA	997
AM08035-SS	csaacguaaAlkCfGfAfuuuAlkcaugAlkaasa(invAb)	557	CAACGUAACGAUUUCAUGAAA	1045
AM08036-SS	csaacAlkguaaCfGfAfuuuAlkcaugAlkaasa(invAb)	558	CAACGUAACGAUUUCAUGAAA	1046
AM08037-SS	csaacAlkguaaAlkCfGfAfuuucaugAlkaasa(invAb)	559	CAACGUAACGAUUUCAUGAAA	1047
AM08038-SS	csaacAlkguaaAlkCfGfAfuuuAlkcaugaasa(invAb)	560	CAACGUAACGAUUUCAUGAAA	1048
AM08092-SS	csaaAlkcguaaCfGfAfuuucaugaasa(invAb)	561	CAACGUAACGAUUUCAUGAAA	998
AM08093-SS	csaacguaaCfGfAfuuucaugaaAlksa(invAb)	562	CAACGUAACGAUUUCAUGAAA	999
AM08108-SS	csaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)	563	CAACGUAACGAUUUCAUGAAA	1000
AM08109-SS	csaacguaaCfGfAfuuucauAlkgaAlkaAlksa(invAb)	564	CAACGUAACGAUUUCAUGAAA	997
AM08110-SS	csaacguaaCfGfAfuuucaAlkugaAlkaAlksa(invAb)	565	CAACGUAACGAUUUCAUGAAA	1001
AM08111-SS	csaacguaaCfGfAfuuucaAlkuAlkgaaAlksa(invAb)	566	CAACGUAACGAUUUCAUGAAA	1002
AM08112-SS	csaacguaaCfGfAfuuucaAlkuAlkgaAlkasa(invAb)	567	CAACGUAACGAUUUCAUGAAA	1002
AM08113-SS	csaacguaaCfGfAfuuucaugaAlkaAlksa(invAb)	568	CAACGUAACGAUUUCAUGAAA	1003
AM08114-SS	csaacguaaCfGfAfuuucaAlkuAlkgaasa(invAb)	569	CAACGUAACGAUUUCAUGAAA	1004
AM08115-SS	csaacguaaCfGfAfuuucauAlkgaAlkasa(invAb)	570	CAACGUAACGAUUUCAUGAAA	1005
AM08116-SS	csaacguaaCfGfAfuuucaAlkugaAlkasa(invAb)	571	CAACGUAACGAUUUCAUGAAA	1006
AM08117-SS	csaacguaaCfGfAfuuucauAlkgaaAlksa(invAb)	572	CAACGUAACGAUUUCAUGAAA	1005
AM08118-SS	csaacguaaCfGfAfuuuAlkcaugAlkaasa(invAb)	573	CAACGUAACGAUUUCAUGAAA	1007

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08119-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	574	CAACGUAACGAUUUCAUGAAA	910
AM08120-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	575	CAACGUAACGAUUUCAUGAAA	1015
AM08121-SS	csaacguaaCfGfAfuuucaAlkuAlkgaAlkaAlksa(invAb)	576	CAACGUAACGAUUUCAUGAAA	1000
AM08122-SS	csaAlkacAlkguAlkaaAlkCfGfAfuuucaugaasa(invAb)	577	CAACGUAACGAUUUCAUGAAA	1033
AM08123-SS	csaAlkaAlkcgAlkuAlkaaCfGfAfuuucaugaasa(invAb)	578	CAACGUAACGAUUUCAUGAAA	1049
AM08124-SS	(invAb)scacauucuCfUfAfuguacuaugus(invAb)	579	CACAUUCUCUAUGUACUAUGU	967
AM08125-SS	(invAb)scacauucuCfUfAfuguAlkacAlkuaAlkugAlkus(invAb)	580	CACAUUCUCUAUGUACUAUGU	1008
AM08126-SS	(invAb)scaAlkcaAlkuuAlkcuAlkCfUfAfuguacuaugus(invAb)	581	CACAUUCUCUAUGUACUAUGU	1009
AM08127-SS	(invAb)scacauucuCfUfAfuguacAlkuAlkauAlkgAlkus(invAb)	582	CACAUUCUCUAUGUACUAUGU	1010
AM08128-SS	(invAb)sacacaacuGfUfCfcauacuaacas(invAb)	583	ACACAACUGUCCAUACUAACA	989
AM08129-SS	(invAb)sacacaacuGfUfCfcauAlkacAlkuaAlkacAlkas(invAb)	584	ACACAACUGUCCAUACUAACA	1011
AM08130-SS	(invAb)sacAlkacAlkaaAlkcuAlkGfUfCfcauacuaacas(invAb)	585	ACACAACUGUCCAUACUAACA	1012
AM08131-SS	(invAb)sacacaacuGfUfCfcauacAlkuAlkaaAlkcAlkas(invAb)	586	ACACAACUGUCCAUACUAACA	1013
AM08132-SS	csaacguaaCfGfAfuuucaugAlkaaAlksa(invAb)	587	CAACGUAACGAUUUCAUGAAA	1003
AM08133-SS	csaacguaaCfGfAfuuucaAlkugAlkaasa(invAb)	588	CAACGUAACGAUUUCAUGAAA	1006
AM08134-SS	csaacguaaCfGfAfuuuAlkcaAlkugaasa(invAb)	589	CAACGUAACGAUUUCAUGAAA	1014
AM08135-SS	csaacguaaCfGfAfuuuAlkcaugaaAlksa(invAb)	590	CAACGUAACGAUUUCAUGAAA	1007
AM08233-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	591	CAACGUAACGAUUUCAUGAAA	1015
AM08234-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	592	CAACGUAACGAUUUCAUGAAA	1015
AM08372-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	593	CAACGUAACGAUUUCAUGAAA	1015

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.	Underlying Base Sequence (5′ → 3′) (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM08394-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)s	594	CAACGUAACGAUUUCAUGAAA	1015
AM08395-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)	595	CAACGUAACGAUUUCAUGAAA	1015
AM08396-SS	csaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s	596	CAACGUAACGAUUUCAUGAAA	1015
AM08397-SS	csasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s	597	CAACGUAACGAUUUCAUGAAA	1015
AM08398-SS	(invAb)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s	598	CAACGUAACGAUUUCAUGAAA	1015
AM08399-SS	csasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)s	599	CAACGUAACGAUUUCAUGAAA	1015
AM10024-SS	csaacguaaCfGfAfuuucaugaasa(invAb)	600	CAACGUAACGAUUUCAUGAAA	910

[0153] As discussed herein, in some embodiments, one or more targeting ligands and/or PK enhancers are linked or conjugated to the RNAi agent. In some embodiments, a targeting ligand (or targeting group) and/or a PK enhancer is linked to the 5' end of the sense strand, the 3' end of the sense strand, and/or to one or more internal nucleotides. The synthesis of the sense strand and/or the antisense strand can be designed such that reactive groups are readily available to facilitate linkage to additional components, such as a targeting ligand or PK enhancer. The following Table 4.3 depicts the sense strand of the HIF-2 alpha RNAi agents disclosed above in Table 4 after linking to one or more targeting ligands and/or PK enhancers (collectively, shown below, as Z).

Table 4.3. HIF-2 alpha RNAi Agent Sense Strand Sequences Showing Targeting Ligand and/or PK enhancer Positions (each X, Y and *Z* is independently a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer); $(Z)_3$ = three Ligands linked (for example, a tridentate targeting group); u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety (for example, targeting ligand, targeting group, and/or PK enhancer) linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group.)

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM05339-SS	Y-(NH-C6)uAuascguaaCfGfAfuuuCfaugaaa(invdT)(C6-S)-X	601
AM05814-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)-X	602
AM05816-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-S)-X	603
AM06490-SS	Y-(NH-C6)scsuggacauAfGfUfaucuuugacas(invAb)(C6-S)-X	604
AM06492-SS	Y-(NH-C6)scscaugcgcUfAfGfacuccgagaas(invAb)(C6-S)-X	605
AM06494-SS	Y-(NH-C6)scscaguaccGfGfAfugcucgcaaas(invAb)(C6-S)-X	606
AM06496-SS	Y-(NH-C6)sgsucaucuaCfAfAfcccucgcaaas(invAb)(C6-S)-X	607
AM06498-SS	Y-(NH-C6)scsuucgggaAfUfCfagaacuucgas(invAb)(C6-S)-X	608
AM06500-SS	Y-(NH-C6)scscacgcccAfAfUfagcccugaaas(invAb)(C6-S)-X	609
AM06502-SS	Y-(NH-C6)sgscaguaccCfAfGfacggauuucas(invAb)(C6-S)-X	610
AM06504-SS	Y-(NH-C6)sgsaugccgGfAfAfgcaaagcauas(invAb)(C6-S)-X	611
AM06524-SS	Y-(NH-C6)scsccuuugaUfGfCfcggacaagcas(invAb)(C6-S)-X	612
AM06526-SS	Y-(NH-C6)sgsgacaagcCfAfCfugagcgcaaas(invAb)(C6-S)-X	613
AM06528-SS	Y-(NH-C6)sasggacuacAfGfCfcugucgucaas(invAb)(C6-S)-X	614
AM06530-SS	Y-(NH-C6)scsggacuuAfCfCfuggcagacuas(invAb)(C6-S)-X	615
AM06532-SS	Y-(NH-C6)sgsaagggucAfAfCfuccaacguaas(invAb)(C6-S)-X	616
AM06534-SS	Y-(NH-C6)scsagggucaAfCfUfccaacguauas(invAb)(C6-S)-X	617
AM06536-SS	Y-(NH-C6)sgsggucaacUfCfCfaacguauguas(invAb)(C6-S)-X	618

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM06538-SS	Y-(NH-C6)scsuccaacgUfAfUfgugguuaucas(invAb)(C6-S)-X	619
AM06550-SS	Y-(NH-C6)sgsccauagGfUfGfugacaauccas(invAb)(C6-S)-X	620
AM06552-SS	Y-(NH-C6)scscauagguGfUfGfacaauccgaas(invAb)(C6-S)-X	621
AM06554-SS	Y-(NH-C6)sgsggucugAfUfGfgcacguuguas(invAb)(C6-S)-X	622
AM06556-SS	Y-(NH-C6)scsugagcuaUfGfUfgacucggauas(invAb)(C6-S)-X	623
AM06558-SS	Y-(NH-C6)sgsgguaagAfGfGfgacgacaccas(invAb)(C6-S)-X	624
AM06560-SS	Y-(NH-C6)scsccuacCfUfGfucaacguaaaas(invAb)(C6-S)-X	625
AM06562-SS	Y-(NH-C6)s(invAb)scccuacCfUfGfucaacguaaaas(invAb)(C6-S)-X	626
AM06564-SS	Y-(NH-C6)scsccuaccuGfUfCfaacguaacgas(invAb)(C6-S)-X	627
AM06566-SS	Y-(NH-C6)scscuaccuGfUfCfaacguaacgas(invAb)(C6-S)-X	628
AM06568-SS	Y-(NH-C6)sascugucaAfCfGfuaacgauuuas(invAb)(C6-S)-X	629
AM06877-SS	Y-(NH-C6)s(invAb)sgcaguuugCfUfCfugaaaacgaas(invAb)(C6-S)-X	630
AM06879-SS	Y-(NH-C6)s(invAb)saggugaaaGfUfCfuacaacaacus(invAb)(C6-S)-X	631
AM06881-SS	Y-(NH-C6)s(invAb)sggacacauCfUfUfuggauaacgas(invAb)(C6-S)-X	632
AM06883-SS	Y-(NH-C6)s(invAb)scgaccugaAfGfAfuugaagugaus(invAb)(C6-S)-X	633
AM06885-SS	Y-(NH-C6)s(invAb)sacgggaagAfCfUfuccagcuaaas(invAb)(C6-S)-X	634
AM06887-SS	Y-(NH-C6)s(invAb)sagcuaacaGfGfAfcauaguaucus(invAb)(C6-S)-X	635
AM06889-SS	Y-(NH-C6)s(invAb)scagauaugAfCfUfgugaggugaas(invAb)(C6-S)-X	636
AM06891-SS	Y-(NH-C6)s(invAb)sggaguacaCfAfAfuuguuuuacas(invAb)(C6-S)-X	637
AM06893-SS	Y-(NH-C6)s(invAb)sggucaaccuCfCfAfacguaugugas(invAb)(C6-S)-X	638
AM06895-SS	Y-(NH-C6)s(invAb)sgucaaccuCfAfAfcguauguggus(invAb)(C6-S)-X	639
AM06897-SS	Y-(NH-C6)s(invAb)sgaugccauAfGfGfugugacaauas(invAb)(C6-S)-X	640

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM06899-SS	Y-(NH-C6)s(invAb)sggaacuacCfAfUfgagaugguuus(invAb)(C6-S)-X	641
AM06901-SS	Y-(NH-C6)s(invAb)sgcuaccauGfAfGfaugguuuagas(invAb)(C6-S)-X	642
AM06903-SS	Y-(NH-C6)s(invAb)scgauaccaAfUfUfacauggaacus(invAb)(C6-S)-X	643
AM06905-SS	Y-(NH-C6)s(invAb)sccuaccugUfCfAfacguaacgaus(invAb)(C6-S)-X	644
AM06981-SS	Y-(NH-C6)scsasascsguaaCfGfAfuuucausgsasasas(invAb)(C6-S)-X	645
AM06983-SS	Y-(NH-C6)scsaascgsuasaCfsGfAfsuusucsausgasaas(invAb)(C6-S)-X	646
AM06984-SS	Y-(NH-C6)scsasacguaaCfGfAfuuucaugasasas(invAb)(C6-S)-X	647
AM06986-SS	Y-(NH-C6)scasacsgusaasCfGfsAfusuuscasugsaasas(invAb)(C6-S)-X	648
AM07071-SS	Y-(NH-C6)csaacguaaCfGfAfuuucaugaasa(invAb)(C6-S)-X	649
AM07138-SS	Y-(NH-C6)s(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)(C6-S)-X	650
AM07139-SS	Y-(NH-C6)s(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)(C6-S)-X	651
AM07141-SS	Y-(NH-C6)s(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)(C6-S)-X	652
AM07142-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)(C6-S)-X	653
AM07145-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)(C6-S)-X	654
AM07146-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)(C6-S)-X	655
AM07224-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	656
AM07225-SS	Y-(NH-C6)s(invAb)scaacguaaCfGfAfuuucaugaaas(invAb)(6-S)-X	657
AM07226-SS	Y-(NH-C6)s(invAb)sgaacguaaCfGfAfuuucaugaaas(invAb)(6-S)-X	658
AM07227-SS	Y-(NH-C6)s(invAb)sga_2NacguaaCfGfAfuuucaugaaas(invAb)(6-S)-X	659
AM07228-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuuucaugaaas(invAb)(6-S)-X	660
AM07229-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuuucauiaaas(invAb)(6-S)-X	661
AM07230-SS	Y-(NH-C6)s(invAb)sggacguaaCfGfAfuUucaugaaas(invAb)(6-S)-X	662

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM07231-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C3-S)-X	663
AM07268-SS	Y-(NH-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)(C6-S)-X	664
AM07269-SS	Y-(NH-C6)scsaascgsuasaCfGfAfuuucaugaaas(invAb)(C6-S)-X	665
AM07270-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucausgsasasas(invAb)(C6-S)-X	666
AM07271-SS	Y-(NH-C6)scsasascsgsuaaCfGfAfuuucaugaaas(invAb)(C6-S)-X	667
AM07272-SS	Y-(NH-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)(C6-S)-X	668
AM07273-SS	Y-(NH-C6)scsaacgusaasCfGfsAfusuucaugaaas(invAb)(C6-S)-X	669
AM07274-SS	Y-(NH-C6)scsaascgsuaaCfGfAfuuucausgasaas(invAb)(C6-S)-X	670
AM07275-SS	Y-(NH-C6)scsasascguaaCfGfAfuuucaugasasas(invAb)(C6-S)-X	671
AM07301-SS	Y-(NH-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)	672
AM07302-SS	Y-(NH-C6)scsaascgsuasaCfGfAfuuucaugaaas(invAb)	673
AM07303-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucausgsasasas(invAb)	674
AM07304-SS	Y-(NH-C6)scsasascsgsuaaCfGfAfuuucaugaaas(invAb)	675
AM07305-SS	Y-(NH-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)	676
AM07306-SS	Y-(NH-C6)scsaacgusaasCfGfsAfusuucaugaaas(invAb)	677
AM07307-SS	Y-(NH-C6)scsaascgsuaaCfGfAfuuucausgasaas(invAb)	678
AM07308-SS	Y-(NH-C6)scsasascguaaCfGfAfuuucaugasasas(invAb)	679
AM07403-SS	$(Z)_3$-(TriAlk1)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	680
AM07404-SS	$(Z)_3$-(TriAlk2)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	681
AM07405-SS	$(Z)_3$-(TriAlk3)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	682
AM07406-SS	$(Z)_3$-(TriAlk6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	683
AM07407-SS	$(Z)_3$-(TriAlk4)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	684

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM07408-SS	(Z)$_3$-(TriAlk5)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	685
AM07493-SS	Y-(NH-C6)scsaacguasaCfsGfAfsuusucaugaaas(invAb)(6-S)-X	686
AM07528-SS	Y-(NH-C6)scsaacguaaCfGfAfuusucsausgasaas(invAb)(6-S)-X	687
AM07530-SS	Y-(NH-C6)s(invAb)scaacuuguAfCfCfugaaaiccuus(invAb)(C6-S)-X	688
AM07532-SS	Y-(NH-C6)s(invAb)sacuuacacAfGfGfuggagcuaaas(invAb)(C6-S)-X	689
AM07534-SS	Y-(NH-C6)s(invAb)saggacauaGfUfAfucuuugacuus(invAb)(C6-S)-X	690
AM07536-SS	Y-(NH-C6)s(invAb)scugugucuGfAfGfaagaguaacus(invAb)(C6-S)-X	691
AM07538-SS	Y-(NH-C6)s(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)(C6-S)-X	692
AM07540-SS	Y-(NH-C6)s(invAb)sccagcacaCfUfAfuuuacaagaus(invAb)(C6-S)-X	693
AM07542-SS	Y-(NH-C6)s(invAb)sgccccuauUfUfUfuaaaguacaas(invAb)(C6-S)-X	694
AM07544-SS	Y-(NH-C6)s(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)(C6-S)-X	695
AM07546-SS	Y-(NH-C6)s(invAb)scaacugucCfAfUfacuaacaagus(invAb)(C6-S)-X	696
AM07548-SS	Y-(NH-C6)s(invAb)sgugguuauCfUfGfugaaaguugas(invAb)(C6-S)-X	697
AM07550-SS	Y-(NH-C6)s(invAb)sgaacuuagAfAfAfcggaaauggas(invAb)(C6-S)-X	698
AM07552-SS	Y-(NH-C6)s(invAb)sgauccgagCfAfGfuggagucauus(invAb)(C6-S)-X	699
AM07554-SS	Y-(NH-C6)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(C6-S)-X	700
AM07556-SS	Y-(NH-C6)s(invAb)sggucagugAfCfAfuguagguagas(invAb)(C6-S)-X	701
AM07558-SS	Y-(NH-C6)s(invAb)sgacacacaCfAfAfagcacauugas(invAb)(C6-S)-X	702
AM07560-SS	Y-(NH-C6)s(invAb)saccggauaGfAfCfuuauuiccaas(invAb)(C6-S)-X	703
AM07562-SS	Y-(NH-C6)s(invAb)sgaaguucuAfUfGfagaaauuccus(invAb)(C6-S)-X	704
AM07564-SS	Y-(NH-C6)s(invAb)sgguuacugAfCfGfuguaaaaugcus(invAb)(C6-S)-X	705
AM07566-SS	Y-(NH-C6)s(invAb)sacguaacgAfUfUfucaugaacgus(invAb)(C6-S)-X	706

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM07568-SS	Y-(NH-C6)s(invAb)sguaacgauUfUfCfaugaacguuas(invAb)(C6-S)-X	707
AM07570-SS	Y-(NH-C6)s(invAb)sgaacgauuUfCfAfugaacguuaus(invAb)(C6-S)-X	708
AM07572-SS	Y-(NH-C6)s(invAb)sggagcuuaAfCfUfuuauaaggaas(invAb)(C6-S)-X	709
AM07619-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(C6-S)-X	710
AM07621-SS	Y-(S-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(C6-S)-X	711
AM07705-SS	$(Z)_3$-(TriAlk7)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	712
AM07706-SS	$(Z)_3$-(TriAlk8)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	713
AM07707-SS	$(Z)_3$-(TriAlk10)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	714
AM07708-SS	$(Z)_3$-(TriAlk11)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	715
AM07709-SS	$(Z)_3$-(TriAlk12)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	716
AM07710-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuca^{Z}ugaasa(invAb)(6-S)-X	717
AM07711-SS	Y-(NH-C6)scsaacgua^{Z}aCfGfAfuuucaugaasa(invAb)(6-S)-X	718
AM07712-SS	Y-(NH-C6)scsaacgua^{Z}aCfGfAfuuuca^{Z}ugaasa(invAb)(6-S)-X	719
AM07713-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(C6-NH2)-X	720
AM07721-SS	Y-(NH-C6)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(6-S)-X	721
AM07722-SS	Y-(NH-C6)s(invAb)sgacauucuCfUfAfuguacuaugus(invAb)(6-S)-X	722
AM07724-SS	Y-(NH-C6)s(invAb)scgcauucuCfUfAfuguacuaugus(invAb)(6-S)-X	723
AM07726-SS	Y-(NH-C6)s(invAb)scccauucuCfUfAfuguacuaugus(invAb)(6-S)-X	724
AM07728-SS	Y-(NH-C6)s(invAb)sggcauucuCfUfAfuguacuaugus(invAb)(6-S)-X	725
AM07730-SS	Y-(NH-C6)s(invAb)scaca_2NuucuCfUfAfuguacuaugus(invAb)(6-S)-X	726
AM07731-SS	Y-(NH-C6)s(invAb)sccca_2NuucuCfUfAfuguacuaugus(invAb)(6-S)-X	727
AM07732-SS	Y-(NH-C6)s(invAb)sgcgaccAfUfGfaggagauucauus(invAb)(6-S)-X	728

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM07734-SS	Y-(NH-C6)s(invAb)scgcucaGfCfCfuaugaauucauus(invAb)(6-S)-X	729
AM07736-SS	Y-(NH-C6)s(invAb)scaagggucAfGfGfuaguaagugas(invAb)(6-S)-X	730
AM07738-SS	Y-(NH-C6)s(invAb)sgacugaauCfCfCfuguucaagcas(invAb)(6-S)-X	731
AM07740-SS	Y-(NH-C6)s(invAb)sucaggccAfUfGfacaaacaucus(invAb)(6-S)-X	732
AM07742-SS	Y-(NH-C6)s(invAb)sgcaccucaCfAfUfuugauguggas(invAb)(6-S)-X	733
AM07744-SS	Y-(NH-C6)s(invAb)sacacaacuGfUfCfcauacuaacas(invAb)(6-S)-X	734
AM07746-SS	Y-(NH-C6)s(invAb)sggcauaaguAfUfCfuuugacuucas(invAb)(6-S)-X	735
AM07776-SS	Y-(NH-C6)s(invAb)sgaguacacAfAfUfuguuuuaccus(invAb)(6-S)-X	736
AM07777-SS	Y-(NH-C6)s(invAb)scuuccuauUfCfAfccaagcuaaas(invAb)(6-S)-X	737
AM07778-SS	Y-(NH-C6)s(invAb)sggucagugAfCfAfuguagguagas(invAb)(6-S)-X	738
AM07801-SS	$(Z)_3$-(TriAlk13)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	739
AM07813-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	740
AM07814-SS	Y-(S-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	741
AM07817-SS	Y-(NH-C6)scsa^{Z}a^{Z}cgu^{Z}a^{Z}aCfGfAfuuuca^{Z}u^{Z}ga^{Z}a^{Z}sa(invAb)(6-S)-X	742
AM07818-SS	Y-(S-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	743
AM07822-SS	Y-(NH-C6)scsaacgua^{Z}aCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	744
AM07823-SS	Y-(NH-C6)scsaa^{Z}cguaaCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	745
AM07824-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuucaugaa^{Z}sa(invAb)(6-S)-X	746
AM07825-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuuca^{Z}ugaasa(invAb)(6-S)-X	747
AM07826-SS	Y-(NH-C6)scsaa^{Z}cgua^{Z}aCfGfAfuuucaugaasa(invAb)(6-S)-X	748
AM07827-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	749
AM07828-SS	Y-(NH-C6)scsaa^{Z}cguaaCfGfAfuuucaugaa^{Z}sa(invAb)(6-S)-X	750

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM07829-SS	Y-(NH-C6)scsaa^{Z}cguaaCfGfAfuuuca^{Z}ugaasa(invAb)(6-S)-X	751
AM07830-SS	Y-(NH-C6)scsaacgua^{Z}aCfGfAfuuucaugaa^{Z}sa(invAb)(6-S)-X	752
AM07831-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaa^{Z}sa(invAb)(6-S)-X	753
AM07832-SS	Y-(NH-C6)scsaa^{Z}cguaaCfGfAfuuucaugaasa(invAb)(6-S)-X	754
AM07833-SS	Y-(NH-C6)scsa^{Z}a^{Z}cguaaCfGfAfuuucauga^{Z}a^{Z}sa(invAb)(6-S)-X	755
AM07834-SS	Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X	756
AM07835-SS	Y-(NH-C6)scsaacg^{Z}uaa^{Z}CfGfAfu^{Z}uuc^{Z}augaasa(invAb)(6-S)-X	757
AM07836-SS	Y-(NH-C6)scsaacgua^{Z}a^{Z}CfGfAfu^{Z}u^{Z}ucaugaasa(invAb)(6-S)-X	758
AM07837-SS	Y-(NH-C6)scsa^{Z}ac^{Z}gu^{Z}aa^{Z}CfGfAfuuucaugaasa(invAb)(6-S)-X	759
AM07838-SS	Y-(NH-C6)scsa^{Z}a^{Z}c^{Z}g^{Z}uaaCfGfAfuuucaugaasa(invAb)(6-S)-X	760
AM07839-SS	Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X	761
AM07840-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X	762
AM07890-SS	Y-(NH-C6)s(invAb)sgcacaacuGfUfCfcauacuaacas(invAb)(6-S)-X	763
AM07892-SS	Y-(NH-C6)s(invAb)sccacaacuGfUfCfcauacuaacas(invAb)(6-S)-X	764
AM07894-SS	Y-(NH-C6)s(invAb)sggacaacuGfUfCfcauacuaacas(invAb)(6-S)-X	765
AM08018-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuca^{Z}u^{Z}ga^{Z}a^{Z}sa(invAb)(6-S)-X	766
AM08019-SS	Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X	767
AM08020-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaug^{Z}aasa(invAb)(6-S)-X	768
AM08021-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuca^{Z}u^{Z}g^{Z}a^{Z}asa(invAb)(6-S)-X	769
AM08022-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuc^{Z}a^{Z}u^{Z}g^{Z}aasa(invAb)(6-S)-X	770
AM08023-SS	Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}c^{Z}a^{Z}u^{Z}gaasa(invAb)(6-S)-X	771
AM08024-SS	Y-(NH-C6)scsaacguaaCfGfAfuu^{Z}u^{Z}c^{Z}a^{Z}ugaasa(invAb)(6-S)-X	772

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM08025-SS	Y-(NH-C6)scsaacguaaCfGfAfu^{Z}u^{Z}u^{Z}c^{Z}augaasa(invAb)(6-S)-X	773
AM08026-SS	Y-(NH-C6)scsaacguaaCfGfAfu^{Z}uu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X	774
AM08027-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X	775
AM08028-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuu^{Z}caug^{Z}aa^{Z}sa(invAb)(6-S)-X	776
AM08029-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuu^{Z}ca^{Z}ugaa^{Z}sa(invAb)(6-S)-X	777
AM08030-SS	Y-(NH-C6)scsaacguaaCfGfAfuuuu^{Z}ca^{Z}ug^{Z}aasa(invAb)(6-S)-X	778
AM08031-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaug^{Z}a^{Z}a^{Z}sa(invAb)(6-S)-X	779
AM08032-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}ga^{Z}a^{Z}sa(invAb)(C6-S)-X	780
AM08033-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}aa^{Z}sa(invAb)(6-S)-X	781
AM08034-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucau^{Z}g^{Z}a^{Z}asa(invAb)(6-S)-X	782
AM08035-SS	Y-(NH-C6)scsaacguaa^{Z}CfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X	783
AM08036-SS	Y-(NH-C6)scsaac^{Z}guaaCfGfAfuuu^{Z}caug^{Z}aasa(invAb)(6-S)-X	784
AM08037-SS	Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuucaug^{Z}aasa(invAb)(6-S)-X	785
AM08038-SS	Y-(NH-C6)scsaac^{Z}guaa^{Z}CfGfAfuuu^{Z}caugaasa(invAb)(6-S)-X	786
AM08092-SS	Y-(NH-C6)scsaa^{Z}cguaaCfGfAfuuucaugaasa(invAb)(C6-S)-X	787
AM08093-SS	Y-(NH-C6)scsaacguaaCfGfAfuuucaugaa^{Z}sa(invAb)(C6-S)-X	788
AM08108-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}u^{Z}ga^{Z}a^{Z}sa(invAb)(C6-S)-X	789
AM08109-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuucau^{Z}ga^{Z}a^{Z}sa(invAb)(C6-S)-X	790
AM08110-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}uga^{Z}a^{Z}sa(invAb)(C6-S)-X	791
AM08111-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}u^{Z}gaa^{Z}sa(invAb)(C6-S)-X	792
AM08112-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}u^{Z}ga^{Z}asa(invAb)(C6-S)-X	793
AM08113-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuucauga^{Z}a^{Z}sa(invAb)(C6-S)-X	794

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM08114-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}u^{Z}gaasa(invAb)(C6-S)-X	795
AM08115-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuucau^{Z}ga^{Z}asa(invAb)(C6-S)-X	796
AM08116-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}uga^{Z}asa(invAb)(C6-S)-X	797
AM08117-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuucau^{Z}gaa^{Z}sa(invAb)(C6-S)-X	798
AM08118-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuu^{Z}caug^{Z}aasa(invAb)(C6-S)-X	799
AM08119-SS	Y-(S-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-NH)-X	800
AM08120-SS	Y-(S-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(C6-NH)-X	801
AM08121-SS	Y-(S-C6)scsaacguaaCfGfAfuuuca^{Z}u^{Z}ga^{Z}a^{Z}sa(invAb)(C6-NH)-X	802
AM08122-SS	Y-(S-C6)scsa^{Z}ac^{Z}gu^{Z}aa^{Z}CfGfAfuuucaugaasa(invAb)(C6-NH)-X	803
AM08123-SS	Y-(S-C6)scsa^{Z}a^{Z}cg^{Z}u^{Z}aaCfGfAfuuucaugaasa(invAb)(C6-NH)-X	804
AM08124-SS	(Z)$_3$-(TriAlk14)s(invAb)scacauucuCfUfAfuguacuaugus(invAb)(C6-S)-X	805
AM08125-SS	(Z)$_3$-(TriAlk14)s(invAb)scacauucuCfUfAfugu^{Z}ac^{Z}ua^{Z}ug^{Z}us(invAb)(C6-S)-X	806
AM08126-SS	(Z)$_3$-(TriAlk14)s(invAb)sca^{Z}ca^{Z}uu^{Z}cu^{Z}CfUfAfuguacuaugus(invAb)(C6-S)-X	807
AM08127-SS	(Z)$_3$-(TriAlk14)s(invAb)scacauucuCfUfAfuguac^{Z}u^{Z}au^{Z}g^{Z}us(invAb)(C6-S)-X	808
AM08128-SS	(Z)$_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcauacuaacas(invAb)(C6-S)-X	809
AM08129-SS	(Z)$_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcau^{Z}ac^{Z}ua^{Z}ac^{Z}as(invAb)(C6-S)-X	810
AM08130-SS	(Z)$_3$-(TriAlk14)s(invAb)sac^{Z}ac^{Z}aa^{Z}cu^{Z}GfUfCfcauacuaacas(invAb)(C6-S)-X	811
AM08131-SS	(Z)$_3$-(TriAlk14)s(invAb)sacacaacuGfUfCfcauac^{Z}u^{Z}aa^{Z}c^{Z}as(invAb)(C6-S)-X	812
AM08132-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuucaug^{Z}aa^{Z}sa(invAb)(C6-S)-X	813
AM08133-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuuca^{Z}ug^{Z}aasa(invAb)(C6-S)-X	814
AM08134-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ugaasa(invAb)(C6-S)-X	815
AM08135-SS	(Z)$_3$-(TriAlk14)scsaacguaaCfGfAfuuu^{Z}caugaa^{Z}sa(invAb)(C6-S)-X	816

Sense Strand ID:	Modified Sense Strand (5′ → 3′)	SEQ ID NO.
AM08233-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)-X	817
AM08234-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)-X	818
AM08372-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)-X	819
AM08394-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)-X	820
AM08395-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksa(invAb)-X	821
AM08396-SS	(Z)3-(TriAlk14)scsaacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)-X	822
AM08397-SS	(Z)3-(TriAlk14)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)-X	823
AM08398-SS	(Z)3-(TriAlk14)s(invAb)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)-X	824
AM08399-SS	(Z)3-(TriAlk14)scsasacguaaCfGfAfuuuAlkcaAlkugAlkaaAlksas(invAb)-X	825
AM10024-SS	(Z)3-(NH2-C6)scsaacguaaCfGfAfuuucaugaasa(invAb)(C6-S)-X	826

[0154] The HIF-2 alpha RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2 or Table 4 (or 4.1, 4.2, or 4.3) can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

[0155] In some embodiments, the antisense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 3. In some embodiments, the sense strand of a HIF-2 alpha RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 4.

[0156] In some embodiments, a HIF-2 alpha RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3. In some embodiments, a HIF-2 alpha RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, or 2-24 of any of the sequences in Table 2 or Table 3. In certain embodiments, a HIF-2 alpha RNAi agent antisense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 3.

[0157] In some embodiments, a HIF-2 alpha RNAi agent sense strand comprises the nucleotide sequence of any of the sequences in Table 2 or Table 4 (or Table 4.1, 4.2, or 4.3). In some embodiments, a HIF-2 alpha RNAi agent sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 2-17, 3-17, 4-17, 1-18, 2-18, 3-18, 4-18, 1-19, 2-19, 3-19, 4-19, 1-20, 2-20, 3-20, 4-20, 1-21, 2-21, 3-21, 4-21, 1-22, 2-22, 3-22, 4-22, 1-23, 2-23, 3-23, 4-23, 1-24, 2-24, 3-24, or 4-24 of any of the sequences in Table 2 or Table 4 (or Table 4.1, 4.2, or 4.3). In certain embodiments, a HIF-2 alpha RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 4 (or Table 4.1, 4.2, or 4.3).

[0158] For the HIF-2 alpha RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) can be perfectly complementary to a HIF-2 alpha gene, or can be non-complementary to a HIF-2 alpha gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) is a U, A, or dT (or a modified version thereof). In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) forms an A:U or U:A base pair with the sense strand.

[0159] In some embodiments, a HIF-2 alpha RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, a HIF-2 alpha RNAi sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17 or 1-18 of any of the sense strand sequences in Table 2 or Table 4 (or Table 4.1, 4.2, or 4.3).

[0160] In some embodiments, a HIF-2 alpha RNAi agent includes (i) an antisense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3, and (ii) a sense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 1-17 or 1-18 of any of the sense strand sequences in Table 2 or Table 4 (or Table 4.1, 4.2, or 4.3).

[0161] A sense strand containing a sequence listed in Table 2 or Table 4 can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence. In some embodiments, the HIF-2 alpha RNAi agent has a sense strand consisting of the modified sequence of any of the modified sequences in Table 4 (or Table 4.1, 4.2, or 4.3), and an antisense strand consisting of the modified sequence of any of the modified sequences in Table 3. Certain representative sequence pairings are exemplified by the Duplex ID Nos. shown in Table 5.

[0162] In some embodiments, a HIF-2 alpha RNAi agent comprises, consists of, or consists essentially of a duplex represented by any one of the Duplex ID Nos. presented herein. In some embodiments, a HIF-2 alpha RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein. In some embodiments, a HIF-2 alpha RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein and a targeting ligand, targeting group, and/or linking group wherein the targeting ligand, targeting group, and/or linking group is covalently linked (conjugated) to the sense strand or the antisense strand. In some embodiments, a HIF-2 alpha RNAi agent includes the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein. In some embodiments, a HIF-2 alpha RNAi agent comprises the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein and a targeting ligand, targeting group, and/or linking group, wherein the targeting ligand,

targeting group, and/or linking group is covalently linked to the sense strand or the antisense strand.

[0163] In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 2 or Table 5, and further comprises a targeting group. In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 5, and further comprises an integrin receptor ligand targeting group.

[0164] In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 5, and further comprises one or more linking groups selected from the group consisting of (NH2-C6), (C6-NH2), (C6-SS-C6), (6-SS-6), (TriAlk1), (TriAlk1)s, (TriAlk2), (TriAlk2)s, (TriAlk3), (TriAlk3)s, (TriAlk4), (TriAlk4)s, (TriAlk5), (TriAlk5)s, (TriAlk6), (TriAlk6)s, (TriAlk7), (TriAlk7)s, (TriAlk8), (TriAlk8)s, (TriAlk9), (TriAlk9)s, (TriAlk10), (TriAlk10)s, (TriAlk11), (TriAlk11)s, (TriAlk12), (TriAlk12)s, (TriAlk13), (TriAlk13)s, (TriAlk14), or (TriAlk14)s, each as defined in Table 7.

[0165] In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequence of any of the antisense strand and/or sense strand nucleotide sequences in Table 3 or Table 4, 4.1, 4.2, or 4.3.

[0166] In some embodiments, a HIF-2 alpha RNAi agent comprises an antisense strand and a sense strand having a modified nucleotide sequence of any of the antisense strand and/or sense strand nucleotide sequences of any of the duplexes Table 5, and further comprises an integrin targeting group.

[0167] In some embodiments, a HIF-2 alpha RNAi agent comprises, consists of, or consists essentially of any of the duplexes of Table 5.

Table 5. HIF-2 alpha RNAi Agents Duplexes with Corresponding Sense and Antisense Strand ID Numbers

Duplex ID	Antisense Strand ID	Sense Strand ID
AD04169	AM03465-AS	AM05339-SS
AD04545	AM05815-AS	AM05814-SS
AD04546	AM05815-AS	AM05816-SS
AD04999	AM06491-AS	AM06490-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05000	AM06493-AS	AM06492-SS
AD05001	AM06495-AS	AM06494-SS
AD05002	AM06497-AS	AM06496-SS
AD05003	AM06499-AS	AM06498-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05004	AM06501-AS	AM06500-SS
AD05005	AM06503-AS	AM06502-SS
AD05006	AM06505-AS	AM06504-SS
AD05018	AM06525-AS	AM06524-SS
AD05019	AM06527-AS	AM06526-SS
AD05020	AM06529-AS	AM06528-SS
AD05021	AM06531-AS	AM06530-SS
AD05022	AM06533-AS	AM06532-SS
AD05023	AM06535-AS	AM06534-SS
AD05024	AM06537-AS	AM06536-SS
AD05025	AM06539-AS	AM06538-SS
AD05034	AM06551-AS	AM06550-SS
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AD05485	AM07143-AS	AM07229-SS
AD05486	AM07143-AS	AM07230-SS
AD05507	AM05815-AS	AM07268-SS
AD05508	AM05815-AS	AM07269-SS
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AD05511	AM05815-AS	AM07272-SS
AD05512	AM05815-AS	AM07273-SS
AD05513	AM05815-AS	AM07274-SS
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AD05716	AM05815-AS	AM07528-SS
AD05718	AM07531-AS	AM07530-SS
AD05719	AM07533-AS	AM07532-SS
AD05720	AM07535-AS	AM07534-SS
AD05721	AM07537-AS	AM07536-SS
AD05722	AM07539-AS	AM07538-SS
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AD05856	AM05815-AS	AM07705-SS
AD05857	AM05815-AS	AM07706-SS
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AD05859	AM05815-AS	AM07708-SS
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Duplex ID	Antisense Strand ID	Sense Strand ID
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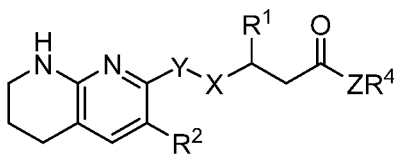
[0168] In some embodiments, a HIF-2 alpha RNAi agent, either before or after being optionally linked or conjugated to one or more targeting ligands, targeting groups, and/or PK enhancers, is prepared or provided as a salt, mixed salt, or a free-acid. The RNAi agents described herein, upon delivery to a cell expressing a HIF-2 alpha gene, inhibit or knockdown expression of one or more HIF-2 alpha genes *in vivo* and/or *in vitro*.

Targeting Ligands and Targeting Groups

[0169] Targeting groups or targeting moieties enhance the pharmacokinetic or biodistribution properties of a conjugate or RNAi agent to which they are attached to improve cell-specific (including, in some cases, organ specific) distribution and cell-specific (or organ specific) uptake of the conjugate or RNAi agent. A targeting group can be monovalent, divalent, trivalent, tetravalent, or have higher valency for the target to which it is directed. Representative targeting groups include, without limitation, compounds with affinity to cell surface molecule, cell receptor ligands, hapten, antibodies, monoclonal antibodies, antibody fragments, and antibody mimics with affinity to cell surface molecules. In some embodiments, a targeting group is linked to an RNAi agent using a linker, such as a PEG linker or one, two, or three abasic and/or ribitol (abasic ribose) residues, which in some instances can serve as linkers. In some embodiments, a targeting group comprises an integrin targeting ligand.

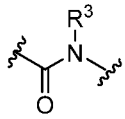
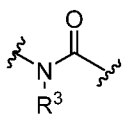
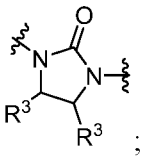
[0170] In some embodiments, RNAi agents described herein are conjugated to targeting groups. In some embodiments, a targeting ligand enhances the ability of the RNAi agent to bind to a particular cell receptor on a cell of interest. In some embodiments, the targeting ligands conjugated to RNAi agents described herein have affinity for integrin receptors. In some embodiments, a suitable targeting ligand for use with the HIF-2 alpha RNAi agents disclosed herein has affinity for integrin alpha-v-beta 3, integrin alpha-v-beta-5, or both of these integrins.

[0171] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein is linked to one or more integrin targeting ligands that include a compound of the formula:



(Formula I),

wherein,

X is -C(R^3)$_2$-, -NR^3-, , , or ;

Y is optionally substituted alkylene with 1 to 8 carbon atoms in the alkylene chain;

Z is O, NR^3, or S;

R^1 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl or R^1 comprises the RNAi agent;

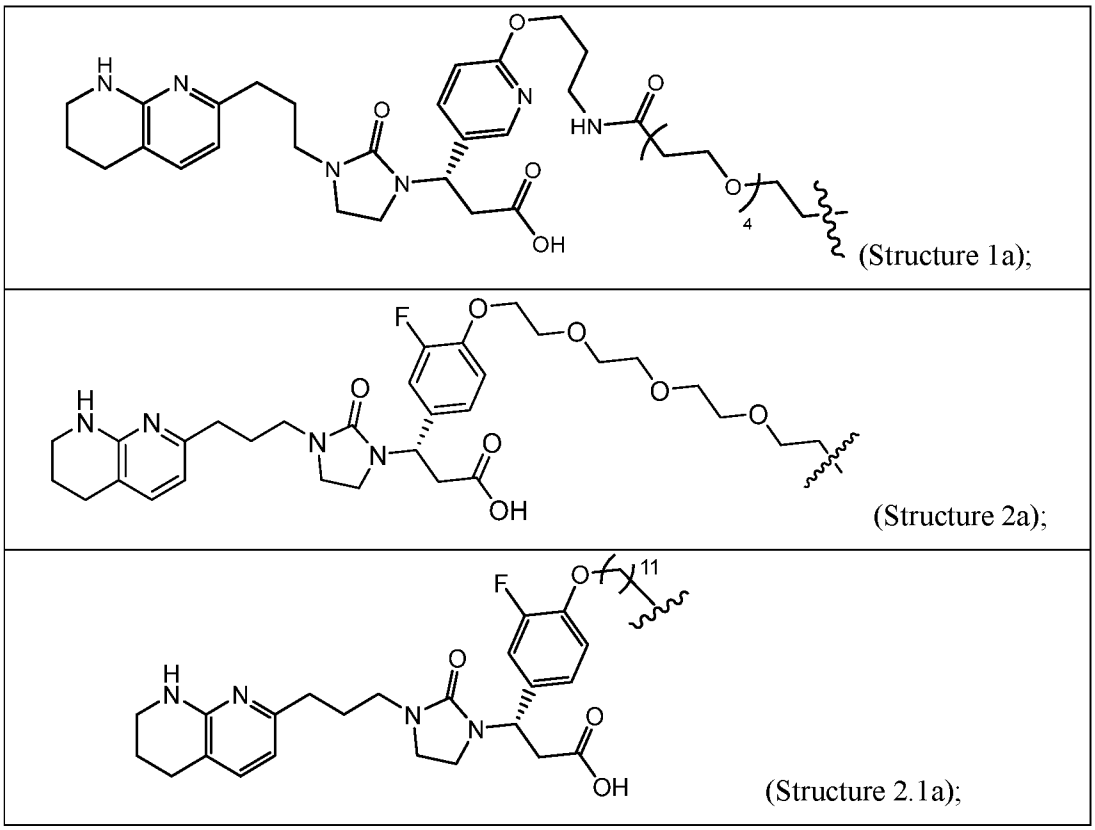
R^2 is H, optionally substituted alkyl, or R^2 comprises the RNAi agent;

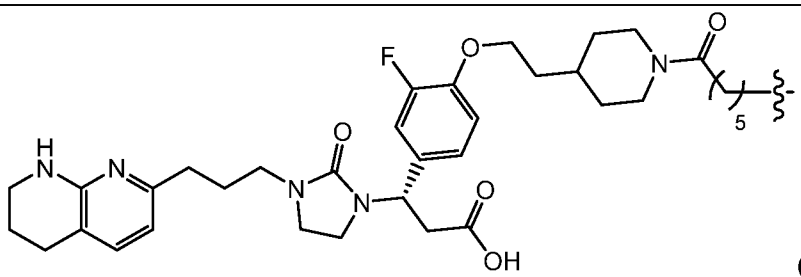
each instance of R^3 is independently selected from the group consisting of H and optionally substituted alkyl, or R^3 comprises the RNAi agent;

R^4 is H or optionally substituted alkyl; and

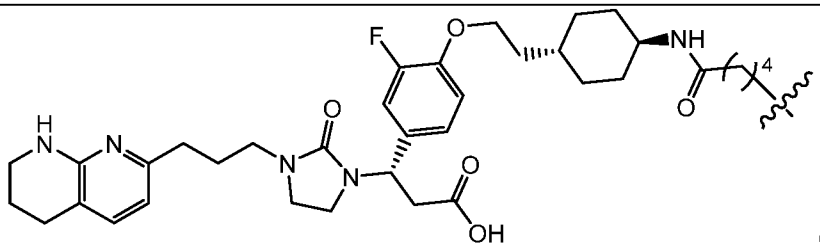
wherein at least one of Y, R^1, R^2, any instance of R^3, and R^4 comprises the RNAi agent.

[0172] In some embodiments, a HIF-2 alpha RNAi agent disclosed herein is linked to one or more integrin targeting ligands that include one of the following structures:

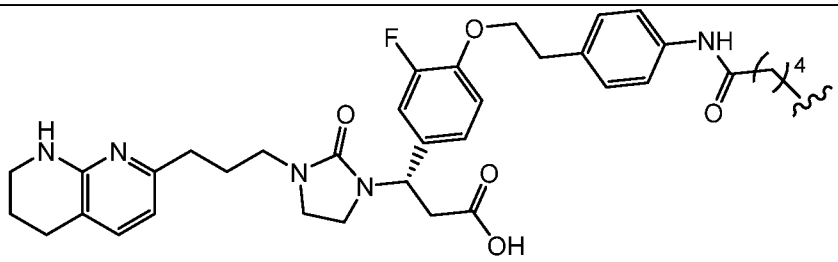




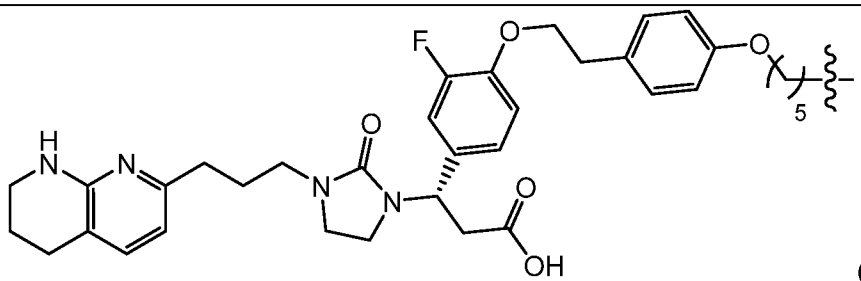
(Structure 2.2a);



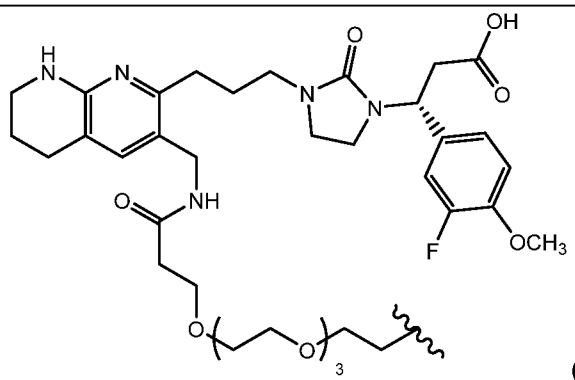
(Structure 2.3a);



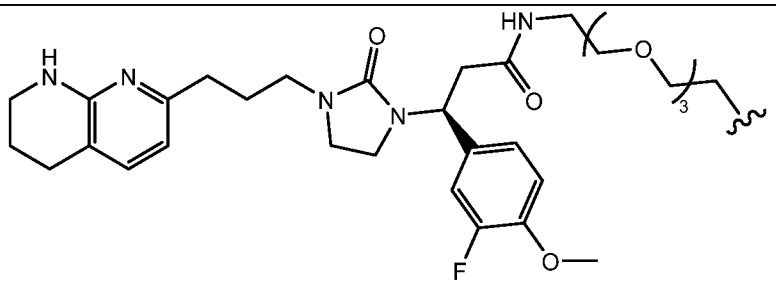
(Structure 2.4a);



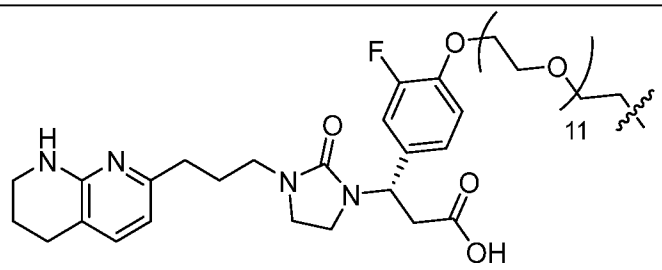
(Structure 2.5a);



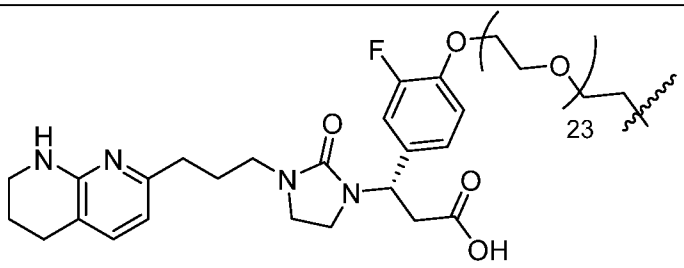
(Structure 2.6a);



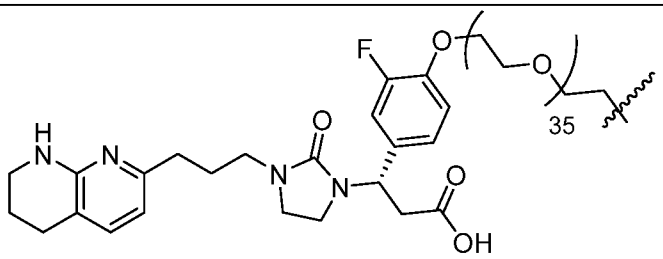
(Structure 2.7a);



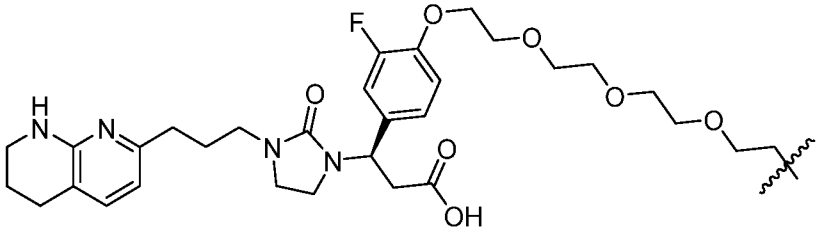
(Structure 2.8a);



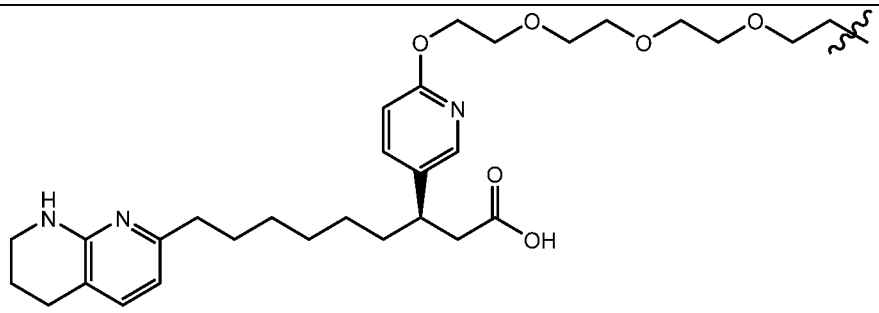
(Structure 2.9a);



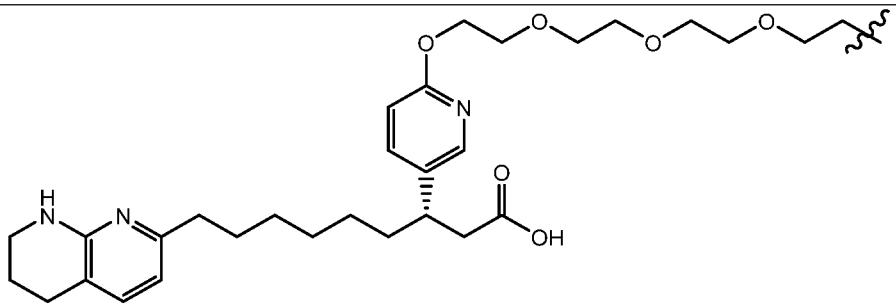
(Structure 2.10a);



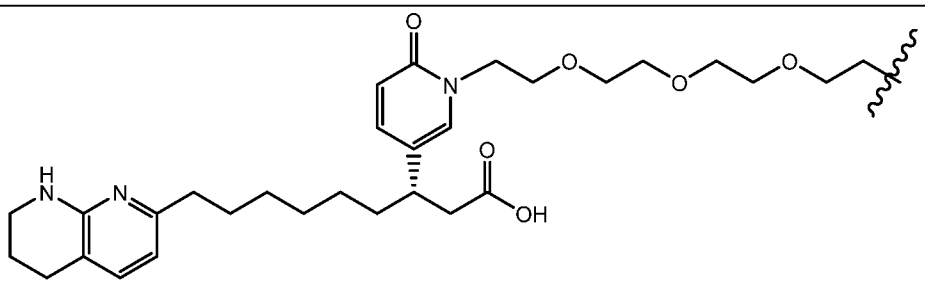
(Structure 2.11a);



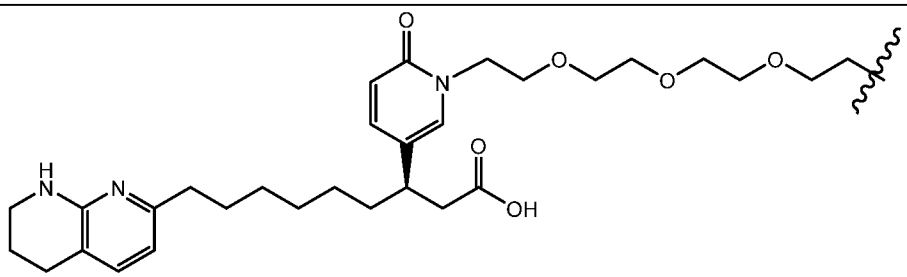
(Structure 28a);



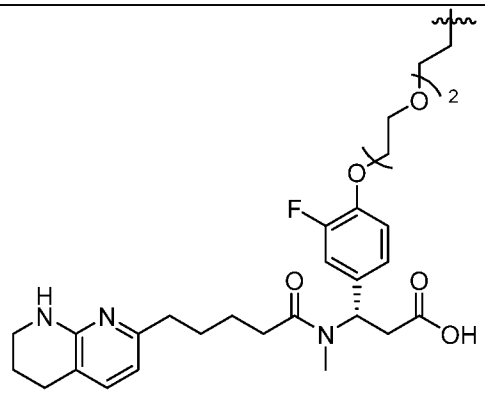
(Structure 29a);



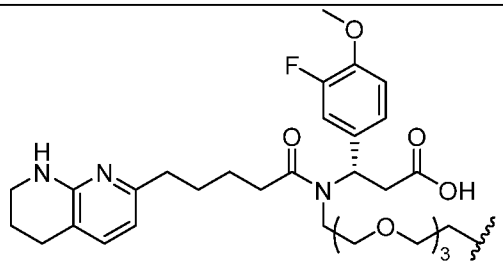
(Structure 30a);



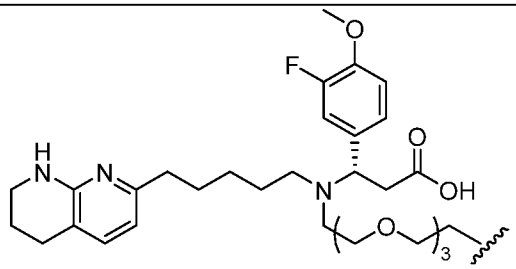
(Structure 31a);



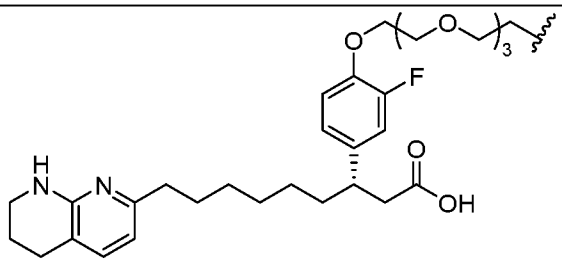
(Structure 32a);



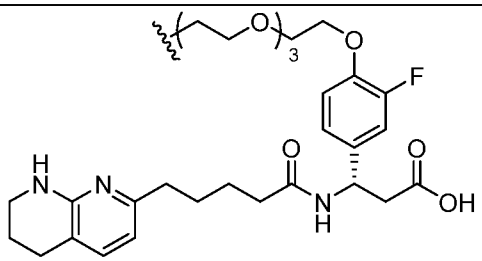
(Structure 33a);



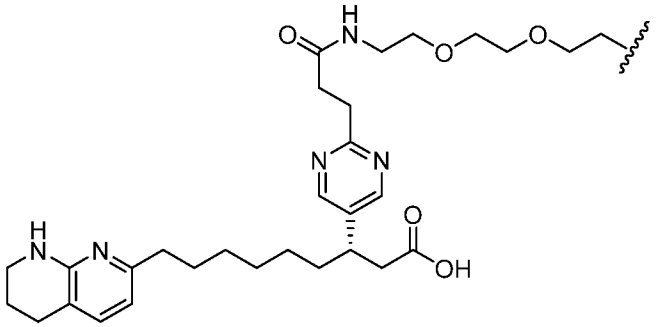
(Structure 34a);



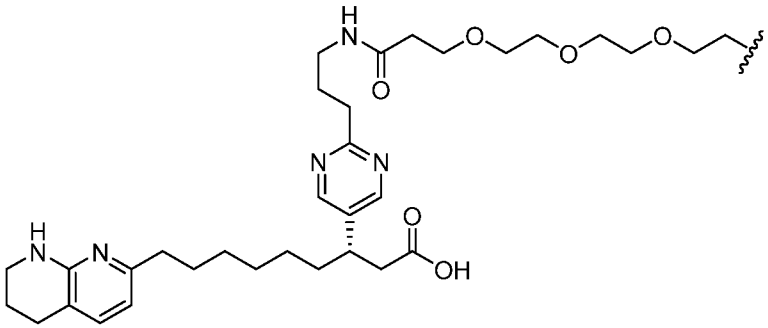
(Structure 36a);



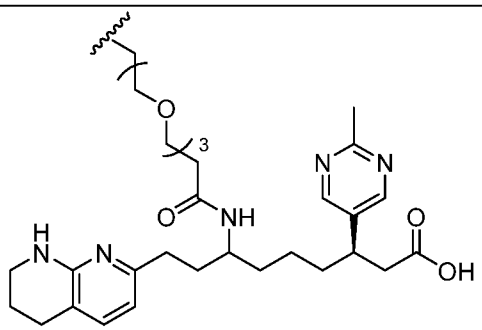
(Structure 37a);



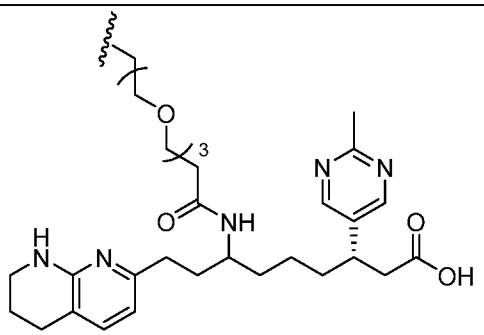
(Structure 38a);



(Structure 39a);



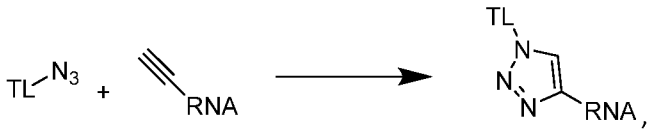
(Structure 40a); and



(Structure 41a)

wherein ≈ indicates the point of connection to a HIF-2 alpha RNAi agent.

[0173] In some embodiments, targeting groups are conjugated to an RNAi agent using a "click" chemistry reaction. In some embodiments, RNAi agents are functionalized with one or more alkyne-containing groups, and targeting ligands include azide-containing groups. Upon reaction, azides and alkynes form triazoles. An example reaction scheme is shown below:



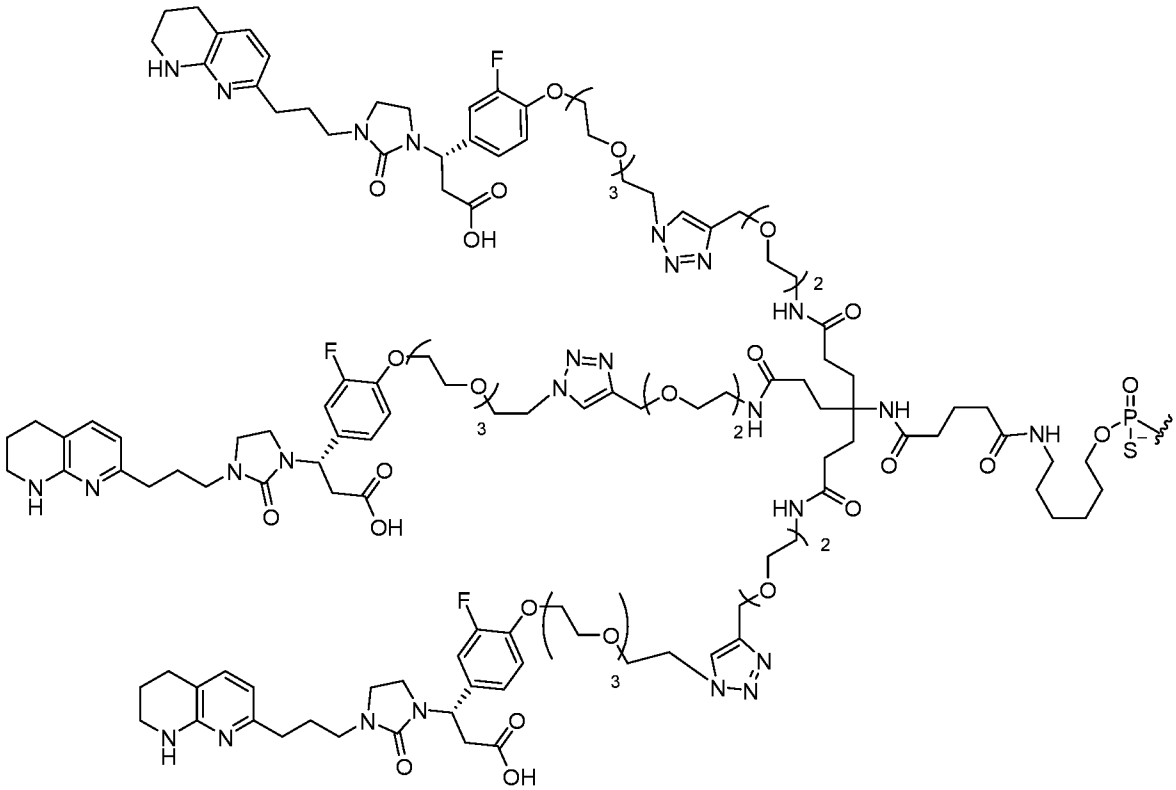
wherein TL comprises a targeting ligand, and RNA comprises an RNAi agent.

[0174] HIF-2 alpha RNAi agents may comprise more than one targeting ligand. In some embodiments, HIF-2 alpha RNAi agents comprise 1-20 targeting ligands. In some embodiments, HIF-2 alpha RNAi agents comprise from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 targeting ligands to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 targeting ligands.

[0175] In some embodiments, HIF-2 alpha RNAi agents comprise a targeting group, which includes 2 or more targeting ligands. In some embodiments, a targeting group may be conjugated at the 5' or 3' end of the sense strand of a HIF-2 alpha RNAi agent. In some embodiments, a targeting group may be conjugated to an internal nucleotide on a HIF-2 RNAi agent. In some embodiments, a targeting group may consist of two targeting ligands linked together, referred to as a "bidentate" targeting group. In some embodiments, a targeting group may consist of three targeting ligands linked together, referred to as a "tridentate" targeting group. In some embodiments, a targeting group may consist of four targeting ligands linked together, referred to as a "tetradentate" targeting group.

[0176] In some embodiments, HIF-2 alpha RNAi agents may comprise both a targeting group conjugated to the 3' or 5' end of the sense strand, and additionally targeting ligands conjugated to internal nucleotides. In some embodiments a tridentate targeting group is conjugated to the 5' end of the sense strand of a HIF-2 alpha RNAi agent, and at least one targeting ligand is conjugated to an internal nucleotide of the sense strand. In further embodiments, a tridentate targeting group is conjugated to the 5' end of the sense strand of a HIF-2 alpha RNAi agent, and four targeting ligands are conjugated to internal nucleotides of the sense strand. In some embodiments, the four targeting ligands are conjugated to the 2, 4, 6, and 8 nucleotide positions of the sense strand.

[0177] In some embodiments, the HIF-2 alpha RNAi agents are linked to one or more targeting groups of the following formula:



wherein ≋ indicates the point of connection. In some embodiments the point of connection is the 5' end of the sense strand of a HIF-2 alpha RNAi agent.

Internally Linked Targeting Ligands

[0178] Some embodiments of HIF-2 alpha RNAi agents described herein include targeting ligands conjugated to internal nucleotides of the sense strand or antisense strand. In some

embodiments, up to 15 targeting ligands may be conjugated to internal nucleotides of the sense strand of a HIF-2 alpha RNAi agent. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 targeting ligands may be conjugated to internal nucleotides of the sense strand of a HIF-2 alpha RNAi agent. In some embodiments, 1 to 5 (for example, 1, 2, 3, 4, or 5) targeting ligands are conjugated to internal nucleotides of the sense strand of a HIF-2 alpha RNAi agent. In some embodiments, 3 to 4 targeting ligands are conjugated to internal nucleotides of the sense strand of a HIF-2 alpha RNAi agent.

[0179] In some embodiments, placement of internal targeting ligands may impact the efficacy or potency of a HIF-2 alpha RNAi agent. In some embodiments of HIF-2 alpha RNAi agents, a targeting group is conjugated to the 5' end of the sense strand, and at least 10 nucleotides are positioned between the tridentate targeting group located on the 5' end of the sense strand and the next closest targeting ligand located of the sense strand. In some embodiments, at least 5 nucleotides are positioned between the tridentate targeting group located on the 5' end of the sense strand and the next closest targeting ligand located of the sense strand.

[0180] In some embodiments where two or more targeting ligands are conjugated to internal nucleotides located of the sense strand of a HIF-2 alpha RNAi agent, there is a space of at least one nucleotide that is not conjugated to a targeting ligand positioned between two internal nucleotides that are conjugated to targeting ligands. In some embodiments where two or more targeting ligands are conjugated to the sense strand of a HIF-2 alpha RNAi agent, at least two nucleotides that are not conjugated to a targeting ligand are positioned between two internal nucleotides that are conjugated to targeting ligands.

[0181] In some embodiments, targeting ligands are conjugated to the 2, 4, and 6 nucleotides of the sense strand as numbered from 3' to 5', starting from the furthest 3' nucleotide that forms a base pair with the 5' terminal nucleotide on the antisense strand. In some embodiments, targeting ligands are conjugated to the 2, 4, 6 and 8 nucleotides (3' → 5') from the 3' terminal nucleotide that forms a base pair with the 5' terminal nucleotide on the antisense strand.

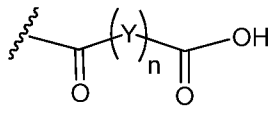
Pharmacokinetic Enhancers

[0182] In some embodiments, a pharmacokinetic (PK) enhancer is linked to the HIF-2 alpha RNAi agents disclosed herein to facilitate the delivery of the RNAi agent to the desired cells or tissues. PK enhancing compounds can be synthetized having reactive groups, such as maleimide or azido groups, readily present to facilitate linkage to one or more linkers on the

HIF-2 alpha RNAi agent. In some embodiments, PK enhancers may be synthesized as maleimides and conjugated to RNAi agents using reactions described herein. Other conjugation reactions such as "click" chemistry or amide conjugation may also be used.

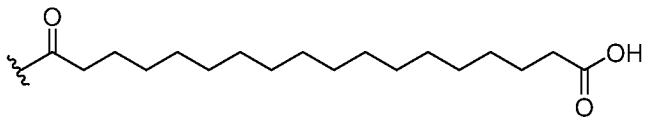
[0183] In some embodiments, PK enhancers may include molecules that are fatty acids, lipids, albumin-binders, antibody-binders, polyesters, polyacrylates, poly-amino acids, and linear or branched polyethylene glycol (PEG) moieties having about 20-1000 ethylene oxide (CH_2-CH_2-O) units.

[0184] In some embodiments, a HIF-2 RNAi agent is linked to a PK enhancer that includes a compound having the structure of the following formula:



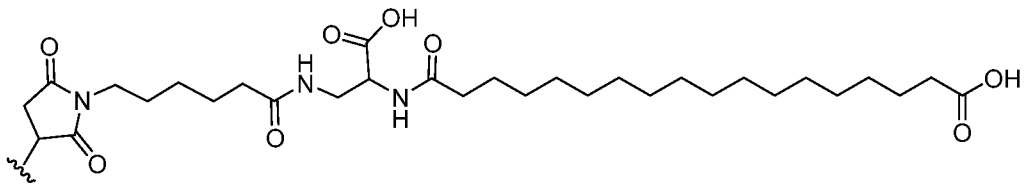
, wherein Y is an optionally substituted saturated or unsaturated aliphatic chain, and n is an integer from 5-25.

[0185] In some embodiments, a HIF-2 RNAi agent is linked to a PK enhancer that includes a compound having the following structure:



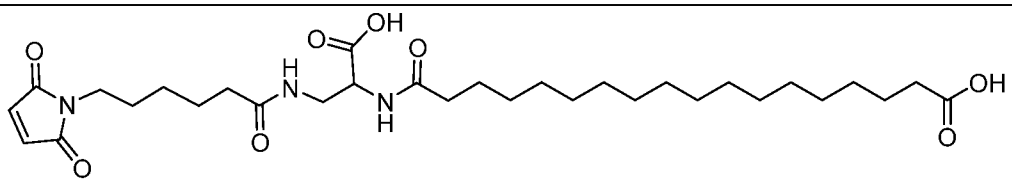
.

[0186] In some embodiments, a HIF-2 RNAi agent is linked to a PK enhancer that includes a compound having the following structure:

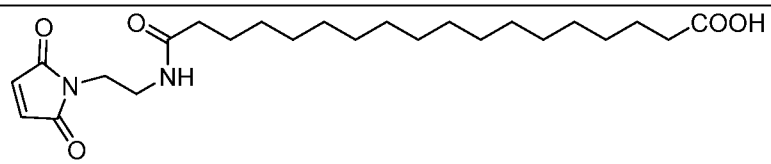


[0187] Table 6, below, shows certain exemplary PK enhancing compounds that can be used as starting materials to link to the HIF-2 alpha RNAi agents disclosed herein. The PK enhancing compounds may be added to a HIF-2 alpha RNAi agent using any known method in the art.

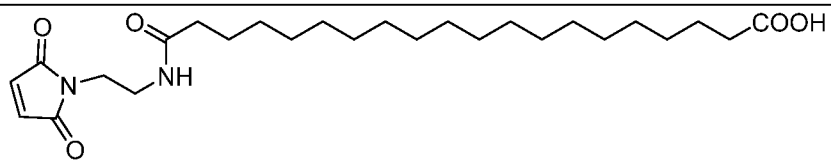
Table 6. Exemplary PK Enhancer Compounds Suitable for Linking to HIF-2 alpha RNAi Agents



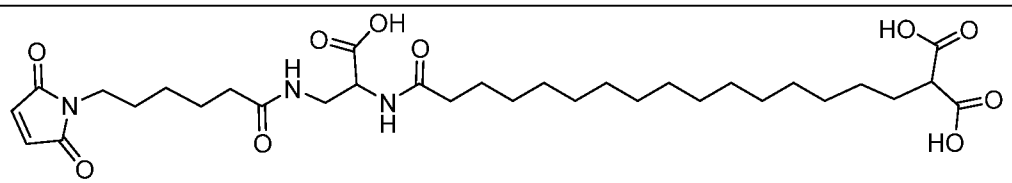
Mal-C_{18}-diacid



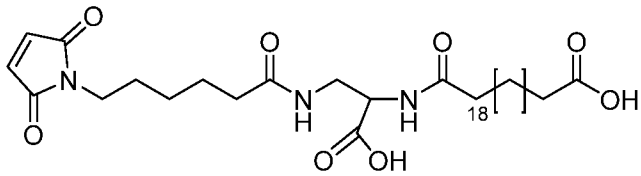
Mal-C_{18}-acid



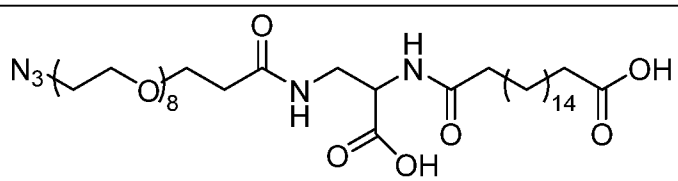
Mal-C_{20}-acid



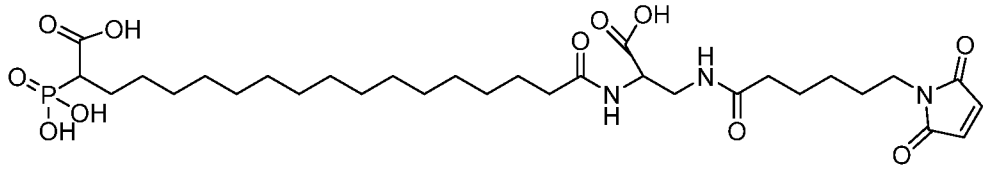
Mal-C_{18}-triacid



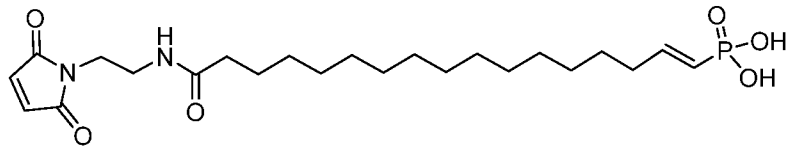
Mal-C_{22}-diacid



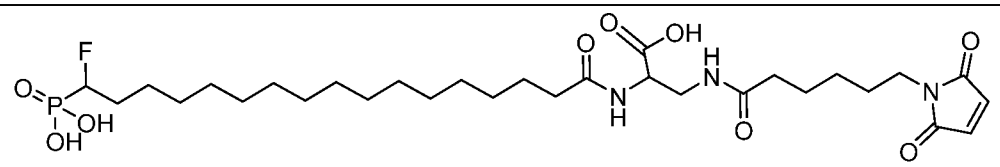
C_{18}-diacid-N_3



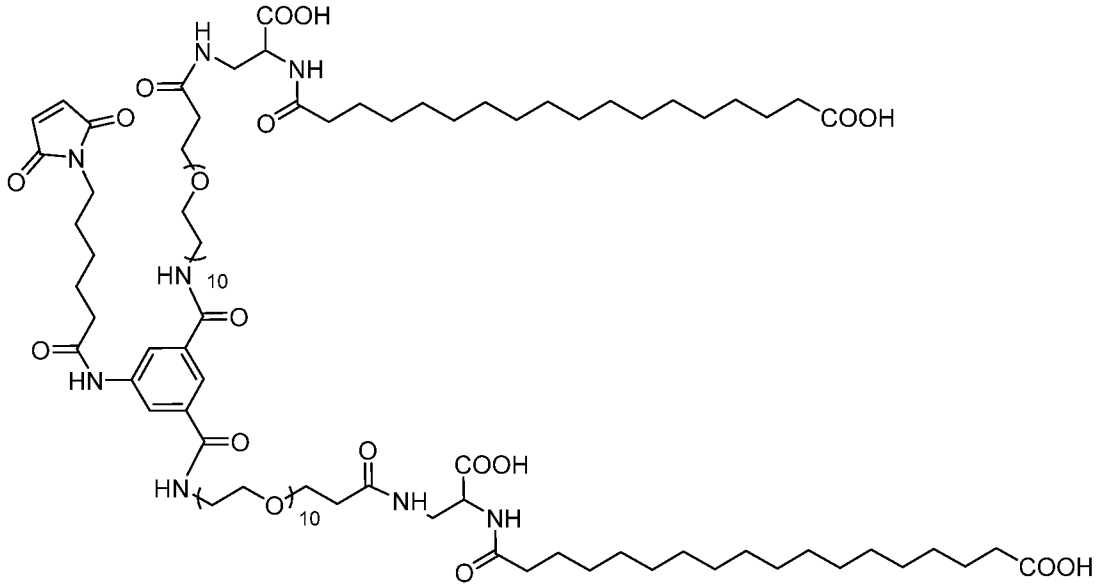
Mal-C_{18}-diacid-PO_3



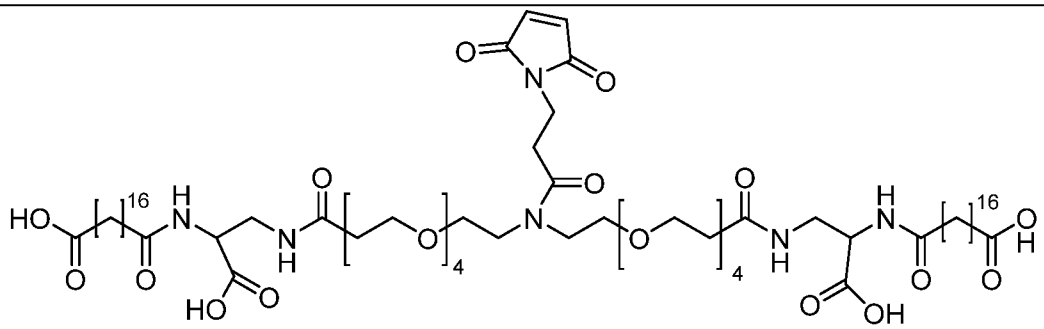
Mal-C_{17}-PO_3



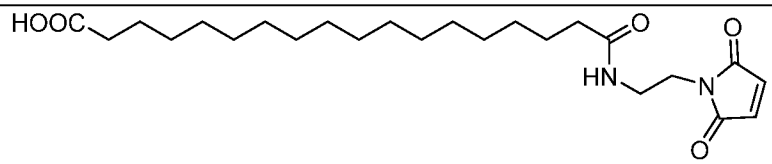
Mal-C_{17}-Fluoro-PO_3 Monoacid



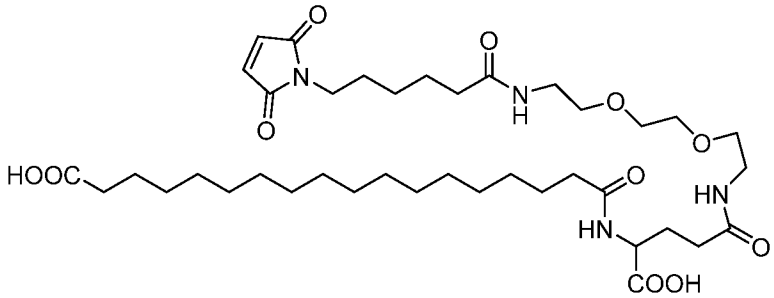
Mal-BisC18-diacid



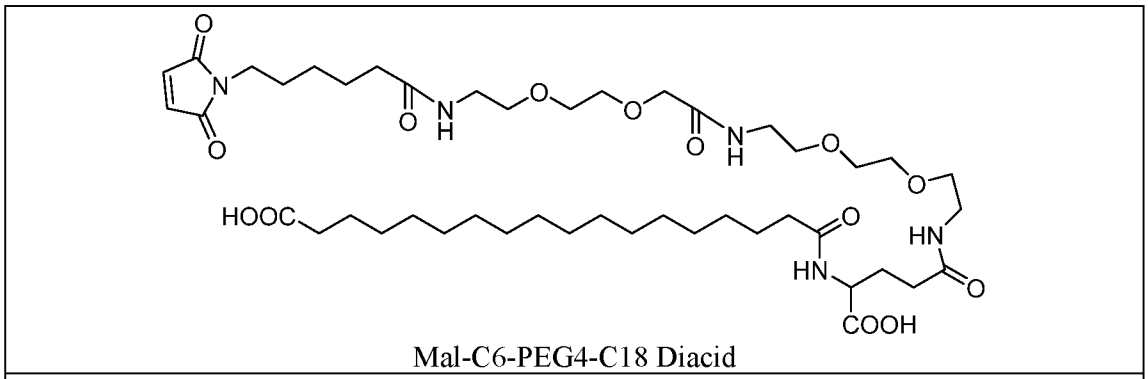
Dual C18-diacid



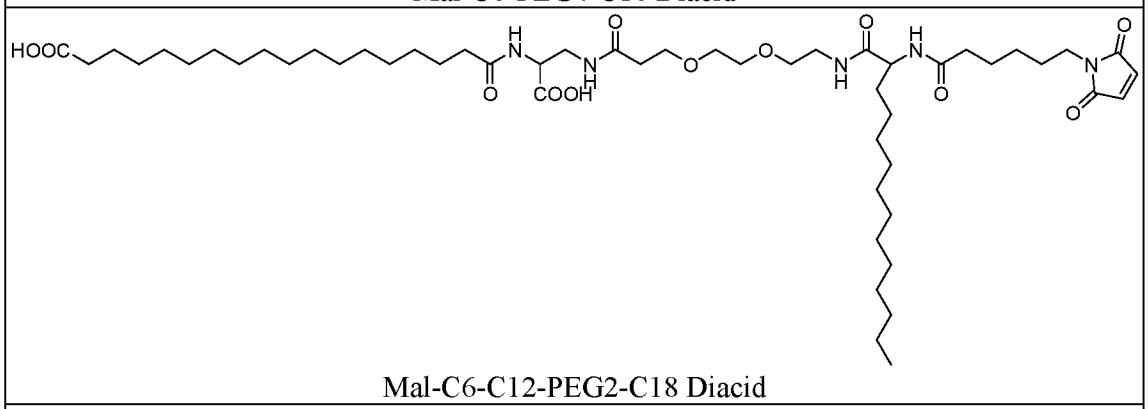
Mal-C18 Acid



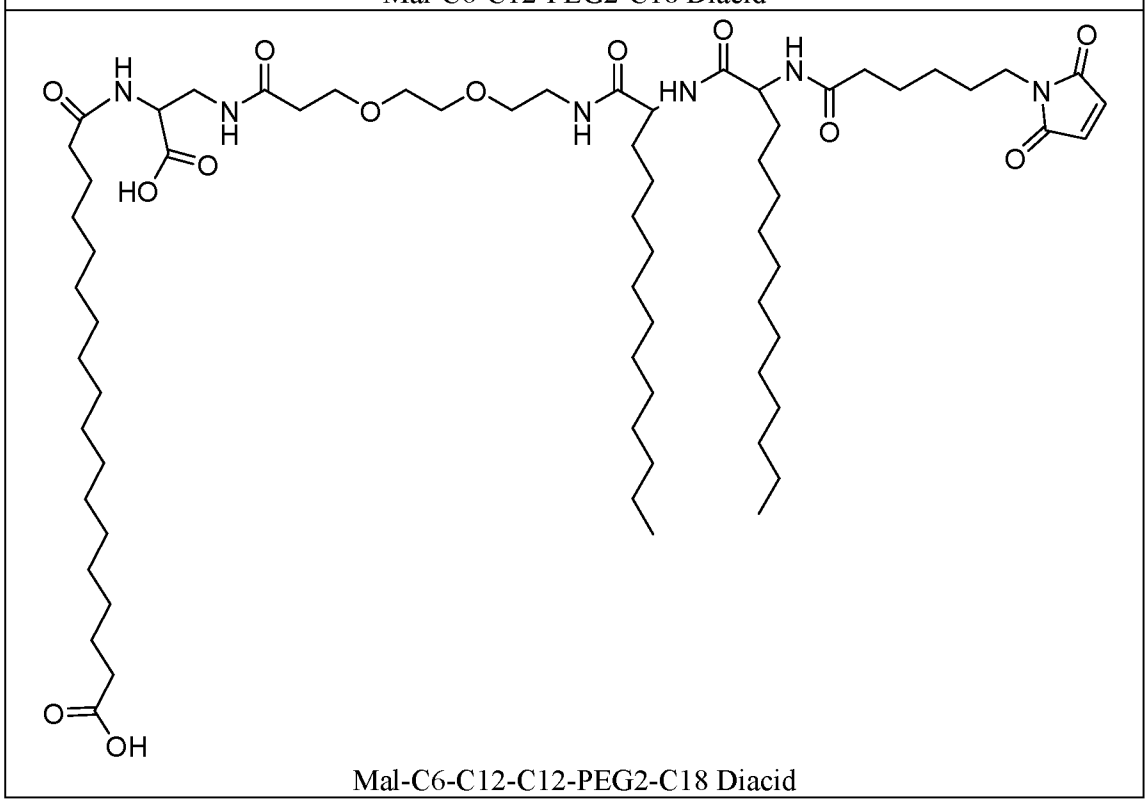
Mal-C6-PEG2-C18 Diacid



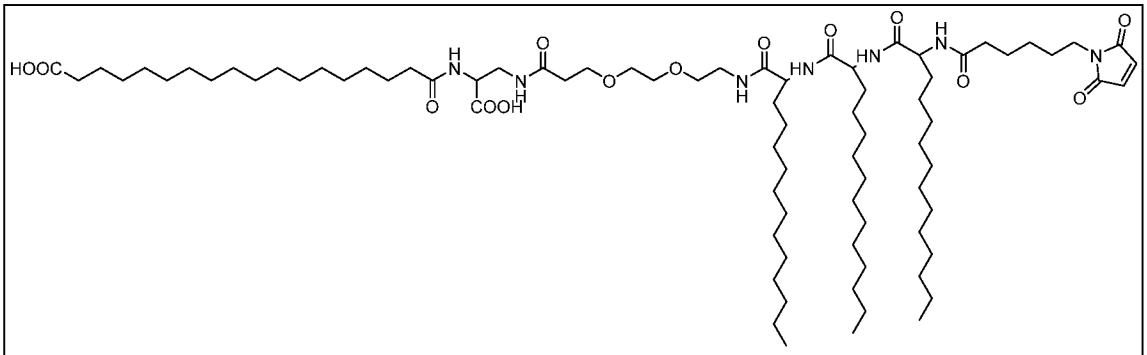
Mal-C6-PEG4-C18 Diacid



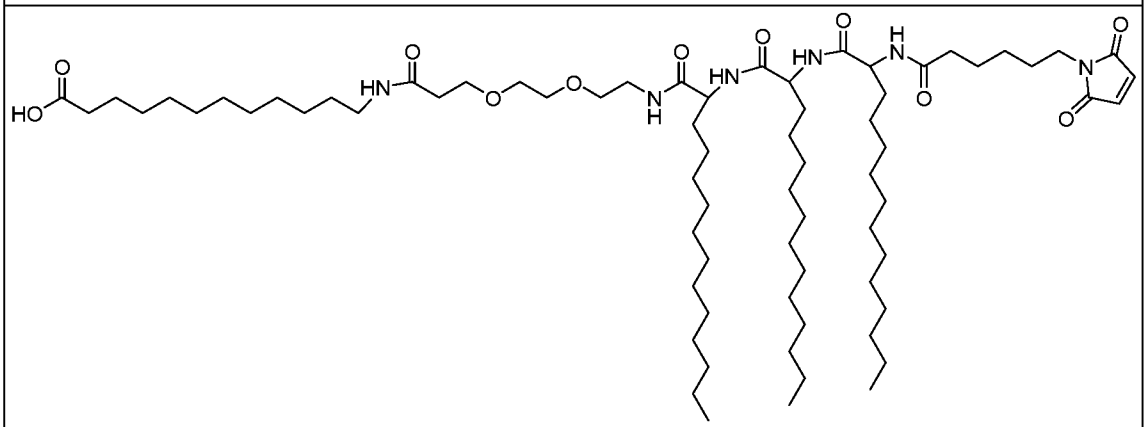
Mal-C6-C12-PEG2-C18 Diacid



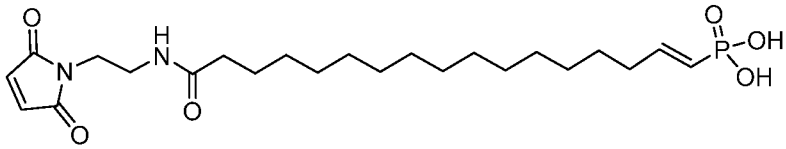
Mal-C6-C12-C12-PEG2-C18 Diacid



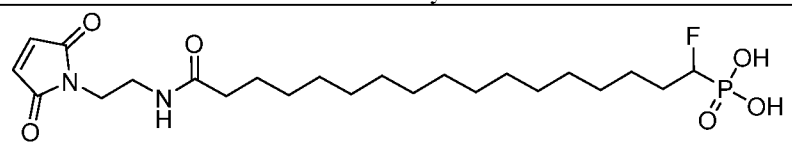
Mal-C6-C12-C12-C12-PEG2 C18 Diacid



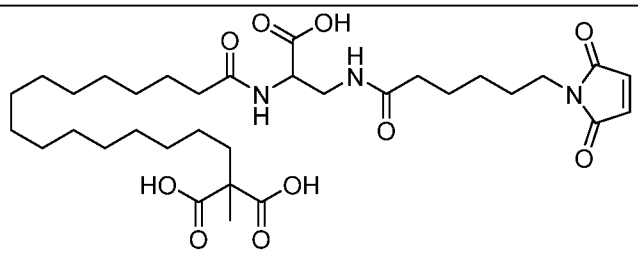
Mal-C6-C12-C12-C12-PEG2-C12 acid



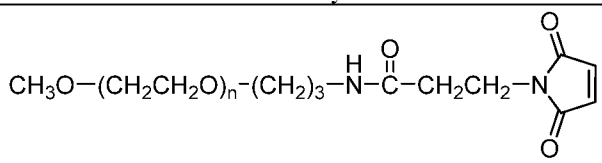
Mal-C_{17}-vinyl-PO_3



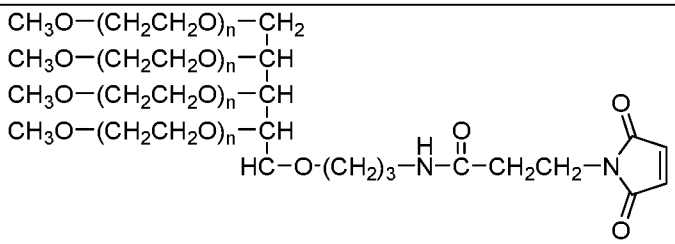
Mal-C_{17}-Fluoro-PO_3



Mal-C_{18}-methyl-triacid

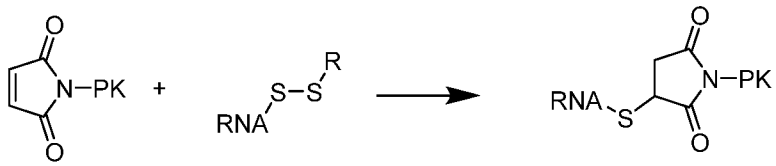


PEG40K,

wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons NOF, Sunbright® ME-400MA
 PEG40K (4-arm), wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons NOF, Sunbright® XY4-400MA

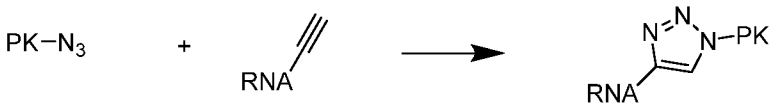
[0188] In some embodiments, HIF-2 alpha RNAi agents may comprise one or more PK enhancers. In some embodiments, HIF-2 alpha RNAi agents comprise one, two, three, four, five, six, seven or more PK enhancers.

[0189] PK enhancers may be conjugated to a HIF-2 alpha RNAi agent using any known method in the art. In some embodiments, PK enhancers may include a maleimide moiety and be reacted with an RNAi agent comprising a disulfide linkage to form an RNAi agent comprising a PK enhancer. The disulfide may be reduced, and added to a maleimide by way of a Michael-Addition reaction. An example reaction scheme is shown below:



wherein PK comprises a PK enhancer, RNA comprises an RNAi agent, and R may be any suitable group known in the art. In some instances of the reaction scheme above, R is an alkyl group such as hexyl (C_6H_{13}).

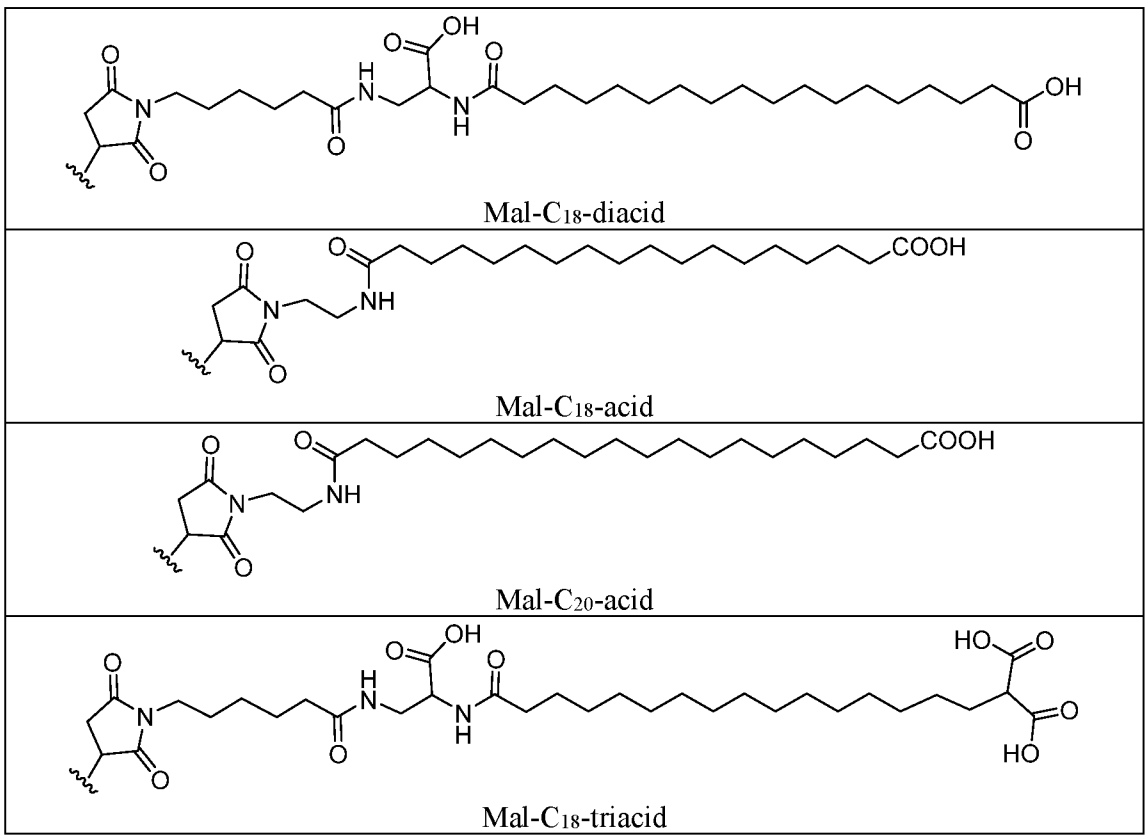
[0190] In some embodiments, PK enhancers may include an azide moiety and be reacted with an RNAi agent comprising an alkyne to form an RNAi agent comprising a PK enhancer. The pair may be reacted using a "click" reaction of the general reaction scheme below:

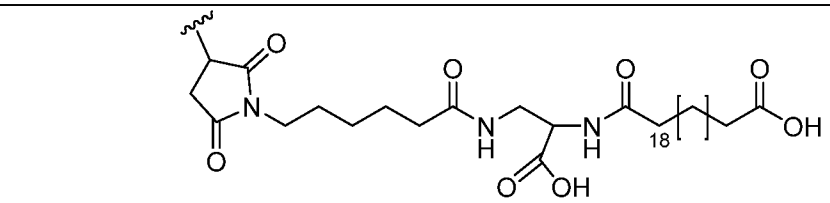


wherein PK comprises a PK enhancer, RNA comprises an RNAi agent.

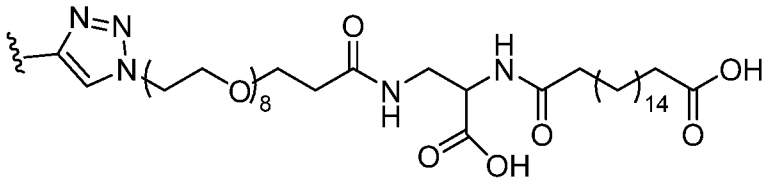
[0191] In some embodiments, PK enhancers may be conjugated to the 5' end of the sense or antisense strand, the 3' end of the sense or antisense strand, or to an internal nucleotide of a HIF-2 alpha RNAi agent. In some embodiments, a HIF-2 alpha RNAi agent is synthesized with a disulfide-containing moiety at the 3' end of the sense strand, and a PK enhancer may be conjugated to the 3' end of the sense strand using the general synthetic scheme shown above. In some embodiments a HIF-2 alpha RNAi agent is synthesized to include a 2'-O-propargyl modified nucleotide (see, for example, Table 7), and a PK enhancer may be conjugated to an internal nucleotide using the general synthetic scheme shown above.

[0192] In some embodiments, after the PK enhancer has been conjugated to the RNAi agent, the PK enhancer may have the formula:

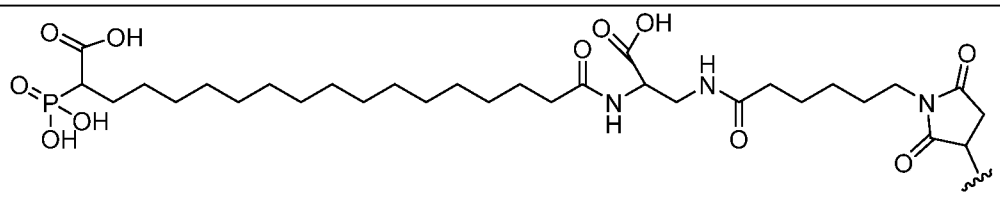




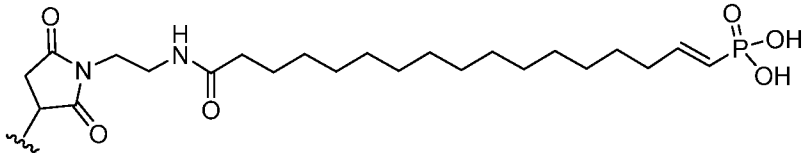
Mal-C_{22}-diacid



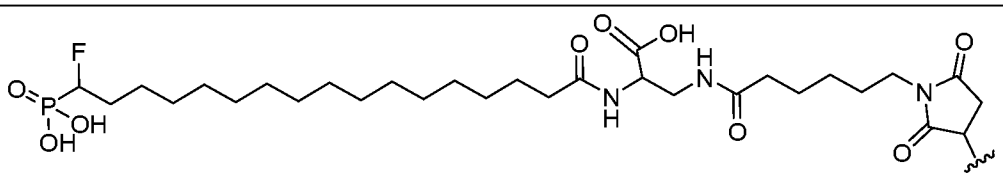
C_{18}-diacid-N_3



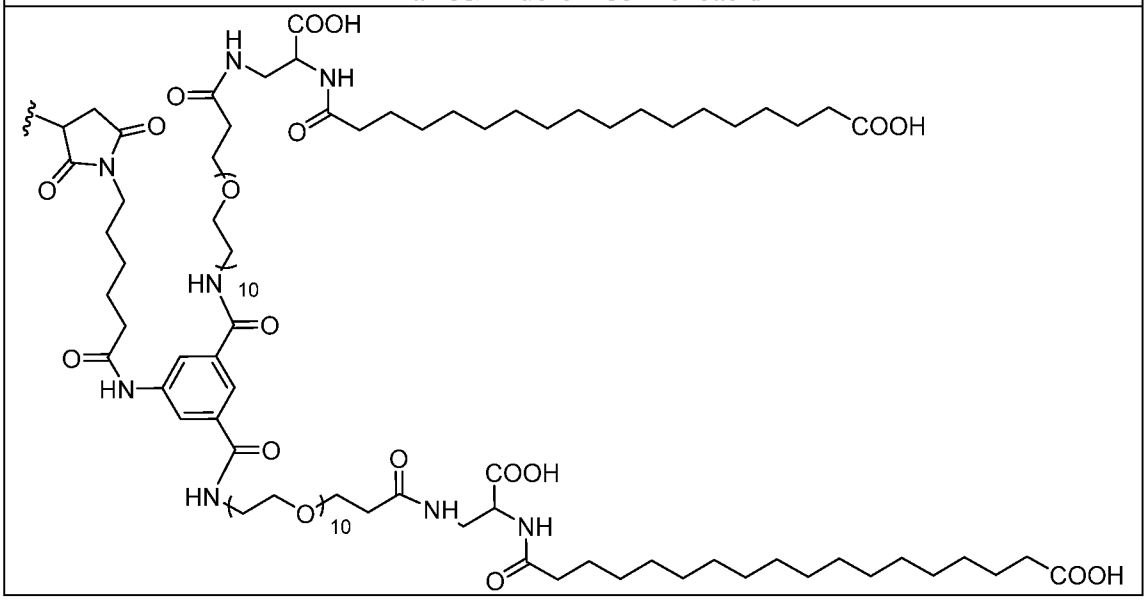
Mal-C_{18}-diacid-PO_3

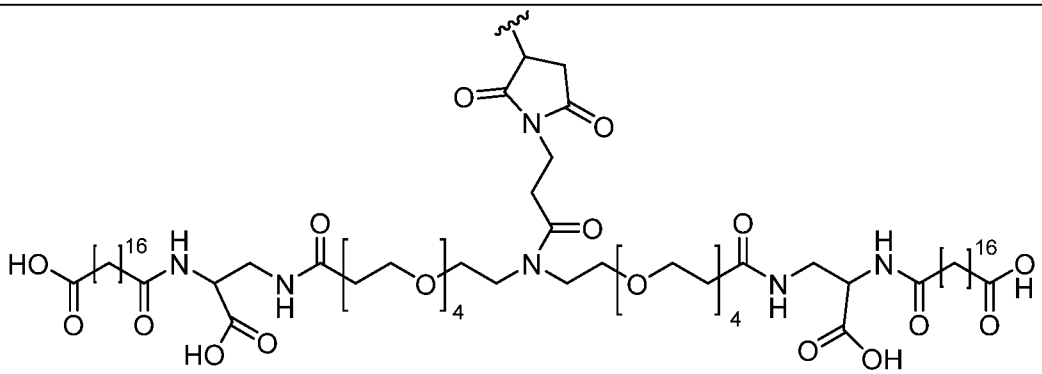
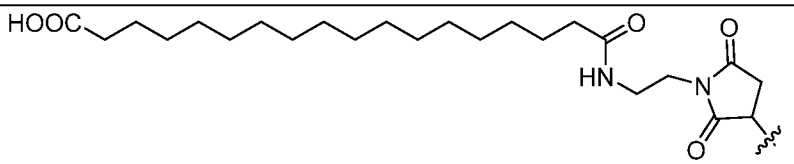
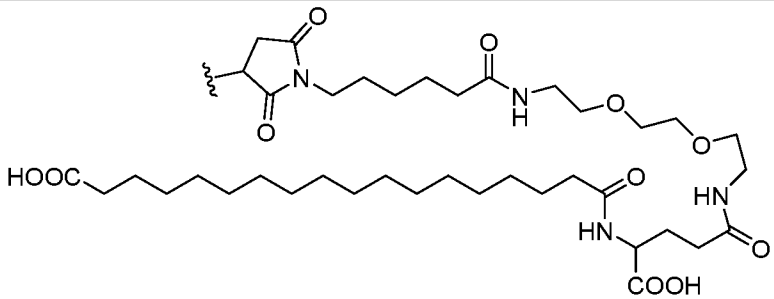
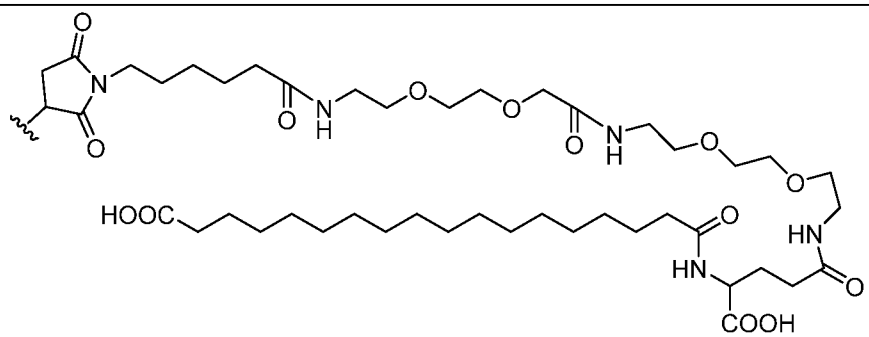


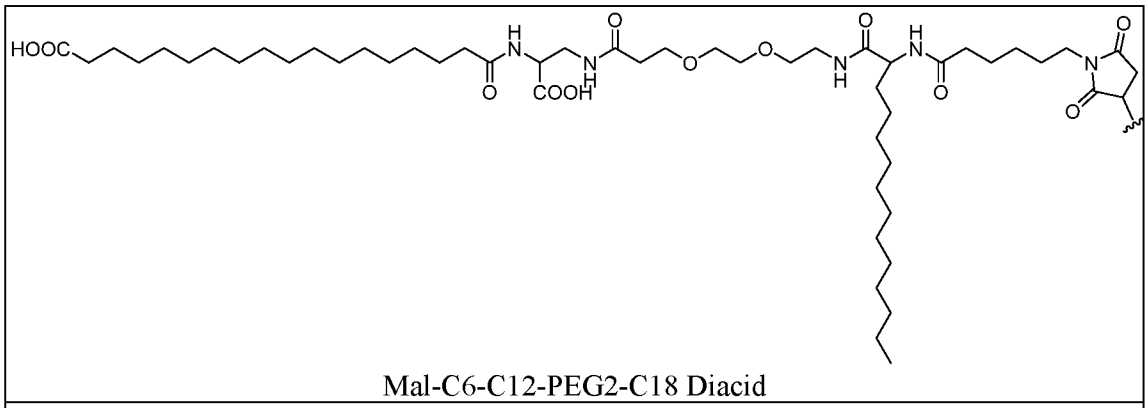
Mal-C_{17}-PO_3



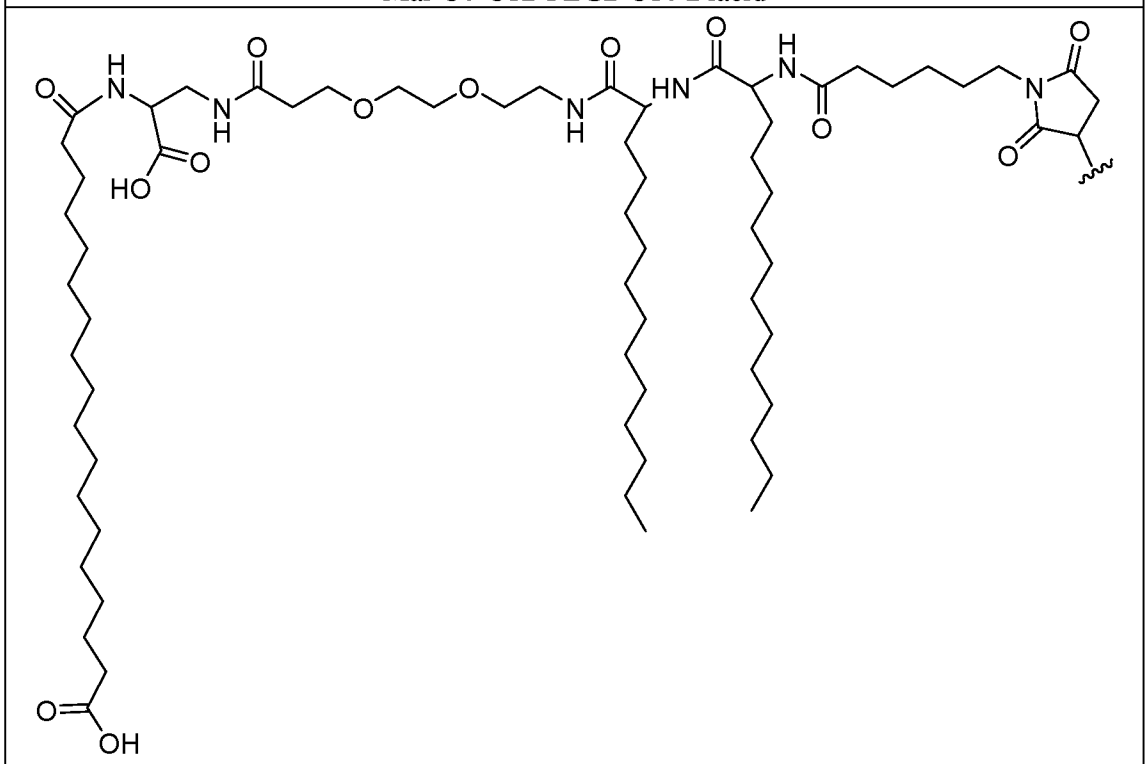
Mal-C_{17}-Fluoro-PO_3 Monoacid



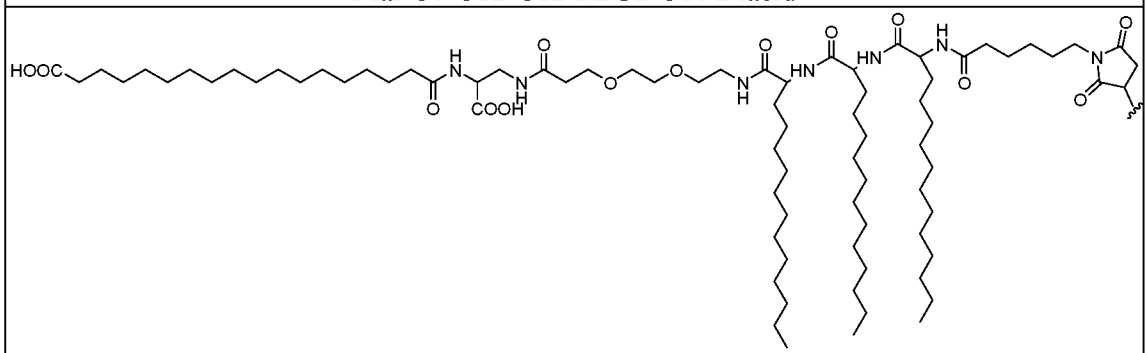
Mal-BisC18-diacid
 Dual C18-diacid
 Mal-C18 Acid
 Mal-C6-PEG2-C18 Diacid
 Mal-C6-PEG4-C18 Diacid



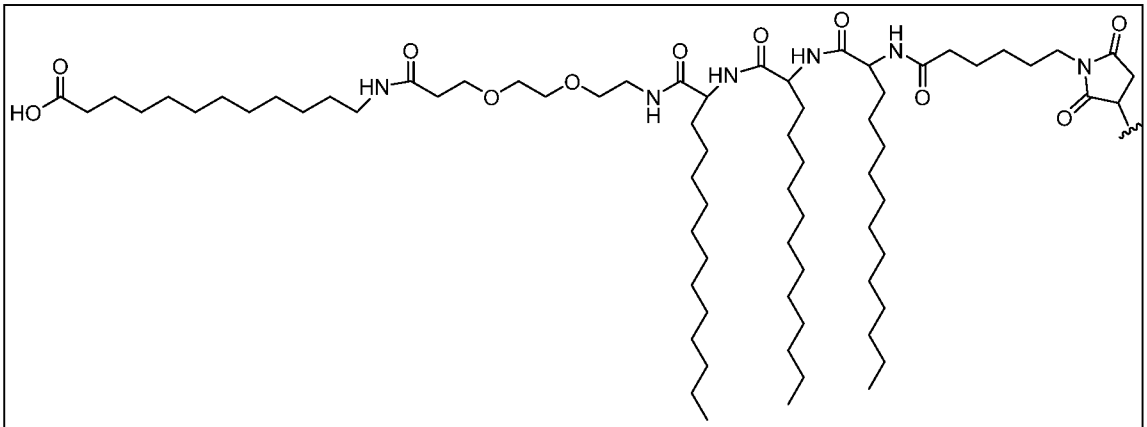
Mal-C6-C12-PEG2-C18 Diacid



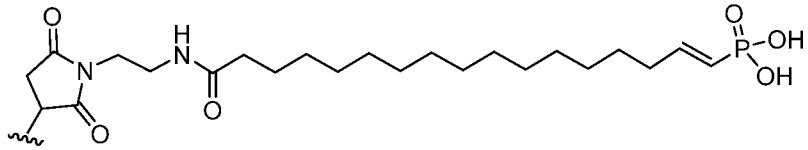
Mal-C6-C12-C12-PEG2-C18 Diacid



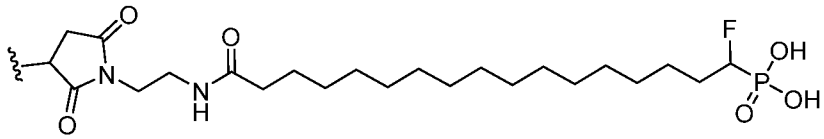
Mal-C6-C12-C12-C12-PEG2 C18 Diacid



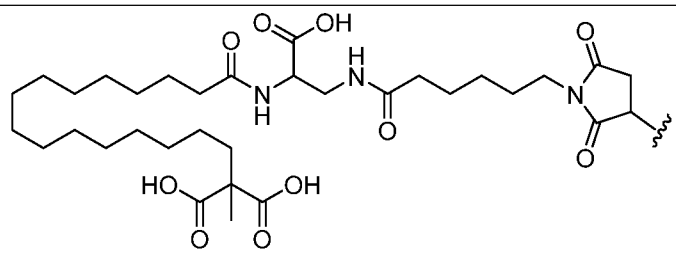
Mal-C6-C12-C12-C12-PEG2-C12 acid



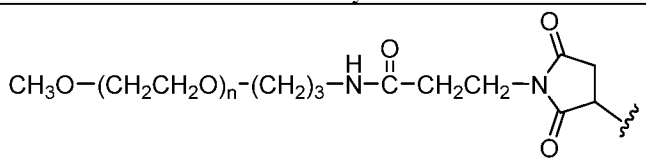
Mal-C_{17}-vinyl-PO_3



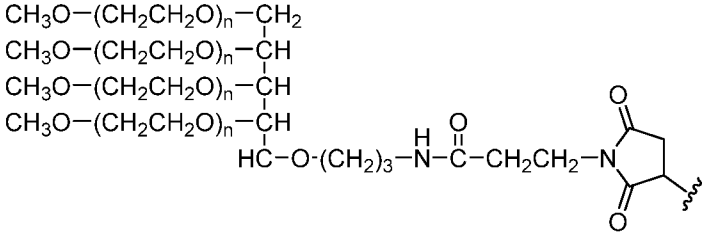
Mal-C_{17}-Fluoro-PO_3



Mal-C_{18}-methyl-triacid



PEG40K,
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



PEG40K (4-arm),
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons

wherein ≀ indicates the point of attachment to the RNAi agent.

Linking Groups and Delivery Vehicles

[0193] In some embodiments, a HIF-2 alpha RNAi agent contains or is conjugated to one or more non-nucleotide groups including, but not limited to a linking group, or a delivery vehicle. The non-nucleotide group can enhance targeting, delivery, or attachment of the RNAi agent. Non-limiting examples of linking groups are provided in Table 7. The non-nucleotide group can be covalently linked to the 3′ and/or 5′ end of either the sense strand and/or the antisense strand. In some embodiments, a HIF-2 alpha RNAi agent contains a non-nucleotide group linked to the 3′ and/or 5′ end of the sense strand. In some embodiments, a non-nucleotide group is linked to the 5′ end of a HIF-2 alpha RNAi agent sense strand. A non-nucleotide group can be linked directly or indirectly to the RNAi agent via a linker/linking group. In some embodiments, a non-nucleotide group is linked to the RNAi agent via a labile, cleavable, or reversible bond or linker.

[0194] In some embodiments, a non-nucleotide group enhances the pharmacokinetic or biodistribution properties of an RNAi agent or conjugate to which it is attached to improve cell- or tissue-specific distribution and cell-specific uptake of the conjugate. In some embodiments, a non-nucleotide group enhances endocytosis of the RNAi agent.

[0195] The HIF-2 alpha RNAi agents described herein can be synthesized having a reactive group, such as an amino group (also referred to herein as an amine), at the 5′-terminus and/or the 3′-terminus. The reactive group can be used subsequently to attach a targeting moiety using methods typical in the art.

[0196] For example, in some embodiments, the HIF-2 alpha RNAi agents disclosed herein are synthesized having an NH_2-C_6 group at the 5′-terminus of the sense strand of the RNAi agent. The terminal amino group subsequently can be reacted to form a conjugate with, for example, a group that includes a compound having affinity for one or more integrins (an integrin targeting ligand) or a PK enhancer. In some embodiments, the HIF-2 alpha RNAi agents disclosed herein are synthesized having one or more alkyne groups at the 5′-terminus of the sense strand of the RNAi agent. The terminal alkyne group(s) can subsequently be reacted to form a conjugate with, for example, a group that includes a targeting ligand.

[0197] In some embodiments, a targeting group comprises an integrin targeting ligand. In some embodiments, an integrin targeting ligand includes a compound that has affinity to integrin alpha-v-beta 3 and/or integrin alpha-v-beta 5. The use of an integrin targeting ligands

can facilitate cell-specific targeting to cells having the respective integrin on its respective surface, and binding of the integrin targeting ligand can facilitate entry of the HIF-2 alpha RNAi agent, to which it is linked, into cells such as ccRCC cells. Targeting ligands, targeting groups, and/or PK enhancers can be attached to the 3′ and/or 5′ end of the HIF-2 alpha RNAi agent, and/or to internal nucleotides on the HIF-2 alpha RNAi agent, using methods generally known in the art. The preparation of targeting ligand and targeting groups, such as integrin αvβ3/αvβ5 is described, for example, in U.S. Provisional Patent Application No. 62/663,763, the contents of which is incorporated herein in its entirety.

[0198] Embodiments of the present disclosure include pharmaceutical compositions for delivering a HIF-2 alpha RNAi agent to a ccRCC cell *in vivo*. Such pharmaceutical compositions can include, for example, a HIF-2 alpha RNAi agent conjugated to a targeting group that comprises an integrin targeting ligand that has affinity for integrin αvβ3 and/or integrin αvβ5 . In some embodiments, the targeting ligand is comprised of a compound having affinity for integrin αvβ3 and/or integrin αvβ5.

[0199] In some embodiments, the HIF-2 alpha RNAi agent is synthesized having a linking group, which can then facilitate covalent linkage of the HIF-2 alpha RNAi agent to a targeting ligand, a targeting group, a PK enhancer, or another type of delivery vehicle such as a delivery polymer. The linking group can be linked to the 3′ and/or the 5′ end of the RNAi agent sense strand or antisense strand. In some embodiments, the linking group is linked to the RNAi agent sense strand. In some embodiments, the linking group is conjugated to the 5′ or 3′ end of an RNAi agent sense strand. In some embodiments, a linking group is conjugated to the 5′ end of an RNAi agent sense strand. Examples of linking groups, include, but are not limited to: Alk-SMPT-C6, Alk-SS-C6, DBCO-TEG, Me-Alk-SS-C6, and C6-SS-Alk-Me, reactive groups such a primary amines and alkynes, alkyl groups, abasic residues/nucleotides, amino acids, trialkyne functionalized groups, ribitol, and/or PEG groups.

[0200] A linker or linking group is a connection between two atoms that links one chemical group (such as an RNAi agent) or segment of interest to another chemical group (such as a targeting ligand, targeting group, PK enhancer, or delivery polymer) or segment of interest via one or more covalent bonds. A labile linkage contains a labile bond. A linkage can optionally include a spacer that increases the distance between the two joined atoms. A spacer may further add flexibility and/or length to the linkage. Spacers include, but are not be limited to, alkyl groups, alkenyl groups, alkynyl groups, aryl groups, aralkyl groups, aralkenyl groups, and aralkynyl groups; each of which can contain one or more heteroatoms, heterocycles, amino

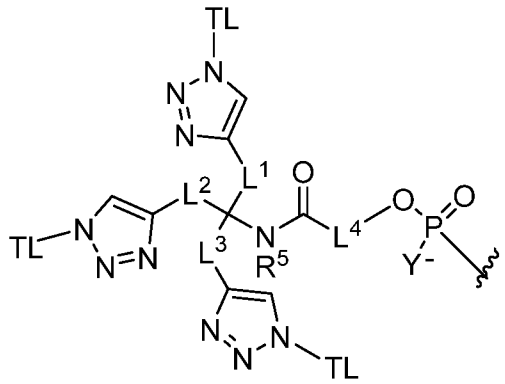
acids, nucleotides, and saccharides. Spacer groups are well known in the art and the preceding list is not meant to limit the scope of the description.

[0201] In some embodiments, targeting groups are linked to the HIF-2 alpha RNAi agents without the use of an additional linker. In some embodiments, the targeting group is designed having a linker readily present to facilitate the linkage to a HIF-2 alpha RNAi agent. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents can be linked to their respective targeting groups using the same linkers. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents are linked to their respective targeting groups using different linkers.

[0202] Any of the HIF-2 alpha RNAi agent nucleotide sequences listed in Tables 2, 3, and 4 (or Table 4.1, 4.2, or 4.3), whether modified or unmodified, may contain 3′ and/or 5′ targeting group(s), linking group(s), and/or pharmacokinetic enhancer(s). Any of the HIF-2 alpha RNAi agent sequences listed in Tables 3 and 4, or are otherwise described herein, which contain a 3′ or 5′ targeting ligand, targeting group, PK enhancer, or linking group, can alternatively contain no 3′ or 5′ targeting ligand, targeting group, linking group, or PK enhancer, or can contain a different 3′ or 5′ targeting ligand, targeting group, linking group, or PK enhancer including, but not limited to, those depicted in Tables 6 and 7. Any of the HIF-2 alpha RNAi agent duplexes listed in Table 5, whether modified or unmodified, can further comprise a targeting ligand, targeting group, linking group, or PK enhancer, including, but not limited to, those depicted in Tables 6 and 7, and the targeting group or linking group can be attached to the 3′ or 5′ terminus of either the sense strand or the antisense strand of the HIF-2 alpha RNAi agent duplex.

[0203] In some embodiments, a linking group may be conjugated synthetically to the 5’ or 3’ end of the sense strand of a HIF-2 alpha RNAi agent described herein. In some embodiments, a linking group is conjugated synthetically to the 5’ end of the sense strand of a HIF-2 alpha RNAi agent. In some embodiments, a linking group conjugated to a HIF-2 alpha RNAi agent may be a trialkyne linking group.

[0204] In some embodiments, the HIF-2 alpha RNAi agents are linked to one or more tridentate targeting groups having the following formula:



Formula II

or a pharmaceutically acceptable salt thereof, wherein,

L^1, L^2 and L^3 are each independently linkers comprising an optionally substituted alkylene;

L^4 is a linker comprising an optionally substituted alkylene, optionally substituted aryl, or optionally substituted cycloalkyl;

R^5 is H or optionally substituted alkyl;

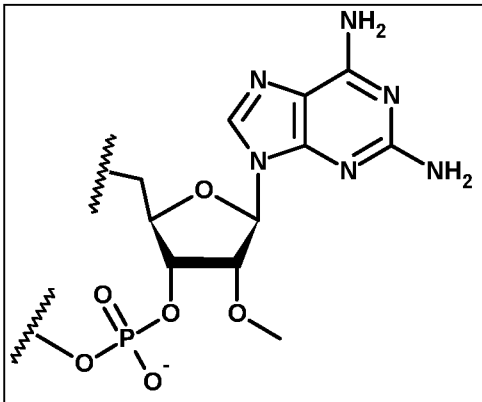
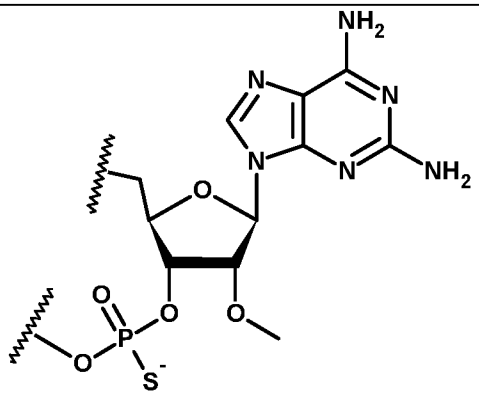
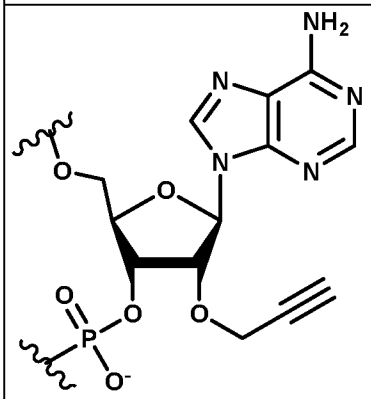
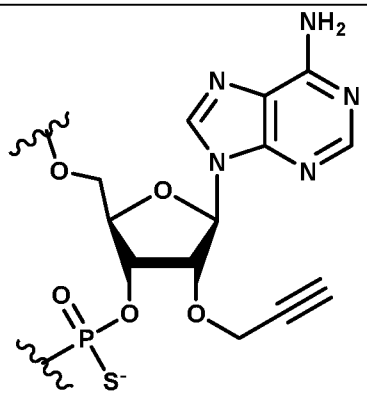
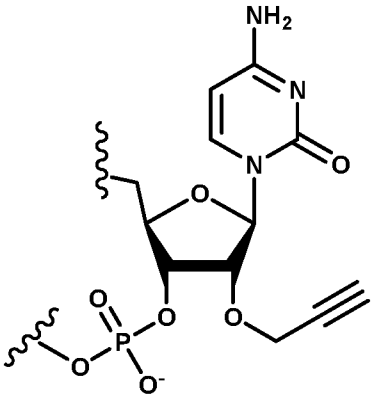
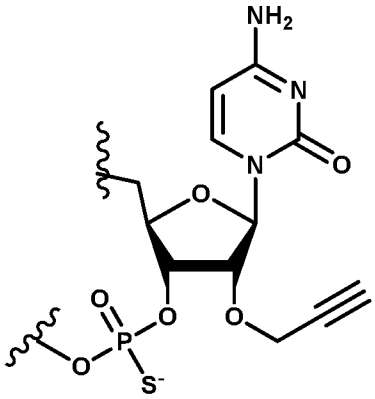
TL is a targeting ligand; and

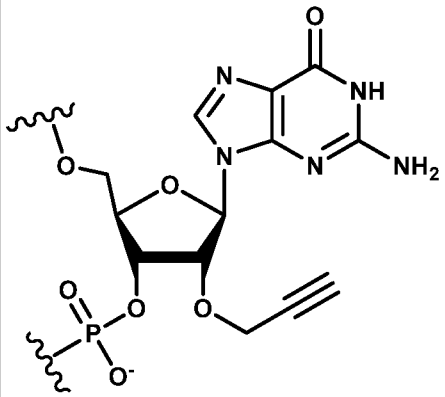
Y is O or S.

[0205] In other embodiments, the HIF-2 alpha RNAi agents are linked to one or more tridentate targeting groups using a linker having the formula of any one of TriAlk 1-14 as shown in Table 7, below. Methods of synthesizing compounds of Formula II are described in PCT Application No. PCT/US19/18232, entitled "Trialkyne Linking Agents and Methods of Use."

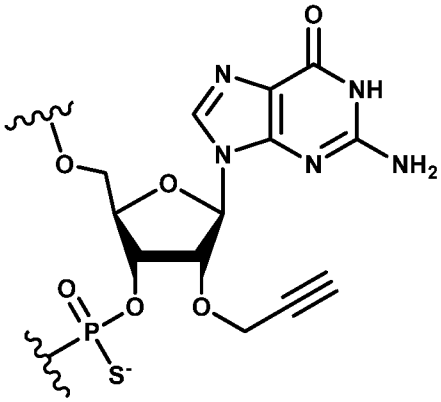
[0206] Examples of certain modified nucleotides and linking groups, are provided in Table 7.

Table 7. Structures Representing Various Modified Nucleotides and Linking Groups

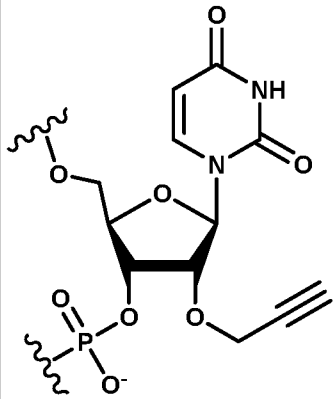
 a_2N	 a_2Ns
 aAlk	 aAlks
 cAlk	 cAlks



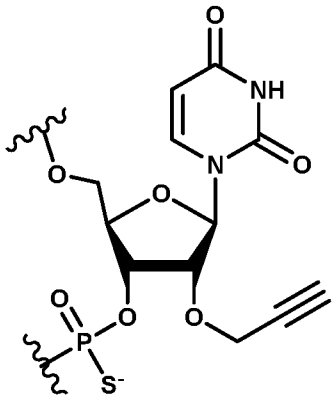
gAlk



gAlks

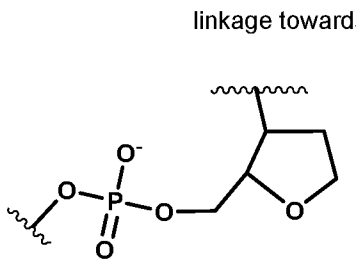


uAlk



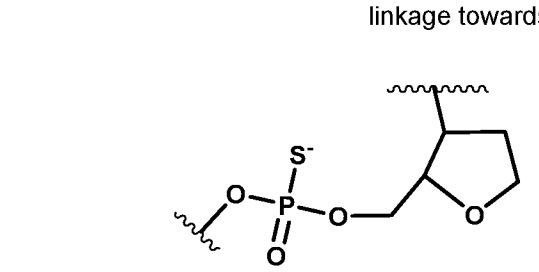
uAlks

When positioned internally in oligonucleotide:



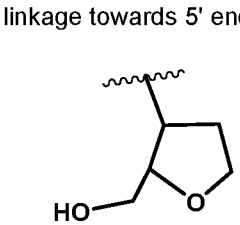
(invAb)

When positioned internally:



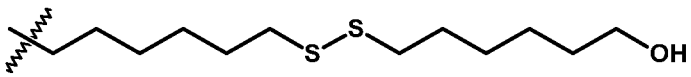
(invAb)s

When positioned at the 3′ terminal end:



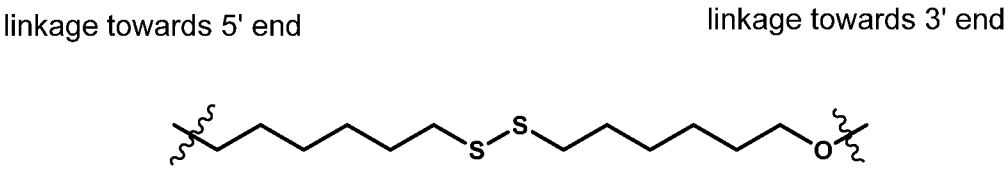
(invAb)

When positioned at the 3′ terminal end:

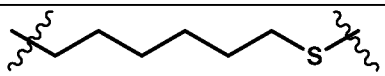


(C6-SS-C6)

When positioned internally:

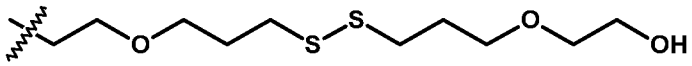


(C6-SS-C6)



(C6-S)

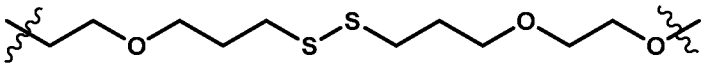
When positioned at the 3′ terminal end:



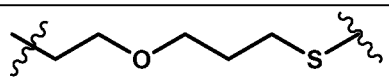
(6-SS-6)

When positioned internally:

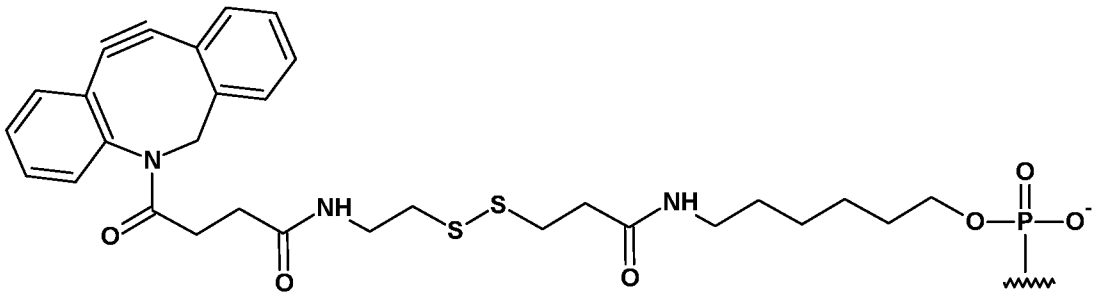
linkage towards 5' end linkage towards 3' end



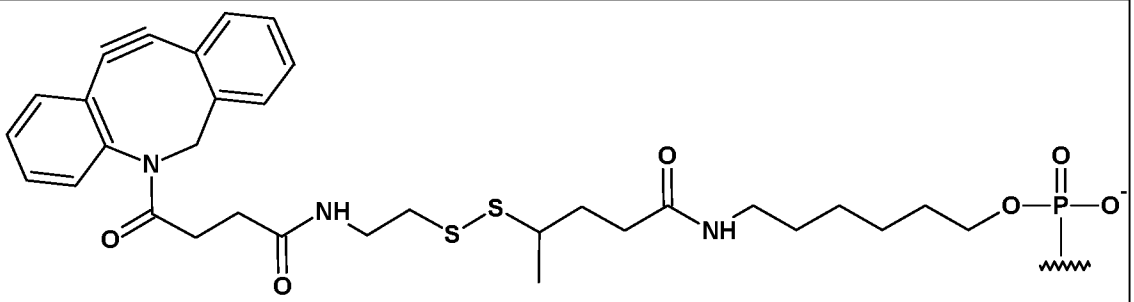
(6-SS-6)



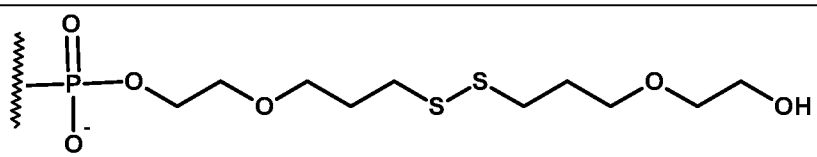
(6-S)



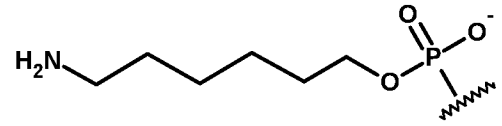
(C6-SS-Alk) or (Alk-SS-C6)



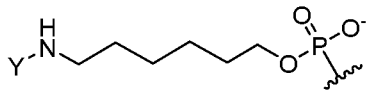
(C6-SS-Alk-Me)



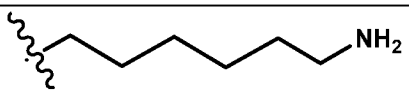
(PEG-C3-SS)



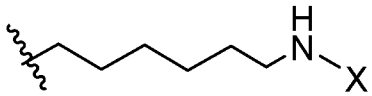
(NH2-C6)



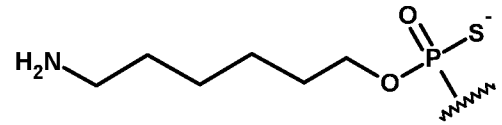
Y-(NH-C6)



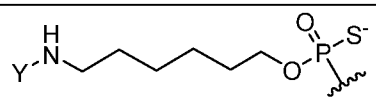
(C6-NH2)



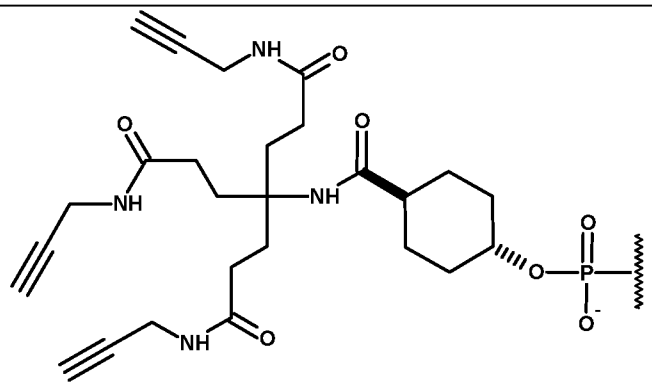
(C6-NH)-X



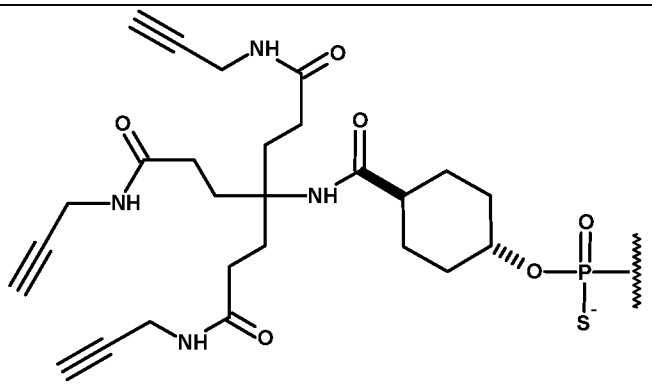
(NH2-C6)s



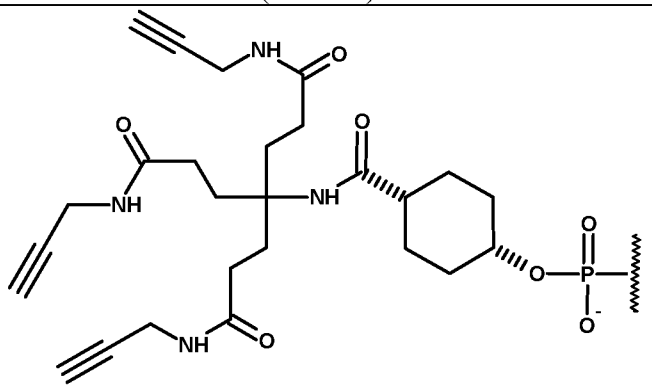
Y-(NH-C6)s



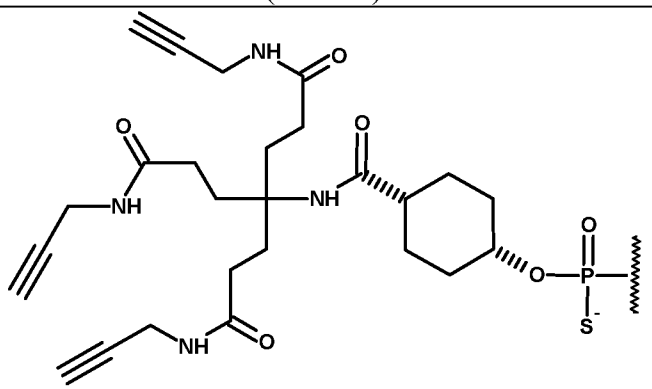
(TriAlk1)



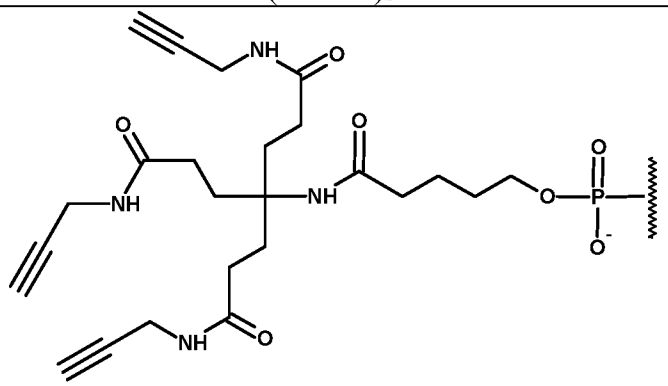
(TriAlk1)s



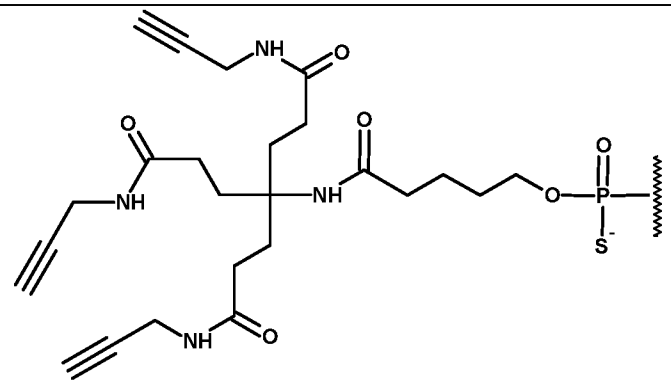
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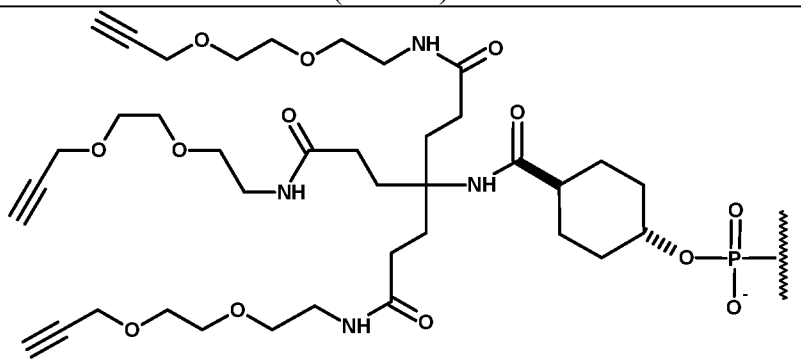
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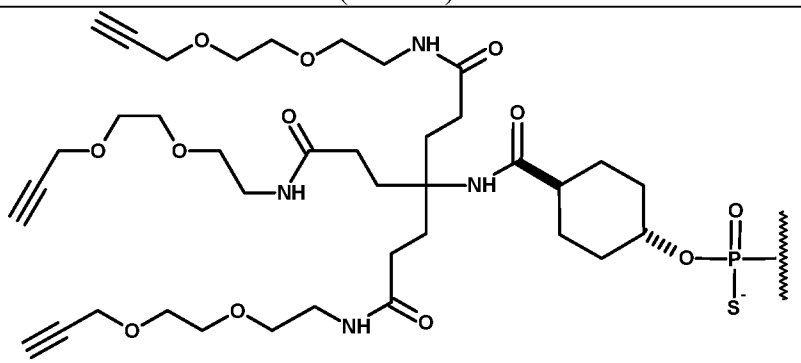
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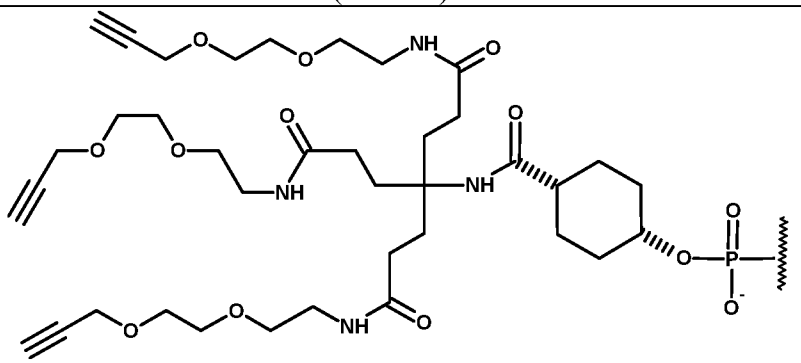
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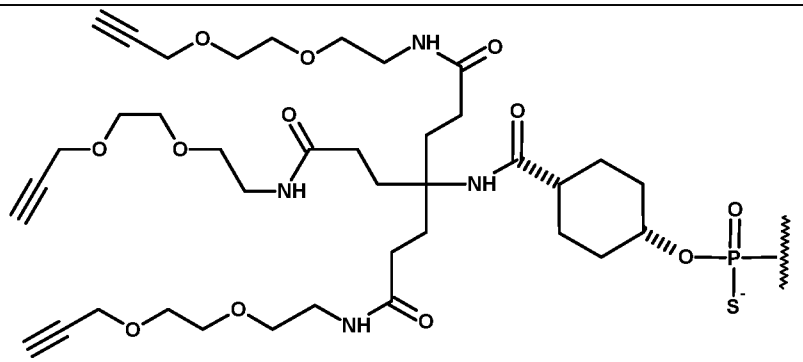
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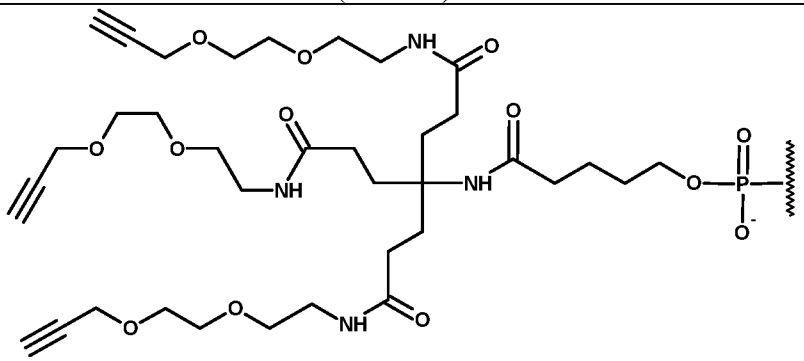
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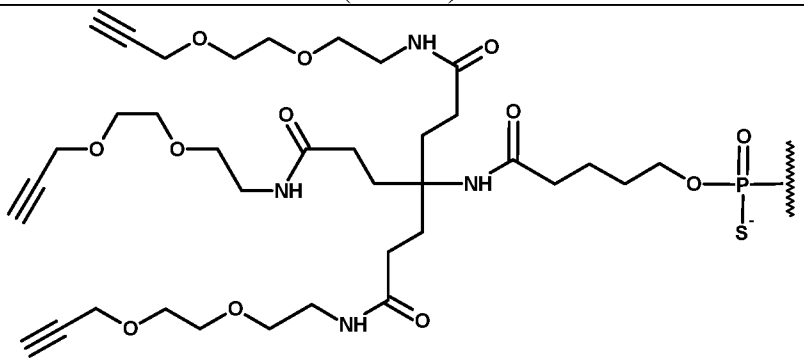
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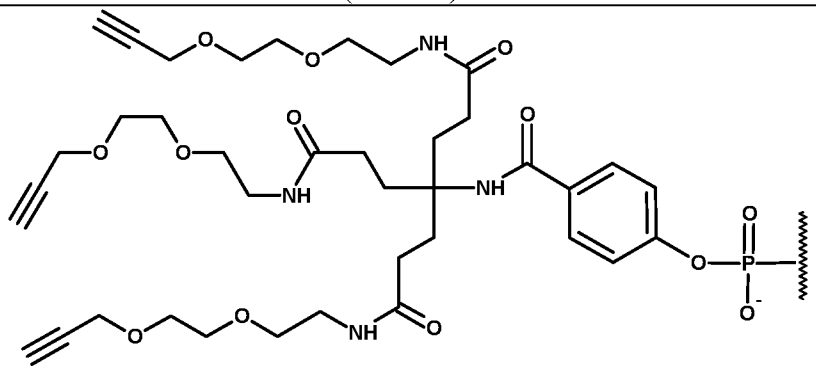
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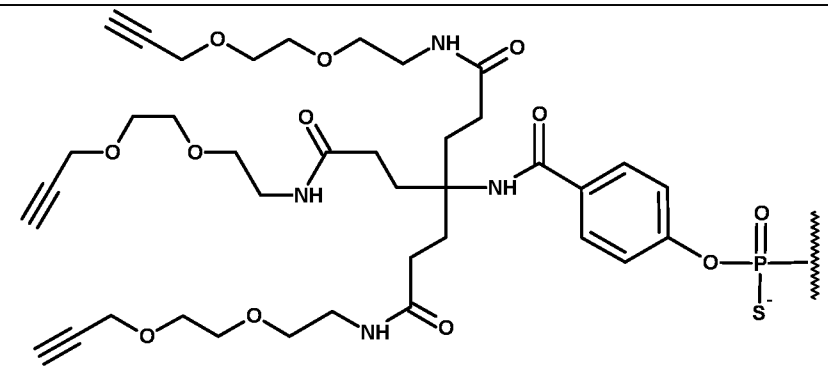
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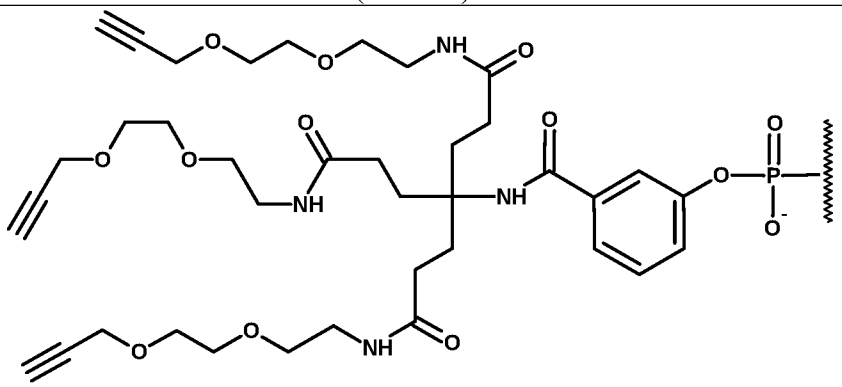
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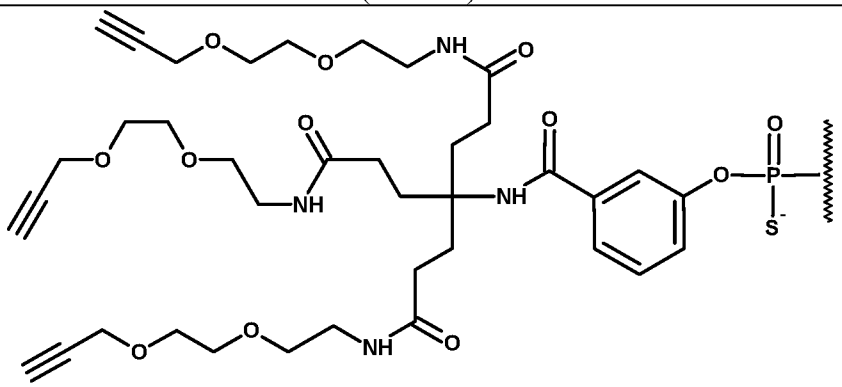
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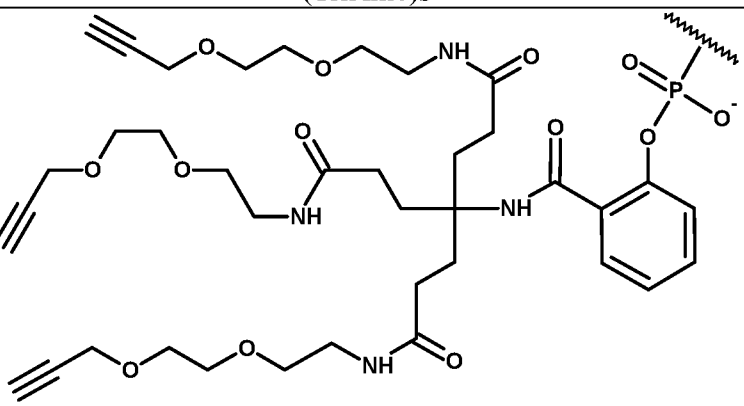
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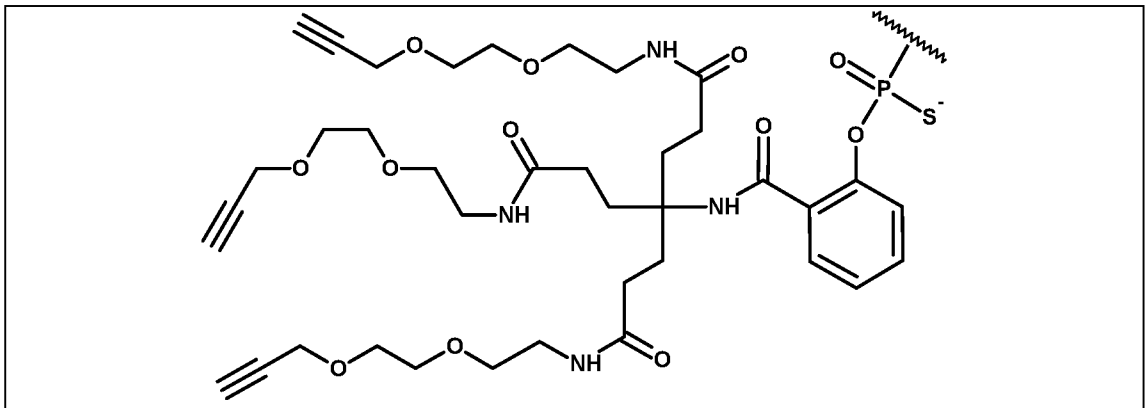
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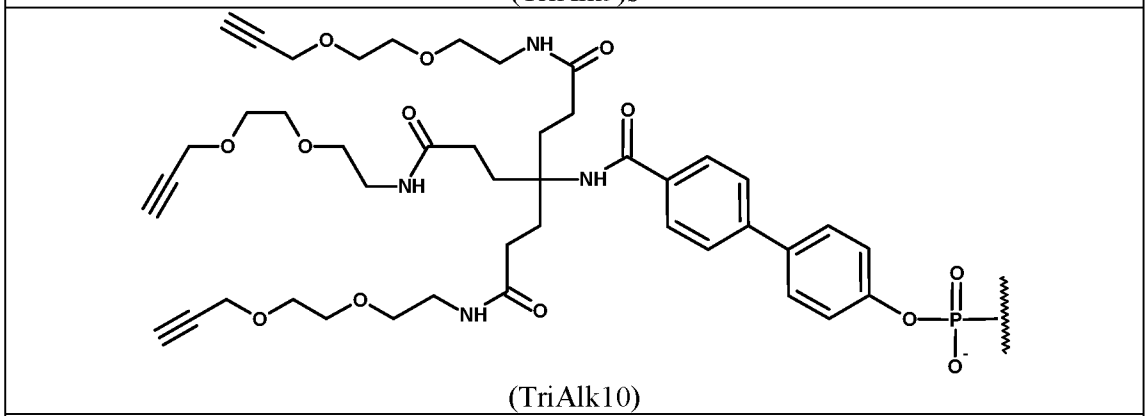
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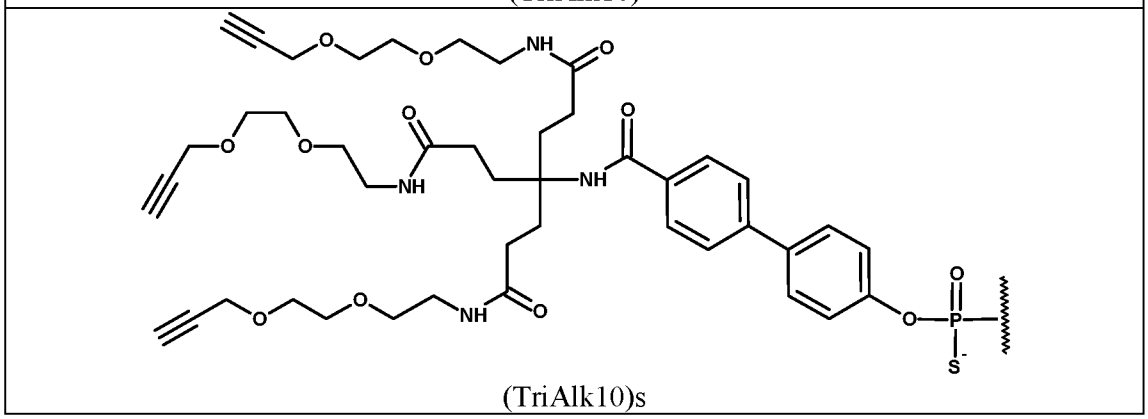
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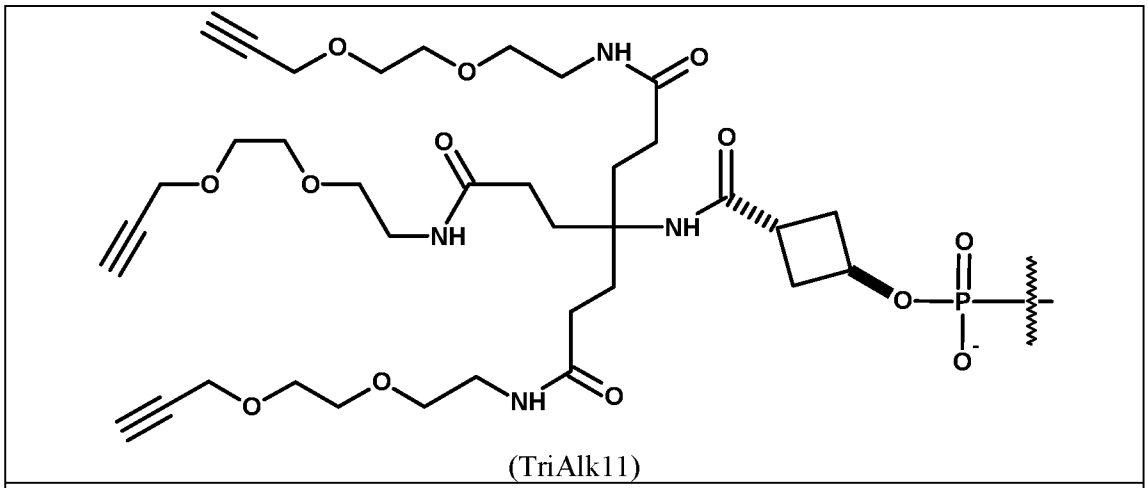
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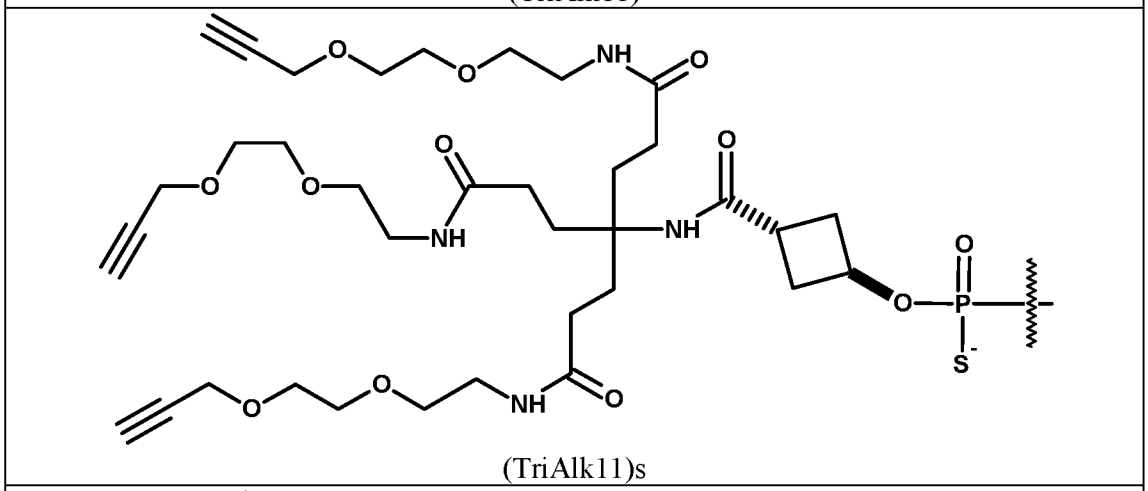
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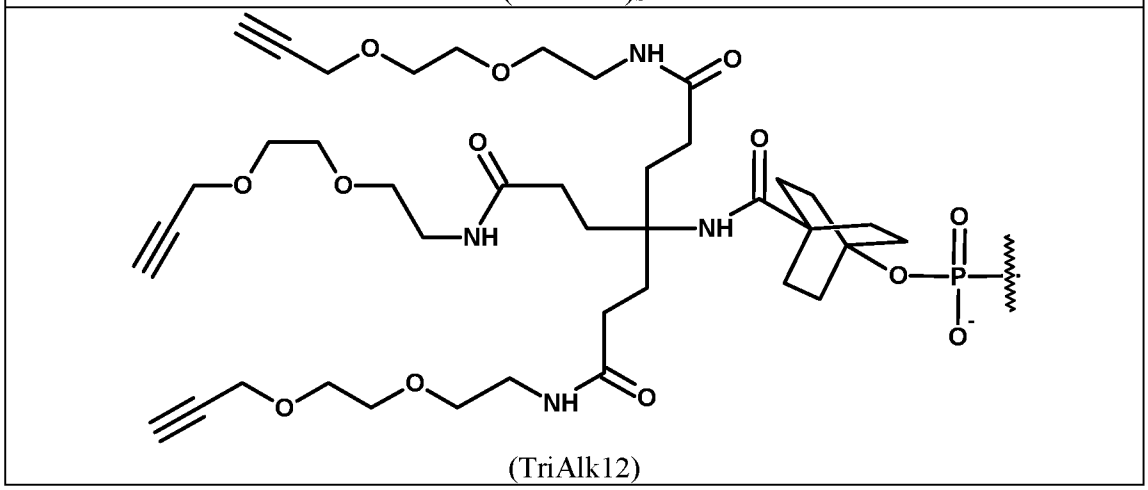
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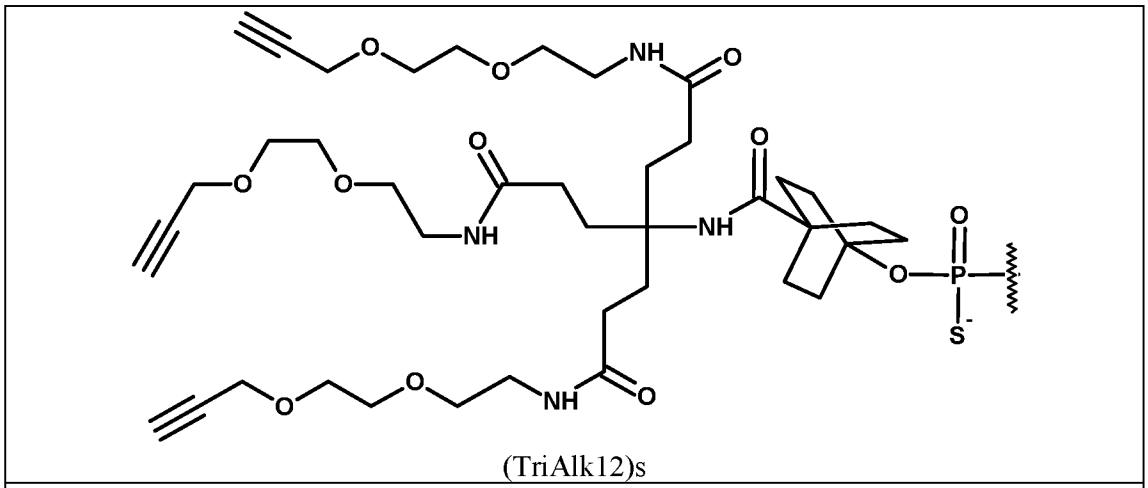
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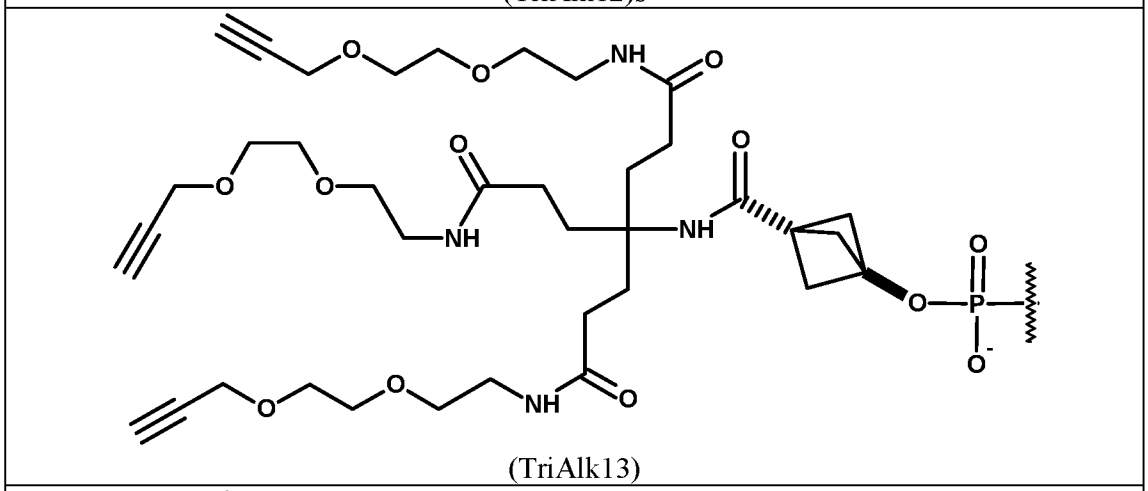
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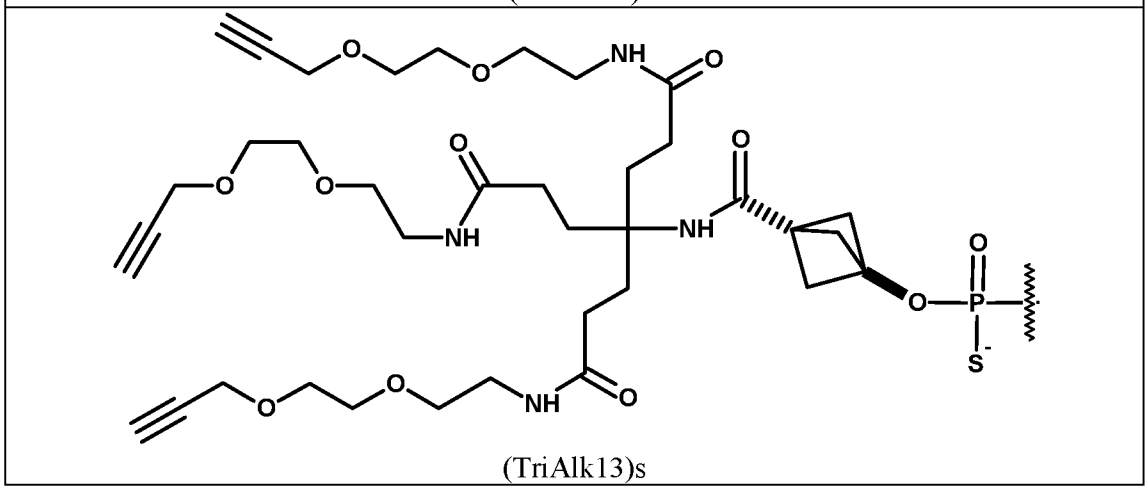
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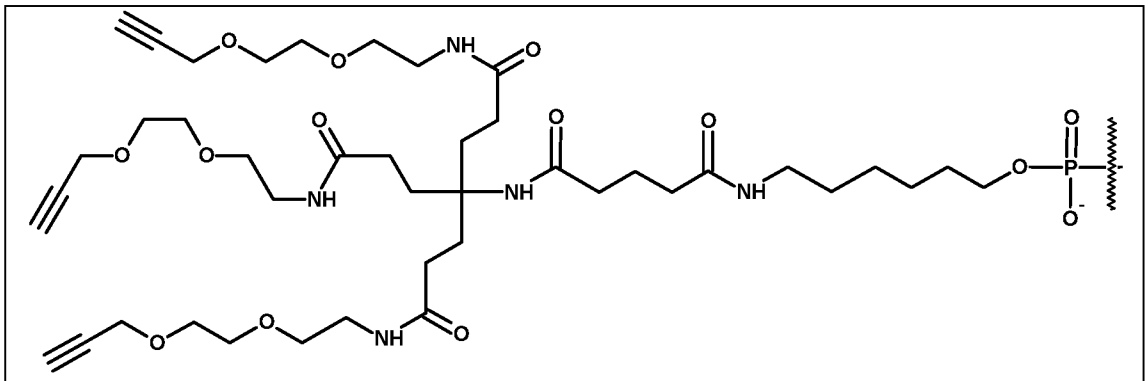
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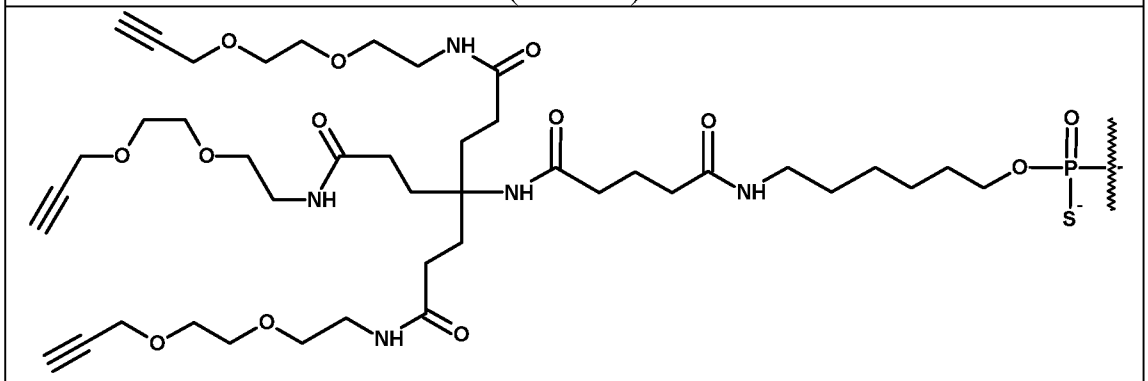
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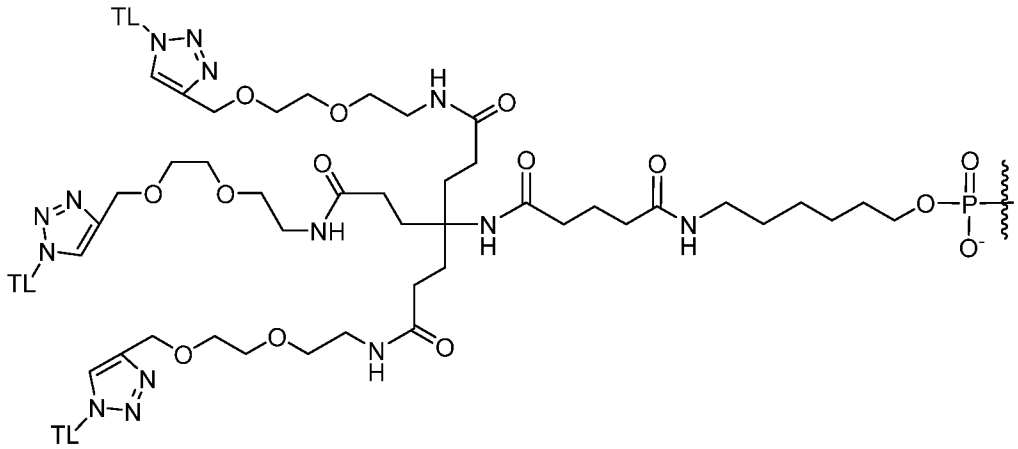


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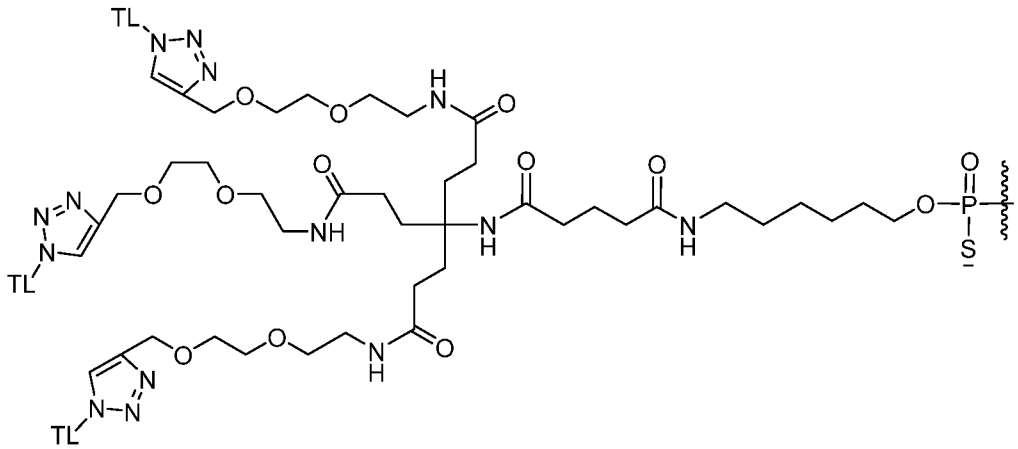


(TriAlk14)s

[0207] In some embodiments, an RNAi agent includes a linker having the structure of TriAlk 14:



or TriAlk 14s:



, wherein TL comprises a targeting ligand, which is the result of a "click" reaction with a compound of (TriAlk14), or (Trialk14)s and a a targeting ligand comprising an azide.

[0208] Alternatively, other linking groups known in the art may be used.

[0209] In addition or alternatively to linking a HIF-2 alpha RNAi agent to one or more targeting ligands, targeting groups, and/or PK enhancers, in some embodiments, a delivery vehicle may be used to deliver an RNAi agent to a cell or tissue. A delivery vehicle is a compound that can improve delivery of the RNAi agent to a cell or tissue, and can include, or consist of, but is not limited to: a polymer, such as an amphipathic polymer, a membrane active polymer, a peptide, a melittin peptide, a melittin-like peptide (MLP), a lipid, a reversibly modified polymer or peptide, or a reversibly modified membrane active polyamine.

[0210] In some embodiments, the RNAi agents can be combined with lipids, nanoparticles, polymers, liposomes, micelles, DPCs or other delivery systems available in the art. The RNAi

agents can also be chemically conjugated to targeting groups, lipids (including, but not limited to cholesterol and cholesteryl derivatives), nanoparticles, polymers, liposomes, micelles, DPCs (see, for example WO 2000/053722, WO 2008/022309, WO 2011/104169, and WO 2012/083185, WO 2013/032829, WO 2013/158141, each of which is incorporated herein by reference), or other delivery systems available in the art.

Pharmaceutical Compositions

[0211] In some embodiments, the present disclosure provides pharmaceutical compositions that include, consist of, or consist essentially of, one or more of the HIF-2 alpha RNAi agents disclosed herein.

[0212] As used herein, a "pharmaceutical composition" comprises a pharmacologically effective amount of an Active Pharmaceutical Ingredient (API), and optionally one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients (excipients) are substances other than the Active Pharmaceutical ingredient (API, therapeutic product) that are intentionally included in the drug delivery system. Excipients do not exert or are not intended to exert a therapeutic effect at the intended dosage. Excipients may act to a) aid in processing of the drug delivery system during manufacture, b) protect, support or enhance stability, bioavailability or patient acceptability of the API, c) assist in product identification, and/or d) enhance any other attribute of the overall safety, effectiveness, of delivery of the API during storage or use. A pharmaceutically acceptable excipient may or may not be an inert substance.

[0213] Excipients include, but are not limited to: absorption enhancers, anti-adherents, anti-foaming agents, anti-oxidants, binders, buffering agents, carriers, coating agents, colors, delivery enhancers, delivery polymers, dextran, dextrose, diluents, disintegrants, emulsifiers, extenders, fillers, flavors, glidants, humectants, lubricants, oils, polymers, preservatives, saline, salts, solvents, sugars, suspending agents, sustained release matrices, sweeteners, thickening agents, tonicity agents, vehicles, water-repelling agents, and wetting agents.

[0214] The pharmaceutical compositions described herein can contain other additional components commonly found in pharmaceutical compositions. In some embodiments, the additional component is a pharmaceutically-active material. Pharmaceutically-active materials include, but are not limited to: anti-pruritics, astringents, local anesthetics, or anti-inflammatory agents (for example, antihistamine, diphenhydramine, etc.), small molecule drug, antibody, antibody fragment, aptamers, and/or vaccines.

[0215] The pharmaceutical compositions may also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents, or antioxidants. They may also contain other agent with a known therapeutic benefit.

[0216] The pharmaceutical compositions can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be made by any way commonly known in the art, such as, but not limited to, topical (for example, by a transdermal patch), pulmonary (for example, by inhalation or insufflation of powders or aerosols, including by nebulizer, intratracheal, intranasal), epidermal, transdermal, oral or parenteral. Parenteral administration includes, but is not limited to, intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal (for example, via an implanted device), intracranial, intraparenchymal, intrathecal, and intraventricular, administration. In some embodiments, the pharmaceutical compositions described herein are administered by subcutaneous injection. The pharmaceutical compositions may be administered orally, for example in the form of tablets, coated tablets, dragées, hard or soft gelatine capsules, solutions, emulsions or suspensions. Administration can also be carried out rectally, for example using suppositories; locally or percutaneously, for example using ointments, creams, gels, or solutions; or parenterally, for example using injectable solutions.

[0217] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the

injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0218] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0219] Formulations suitable for intra-articular administration can be in the form of a sterile aqueous preparation of any of the ligands described herein that can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present any of the ligands described herein for both intra-articular and ophthalmic administration.

[0220] The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0221] A pharmaceutical composition can contain other additional components commonly found in pharmaceutical compositions. Such additional components include, but are not limited to: anti-pruritics, astringents, local anesthetics, or anti-inflammatory agents (for example, antihistamine, diphenhydramine, etc.). As used herein, "pharmacologically effective amount," "therapeutically effective amount," or simply "effective amount" refers to that amount of an the pharmaceutically active agent to produce a pharmacological, therapeutic or preventive result.

[0222] Medicaments containing a HIF-2 alpha RNAi agent are also an object of the present invention, as are processes for the manufacture of such medicaments, which processes comprise bringing one or more compounds containing a HIF-2 alpha RNAi agent, and, if

desired, one or more other substances with a known therapeutic benefit, into a pharmaceutically acceptable form.

[0223] The described HIF-2 alpha RNAi agents and pharmaceutical compositions comprising HIF-2 alpha RNAi agents disclosed herein may be packaged or included in a kit, container, pack, or dispenser. The HIF-2 alpha RNAi agents and pharmaceutical compositions comprising the HIF-2 alpha RNAi agents may be packaged in pre-filled syringes or vials.

Methods of Treatment and Inhibition of Expression

[0224] The HIF-2 alpha RNAi agents disclosed herein can be used to treat a subject (for example, a human or other mammal) having a disease or disorder that would benefit from administration of the RNAi agent. In some embodiments, the RNAi agents disclosed herein can be used to treat a subject (for example, a human) that would benefit from reduction and/or inhibition in expression of HIF-2 alpha mRNA and/or HIF-2 alpha (EPAS1) protein levels, for example, a subject that has been diagnosed with or is suffering from symptoms related to cancer, renal cancer, clear cell renal cell carcinoma, non-small cell lung cancer, astrocytoma (brain cancer), bladder cancer, breast cancer, chondrosarcoma, colorectal carcinoma, gastric carcinoma, glioblastoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, neuroblastoma, melanoma, multiple myeloma, ovarian cancer, rectal cancer, metastases, gingivitis, psoriasis, Kaposi's sarcoma-associated herpesvirus, preeclampsia, inflammation, chronic inflammation, neovascular diseases, and rheumatoid arthritis.

[0225] In some embodiments, the subject is administered a therapeutically effective amount of any one or more HIF-2 alpha RNAi agents. Treatment of a subject can include therapeutic and/or prophylactic treatment. The subject is administered a therapeutically effective amount of any one or more HIF-2 alpha RNAi agents described herein. The subject can be a human, patient, or human patient. The subject may be an adult, adolescent, child, or infant. Administration of a pharmaceutical composition described herein can be to a human being or animal.

[0226] The HIF-2 alpha RNAi agents described herein can be used to treat at least one symptom in a subject having a HIF-2 alpha-related disease or disorder, or having a disease or disorder that is mediated at least in part by HIF-2 alpha gene expression. In some embodiments, the HIF-2 alpha RNAi agents are used to treat or manage a clinical presentation of a subject with a disease or disorder that would benefit from or be mediated at least in part by a reduction

in HIF-2 alpha mRNA. The subject is administered a therapeutically effective amount of one or more of the HIF-2 alpha RNAi agents or HIF-2 alpha RNAi agent-containing compositions described herein. In some embodiments, the methods disclosed herein comprise administering a composition comprising a HIF-2 alpha RNAi agent described herein to a subject to be treated. In some embodiments, the subject is administered a prophylactically effective amount of any one or more of the described HIF-2 alpha RNAi agents, thereby treating the subject by preventing or inhibiting the at least one symptom.

[0227] In certain embodiments, the present disclosure provides methods for treatment of diseases, disorders, conditions, or pathological states mediated at least in part by HIF-2 alpha gene expression, in a patient in need thereof, wherein the methods include administering to the patient any of the HIF-2 alpha RNAi agents described herein.

[0228] In some embodiments, the gene expression level and/or mRNA level of a HIF-2 alpha gene in a subject to whom a described HIF-2 alpha RNAi agent is administered is reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 95%, 96%, 97%, 98%, 99%, or greater than 99% relative to the subject prior to being administered the HIF-2 alpha RNAi agent or to a subject not receiving the HIF-2 alpha RNAi agent. The gene expression level and/or mRNA level in the subject may be reduced in a cell, group of cells, and/or tissue of the subject.

[0229] In some embodiments, the HIF-2 alpha protein level in a subject to whom a described HIF-2 alpha RNAi agent has been administered is reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or greater than 99% relative to the subject prior to being administered the HIF-2 alpha RNAi agent or to a subject not receiving the HIF-2 alpha RNAi agent. The protein level in the subject may be reduced in a cell, group of cells, tissue, blood, and/or other fluid of the subject.

[0230] A reduction in HIF-2 alpha mRNA levels and HIF-2 alpha protein levels can be assessed by any methods known in the art. As used herein, a reduction or decrease in HIF-2 alpha mRNA level and/or protein level are collectively referred to herein as a reduction or decrease in HIF-2 alpha or inhibiting or reducing the expression of HIF-2 alpha. The Examples set forth herein illustrate known methods for assessing inhibition of HIF-2 alpha gene expression.

[0231] In some embodiments, HIF-2 alpha RNAi agents may be used in the preparation of a pharmaceutical composition for use in the treatment of a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha gene expression. In some embodiments, the disease,

disorder, or symptom that is mediated at least in part by HIF-2 alpha gene expression is cancer, renal cancer, clear cell renal cell carcinoma, non-small cell lung cancer, astrocytoma (brain cancer), bladder cancer, breast cancer, chondrosarcoma, colorectal carcinoma, gastric carcinoma, glioblastoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, neuroblastoma, melanoma, multiple myeloma, ovarian cancer, rectal cancer, metastases, gingivitis, psoriasis, Kaposi's sarcoma-associated herpesvirus, preeclampsia, inflammation, chronic inflammation, neovascular diseases, or rheumatoid arthritis.

[0232] In some embodiments, methods of treating a subject are dependent on the body weight of the subject. In some embodiments, HIF-2 alpha RNAi agents may be administered at a dose of about 3 mg/kg to about 80 mg/kg of body weight of the subject. In other embodiments HIF-2 alpha RNAi agents may be administered at a dose of about 5 mg/kg to about 20 mg/kg of body weight of the subject.

[0233] In some embodiments, HIF-2 alpha RNAi agents may be administered in a split dose, meaning that two doses are given to a subject in a short (for example, less than 24 hour) time period. In some embodiments, about half of the desired daily amount is administered in an initial administration, and the remaining about half of the desired daily amount is administered approximately four hours after the initial administration.

[0234] In some embodiments, HIF-2 alpha RNAi agents may be administered once a week (weekly). In other embodiments, HIF-2 alpha RNAi agents may be administered biweekly (once every other week).

[0235] In some embodiments, the dose of the HIF-2 alpha RNAi agent administered is a fixed dose of 225 mg administered weekly. In some embodiments, the dose of the HIF-2 alpha RNAi agent administered is a fixed dose of 525 mg administered weekly. In some embodiments, the dose of the HIF-2 alpha RNAi agent administered is a fixed dose of 1,050 mg administered weekly. In some embodiments, the HIF-2 alpha RNAi agent is administered by intravenous infusion.

[0236] In some embodiments, HIF-2 alpha RNAi agents or compositions containing HIF-2 alpha RNAi agents may be used for the treatment of a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression. In some embodiments, the disease, disorder or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression is ccRCC.

Cells, Tissues, and Non-Human Organisms

[0237] Cells, tissues, and non-human organisms that include at least one of the HIF-2 alpha RNAi agents described herein is contemplated. The cell, tissue, or non-human organism is made by delivering the HIF-2 alpha RNAi agent to the cell, tissue, or non-human organism by any means available in the art. In some embodiments, the cell is a mammalian cell, including, but not limited to, a human cell.

[0238] The above provided embodiments and items are now illustrated with the following, non-limiting examples.

EXAMPLES

[0239] The following examples are not limiting and are intended to illustrate certain embodiments disclosed herein.

***Example 1.* Syntheses of HIF-2 alpha RNAi agents and Compositions Containing HIF-2 alpha RNAi agents.**

[0240] The following describes the general procedures for the syntheses of certain HIF-2 alpha RNAi agents, and conjugates thereof, that are illustrated in the non-limiting Examples set forth herein.

[0241] *Synthesis of RNAi Agents*. RNAi agents can be synthesized using methods generally known in the art. For the synthesis of the RNAi agents illustrated in the Examples set forth herein, the sense and antisense strands of the RNAi agents were synthesized according to phosphoramidite technology on solid phase used in oligonucleotide synthesis. Depending on the scale, a MerMade96E® (Bioautomation), a MerMade12® (Bioautomation), or an Oligopilot 100 (GE Healthcare) was used. Syntheses were performed on a solid support made of controlled pore glass (CPG, 500 Å or 600Å, obtained from Prime Synthesis, Aston, PA, USA) or polystyrene (obtained from Kinovate, Oceanside, CA, USA). All RNA and 2′-modified RNA phosphoramidites were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA), ChemGenes (Wilmington, MA, USA), or Hongene Biotech (Morrisville, NC, USA). Specifically, the following 2′-O-methyl phosphoramidites that were used include the following: (5′-O-dimethoxytrityl-N^6-(benzoyl)-2′-O-methyl-adenosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, 5′-O-dimethoxy-trityl-N^4-(acetyl)-2′-O-methyl-cytidine-3′-O-(2-cyanoethyl-N,N-diisopropyl-amino) phosphoramidite, (5′-O-dimethoxytrityl-N^2-(isobutyryl)-2′-O-methyl-guanosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, and 5′-O-dimethoxytrityl-2′-O-methyl-uridine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite. The 2′-deoxy-2′-fluoro-phosphoramidites and 2′-O-propargyl phosphoramidites carried the same protecting groups as the 2′-O-methyl phosphoramidites. 5′-dimethoxytrityl-2′-O-methyl-inosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidites were purchased from Glen Research (Virginia). The inverted abasic (3′-O-dimethoxytrityl-2′-deoxyribose-5′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidites were purchased from ChemGenes. The following UNA phosphoramidites that were used included the following: 5′-(4,4'-Dimethoxytrityl)-N6-(benzoyl)-2′,3′-seco-

adenosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5′-(4,4'-Dimethoxytrityl)-N-acetyl-2′,3′-seco-cytosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diiso-propyl)]-phosphoramidite, 5′-(4,4'-Dimethoxytrityl)-N-isobutyryl-2′,3′-seco-guanosine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, and 5′-(4,4'-Dimethoxy-trityl)-2′,3′-seco-uridine, 2′-benzoyl-3′-[(2-cyanoethyl)-(N,N- diiso-propyl)]-phosphoramidite. In order to introduce phosphorothioate linkages, a 100 mM solution of 3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, MA, USA) in anhydrous acetonitrile or a 200mM solution of xanthane hydride (TCI America, Portland, OR, USA) in pyridine was employed.

[0242] TFA aminolink phosphoramidites were also commercially purchased (ThermoFisher) to introduce the (NH2-C6) reactive group linkers. TFA aminolink phosphoramidite was dissolved in anhydrous acetonitrile (50 mM) and molecular sieves (3Å) were added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 10 min (RNA), 90 sec (2′ O-Me), and 60 sec (2′ F). Trialkyne-containing phosphoramidites were synthesized to introduce the respective (TriAlk#) linkers. When used in connection with the RNAi agents presented in certain Examples herein, trialkyne-containing phosphoramidites were dissolved in anhydrous dichloromethane or anhydrous acetonitrile (50 mM), while all other amidites were dissolved in anhydrous acetonitrile (50 mM), and molecular sieves (3Å) were added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 10 min (RNA), 90 sec (2′ O-Me), and 60 sec (2′ F).

[0243] For some RNAi agents, a linker, such as a C6-SS-C6 or a 6-SS-6 group, was introduced at the 3' terminal end of the sense strand. Pre-loaded resin was commercially acquired with the respective linker. Alternatively, for some sense strands, a dT resin was used and the respective linker was then added via standard phosphoramidite synthesis.

[0244] *Cleavage and deprotection of support bound oligomer.* After finalization of the solid phase synthesis, the dried solid support was treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% to 31% ammonium hydroxide solution (Aldrich) for 1.5 hours at 30 °C. The solution was evaporated and the solid residue was reconstituted in water (see below).

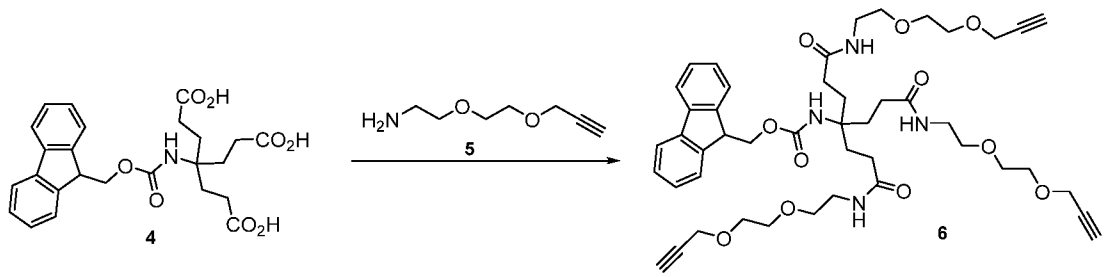
[0245] *Purification.* Crude oligomers were purified by anionic exchange HPLC using a TSKgel SuperQ-5PW 13µm column and Shimadzu LC-8 system. Buffer A was 20 mM Tris, 5

mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B was the same as buffer A with the addition of 1.5 M sodium chloride. UV traces at 260 nm were recorded. Appropriate fractions were pooled then run on size exclusion HPLC using a GE Healthcare XK 16/40 column packed with Sephadex G25 fine with a running buffer of 100mM ammonium bicarbonate, pH 6.7 and 20% Acetonitrile or filtered water.

[0246] *Annealing.* Complementary strands were mixed by combining equimolar RNA solutions (sense and antisense) in 1× PBS (Phosphate-Buffered Saline, 1×, Corning, Cellgro) to form the RNAi agents. Some RNAi agents were lyophilized and stored at −15 to −25 °C. Duplex concentration was determined by measuring the solution absorbance on a UV-Vis spectrometer in 1× PBS. The solution absorbance at 260 nm was then multiplied by a conversion factor and the dilution factor to determine the duplex concentration. The conversion factor used was either 0.037 mg/(mL·cm) or was calculated from an experimentally determined extinction coefficient.

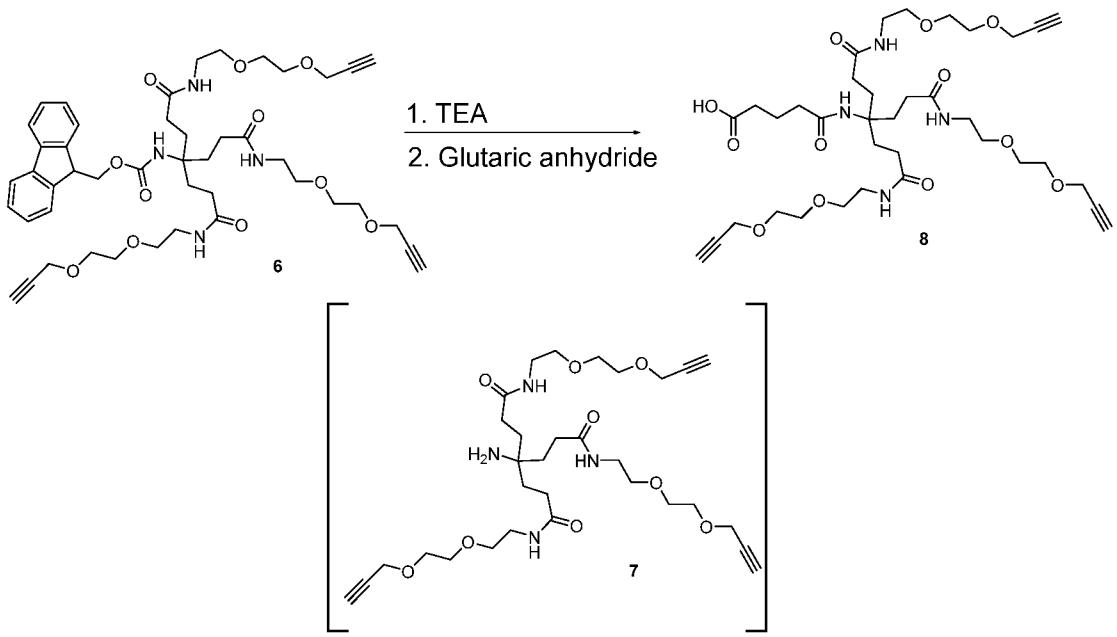
Synthesis of Linking Agent TriAlk 14

[0247] In some embodiments, linking agents such as TriAlk 14 may be attached to the RNAi agent in the form of phosphoramidites, by reacting a phosphoramidite comprising the trialkyne, or by synthesizing an RNAi agent comprising a reactive group such as a terminal amine and reacting the RNAi agent with a trialkyne moiety comprising an activated ester after the RNAi agent has been cleaved from the resin. The following procedures provide a method for synthesizing an activated ester version of TriAlk 14 (compound 22) or a phosphoramidite version of TriAlk 14 (compound 14.)



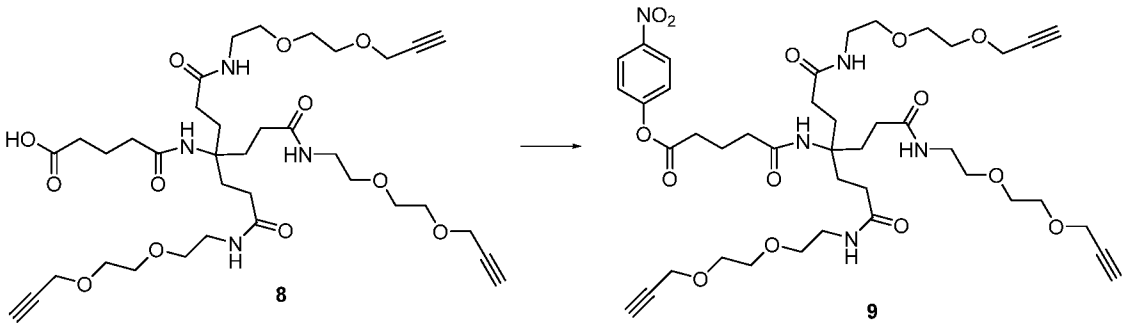
[0248] To a 3-L jacketed reactor was added 500 mL DCM and **4** (75.0 g, 0.16 mol). The internal temperature of the reaction was cooled to 0 °C and TBTU (170.0 g, 0.53 mol) was added. The suspension was then treated with the amine **5** (75.5 g, 0.53 mol) dropwise keeping the internal temperature less than 5 °C. The reaction was then treated with DIPEA (72.3 g, 0.56 mol) slowly, keeping the internal temperature less than 5 °C. After the addition

was complete, the reaction was warmed up to 23 °C over 1 hour, and allowed to stir for 3 hours. A 10% kicker charge of all three reagents were added and allowed to stir an additional 3 hours. The reaction was deemed complete when <1% of **4** remained. The reaction mixture was washed with saturated ammonium chloride solution (2 x 500 mL) and once with saturated sodium bicarbonate solution (500 mL). The organic layer was then dried over sodium sulfate and concentrated to an oil. The mass of the crude oil was 188 g which contained 72% **6** by QNMR. The crude oil was carried to the next step. Calculated mass for $C_{46}H_{60}N_4O_{11}$ = 845.0 m/z. Found [M+H] = 846.0.



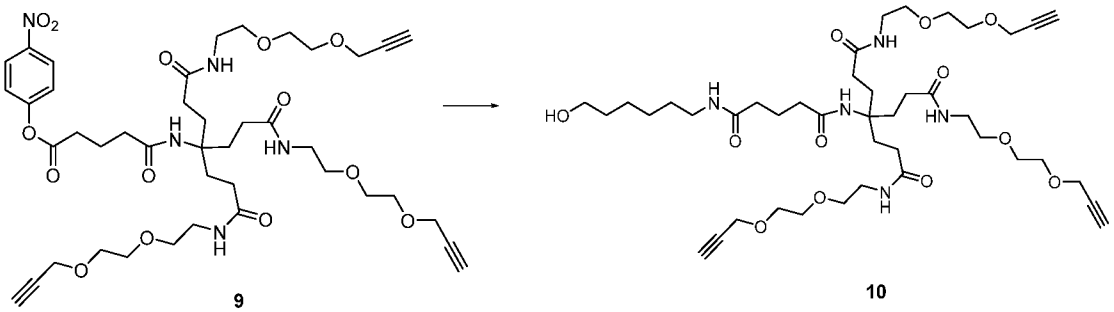
[0249] The 121.2 g of crude oil containing 72 wt% compound **6** (86.0 g, 0.10 mol) was dissolved in DMF (344 mL) and treated with TEA (86 mL, 20 v/v%), keeping the internal temperature below 23 °C. The formation of dibenzofulvene (DBF) relative to the consumption of Fmoc-amine **6** was monitored via HPLC method 1 (Figure 2) and the reaction was complete within 10 hours. To the solution was added glutaric anhydride (12.8 g, 0.11 mol) and the intermediate amine **7** was converted to compound **8** within 2 hours. Upon completion, the DMF and TEA were removed at 30 °C under reduced pressure resulting in 100 g of a crude oil. Due to the high solubility of compound **7** in water, an aqueous workup could not be used, and chromatography is the only way to remove DBF, TMU, and glutaric anhydride. The crude oil (75 g) was purified on a Teledyne ISCO Combi-flash® purification system in three portions. The crude oil (25 g) was loaded onto a 330 g silica column and

eluted from 0 – 20% methanol/DCM over 30 minutes resulting in 42 g of compound **8** (54% yield over 3 steps). Calculated mass for $C_{36}H_{55}N_4O_{12}$ = 736.4 m/z. Found [M+H] = 737.0.



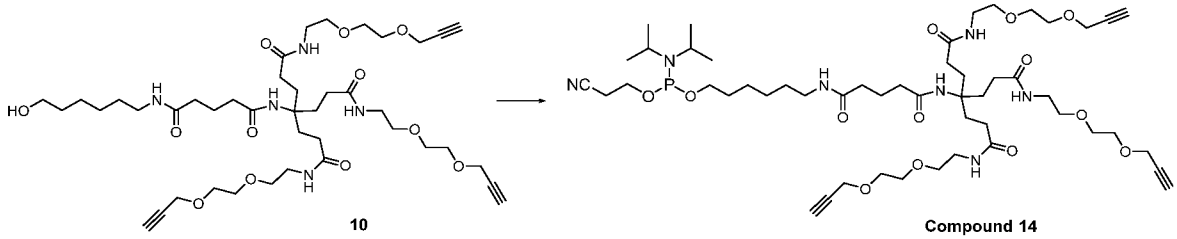
Compound 22

[0250] Compound **8** (42.0 g, 0.057 mol) was co-stripped with 10 volumes of acetonitrile prior to use to remove any residual methanol from chromatography solvents. The oil was redissolved in DMF (210 mL) and cooled to 0 °C. The solution was treated with 4-nitrophenol (8.7 g, 0.063 moL) followed by EDC-hydrochloride (12.0 g, 0.063 mol) and found to reach completion within 10 hours. The solution was cooled to 0 °C and 10 volumes ethyl acetate was added followed by 10 volumes saturated ammonium chloride solution, keeping the internal temperature below 15 °C. The layers were allowed to separate and the ethyl acetate layer was washed with brine. The combined aqueous layers were extracted twice with 5 volumes ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The crude oil (55 g) was purified on a Teledyne ISCO Combi-Flash® purification system in three portions. The crude oil (25 g) was loaded onto a 330 g silica column and eluted from 0 – 10% methanol/DCM over 30 minutes resulting in 22 g of pure **9 (Compound 22)** (50% yield). Calculated mass for $C_{42}H_{59}N_5O_{14}$ = 857.4 m/z. Found [M+H] = 858.0.



[0251] A solution of ester **9** (49.0 g, 57.1 mmol) and 6-amino-1-hexanol (7.36 g, 6.28 mmol) in dichloromethane (3 volumes) was treated with triethylamine (11.56g, 111.4 mmol)

dropwise. The reaction was monitored by observing the disappearance of compound 9 on HPLC Method 1 and was found to be complete in 10 minutes. The crude reaction mixture was diluted with 5 volumes dichloromethane and washed with saturated ammonium chloride (5 volumes) and brine (5 volumes). The organic layer was dried over sodium sulfate and concentrated to an oil. The crude oil was purified on a Teledyne ISCO Combi-flash® purification system using a 330 g silica column. The 4-nitrophenol was eluted with 100% ethyl acetate and **10** was flushed from the column using 20% methanol/DCM resulting in a colorless oil (39 g, 81% yield). Calculated mass for $C_{42}H_{69}N_5O_{12}$ = 836.0 m/z. Found [M+H] = 837.0.

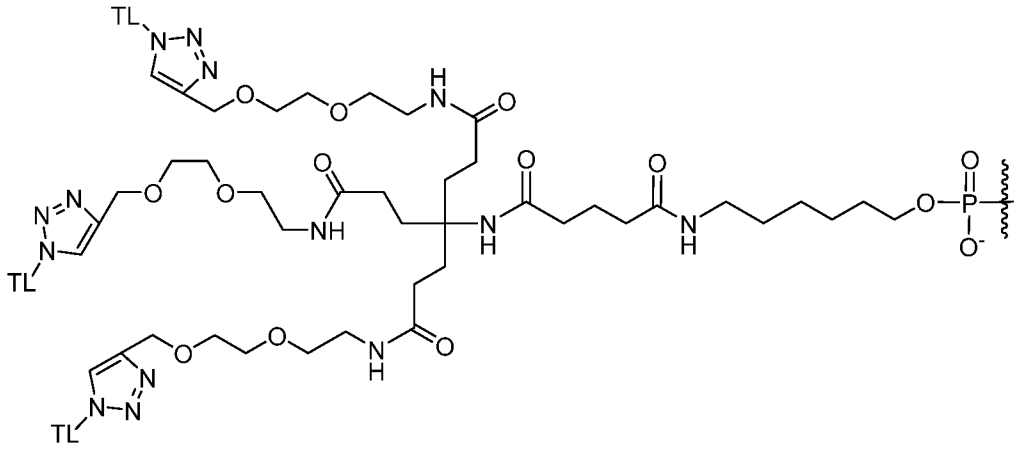


[0252] Alcohol **10** was co-stripped twice with 10 volumes of acetonitrile to remove any residual methanol from chromatography solvents and once more with dry dichloromethane (KF < 60 ppm) to remove trace water. The alcohol **10** (2.30 g, 2.8 mmol) was dissolved in 5 volumes dry dichloromethane (KF < 50 ppm) and treated with diisopropylammonium tetrazolide (188 mg, 1.1 mmol). The solution was cooled to 0 °C and treated with 2-cyanoethyl N,N,N',N'-tetraisopropylphosphoramidite (1.00 g, 3.3 mmol) dropwise. The solution was removed from ice-bath and stirred at 20 °C. The reaction was found to be complete within 3 – 6 hours. The reaction mixture was cooled to 0 °C and treated with 10 volumes of a 1:1 solution of saturated ammonium bicarbonate/brine and then warmed to ambient over 1 minute and allowed to stir an additional 3 minutes at 20 °C. The biphasic mixture was transferred to a separatory funnel and 10 volumes of dichloromethane was added. The organic layer was separated, and washed with 10 volumes of saturated sodium bicarbonate solution to hydrolyze unreacted bis-phosphorous reagent. The organic layer was dried over sodium sulfate and concentrated to an oil resulting in 3.08 g of 94 wt% Compound 14. Calculated mass for $C_{51}H_{86}N_7O_{13}P$ = 1035.6 m/z. Found [M+H] = 1036.

[0253] *Post-Synthetic Conjugation of Trialkyne scaffold.* Either prior to or after annealing, the 5′ or 3′ amine functionalized sense strand of an RNAi agent can be conjugated to a trialkyne scaffold. The following describes the conjugation of trialkyne scaffold to the annealed duplex:

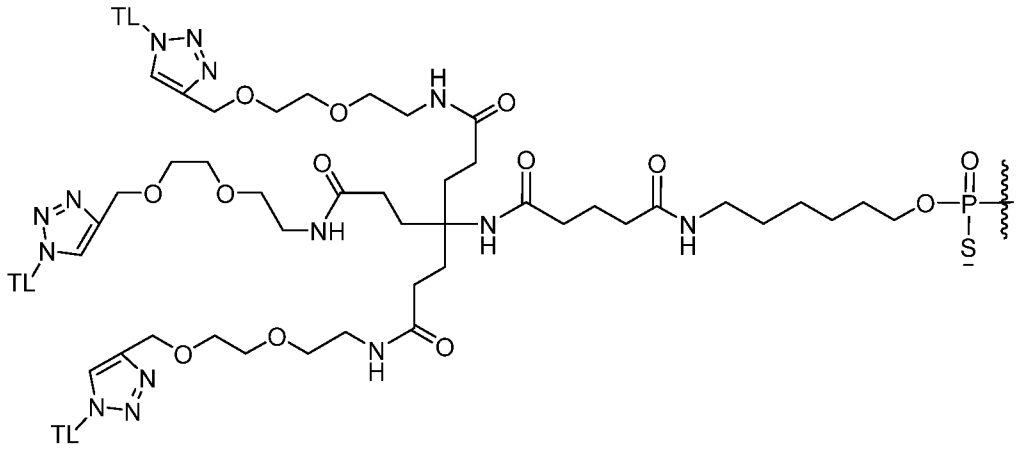
Amine functionalized duplex was dissolved in 90% DMSO/10% H_2O, at ~50-70 mg/mL. 40 eq triethylamine was added, followed by 3 eq trialkyne-PNP. Once complete, the conjugate was precipitated twice in a solvent system of 1x phosphate buffered saline/acetonitrile (1:14 ratio), and dried.

[0254] *Conjugation of Targeting Ligands to the HIF-2 RNAi Agents.* Either prior to or after annealing and prior to or after conjugation of a PK enhancer, one or more targeting ligands can be linked to the HIF-2 RNAi agents disclosed herein. The following describes the general conjugation process used to link integrin targeting ligands to an alkyne-functionalized linker (for example, (TriAlk) or a 2'-O-propargyl group on an internal nucleotide). The procedure describes the addition of three targeting ligands to a tridentate targeting group scaffold. The same procedure may be used to link targeting ligands to internal nucleotides, though the number of equivalents of targeting ligands may be adjusted in view of the number of targeting ligands to be added: Stock solutions of 0.5M Tris(3-hydroxypropyltriazolylmethyl)amine (THPTA), 0.5M of Cu(II) sulfate pentahydrate ($Cu(II)SO_4 \cdot 5\ H_2O$) and 2M solution of sodium ascorbate were prepared in deionized water. A 75 mg/mL solution in DMSO of the desired integrin ligand was made. In a vial containing the sense strand (75mg/mL in deionized water), integrin ligands were added to the reaction (2 eq/alkyne) with stirring. Triethylamine (40eq/sense strand) was added to the reaction vial. In a separate vial, 5 parts 0.5M THPTA was mixed with 1 part 0.5M $Cu(II)SO_4 \cdot 5\ H_2O$, vortexed, and incubated at room temp for 5 min. After 5 min, THPTA/Cu solution (0.5 eq Cu/alkyne) was added to the reaction vial. Immediately afterwards, 2M ascorbate (5eq/Cu) was added to the reaction vial. Once the reaction was complete (typically complete in 0.5-1h), the reaction was immediately purified by non-denaturing anion exchange chromatography. Unless otherwise specified, all constructs described in the examples below including a tridentate targeting group include a group having the structure TriAlk14:



or

TriAlk14s:



, wherein

TL comprises a targeting ligand and ≈ indicates the point of connection to the RNAi agent.

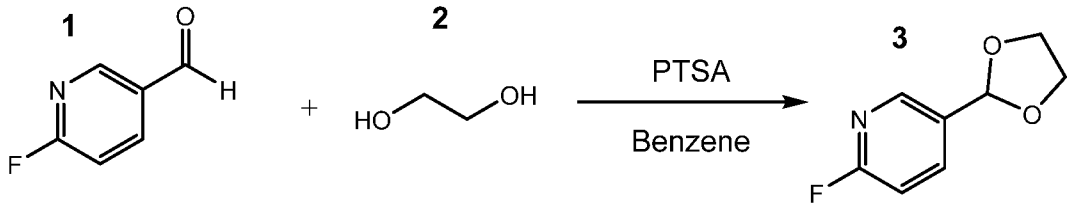
[0255] *Conjugation of PK Enhancers to the HIF-2 RNAi Agents.* Either prior to or after annealing and prior to or after conjugation of one or more targeting ligands, one or more PK enhancers can be linked to the HIF-2 alpha RNAi agents disclosed herein. The following describes the general conjugation process used to link PK enhancers to the constructs set forth in the Examples depicted herein. The following describes the general process used to link the maleimide-functionalized PK enhancer to the (C6-SS-C6) or (6-SS-6) functionalized sense strand of a HIF-2 alpha RNAi agent by undertaking a dithiothreitol reduction of disulfide followed by a thiol-Michael Addition of the respective PK enhancer: In a vial, functionalized sense strand was dissolved at 75mg/mL in 0.1M Hepes pH 8.5 buffer, and 25 eq of dithiothreitol was added. Once the reaction was complete (typically complete in 0.5-1h), the conjugate was precipitated three times in a solvent system of 1x phosphate buffered

saline/acetonitrile (1:40 ratio), and dried. A 75 mg/mL solution of maleimide functionalized PK enhancer in DMSO was then made. The disulfide-reduced (3′ C6-SH, 5′ HS-C6, or 3’ 6-SH functionalized) sense strand was dissolved 100mg/mL in deionized water, and three equivalents of maleimide-functionalized PK enhancer was added. Once the reaction was complete (typically complete in 1h-3h), the conjugate was precipitated in a solvent system of 1x phosphate buffered saline/acetonitrile (1:40 ratio), and dried.

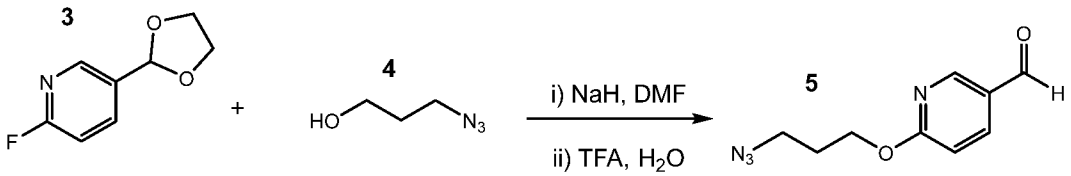
Methods of Making Targeting Ligands

[0256] Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined as follows: h or hr = hour(s); min = minute(s); mol = mole(s); mmol = millimole(s); M = molar; μM = micromolar; g = gram(s); μg = microgram(s); rt or RT = room temperature; L= liter(s); mL = milliliter(s); wt = weight; Et_2O = diethyl ether; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; EtOAc = ethyl acetate; Et_3N or TEA = triethylamine; *i*–Pr_2NEt or DIPEA or DIEA = diisopropylethylamine; CH_2Cl_2 or DCM = methylene chloride; $CHCl_3$ = chloroform; $CDCl_3$ = deuterated chloroform; CCl_4 = carbon tetrachloride; MeOH = methanol; EtOH = ethanol; DMF = dimethylformamide; BOC = *t*–butoxycarbonyl; CBZ = benzyloxycarbonyl; TBS = *t*–butyldimethylsilyl; TBSCl or TBDMSCl = *t*–butyldimethylsilyl chloride; TFA = trifluoroacetic acid; DMAP = 4–dimethylaminopyridine; NaN_3 = sodium azide; Na_2SO_4 = sodium sulfate; $NaHCO_3$ = sodium bicarbonate; NaOH = sodium hydroxide; $MgSO_4$ = magnesium sulfate; K_2CO_3 = potassium carbonate; KOH = potassium hydroxide; NH_4OH = ammonium hydroxide; NH_4Cl = ammonium chloride; SiO_2 = silica; Pd–C = palladium on carbon; HCl = hydrogen chloride or hydrochloric acid; NMM = *N*-methylmorpholine; H_2 = hydrogen gas; KF = potassium fluoride; EDC-HCl = N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride; MTBE = methyl-*tert*-butyl ether; MeOH = methanol; Ar = argon; N_2 = nitrogen; SiO_2 = silica; R_T = retention time; PTSA = *para*-toluenesulfonic acid; PPTS = pyridinium *para*-toluenesulfonate.

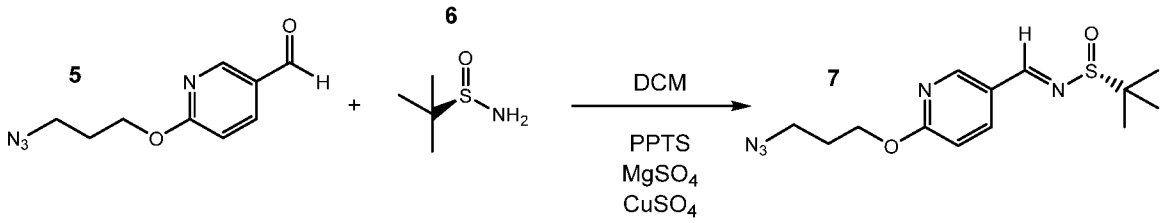
Synthesis of Structure 1c ((S)-3-(6-((1-azido-15-oxo-3,6,9,12-tetraoxa-16-azanonadecan-19-yl)oxy)pyridin-3-yl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).



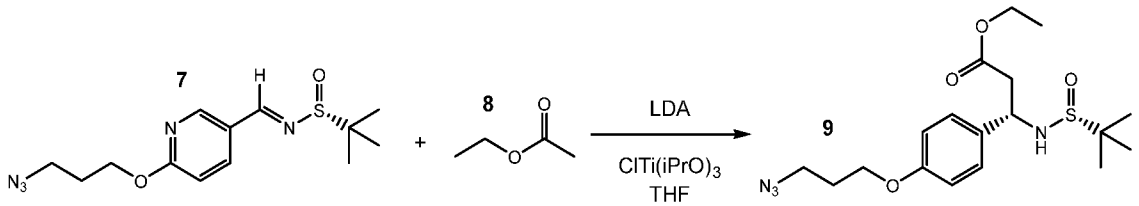
[0257] A mixture containing compound 1 (1.03 g, 8.23 mmol), compound 2 (0.92 g 14.8 mol), and PTSA hydrate (156 mg, 0.82 mmol) in benzene (25 mL) was refluxed in a Dean Stark apparatus overnight. The following morning, the reaction mixture was poured into saturated sodium bicarbonate, and ethyl acetate was subsequently added. The organic phase was separated, filtered over sodium sulfate, and concentrated to afford compound 3 in 95% yield, which was subsequently used without further purification.



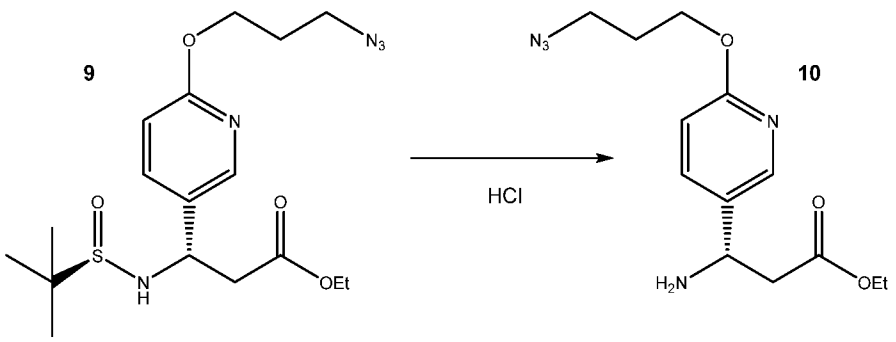
[0258] To a solution containing compound 4 (5.39 g, 53.3 mmol) and 3Å molecular sieves in DMF (100 mL) was added sodium hydride (60 wt%, 2.13 g, 53.3 mmol), and the reaction was agitated for 1 hour. A solution of compound 3 (7.52 g, 7.52 g) in DMF (20 mL) was subsequently added and the suspension was heated at 80 °C overnight. Upon completion, the suspension was filtered over a cotton plug and concentrated under reduced pressure. The residue was partitioned between diethyl ether and water, and the organic phase was separated, filtered over sodium sulfate, and concentrated under reduced pressure. The residue was treated with 20 ml of 10% H_2O in TFA and stirred for 30 minutes. Upon completion, the solution was chilled to 0 °C and the pH was adjusted to 11 with 6M NaOH, upon which the product precipitated as an oil. Compound 5 was extracted three times from the oily suspension with diethyl ether. The organic phases were combined, filtered over sodium sulfate, and concentrated. Compound 5 was then isolated in 26% yield by separation on silica eluting a gradient of ethyl acetate in hexanes.



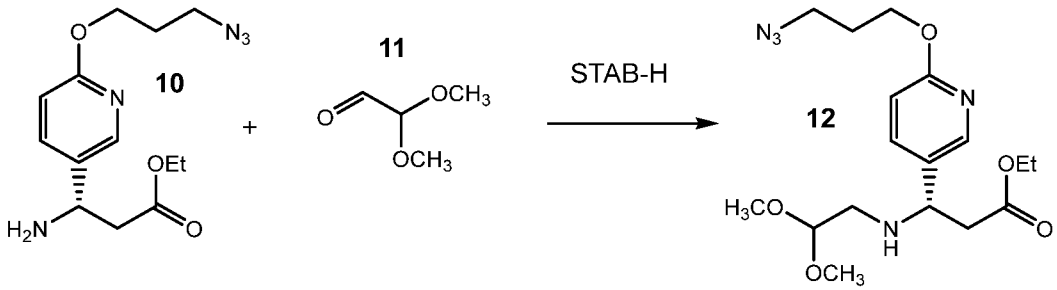
[0259] A mixture containing compound 5 (2.29 g, 9.94 mmol), compound 6 (4.82 g, 39.8 mmol), PPTS (125 mg, 0.50 mmol), magnesium sulfate (3 g, 24.9 mmol), copper sulfate (3.97 g, 24.9 mmol), and 3 angstrom molecular sieves in DCM (22 mL) was heated to reflux overnight. Upon completion, the mixture was filtered and concentrated under reduced pressure. Compound 7 was then isolated in 76% yield by separation on silica eluting a gradient of ethyl acetate in hexanes.



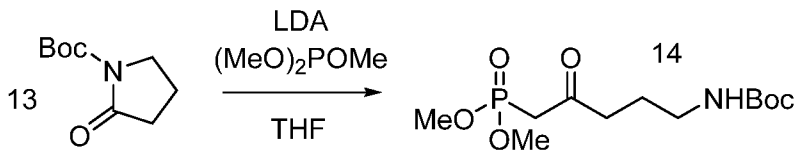
[0260] A flame dried flask was charged with THF (40 mL) and diisopropylamine (2.29 g, 22.6 mmol). It was cooled to -20 °C and n-BuLi (2.5 M, 8.64 mL, 21.6 mmol) was added via cannula. The solution was stirred for 10 min at -20 °C then cooled to -78 °C. Compound 8 (2.02 mL, 20.6 mmol) was added dropwise with vigorous stirring. After addition, the solution was stirred for 30 min at -78 °C. Next, $ClTi(iPrO)_3$ (11.26 g, 43.2 mmol) as a solution in THF (10 mL) was added via addition funnel over approximately 10 minutes with vigorous stirring. The reaction was stirred for 30 minutes at -78 °C. Finally, compound 7 (2.29 g. 6.86 mmol) was added dropwise as a suspension in THF and stirred at -78 °C for 1.25 hours until the reaction was complete. To the reaction at -78 °C was added saturated aqueous ammonium chloride. The reaction was then removed from cooling and the aqueous phase was allowed to gradually thaw and quench (yellow orange color disappears). The mixture was portioned between EtOAc and saturated aqueous ammonium chloride. The organic phase was separated and aqueous phase was extracted two times with EtOAc. The organic phases were combined and dried over brine, then over sodium sulfate, and then filtered and concentrated. The residue was purified over silica eluting a gradient of ethyl acetate in hexanes. Compound 9 was obtained in 75% yield as single diastereomer after purification.



[0261] Compound 9 (1.28 g, 3.21 mmol) in MeOH (3.2 mL) was treated with HCl in dioxane (4M, 3.2 mL, 12.9 mmol) and stirred at room temperature for 30 minutes. Upon completion, the reaction mixture was diluted with water and washed with diethyl ether. Subsequently, the pH was adjusted to 11 using 2 N aqueous NaOH and the product was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated, yielding compound 10 in 92% yield, which was subsequently used without further purification.

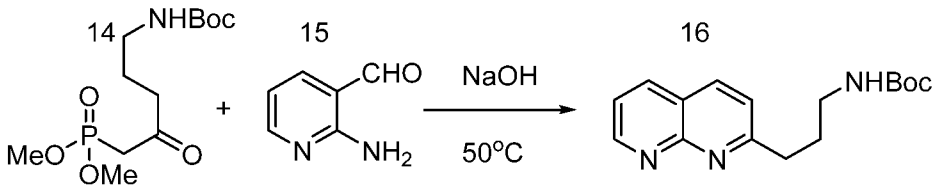


[0262] To a mixture of compound 10 (0.78 g, 2.67 mmol) and compound 11 (0.60 g, 3.46 mmol) in THF (6 mL) at 15 °C was added STAB-H (1.29g, 6.12 mmol) portion-wise as solid. After the addition, cooling was removed and the mixture was stirred for approximately 2.5 hours to completion. The reaction was quenched by addition of saturated aqueous sodium bicarbonate and pH was brought to 9. The product was extracted three times with EtOAc, the organic phases were combined, dried with brine, then filtered over sodium sulfate and concentrated. Compound 12 was isolated in 85% yield by separation on silica eluting a gradient of ethyl acetate in hexanes.

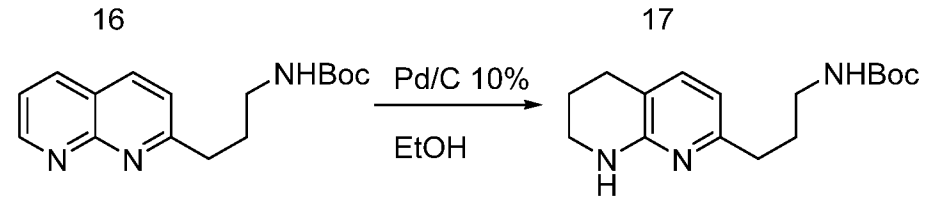


[0263] To DIPEA (7.53 mL, 53.75 mmol) in THF (35 mL) was added n-BuLi (2.5 M, 19.9 mL, 49.8 mmol) via oven dried gastight syringe over 2 minutes at -10 °C. The mixture was stirred for 10 minutes at -10 °C, then cooled to -60 °C and a solution of dimethyl

methylphosphonate (6.42 g, 51.8 mmol) in THF (8 mL) was added dropwise over 5-10 minutes. After aging at -60 °C for about 1 hour, compound 13 (7.37 g. 39.82 mmol) was added as solution in THF (15 mL) dropwise over 5 minutes at -60 °C. The reaction mixture was stirred at -60 °C for 1 hour and then -41 °C for about 1.5 hours. The reaction was quenched by addition of 2.6 equivalents of H_2SO_4 (2.0 M) and extracted three times with ethyl acetate (~50 mL). The organic phases were combined and dried with brine, filtered over sodium sulfate, and concentrated briefly to determine crude weight and take sample for NMR. Upon determination of dry weight, compound 14 was dissolved in MeOH for use in next reaction without further purification. Calculated to be 75.83% yield. Crude wt/wt% 76.3% by NMR. **^{1}H NMR:** 400 MHz $CDCl_3$ δ 4.75 (s, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.10 - 3.14 (m, 2 H), 3.04 - 3.09 (m, 2 H), 2.68 (t, 2 H), 1.82-1.75 (m, 2 H), 1.44 (s, 9 H).

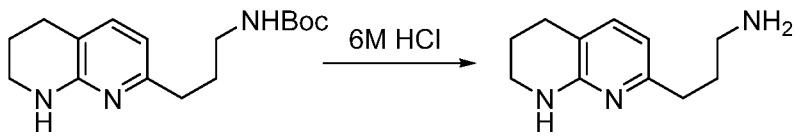


[0264] To compound 14 (9.33g by weight from NMR of ~12g crude, 30.16 mmol) in MeOH (40 mL), was added solution of NaOH (1.45 g, 36.2 mmol) in water (1.5 mL). The mixture was heated to 50 °C and compound 15 (2.76 g, 22.62 mmol) was added. After stirring for 30 minutes, a second portion of compound 15 (736 mg, 6.03 mmol) was added, and the reaction mixture was stirred overnight at 50 °C. The reaction mixture was then concentrated to an oil and partitioned between 2 volumes EtOAc and 1 volume H_2O. The organic phase was separated and washed with 1 volume of water. The aqueous washes were combined and back extracted (2x, 1 vol) with EtOAc. The combined organic phase was dried over sodium sulfate, filtered, and concentrated. The crude was dried onto approximately 20g of silica compound 16 was isolated in 69% yield by separation on silica eluting a gradient of ethyl acetate in hexanes containing 1% triethylamine. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 9.09 (dd, 1 H), 8.17 (dd, 1 H), 8.12 (d, 1 H), 7.46 (dd, 1 H), 7.41 (d, 1 H), 4.78 (s, 1 H), 3.24 (q, 2 H), 3.10 (t, 2 H), 2.12 (quin, 2 H), 1.43 (s, 9 H).



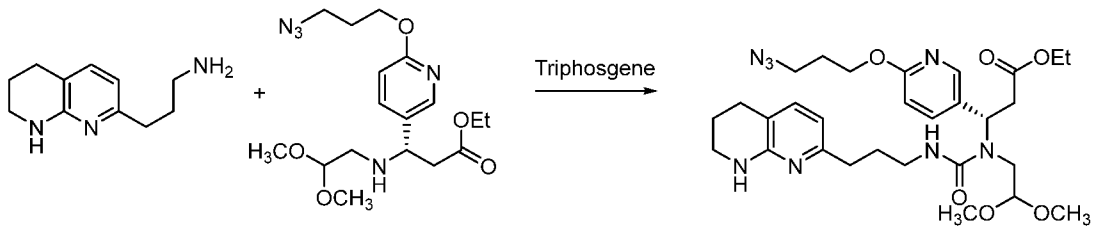
[0265] To a solution of compound 16 (5.98 g, 20.8 mmol) in EtOH (50 mL) was charged with palladium (10% on Carbon, 2.22 g, 2.08 mmol) and hydrogen at 1 atmosphere. The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was filtered over Celite® and concentrated. Compound 17 was isolated in 79% yield by separation on silica eluting a gradient of ethyl acetate in hexanes containing 1% triethylamine. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 7.05 (d, 1 H), 6.34 (d, 1 H), 5.48 (s, 1 H), 4.81 (s, 1 H), 3.36 - 3.43 (m, 2 H), 3.16 (q, 2 H), 2.68 (t, 2 H), 2.59 (t, 2 H), 1.90 (dt, 2 H), 1.83 (quin, 2 H), 1.44 (s, 9 H).

17 18



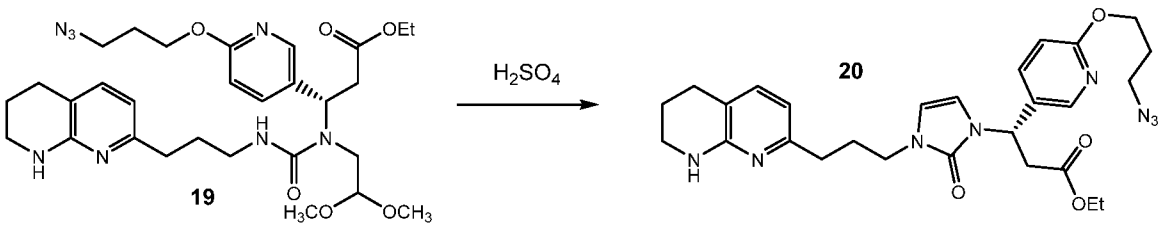
[0266] Compound 17 (4.81 g, 16.53 mmol) was dissolved in aqueous 6 M HCl (16.4 mL) and heated at 42 °C for 2 hours. An additional portion of 6 M HCl (2.8 mL) was then added and the reaction mixture was stirred for an additional 2 hours. To the reaction was added sodium chloride followed by aqueous 2 N NaOH until the product precipitated as an oil (pH was greater than 12). The mixture was extracted three times with 2-Butanol. The combined organic phase was dried over sodium sulfate, filtered and concentrated. Compound 18 was obtained in 85% yield and subsequently used without further purification. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 7.06 (d, 1 H), 6.35 (d, 1 H), 4.83 (s, 1 H), 3.35 - 3.46 (m, 2 H), 2.75-2.67 (m, 4 H), 2.58 (t, 2 H), 1.88 - 1.95 (m, 2 H), 1.84-1.76 (m, 4 H).

18 12 19

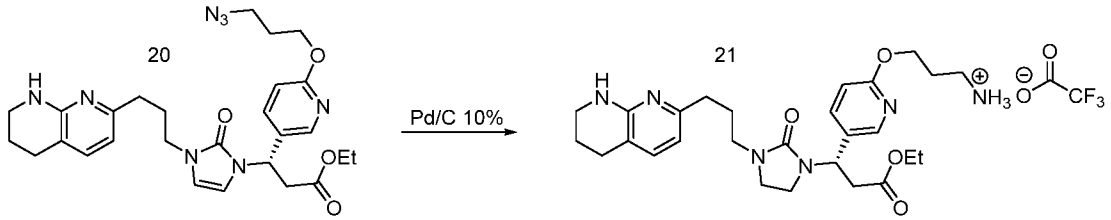


[0267] To a solution of triphosgene (85 mg, 0.28 mmol) in THF (0.9 mL) in a flame dried flask at -10 °C was added dropwise a solution of compound 18 (236 mg, 0.62 mmol) and TEA (0.134 mL, 0.96 mmol) in THF (0.5 mL). The reaction mixture was warmed to room temperature. After TLC indicated a complete reaction, additional TEA (0.134 mL) was added followed by addition of compound 12 (166 mg, 0.87 mmol) as a solid. The heterogenous mixture was heated at 50 °C for 2 hours with vigorous stirring. Upon completion, the reaction mixture was quenched with 1 volume of water and extracted three times with EtOAc. The combined organic

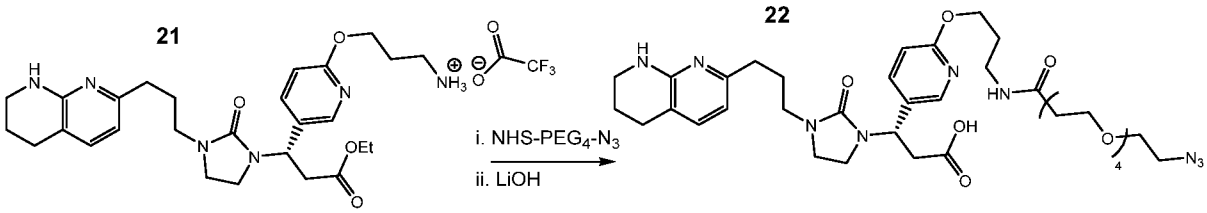
phase was dried with brine, filtered over sodium sulfate and concentrated. Compound 19 was obtained assuming 100% yield and subsequently used without further purification.



[0268] To crude compound 19 (400 mg, 0.62 mmol assumed) dissolved in THF (37 mL) was added H_2SO_4(2M, 0.6 mL) and the mixture was stirred at room temperature overnight. The following morning, an additional portion of H_2SO_4 (0.65 equivalents) was added. Four hours later the reaction was complete. The reaction mixture was diluted with ethyl acetate. The organic phase was separated and the aqueous phase was back extracted once with ethyl acetate. The combined organic phase was filtered over sodium sulfate and concentrated. Compound 20 was isolated in 75% yield by separation over silica eluting a gradient of MeOH in DCM.



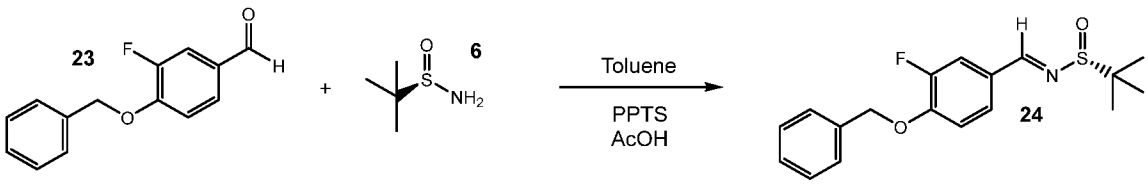
[0269] To a suspension of compound 20 (251 mg, 0.47 mmol) and Pd/C (10 wt%, 100mg, 0.094 mmol) in ethanol (9 mL) was charged H_2 to 1 atmosphere and stirred at 35 °C overnight. Upon completion, palladium was removed by filtration over Celite®. Compound 21 was isolated in 20 % yield as TFA salt by reverse phase HPLC using a C_{18} 5u 19x250 mm BEH column (Waters Corp.) eluting a gradient of acetonitrile in H_2O containing 1% TFA.



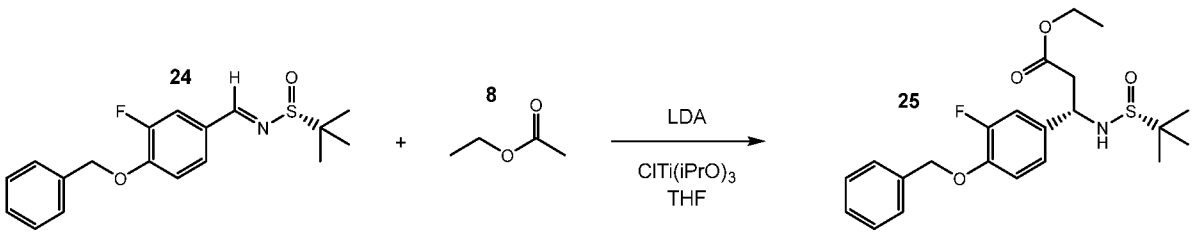
[0270] To a solution of compound 21 (61 mg, 0.097 mmol) in DCM (250uL) was added TEA (8 uL, 0.24 mmol) followed by addition of NHS-PEG_4-N_3 (41.4 mg, 0.11 mmol) as a solution in DCM (275 µL). The reaction mixture was stirred for 15 minutes and checked by LC-MS, which showed that the reaction was complete. All volatiles were removed, and the residue was dissolved in EtOH (0.4 mL) and water (0.4 mL). LiOH (11.2 mg, 0.47 mmol) was added and

the reaction mixture was heated at 40 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. Compound 22 (Structure 1c) was isolated in 42% yield by reverse phase HPLC using a C_{18} 5u 19x250 mm BEH column (Waters Corp.) eluting a gradient of acetonitrile in H_2O containing 1% TFA.

Synthesis of Structure 2c ((S)-3-(4-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

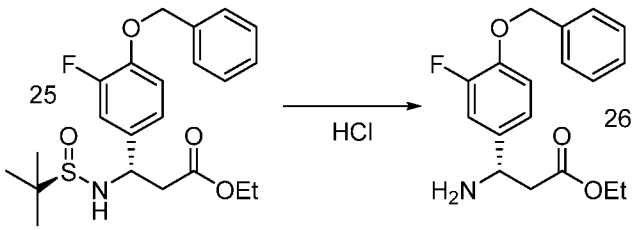


[0271] To a solution of compound 23 (10 g, 43.4 mmol) in toluene (80 mL) was added compound 6 (21.1g, 0.17 mol), PPTS (0.55g, 2.2 mmol), and then acetic acid (1.24 mL, 21.7 mmol)). The reaction vessel was equipped with a Dean Stark trap and then heated to reflux overnight. Upon completion the reaction mixture was concentrated and dried onto 60 grams of silica and purified over SiO_2 with a gradient of ethyl acetate in hexanes, yielding compound 24 in 66% yield. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 8.47 (s, 1 H), 7.68 (d, 1 H), 7.31 - 7.56 (m, 6 H), 6.98 - 7.16 (m, 1 H), 5.23 (s, 2 H), 1.26 (s, 9 H).

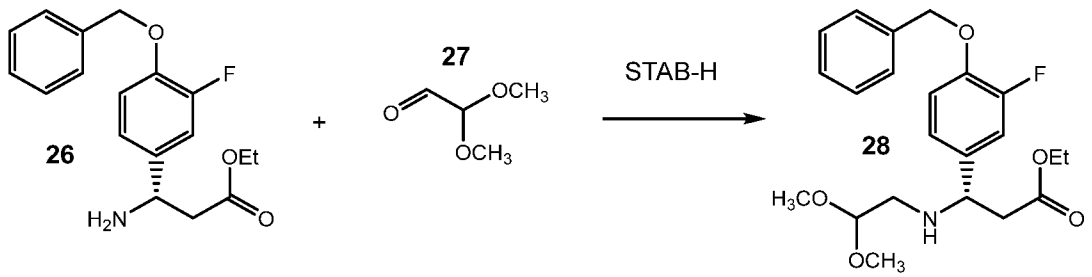


[0272] A flame dried flask was charged with THF (190 mL) and DIPEA (9.07 g, 89.7 mmol), cooled to -20 °C, and then charged with n-BuLi (2.5M, 34.2 mL, 85.6 mmol) via cannula. The solution was stirred for 10 min at -20 °C then cooled to -78 °C. Compound 8 (8 mL, 81.5 mmol) was added dropwise with vigorous stirring. After addition, stirred for 30 min at -78 °C. Next, $ClTi(iPrO)_3$ (44.6g, 0.171 mol) as solution in THF (40 mL) was added via addition funnel over 10 minutes. The reaction was stirred for 30 minutes at -78 °C. Finally, compound 24 (9.06g, 27.2 mmol) was added dropwise as a suspension in THF (20 mL) and stirred at -78 °C for 1.25 hour until the reaction was complete. To the reaction at -78 °C was added saturated aqueous ammonium chloride. The reaction was then removed from cooling and the aqueous

phase was allowed to gradually thaw and quench (yellow orange color disappears). The mixture was partitioned between EtOAc and saturated aqueous ammonium chloride. The organic phase was separated and the aqueous phase was washed two times with EtOAc. The organic phases were combined and dried over brine, then over sodium sulfate, filtered, and concentrated. Compound 25 was obtained in 70% yield as a single diastereomer by separation on silica eluting a gradient of ethyl acetate in hexanes. **^{1}H NMR**:400 MHz $CDCl_3$ δ 7.31 - 7.48 (m, 5 H), 7.09 (dd, 1 H), 6.89 - 7.04 (m, 2 H), 5.13 (s, 2 H), 4.59 - 4.76 (m, 2 H), 4.13 (q, 2 H), 2.81 (dd, 2 H), 1.21 - 1.25 (m, 12 H).

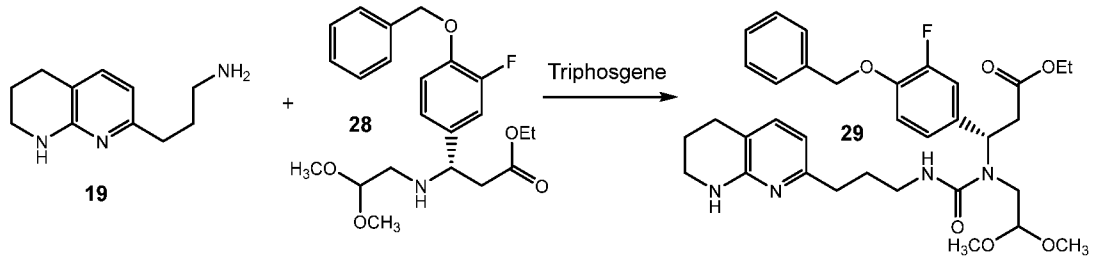


[0273] To compound 25 (8.07g, 19.1 mmol) was added aqueous HCl (6M, 20.7 mL, 0.124 mol) followed by MeOH (60 mL). THF was added until homogenous solution was obtained and the reaction mixture was stirred for 6 hours at room temperature. The reaction mixture was basified to a of pH 10 with aqueous 2 N NaOH and then was extracted three times with EtOAc. The combined organic phases were dried with brine, filtered over sodium sulfate, and concentrated. Compound 26 was obtained in 95% yield and was subsequently used without further purification. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 7.28 - 7.46 (m, 6 H), 7.18 (d, 1 H), 6.99 (t, 1 H), 5.11 (s, 2 H), 4.57 (t, 1 H), 4.09 (q, 2 H), 2.97 - 3.09 (m, 1 H), 2.81 - 2.93 (m, 1 H), 1.18 (t, 3 H).

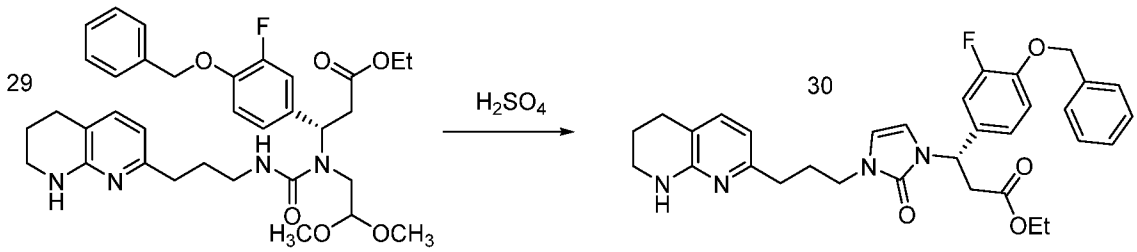


[0274] To a mixture of compound 26 (5.76g, 18.2 mmol) and compound 27 (4.09g, 23.6 mmol) in THF (40 mL) at 0 °C was added STAB-H (8.85g, 41.8 mmol) portionwise as solid. After final addition cooling was removed and the mixture was stirred for approximately 2.5 hours to completion. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate. The mixture was extracted three times with EtOAc. The combined organic phases were dried with brine, filtered over sodium sulfate, and concentrated. Compound 28 was

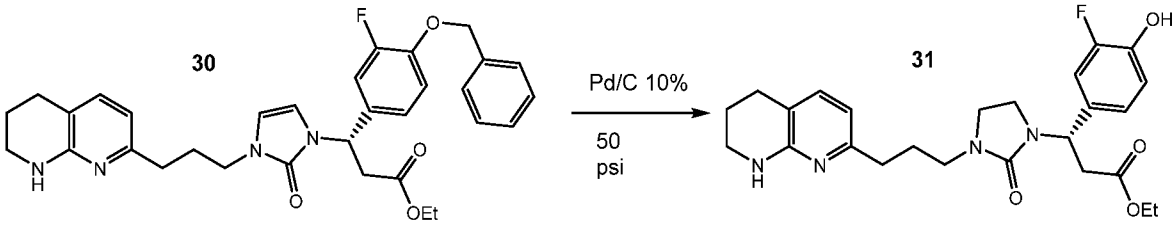
isolated in 73% yield by separation on silica eluting a gradient of ethyl acetate in hexanes. **^{1}H NMR**: 400 MHz $CDCl_3$ δ 7.30 - 7.49 (m, 5 H), 7.11 (dd, 1 H), 6.88 - 7.02 (m, 2 H), 5.13 (s, 2 H), 4.40 (t, 1 H), 4.10 (q, 2 H), 4.00 (dd, 1 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 2.47 - 2.75 (m, 4 H), 1.20 (t, 3 H).



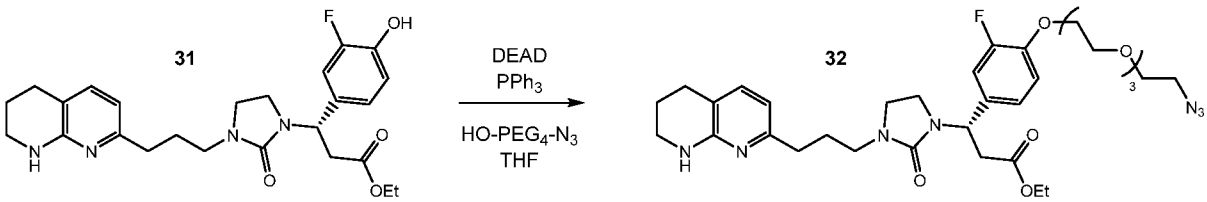
[0275] To a solution of triphosgene (1.2 g, 4.04 mmol) in THF (24 mL) in flame dried flask at -10 °C was added dropwise a solution of compound 19 (3.64 g, 8.99 mmol) and TEA (1.94 mmol, 13.9 mmol) in THF (6 mL). The reaction mixture was warmed to room temperature. After TLC indicated a complete reaction, additional TEA (3.3 mL, 23.6 mmol) was added followed by the addition of compound 28 (2.61 g, 13.7 mmol) as a solid. The heterogenous mixture was heated at 50 °C for 2 hours with vigorous stirring. Upon completion, the reaction mixture was quenched with 1 volume of water and extracted three times with EtOAc. The combined organic phase was dried with brine, filtered over sodium sulfate and concentrated. Compound 29 was obtained assuming 100% yield and the crude was subsequently used without further purification.



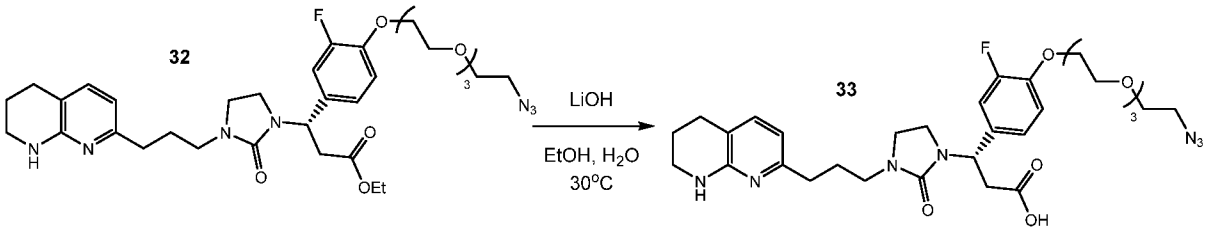
[0276] To compound 29 (5.59g, 8.97 mmol) dissolved in THF (37 mL) was added water (0.8 mL) and H_2SO_4 (2M, 8.07 ml, 16.2 mmol) and the reaction mixture was stirred at 28 °C overnight. The following morning, the pH of the mixture was adjusted to 9 using sodium bicarbonate and extracted three times with DCM. The combined organic phases were dried with brine, filtered over sodium sulfate, and concentrated. Compound 30 was isolated in 82% yield by separation on silica eluting a gradient of MeOH in DCM containing 1% TEA.



[0277] To compound 30 (4.13 g, 7.39 mmol) dissolved in EtOH (30 mL) was charged Degussa® palladium (10 wt%, 3.15 g, 2.96 mmol) and hydrogen to 50psi. The mixture was stirred at room temperature overnight. The next day, reaction was 64% complete. The reaction mixture was filtered over Celite® and concentrated. The residue was dissolved in EtOH and charged with palladium (10 wt%, 1.57 g, 1.48 mmol)) and hydrogen to 50 psi. After stirring for 48 hours the reaction mixture was heated to 30 °C and stirred for a further 24 hours. Upon completion the suspension was filtered over Celite® and all volatiles were removed in vacuo. The residue was purified over silica eluting a gradient of MeOH in DCM, yielding compound 31 in 72% yield. **^{1}H NMR**: 400 MHz DMSO-d_6 δ 9.88 (s, 1 H), 7.02 - 7.14 (m, 2 H), 6.86 - 6.93 (m, 2 H), 6.50 - 6.76 (m, 1 H), 6.31 (d, 1 H), 5.17 (t, 1 H), 4.00 (q, 2 H), 3.23 - 3.28 (m, 4 H), 2.79 - 3.18 (m, 7 H), 2.61 (t, 2 H), 2.41 (t, 2 H), 1.65 - 1.78 (m, 4 H), 1.09 (t, 3 H).

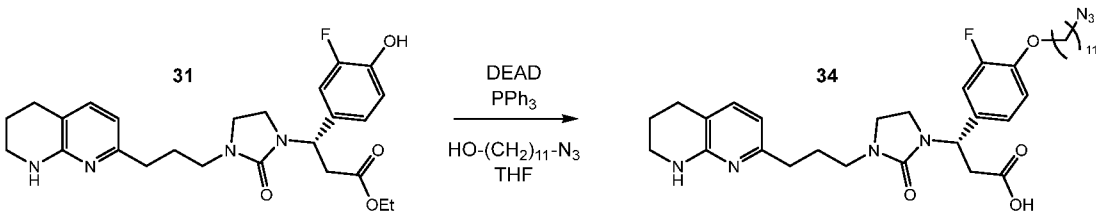


[0278] To a solution of PPh_3 (699 mg, 2.66 mmol) in THF (0.47 mL) at -10 °C was added dropwise a solution of DEAD. The mixture was warmed to room temperature and added to a neat mixture of compound 31 (600mg, 1.33 mmol) and HO-PEG_4-N_3, (466 mg, 3.06 mmol) and stirred overnight. The reaction mixture was then concentrated under reduced pressure, and the residue was purified over silica eluting a gradient of MeOH in DCM, yielding compound 32 in 50% yield. **^{1}H NMR**: 400 MHz DMSO-d_6 δ 7.10 - 7.19 (m, 2 H), 6.97 - 7.06 (m, 2 H), 6.18 - 6.31 (m, 2 H), 5.20 (t, 1 H), 4.13 - 4.16 (m, 1 H), 3.98 - 4.04 (m, 2 H), 3.71 - 3.80 (m, 2 H), 3.52 - 3.61 (m, 8 H), 3.38 - 3.37 (m, 5 H), 3.10 - 3.25 (m, 5 H), 2.79 - 3.08 (m, 5 H), 2.59 (t, 2 H), 2.31 - 2.42 (m, 2 H), 1.65 - 1.75 (m, 4 H), 1.10 (t, 3 H).



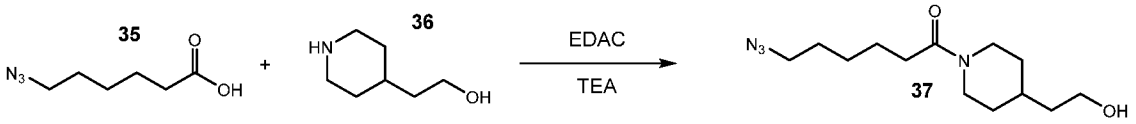
[0279] To compound 32 (826 mg, 1.23 mmol) was added EtOH (3 mL) and H_2O (3 mL), followed by LiOH (97 mg, 4.05 mmol). The mixture was stirred at 30 °C overnight. Upon completion the mixture was neutralized to pH=5 using 6 M aqueous HCl and concentrated. The residue was purified by reverse phase HPLC with a Phenomenex Gemini C18, 50 x 250 mm, 10 µm column eluting a gradient of acetonitrile in water containing 0.1%, yielding compound 33 (Structure 2c) in 81% yield. **^{1}H NMR**: 400 MHz D_2O δ 7.30 (d, 1 H), 7.01 - 7.19 (m, 3 H), 6.45 (d, 1 H), 5.24 (t, 1 H), 4.14 - 4.32 (m, 2 H), 3.84 - 3.92 (m, 2 H), 3.59 - 3.77 (m, 10 H), 3.14 - 3.45 (m, 8 H), .02 - 3.12 (m, 1 H), 2.97 (d, 2 H), 2.85 (q, 1 H), 2.50 - 2.72 (m, 4 H), 1.68 - 1.94 (m, 4 H).

Synthesis of Structure 2.1c ((S)-3-(4-((11-azidoundecyl)oxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

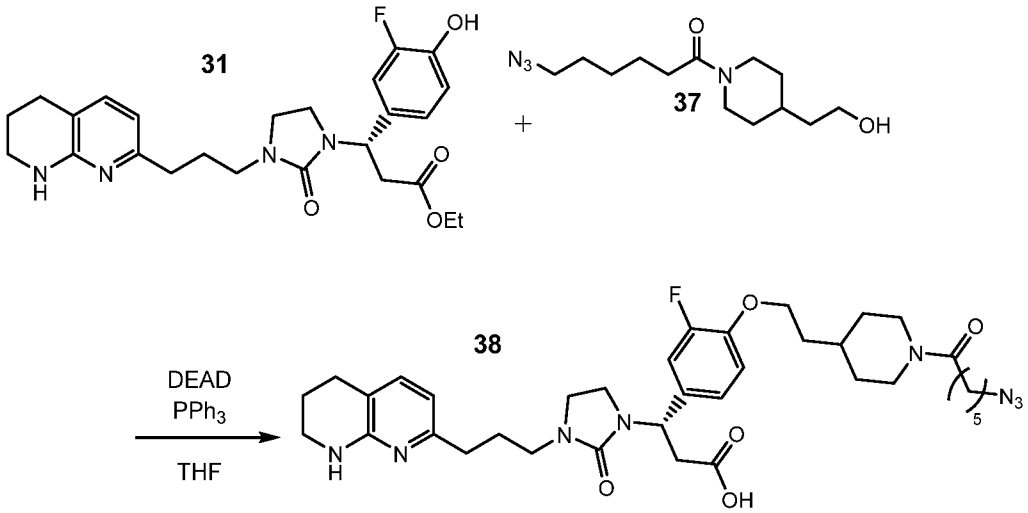


[0280] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at room temperature. The mixture was transferred to a vial containing mixture of compound 31 and OH-$(CH_2)_{11}$-N_3, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed from the reaction mixture and the crude was dissolved in EtOH. LiOH was added as a solution in H_2O, and additional water/EtOH was added until the reaction mixture became homogenous. After stirring at room temperature for 1.5 hours, the mixture was acidified to a pH of 3 with H_2SO_4, concentrated, and purified by reverse phase HPLC (Phenomenex Gemini C18, 50 x 250 mm, 10 µm, 0.1% TFA in acetonitrile/water, gradient elution).

Synthesis of Structure 2.2c ((S)-3-(4-(2-(1-(6-azidohexanoyl)piperidin-4-yl)ethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

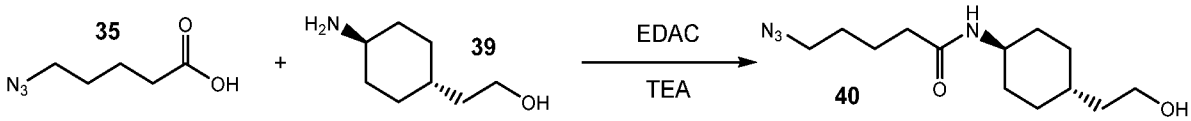


[0281] Compound 35 dissolved in DCM at 0 °C was treated with EDAC and acetonitrile was added to aid in solubility. After 5 minutes, TEA and compound 36 were added, cooling was removed, and stirring continued for 2 hours. Upon completion, saturated ammonium chloride was added and the organic phase was separated, filtered over sodium sulfate, and concentrated. The crude obtained was used subsequently without further purification.

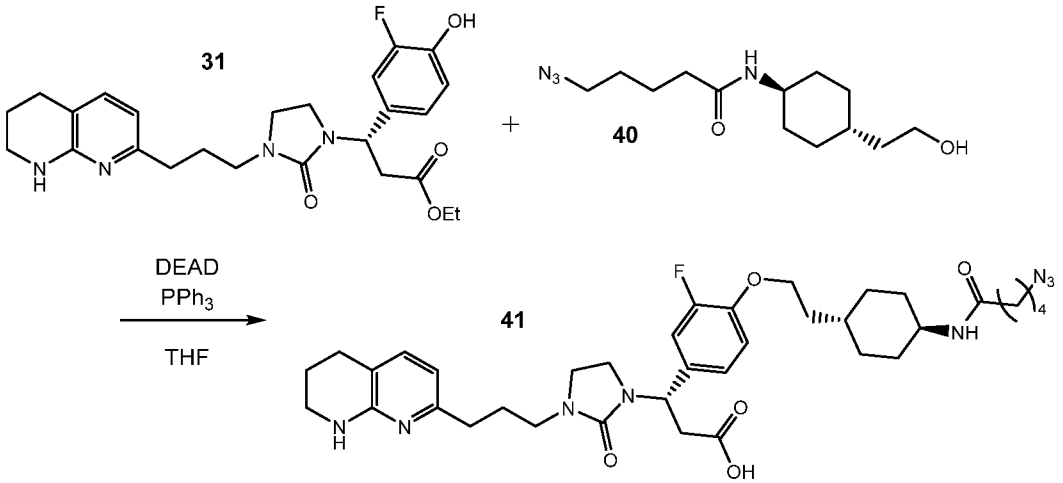


[0282] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at room temperature with vigorous stirring. The mixture was transferred to a vial containing a mixture of compound 31 and compound 37, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed from the reaction mixture and the crude was dissolved in EtOH. LiOH was added as a solution in H_2O, and additional water was added until the reaction mixture became homogeneous. After stirring at room temperature for 1.5 hours, the mixture was acidified to a pH of 3 with H_2SO_4, concentrated, and purified by reverse phase HPLC (Phenomenex Gemini C18, 50 x 250 mm, 10 µm, 0.1% TFA in acetonitrile/water, gradient elution), yielding compound 38 (Structure 2.2c).

Synthesis of Structure 2.3c ((S)-3-(4-(2-((1r,4S)-4-(5-azidopentanamido)cyclohexyl)ethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

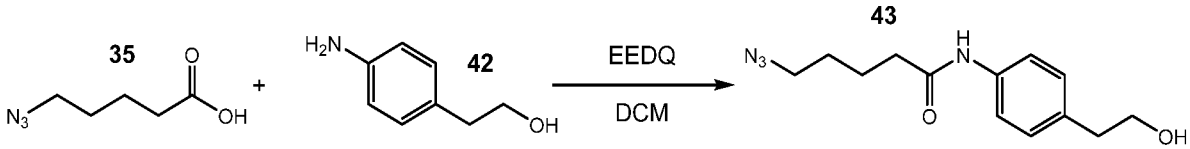


[0283] To a suspension of compound 35 in DCM at 0 °C was added EDAC as a solution in DCM. After 5 minutes, cooling was removed and compound 39 was added, followed by the addition of TEA. The heterogeneous mixture was stirred overnight at room temperature. The next day, the reaction was diluted with DCM and the precipitate dissolved. The mixture was washed twice with 5% $KHSO_4$ and once with brine. The organic phase was filtered over sodium sulfate and concentrated. The crude residue containing compound 40 was used without further purification.

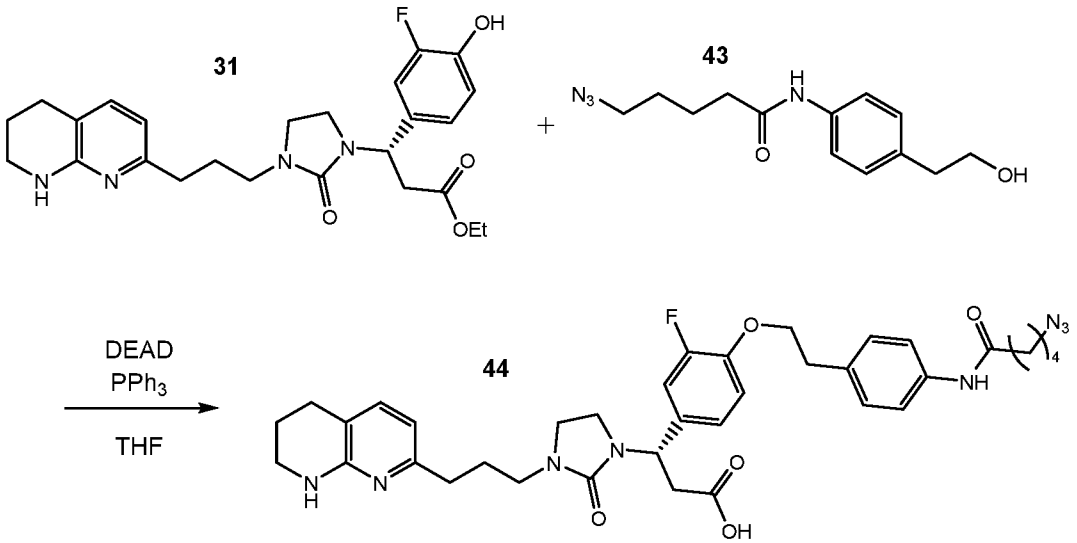


[0284] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at room temperature with vigorous stirring. The mixture was transferred to a vial containing a mixture of compound 31 and compound 40, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed from the reaction mixture and the crude was dissolved in EtOH. LiOH was added as a solution in H_2O, and additional water was added until the reaction mixture became homogeneous After stirring at room temperature for 1.5 hours, the mixture was acidified to a pH of 3 with H_2SO_4, concentrated, and purified by reverse phase HPLC (Phenomenex Gemini C18, 50 x 250 mm, 10 µm, 0.1% TFA in acetonitrile/water, gradient elution), yielding compound 41 (Structure 2.3c).

Synthesis of Structure 2.4c ((S)-3-(4-(4-(5-azidopentanamido)phenethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

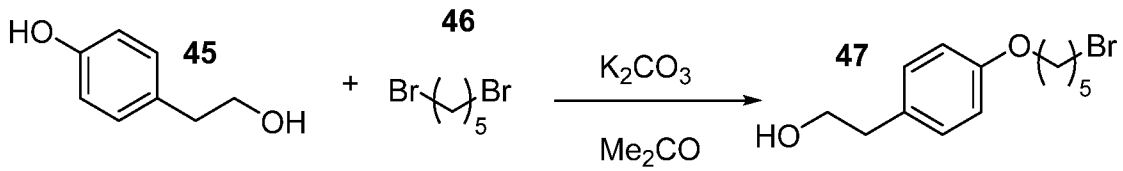


[0285] To a mixture of compound 35 and compound 42 in DCM was added EEDQ, and the solution was stirred at room temperature overnight. The reaction mixture was then diluted with DCM, washed three times with 1M HCl, and washed once with brine. The organic phase was dried over sodium sulfate, filtered, and concentrated. Compound 43 was then used without further purification.

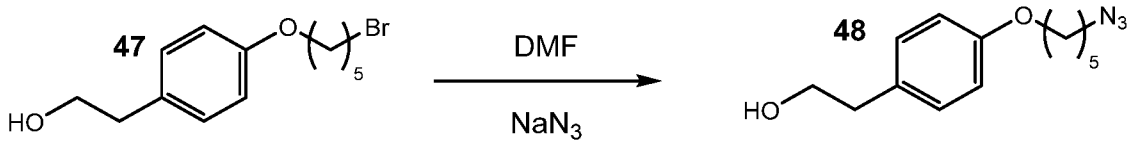


[0286] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at room temperature with vigorous stirring. The mixture was transferred to a vial containing a mixture of compound 31 and compound 43, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed from the reaction mixture and the crude was dissolved in EtOH. LiOH was added as a solution in H_2O, and additional water was added until the reaction mixture became homogeneous. After stirring at room temperature for 1.5 hours, the mixture was acidified to a pH of 3 with H_2SO_4, concentrated, and purified by reverse phase HPLC (Phenomenex Gemini C18, 50 x 250 mm, 10 µm, 0.1% TFA in acetonitrile/water, gradient elution), yielding compound 44 (Structure 2.4c).

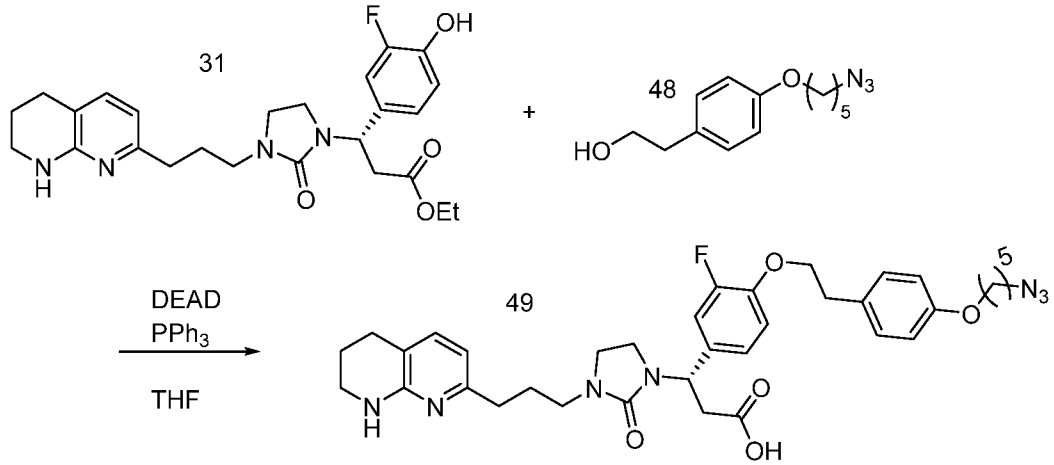
Synthesis of Structure 2.5c ((S)-3-(4-(4-((5-azidopentyl)oxy)phenethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).



[0287] To a solution of compound 45 and compound 46 in acetone was added potassium carbonate. The mixture was heated to 65 °C in a sealed vial as a suspension with vigorous stirring overnight under N_2 protection. The reaction was then filtered, concentrated, and purified over silica eluting a gradient of ethyl acetate in hexanes, yielding compound 47.



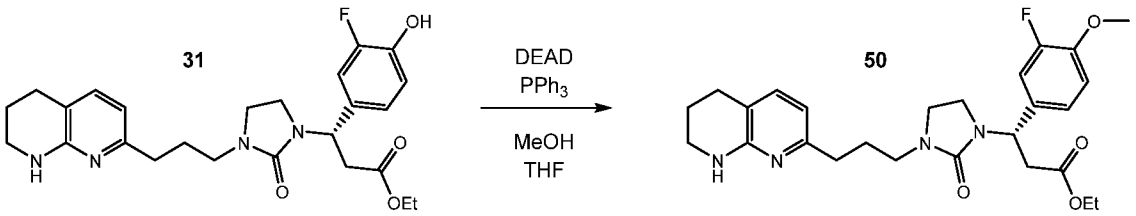
[0288] To a solution of compound 47 in DMF was added sodium azide and the mixture was stirred at 80 °C in a sealed vial under nitrogen protection overnight. Upon completion, 1 volume of water was added and the product was extracted with ethyl acetate. The separated organic phase was filtered over sodium sulfate and concentrated. Crude of compound 48 was used without further purification.



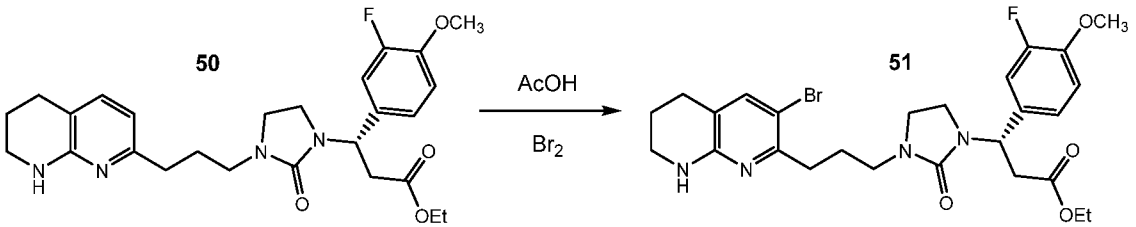
[0289] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at room temperature with vigorous stirring. The mixture was transferred to a vial containing a mixture of compound 31 and compound 48, and the reaction mixture was stirred at room temperature overnight. Volatiles were removed from the reaction mixture and the crude was dissolved in EtOH. LiOH was added as a solution in H_2O, and additional water was added until the reaction

mixture became homogeneous. After stirring at room temperature for 1.5 hours, the mixture was acidified to a pH of 3 with H_2SO_4, concentrated, and purified by reverse phase HPLC (Phenomenex Gemini C18, 50 x 250 mm, 10 µm, 0.1% TFA in acetonitrile/water, gradient elution), yielding compound 49 (Structure 2.5c).

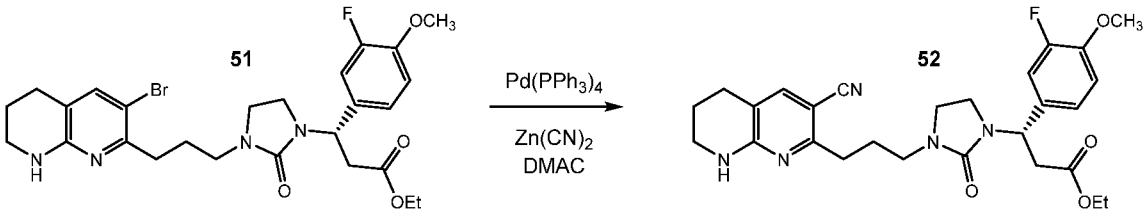
Synthesis of Structure 2.6c ((S)-3-(3-(3-(3-(17-azido-3-oxo-6,9,12,15-tetraoxa-2-azaheptadecyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)-2-oxoimidazolidin-1-yl)-3-(3-fluoro-4-methoxyphenyl)propanoic acid).



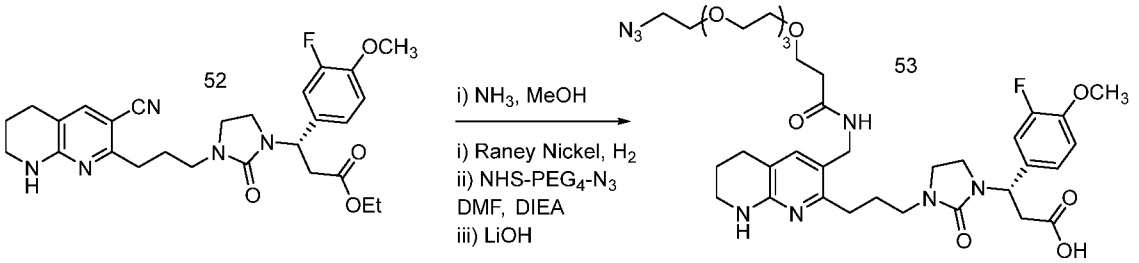
[0290] To a solution of PPh_3 in THF was added dropwise a solution of DEAD at 0 °C. After complete addition, the mixture was transferred to a vial containing a neat mixture of compound 31 and MeOH. The vial was capped with N_2 and stirred at room temperature overnight. Upon completion all volatiles were removed and the crude obtained was purified over silica eluting a gradient of MeOH in DCM, yielding compound 50.



[0291] To a solution of compound 50 in AcOH was added bromine, and the mixture was stirred for 0.5 hours. Upon completion, the reaction was diluted with 5 volumes of ethyl acetate and 2.5 volumes of water. The aqueous layer was neutralized to pH 7 with saturated aqueous sodium bicarbonate, and the organic phase was separated. The aqueous layer was extracted two additional times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and concentrated. Crude obtained of compound 51 was subsequently used without further purification.

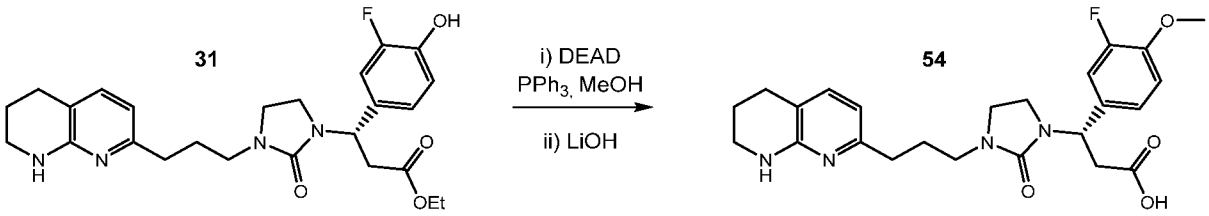


[0292] A solution of compound 51, $Pd(PPh_3)_4$, and $Zn(CN)_2$ in DMAC was degassed with nitrogen for 30 minutes The mixture was heated at 128 °C in a sealed vial overnight. Upon completion, mixture was diluted with 5 volumes of EtOAc. The organic phase was separated then washed two times with water, washed two times with brine, and then the organic phase was filtered over sodium sulfate and concentrated. The residue was purified over silica eluting 100% EtOAc, yielding compound 52.

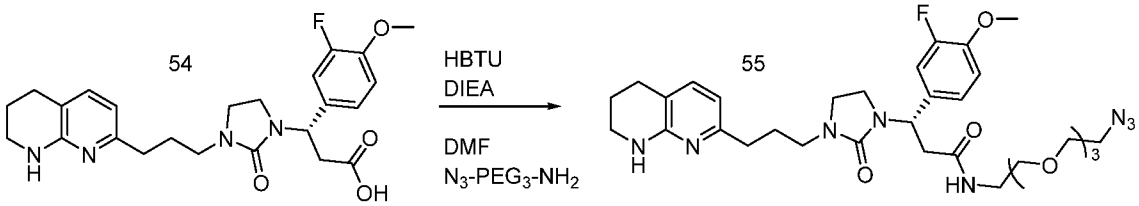


[0293] To a solution of compound 52 in MeOH was added ammonia, then a slurry of Raney nickel that was pre-rinsed three times with methanol. A Parr® flask was charged to 60 psi with hydrogen and stirred at room temperature for 16 hours. Upon completion, the suspension was filtered and concentrated. The crude residue obtained was redissolved in DMF. DIEA and $NHS\text{-}PEG_4\text{-}N_3$ were added and the mixture was stirred for one hour. Upon completion, all volatiles were removed and the crude residue was redissolved in a mixture of MeOH and THF. LiOH in H_2O was added and the mixture was stirred at room temperature for 17 hours. Upon reaction completion, the pH was adjusted to 3 with TFA and the mixture was directly injected onto semi-preparative reverse phase HPLC (Phenomenex Gemini C18, 250 x 21.2 mm, 5 µm, 0.1% TFA in water/ACN, gradient elution), yielding compound 53 (Structure 2.6c).

Synthesis of Structure 2.7c ((S)-N-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-3-(3-fluoro-4-methoxyphenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanamide), Structure 2.8c, Structure 2.9c, and Structure 2.10c.



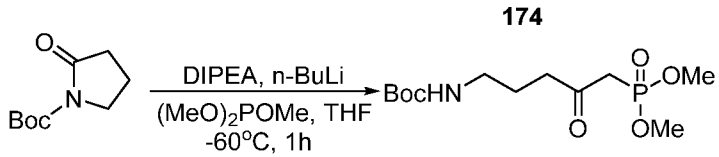
[0294] To compound 31 was added sequentially THF, PPh_3, and a solution of DEAD dropwise at 0 °C. The mixture was stirred for 16 hours at room temperature. The mixture was then cooled to -20 °C for 1 hour and filtered to remove triphenylphosphine oxide. The filtrate was concentrated and intermediate of O-alkylation isolated by purification on silica eluting a gradient of ethyl acetate in hexanes containing 1% TEA. Isolated intermediate was then suspended in a mixture of THF and H_2O, treated with LiOH in H_2O, and stirred at 35 °C for 16 hours. Upon completion, the pH was adjusted to 7 with 2 M HCl and all volatiles were removed. Crude was suspended in H_2O; sodium chloride was added and compound 54 was extracted with ethyl acetate five times. The organic phases were combined, filtered over sodium sulfate and concentrated. Compound 54 was subsequently used without further purification.



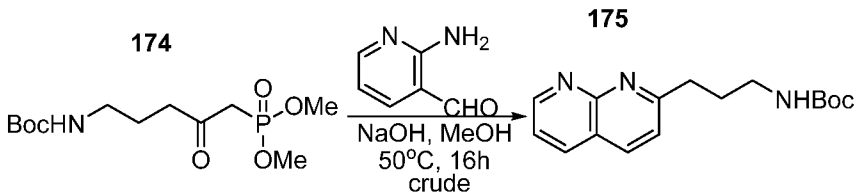
[0295] A solution of compound 54 in DMF was treated with HBTU and stirred for 5 minutes. DIEA and N_3-PEG_3-NH_2 were subsequently added, and the mixture was stirred at room temperature for 16 hours. Upon completion, the pH was adjusted to 3 with TFA and compound 55 was isolated by direct injection into semi-preparative reverse phase HPLC (Phenomenex Gemini C18, 250 x 21.2 mm, 5 µm, 0.1% TFA in water/ACN, gradient elution), yielding compound 55.

[0296] Similar procedures were used to synthesize compounds 2.8c, 2.9c and 2.10c, using N_3-PEG_{11}-NH_2, N_3-PEG_{23}-NH_2 and N_3-PEG_{35}-NH_2, respectively.

Synthesis of Structure 2.11c ((R)-3-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-3-fluorophenyl)-3-(2-oxo-3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)imidazolidin-1-yl)propanoic acid).

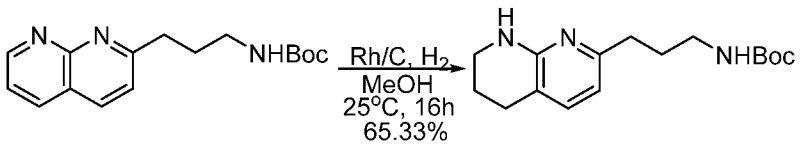


[0297] Into a 3-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed THF (1.50 L), DIPEA (150.00 mL, 716.000 mmol, 0.88 equiv.), n-BuLi (430.00 mL, 680.000 mmol, 0.84 equiv.) This was followed by the addition of trimethyl phosphite (195.00 mL) at -60°C and stirred for 1h at -60°C. To this was added tert-butyl 2-oxopyrrolidine-1-carboxylate (150.00 g, 809.835 mmol, 1.00 equiv.) at -60°C. The resulting solution was stirred for 1h at -60°C in a liquid nitrogen bath. The reaction was then quenched by the addition of 350 mL of H_2SO_4 (2N) and diluted with 1.5 L of H_2O. The resulting solution was extracted with 2x1 L of ethyl acetate. The resulting mixture was washed with 1x1 L of H_2O, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 200 g (crude) of tert-butyl N-[5-(dimethoxyphosphoryl)-4-oxopentyl]carbamate as yellow oil.



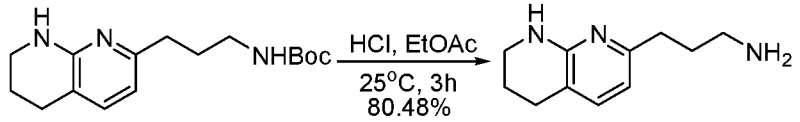
[0298] Into a 3-L round-bottom flask, was placed tert-butyl N-[5-(dimethoxyphosphoryl)-4-oxopentyl]carbamate (200.00 g, 1500.00 mmol, 1.50 equiv.), MeOH (1.50 L), 2-aminopyridine-3-carbaldehyde (53.00 g, 1000.00 mmol, 1.00 equiv.), NaOH (50.00 g, 1500.00 mmol, 1.50 equiv.). The resulting solution was stirred for 16 h at 50°C in an oil bath. The pH value of the solution was adjusted to 8 with $NaHCO_3$ (aq.). The resulting mixture was concentrated. The reaction was then quenched by the addition of 1.5 L of water and extracted with 2x1.5 L of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 160 g (crude) of tert-butyl N-[3-(1,8-naphthyridin-2-yl)propyl]carbamate as yellow oil.

175 176



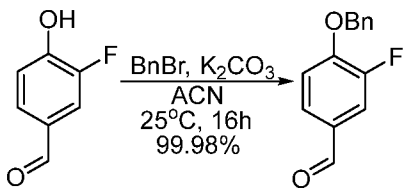
[0299] Into a 5-L round-bottom flask, was placed tert-butyl N-[3-(1,8-naphthyridin-2-yl)propyl]carbamate (160.00 g, 556.787 mmol, 1.00 equiv.), MeOH (2.00 L), Rh/C (140.00 g, 1.360 mmol), H_2 (40 Psi). The resulting solution was stirred for 16 h at 25°C. The solids were filtered out. The resulting mixture was concentrated. This resulted in 106 g (65.33%) of tert-butyl N-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]carbamate as a yellow solid.

176 177

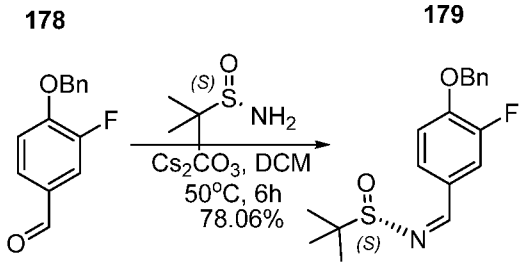


[0300] Into a 1-L round-bottom flask, was placed tert-butyl N-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]carbamate (106.00 g, 363.767 mmol, 1.00 equiv.), EtOAc (500.00 mL), HCl in EtOAc (4M, 400.00 mL). The resulting solution was stirred for 3 h at 25°C. The resulting solution was diluted with 1 L of H_2O. NaOH (aq.) was employed to adjust the pH to 11. The resulting solution was extracted with 2x1 L of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 56 g (80.48%) of 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine as a yellow solid.

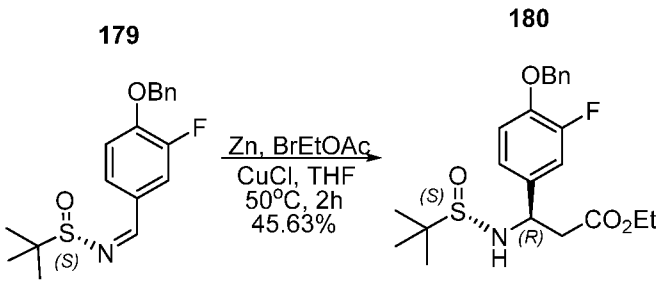
178



[0301] Into a 2-L round-bottom flask, was placed 3-fluoro-4-hydroxybenzaldehyde (140.00 g, 999.194 mmol, 1.00 equiv.), ACN (1000 mL), (bromomethyl)benzene (205.08 g, 1199.039 mmol, 1.20 equiv.), K_2CO_3 (414.28 g, 2997.581 mmol, 3.00 equiv.). The resulting solution was stirred for 16 h at 25°C. The solids were filtered out. The resulting mixture was concentrated. This resulted in 230 g (99.98%) of 4-(benzyloxy)-3-fluorobenzaldehyde as a white solid.

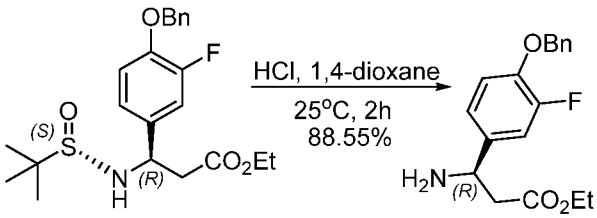


[0302] Into a 3-L round-bottom flask, was placed 4-(benzyloxy)-3-fluorobenzaldehyde (230.00 g, 998.966 mmol, 1.00 equiv.), DCM (1600 mL), (S)-2-methylpropane-2-sulfinamide (145.29 g, 1198.762 mmol, 1.20 equiv.), Cs_2CO_3 (650.97 g, 1997.933 mmol, 2.00 equiv.). The resulting solution was stirred for 6 h at 50°C in an oil bath. The solids were filtered out. The resulting mixture was concentrated. This resulted in 260 g (78.06%) of (S)-N-[[4-(benzyloxy)-3-fluorophenyl]methylidene]-2-methylpropane-2-sulfinamide as a white solid.



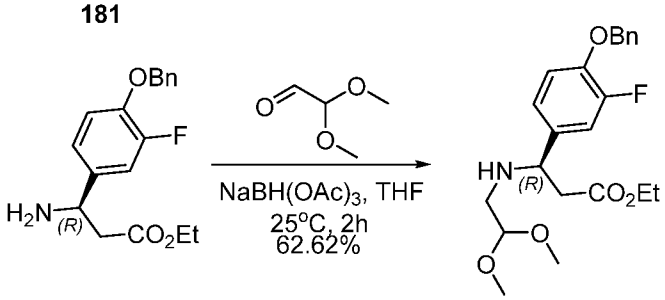
[0303] Into a 3-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed THF (2.0 L), Zn (1.02 kg, 15595.945 mmol, 20.00 equiv.), CuCl (115.80 g, 1169.696 mmol, 1.50 equiv.), ethyl 2-bromoacetate (325.57 g, 1949.498 mmol, 2.50 equiv.), (S)-N-[[4-(benzyloxy)-3-fluorophenyl]methylidene]-2-methylpropane-2-sulfinamide (260.00 g, 779.797 mmol, 1.00 equiv.). The resulting solution was stirred for 30 min at 0°C in a water/ice bath. The resulting solution was allowed to react, with stirring, for an additional 2 h while the temperature was maintained at 50°C in an oil bath. The solids were filtered out. The resulting mixture was concentrated. The reaction was then quenched by the addition of 2 L of water and extracted with 2x2 L of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 150 g (45.63%) of ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[[(S)-2-methylpropane-2-sulfinyl]amino]propanoate as yellow oil.

180 181

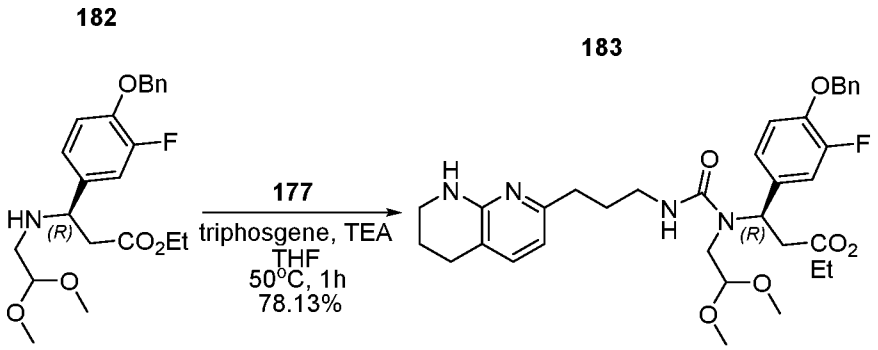


[0304] Into a 1-L round-bottom flask, was placed ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[[(S)-2-methylpropane-2-sulfinyl]amino]propanoate (150.00 g, 355.847 mmol, 1.00 equiv.), HCl in 1,4-dioxane (400.00 mL, 4M). The resulting solution was stirred for 2 h at 25°C. The resulting mixture was concentrated. The reaction was then quenched by the addition of 1 L of water. $NaHCO_3$ (aq.) was employed to adjust the pH to 8. The resulting solution was extracted with 2x1 L of ethyl acetate dried over anhydrous sodium sulfate and concentrated. This resulted in 100 g (88.55%) of ethyl (3R)-3-amino-3-[4-(benzyloxy)-3-fluorophenyl]propanoate as yellow oil.

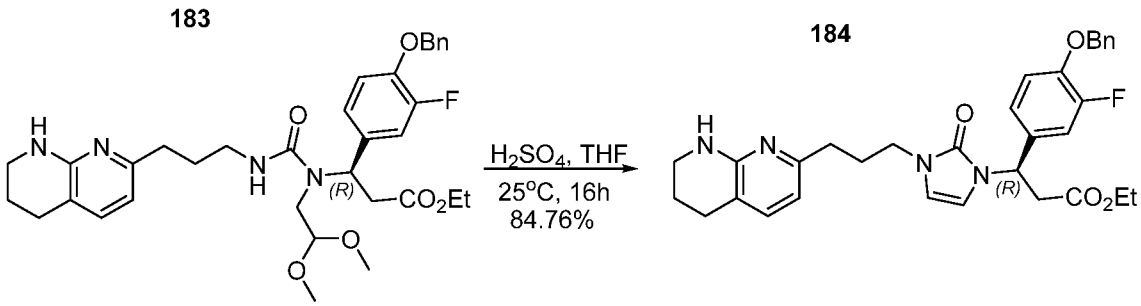
181 182



[0305] Into a 2-L round-bottom flask, was placed ethyl (3R)-3-amino-3-[4-(benzyloxy)-3-fluorophenyl]propanoate (100.00 g, 315.100 mmol, 1.00 equiv.), THF (1.00 L), 2,2-dimethoxyacetaldehyde (49.21 g, 472.696 mmol, 1.50 equiv.), $NaBH(OAc)_3$ (133.57 g, 630.199 mmol, 2.00 equiv.). The resulting solution was stirred for 2 h at 25°C. The reaction was then quenched by the addition of 1 L of water. The resulting solution was extracted with 2x1 L of ethyl acetate dried over Na_2SO_4 and concentrated under vacuum. This resulted in 80 g (62.62%) of ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[(2,2-dimethoxyethyl)amino]propanoate as yellow oil.

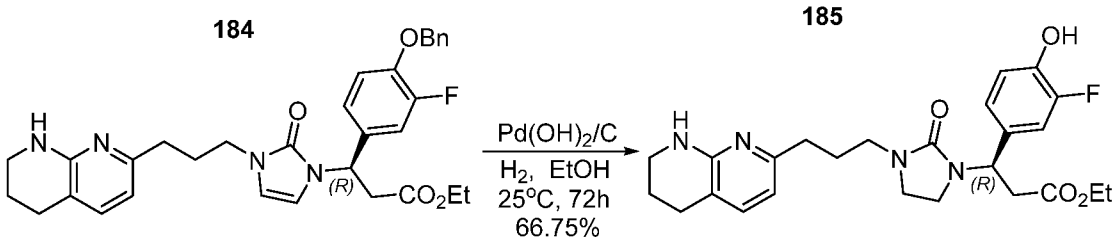


[0306] Into a 2-L 3-necked round-bottom flask, was placed Triphosgene (22.25 g, 74.975 mmol, 0.38 equiv.), THF (500 mL), ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[(2,2-dimethoxyethyl)amino]propanoate (80.00 g, 197.304 mmol, 1.00 equiv.), TEA (29.95 g, 295.956 mmol, 1.50 equiv.), 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine (Compound 177, 33.97 g, 177.573 mmol, 0.90 equiv.). The resulting solution was stirred for 1 h at 50°C in an oil bath. The reaction was then quenched by the addition of 1 L of water. $NaHCO_3$ (aq.) was employed to adjust the pH to 8. The resulting solution was extracted with 2x1 L of ethyl acetate dried over anhydrous sodium sulfate and concentrated. This resulted in 96 g (78.13%) of ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[(2,2-dimethoxyethyl)([[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]carbamoyl])amino]propanoate as yellow crude oil.



[0307] Into a 1000-mL round-bottom flask, was placed ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[(2,2-dimethoxyethyl)([[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]carbamoyl])amino]propanoate (96.00 g, 154.158 mmol, 1.00 equiv.), THF (500.00 mL), H_2SO_4 (180.00 mL, 2M). The resulting solution was stirred for 16 h at 25°C. NaOH (5M) was employed to adjust the pH to 8. The resulting solution was extracted with 2x1 L of dichloromethane dried over anhydrous sodium sulfate and concentrated. The residue was applied onto a silica gel column with dichloromethane/methanol (50/1). The collected

fractions were combined and concentrated. This resulted in 73 g (84.76%) of ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-2,3-dihydro-1H-imidazol-1-yl]propanoate as yellow oil.

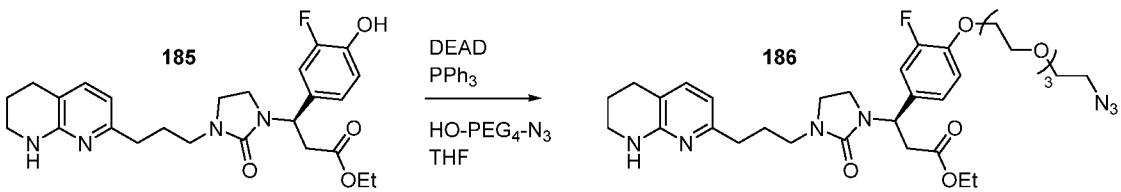


[0308] Into a 3-L round-bottom flask, was placed ethyl (3R)-3-[4-(benzyloxy)-3-fluorophenyl]-3-[2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-2,3-dihydro-1H-imidazol-1-yl]propanoate (73.00 g, 130.671 mmol, 1.00 equiv.), EtOH (1.50 L), $Pd(OH)_2/C$ (60.00 g, 427.259 mmol, 3.27 equiv.), H_2 (50 atm). The resulting solution was stirred for 72 h at 25°C. The solids were filtered out. The residue was applied onto a silica gel column with dichloromethane/methanol (9/1). The collected fractions were combined and concentrated. This resulted in 41.0415 g (66.75%) of ethyl (3R)-3-(3-fluoro-4-hydroxyphenyl)-3-[2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]imidazolidin-1-yl]propanoate as yellow oil.

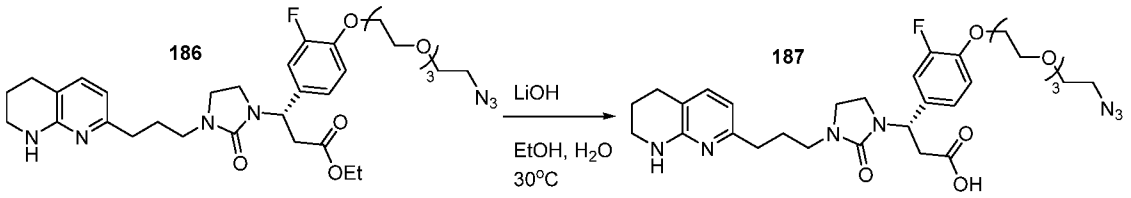
[0309] LCMS-PH-ARP-052-0: [MS+1]+=471

[0310] Rotation Optical $[a]_D^{20.0}$ = +37.5° (C=1 g/100ml in MeOH)

H-NMR: (300 MHz, DMSO-*d6*, *ppm*) δ 9.84 (s, 1H), 7.07 – 7.00 (m, 2H), 6.95 – 6.850 (m, 2H), 6.24 (d, 2H), 5.18 (t, 1H), 4.06 – 3.96 (m, 2H), 3.32 – 2.75 (m, 10H), 2.60 (t, 2H), 2.37 (t, 2H), 1.77 – 1.67 (m, 4H), 1.10 (t, 3H).

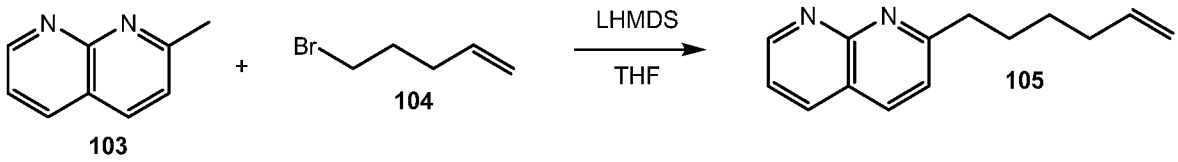


[0311] To a solution of PPh_3 in THF at -10 °C was added dropwise a solution of DEAD. The mixture was warmed to room temperature and added to a neat mixture of compound 185 and $HO\text{-}PEG_4\text{-}N_3$, and stirred overnight. The reaction mixture was then concentrated under reduced pressure, and the residue was purified over silica eluting a gradient of MeOH in DCM, yielding compound 186.

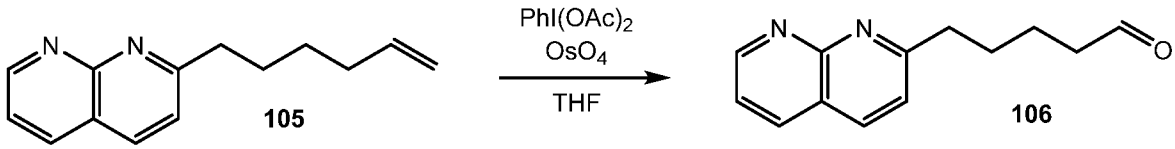


[0312] To compound 186 was added EtOH and H_2O, followed by LiOH. The mixture was stirred at 30 °C overnight. Upon completion the mixture was neutralized to pH=5 using 6 M aqueous HCl and concentrated. The residue was purified by reverse phase HPLC with a Phenomenex Gemini C18, 50 x 250 mm, 10 µm column eluting a gradient of acetonitrile in water containing 0.1%, yielding compound 187 (Structure 2.11c).

Synthesis of Structure 28c (Compound 118a) Structure 29c (Compound 118b), Structure 31c (Compound 119a), and Structure 30c (Compound 119b).

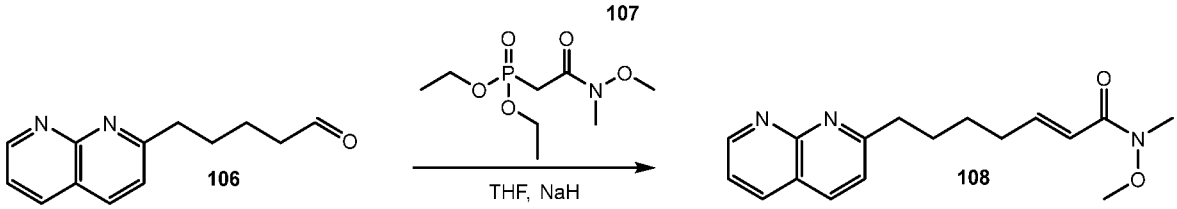


[0313] To a solution of LHMDS (1.0 M in THF, 95 mL, 95 mmol) and THF (60 mL) was added a solution of compound 103 (2-methyl-[1,8]naphthyridine (12.5 g, 86.7 mmol)) in THF (180 mL) dropwise at -78 °C. After stirring for 30 minutes, a solution of compound 104 (5-bromo-1-pentene (19.4 g, 130 mmol)) in THF (120 mL) was added to the reaction mixture dropwise. The reaction mixture was warmed to 0 °C and stirred for 4 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and deionized water (100 mL), then extracted with ethyl acetate (2 x 400 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated, and compound 105 was isolated by CombiFlash® eluting a gradient of 50-100% ethyl acetate in hexanes. Yield of compound 105: 7.93 g (43%).

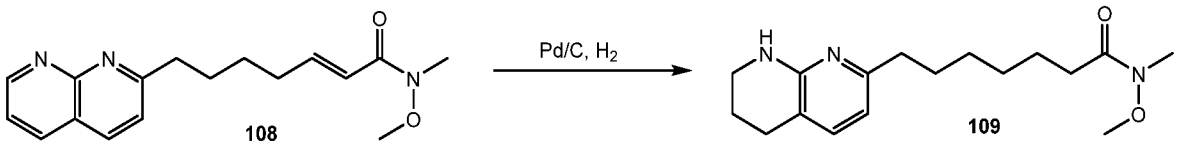


[0314] To a solution of compound 105 (2.50 g, 11.8 mmol) in acetone (67.5 mL), water (7.5 mL), and 2,6 lutidine (2.74 mL, 23.6 mmol) was added 4-methylmorpholine N-oxide (2.07 g, 17.7 mmol) and osmium tetroxide (2.5 wt% in t-butanol, 2.40 g, 0.24 mmol) at room temperature. After stirring for 75 minutes, (diacetoxyiodo)benzene (5.69 g, 17.7 mmol) was added to the reaction mixture. The reaction mixture was stirred for 2 hours then quenched with

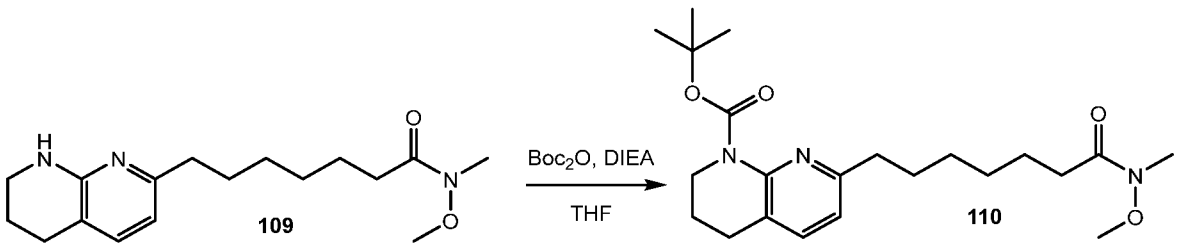
saturated aqueous sodium thiosulfate solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated, and compound 106 was isolated by CombiFlash® eluting a gradient of 0-5% methanol in ethyl acetate. Yield of compound 106: 1.12 g (44%).



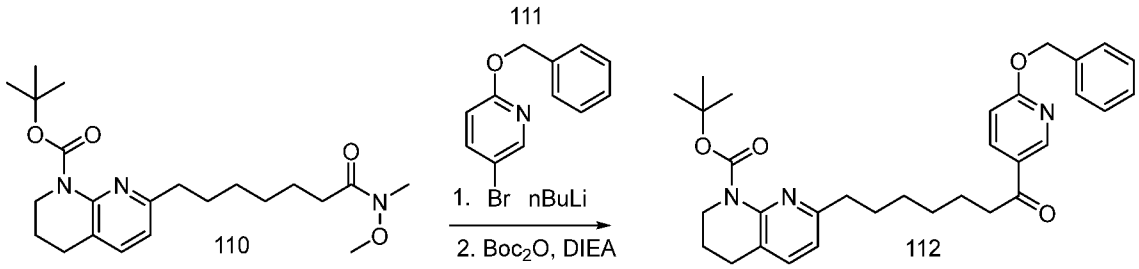
[0315] To a suspension of sodium hydride (60% dispersion in mineral oil, 0.185 g, 4.64 mmol) in THF (9 mL) was added a solution of compound 107 (diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate) (1.06 g, 4.43 mmol) in THF (5 mL) at 0 °C. After stirring for 30 minutes, a solution of compound 106 (0.903 g, 4.21 mmol) in THF (9 mL) was added dropwise. The reaction mixture was stirred for 10 minutes at 0 °C then quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed twice with half saturated aqueous $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Yield of compound 108: 1.40 g (assumed 100% yield and used in the subsequent step without further purification).



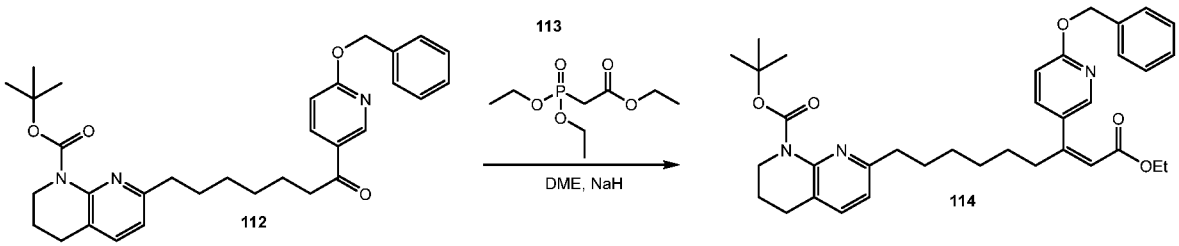
[0316] To a solution of compound 108 (1.31 g, 4.38 mmol) in ethyl acetate (20 mL) was added Pd/C (10% loading, 0.466 g, 0.44 mmol). The reaction vessel was pressurized with H_2 to 50 PSI. After stirring for 3.5 hours, the reaction mixture was filtered over Celite® and rinsed with methanol. The filtrate was concentrated and compound 109 was isolated by CombiFlash® eluting a gradient of 50-100% ethyl acetate in hexanes containing 1% triethylamine. Yield of compound 109: 0.833 g (62%).



[0317] To a solution of compound 109 (0.833 g, 2.73 mmol) in THF (10 mL) was added DIEA (0.590 mL, 3.41 mmol) and di-tert-butyl dicarbonate (0.744 g, 3.41 mmol). The reaction mixture was heated to 50 °C for 5 hours. The reaction was incomplete based on LC/MS and additional portions of DIEA (0.590 mL, 3.41 mmol) and di-tert-butyl dicarbonate (0.744 g, 3.41 mmol) were added. The reaction mixture was heated at 50 °C for an additional 16 hours. The reaction mixture was concentrated and compound 110 was isolated by CombiFlash® eluting a gradient of 50-100% ethyl acetate in hexanes. Yield of compound 110: 0.934 g (84%).

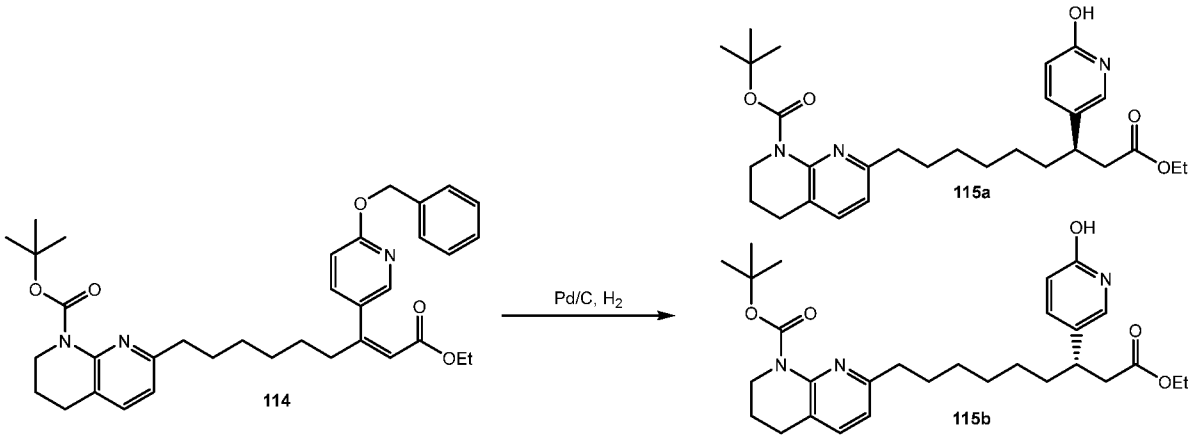


[0318] To a solution of n-butyl lithium (2.5 M in hexanes, 0.70 mL, 1.8 mmol) and THF (1.5 mL) was added compound 111 (5-bromo-2-(phenylmethoxy)-pyridine) (0.465 g, 1.8 mmol) as a solution in THF (0.8 mL) dropwise over 3 minutes at -78 °C. Compound 110 (0.535 g, 1.3 mmol) was then added as a solution in THF (1 mL). After stirring for 30 minutes, the reaction was warmed to 0 °C, quenched with saturated aqueous NH_4Cl solution (10 mL), and acidified further with 6 M aqueous HCl to a pH of 7. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. To a solution of the crude in THF (8 mL) was added DIEA (0.94 mL, 5.4 mmol) and di-tert-butyl dicarbonate (1.18 g, 5.4 mmol). The mixture was stirred at 40 °C overnight. The reaction mixture was concentrated and compound 112 was isolated by CombiFlash® eluting a gradient of 0-40% ethyl acetate in hexanes. Yield of compound 112: 471 mg (50%).



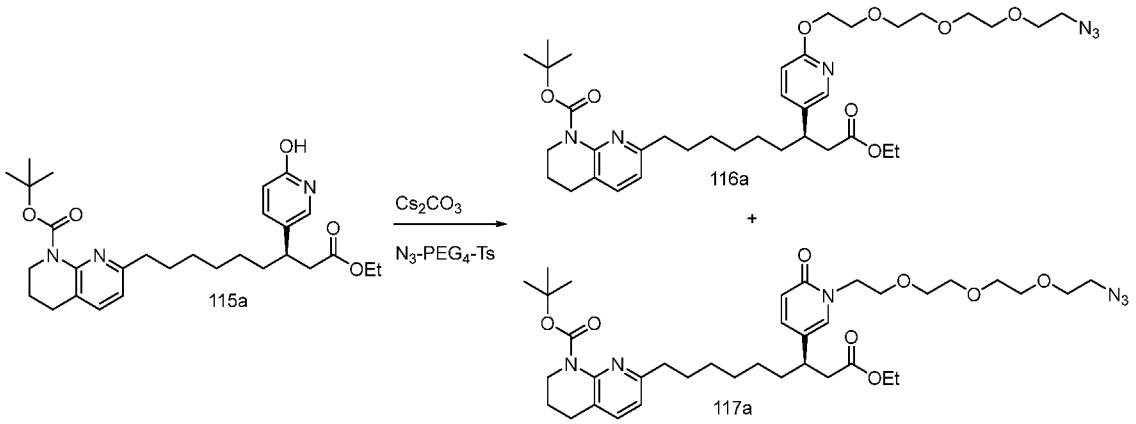
[0319] To a suspension of sodium hydride (60% dispersion in mineral oil, 0.106 g, 2.65 mmol) in dimethoxyethane (2 mL) was added compound 113 (triethyl phosphonoacetate) (0.593 g, 2.65 mmol) as a solution in dimethoxyethane (1 mL) at 0 °C. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and a solution of compound 112 (0.467 g,

0.88 mmol) in dimethoxyethane (2 mL) was added. The reaction mixture was heated at 70 °C for 4 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and the product was extracted with ethyl acetate (3 x 15 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated, and compound 114 was isolated as a 1:1 mixture of cis:trans isomers by CombiFlash® eluting a gradient of 0-30% ethyl acetate in hexanes. Yield of compound 114: 392 mg (74%.).

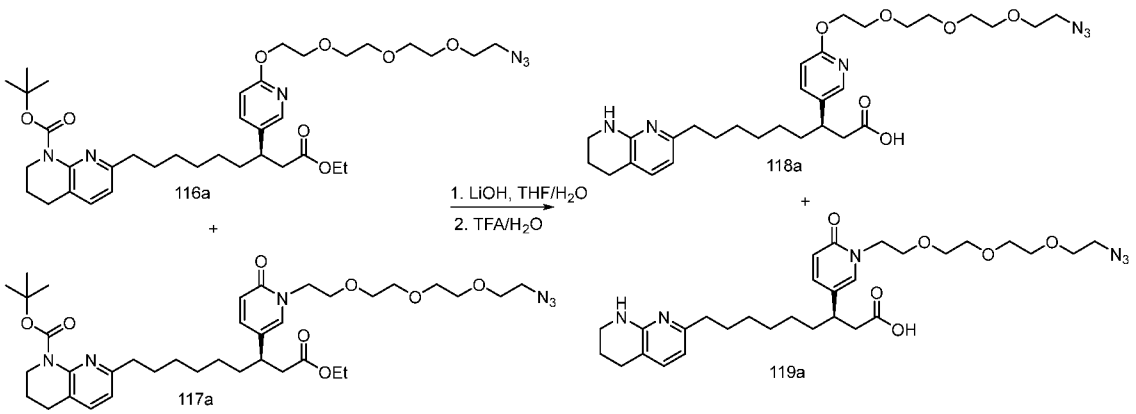


[0320] To a solution of compound 114 (390 mg, 0.65 mmol) in ethanol (6 mL) was added Pd/C (10% loading, 69 mg, 0.07 mmol). The reaction vessel was pressurized with H_2 to 50 PSI. After stirring for 4 hours, the reaction mixture was filtered over Celite® and rinsed with methanol. The filtrate was concentrated and compound 115 was isolated as a racemic mixture by CombiFlash® eluting a gradient of 0-10% methanol in DCM. Yield of compound 115: 95 mg (29%). Chiral semi-preparative HPLC (250 x 21 mm Chiralpak® AD column, 5 μm, 90/10 hexanes/EtOH, 40 mL/min) was used to isolate 42 mg of the first eluting *R*-isomer (R_T = 12-14 m, >99% ee, compound 115a) and 40 mg of the second eluting *S*-isomer (R_T = 15-18 m, >98% ee, compound 115b). The identity of the *R*- and *S*-isomers were assigned based on the order of elution of a structurally similar compound reported by Coleman et al. 47 *J. Med. Chem.* 4834 (2004).

Structures 28c ((R)-3-(6-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)pyridin-3-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid) and 31c ((R)-3-(1-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-6-oxo-1,6-dihydropyridin-3-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid)



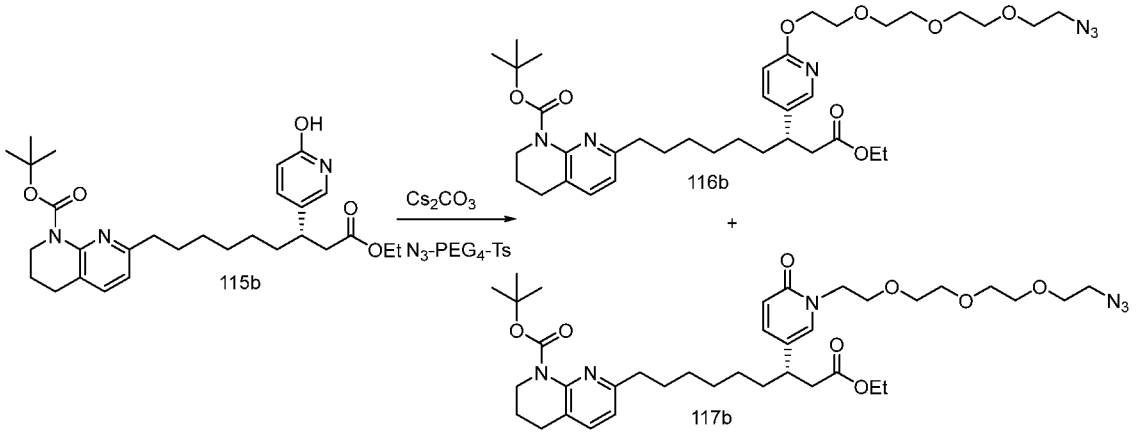
[0321] To a solution of compound 115a (41 mg, 0.08 mmol) and N_3-PEG_4-OTs (61 mg, 0.16 mmol) in DMF (0.5 mL) was added cesium carbonate (53 mg, 0.16 mmol). The reaction mixture was stirred at 40 °C for 1 hour. The reaction mixture was quenched with aqueous $NaHCO_3$ solution (1 mL) then extracted with ethyl acetate (3 x 3 mL). The organic phase was concentrated under reduced pressure. The crude mixture of *N*- and *O*- alkylated regioisomers was subsequently used without further purification.



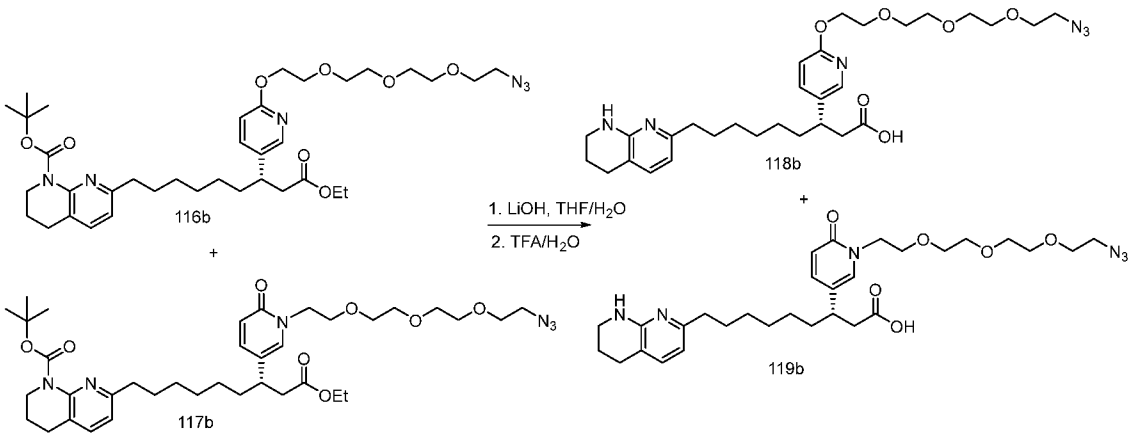
[0322] To a solution of compounds 116a and 117a (58 mg, 0.08 mmol, 4:6 mixture of 9a:10a) in THF (1.0 mL) and deionized water (1.0 mL) was added lithium hydroxide (6 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 1 hour and then at 35 °C for 2 hours. An additional portion of lithium hydroxide (4 mg, 0.16 mmol) was added and the reaction temperature was increased to 40 °C. After stirring for 3 hours, a final portion of lithium hydroxide (4 mg, 0.25 mmol, total 16 mg, 0.66 mmol) was added. The reaction mixture was stirred at 50 °C for 3 hours. The reaction mixture was acidified to a pH of 7 with 6 N aqueous HCl and concentrated under reduced pressure. The regioisomers, compounds 118a and 119a, were separated by CombiFlash® eluting a gradient of 0-5% methanol in DCM containing 0.5% acetic acid. Compound 118a was further purified by reverse phase HPLC (Thermo Scientific™

Aquasil™ C18, 250 x 21.2 mm, 5 µm, 20 mL/min, 0.1% TFA in water/ACN, gradient elution), yielding 13 mg of compound 118a (Structure 28c). Compound 119a was purified under the same conditions, yielding 16 mg of compound 119a (Structure 31c).

Structures 29c ((S)-3-(6-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)pyridin-3-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid) and 30c ((S)-3-(1-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-6-oxo-1,6-dihydropyridin-3-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid)

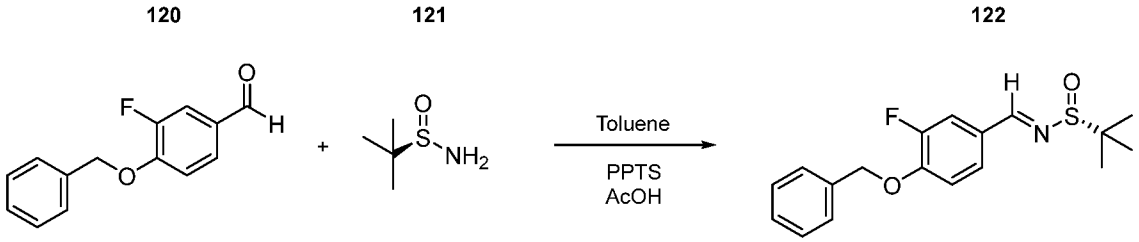


[0323] To a solution of compound 115b (40 mg, 0.08 mmol) and N_3-PEG_4-OTs (58 mg, 0.16 mmol) in DMF (0.5 mL) was added cesium carbonate (51 mg, 0.16 mmol). The reaction mixture was stirred at 40 °C for 30 minutes. The reaction mixture was quenched with aqueous $NaHCO_3$ solution (1 mL) then extracted with ethyl acetate (3 x 3 mL). The organic phase was concentrated under reduced pressure. The crude mixture of *N*- and *O*- alkylated regioisomers was subsequently used without further purification.

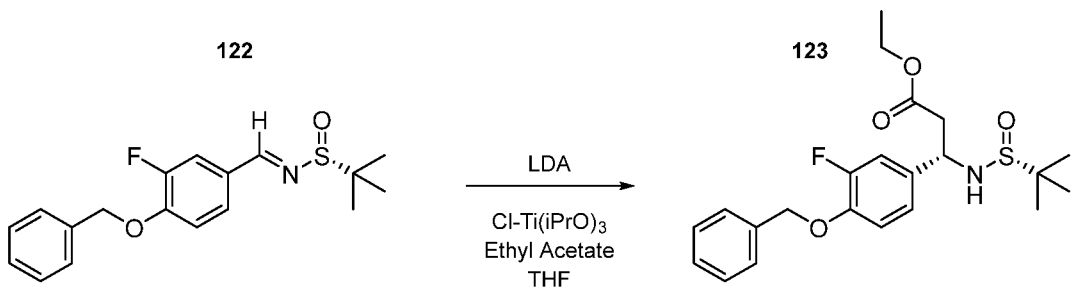


[0324] To a solution of compounds 116b and 117b (56 mg, 0.08 mmol, 4:6 mixture of 9a:10a) in THF (0.75 mL) and deionized water (0.75 mL) was added lithium hydroxide (6 mg, 0.25 mmol). The reaction mixture was stirred at 45 °C for 2.5 hours. An additional portion of lithium hydroxide (6 mg, 0.25 mmol) was added and the reaction mixture was stirred for 2.5 hours. The reaction temperature was lowered to 35 °C and the mixture was stirred overnight. The reaction mixture was acidified to pH = 7 with 6 N aqueous HCl and concentrated under reduced pressure. The regioisomers, compounds 118b and 119b, were separated by CombiFlash eluting a gradient of 0-5% methanol in DCM containing 0.5% acetic acid. Compound 118b was further purified by reverse phase HPLC (Thermo Scientific™ Aquasil™ C18, 250 x 21.2 mm, 5 µm, 20 mL/min, 0.1% TFA in water/ACN, gradient elution), yielding 14 mg of compound 118b (Structure 29c). Compound 119b was purified under the same conditions, yielding 18 mg of compound 119b (Structure 30c).

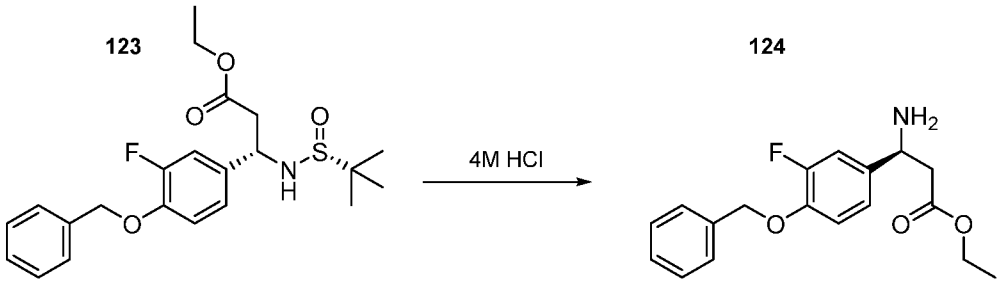
Synthesis of Structure 32c ((R)-3-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-3-fluorophenyl)-3-(N-methyl-5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid)



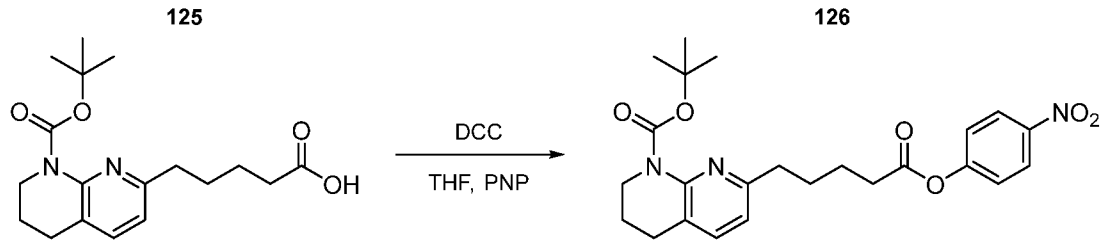
[0325] To compound 120 (2.75 g, 11.94 mmol) in toluene (80 mL) over 3Å sieves was added compound 121 (5.79 g, 47.78 mmol), followed by PPTS (300 mg, 1.19 mmol) then AcOH (683 uL, 11.94 mmol). The reaction was brought to reflux overnight. Upon completion the reaction was quenched by addition of saturated sodium bicarbonate. The organic layer was diluted with 2 volumes of ethyl acetate, separated, and filtered over sodium sulfate. The product was isolated over silica eluting a gradient of ethyl acetate (0-30%) in hexane to yield 2.054 g (54%).



[0326] To DIA (2.85 mL, 20.33 mmol) in THF (15 mL) at -78°C was added a 2.5M solution of n-BuLi (7.76 mL, 19.41 mmol) was added dropwise. Stirring was continued for 5 minutes at -78C and ethyl acetate (1.81 mL, 18.48 mmol) was added dropwise. Stirring was continued for a further 10 minutes at -78°C and a solution of chloro titanium triisopropoxide (9.27 mL, 38.381 mmol) in THF (10 mL) was added dropwise. Stirring was continued for a further 15 minutes at -78°C and a solution of compound 122 (2.054 g, 6.16 mmol) in THF (10 mL) was added dropwise. Stirring was continued for 1.5 hours at -78°C. Upon completion the reaction was quenched by addition of saturated ammonium bicarbonate. The suspension was diluted with 6 volumes of ethyl acetate and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The product was isolated over silica eluting a gradient of ethyl acetate in hexanes to yield 1.043 g (53%).

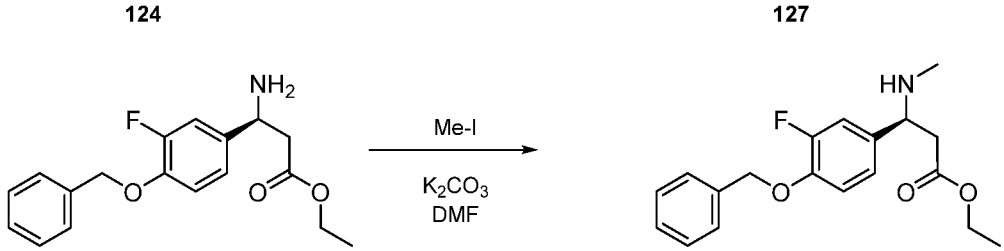


[0327] To compound 123 (1.043 g, 2.47 mmol) stirring in MeOH (3 mL) was added a 4M HCl solution in dioxane (3.09 mL, 12.37 mmol). Upon completion of deprotection the solution was diluted with water (8 mL) and washed twice with diethyl ether (6 mL). The aqueous layer was subsequently adjusted to a pH of 11 with sodium hydroxide. The precipitate was extracted with ethyl acetate, and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated yielding 0.616 g (78.5%) of product 124 that was used without further purification.

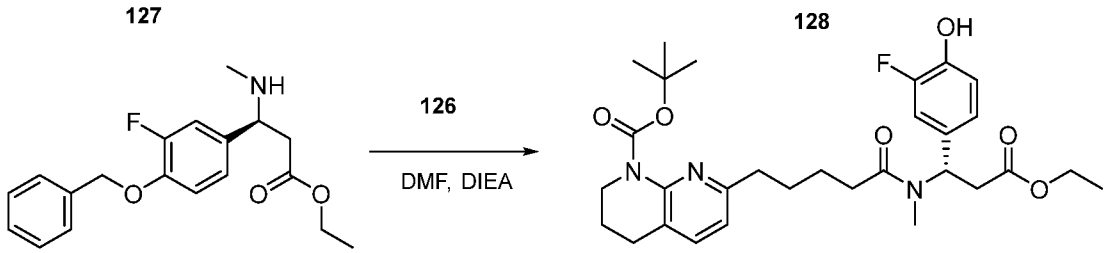


[0328] To compound 125 (92.1 mg, 0.275 mmol) in THF (1.5 mL) at 0°C was added DCC (68.1 mg, 0.331 mmol). After 5 minutes PNP (106.1 mg, 0.331 mmol) was added, the ice bath was removed, and stirring continued for 1 hour. Upon completion the suspension was chilled to -20°C for 1 hour and the precipitate was removed by filtration. The supernatant was

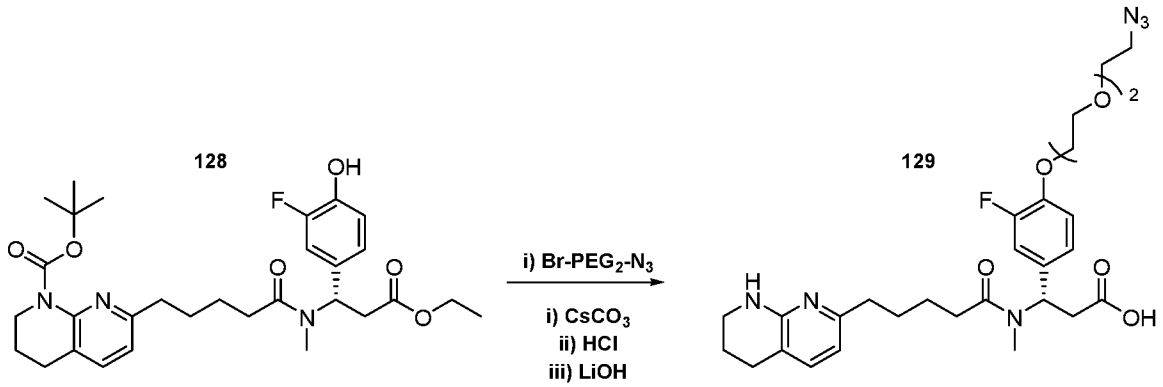
concentrated and yielded 129 mg (103%) of crude product 126 that was subsequently used without further purification.



[0329] A mixture containing compound 124 (148.6 mg, 0.468 mmol) and potassium carbonate (129 mg, 0.937 mmol) in DMF (2 mL) was treated with methyl iodide (66.5 mg, 0.468 mmol) and stirred at 50°C for 3 hours. Upon completion of alkylation all volatiles were removed and the product was isolated over silica eluting a gradient of ethyl acetate in hexanes, each buffered with 1% TEA, to yield 94.6 mg (61%).



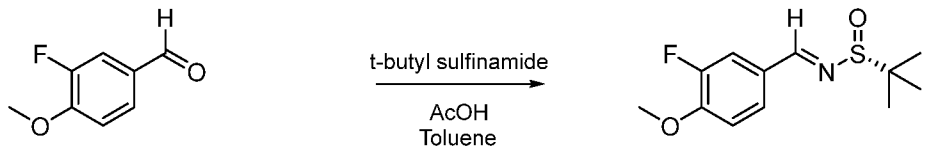
[0330] To compound 127 (94.5 mg, 0.285 mmol) in DMF (2 mL) was added DIEA (149 uL, 0.856 mmol) followed by Compound 126 (129.9 mg, 0.285 mmol) and the mixture was stirred for 1 hour at 80°C. Upon completion all volatiles were removed and the crude was dissolved in MeOH, treated with 10% palladium on carbon (20 mg), and the flask was charged with 60 PSI of hydrogen. Upon completion the suspension was filtered. The supernatant was concentrated and the crude product obtained was used subsequently without further purification.



[0331] A mixture containing compound 128 (159 mg, 0.285 mmol), Bromo-PEG_2-Azide (74.7 mg, 0.314 mmol) and cesium carbonate (204 mg, 0.627 mmol) in DMF (2 mL) was heated to 60° C for 2 hours. Upon completion all volatiles were removed and the crude was treated with 4M HCl in dioxane (0.5 mL, 2 mmol) and heated to 40° C for 3 hours. Upon completion all volatiles were removed. The crude was suspended in a mixture of THF (1 mL), MeOH (1.5 mL) and H_2O (1.5 mL), treated with lithium hydroxide (83.5 mg, 3.48 mmol) and heated to 40°C for 16 hours. Upon completion the pH was adjusted to 3 with TFA, and the product was isolated by separation over a Phenomenex® Gemini® C18 column (21.2x250mm, 5 micron) eluting a gradient of acetonitrile in water containing 0.1% TFA to yield 33.1 mg (20%).

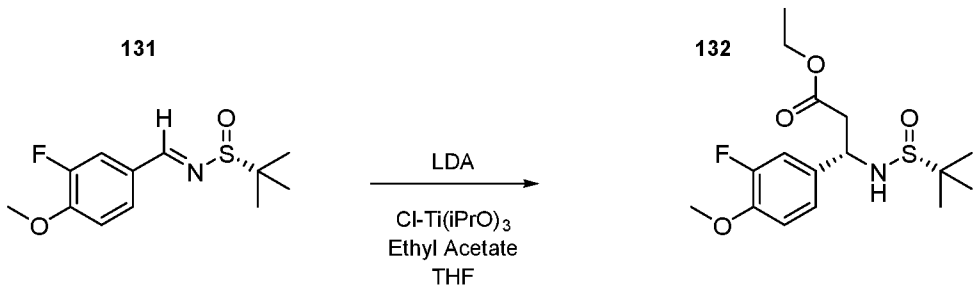
Synthesis of Structure 33c ((R)-1-azido-13-(3-fluoro-4-methoxyphenyl)-12-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanoyl)-3,6,9-trioxa-12-azapentadecan-15-oic acid)

130 131



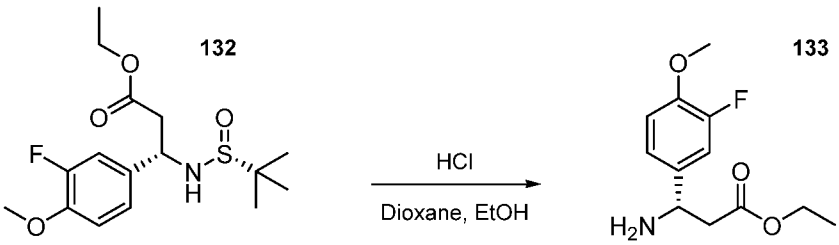
[0332] A mixture containing compound 130 (1.5 g, 9.73 mmol), (R) t-butyl sulfinamide (2.36 g, 19.46 mmol), and AcOH (0.14 mL) in toluene (45 mL) was refluxed in a flask fitted with a Dean-Stark trap for 16 hours. Upon completion the reaction was quenched by addition of saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The product was isolated by separation over silica eluting a gradient of ethyl acetate in hexanes to yield 1.714 g (68.4%).

131 132

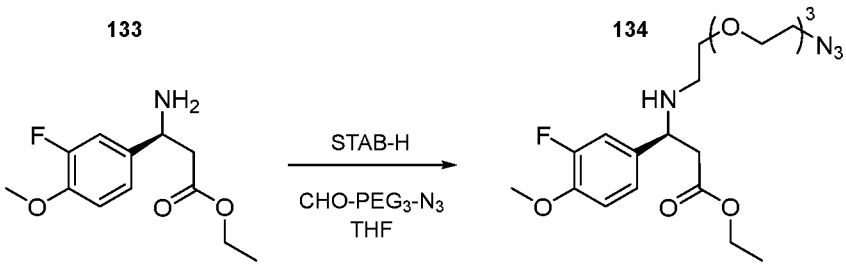


[0333] To DIA (3.056 mL, 21.80 mmol) in THF (18 mL) at -78°C was added a 2.5M solution of n-BuLi (8.324 mL, 20.81 mmol) was added dropwise. Stirring was continued for 5 minutes at -78°C and ethyl acetate (1.94 mL, 19.82 mmol) was added dropwise. Stirring was continued for a further 10 minutes at -78°C and a solution of chloro titanium

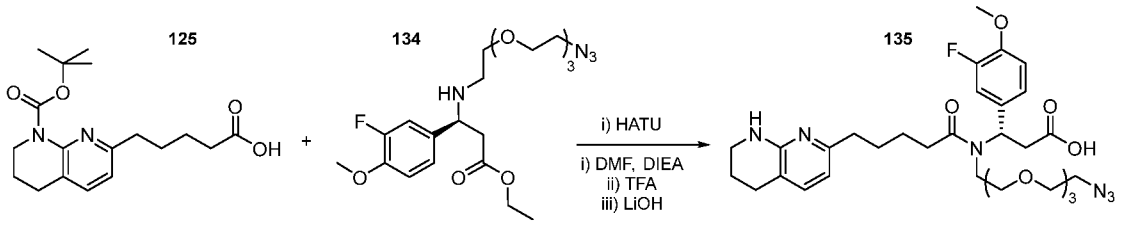
triisopropoxide (9.94 mL, 41.62 mmol) in THF (10 mL) was added dropwise. Stirring was continued for a further 15 minutes at -78°C and a solution of compound 131 (1.70 g, 6.61 mmol) in THF (12 mL) was added dropwise. Stirring was continued for 1.5 hours at -78°C. Upon completion the reaction was quenched by addition of saturated ammonium bicarbonate. The suspension was diluted with 7 volumes of ethyl acetate and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The product was isolated over silica eluting a gradient of ethyl acetate in hexanes to yield 0.984 g (43%).



[0334] To compound 132 (0.975 g, 2.82 mmol) in EtOH (6 mL) at 0°C was added 4 M HCl (2.12 mL, 8.47 mmol) in dioxane and stirred for 30 minutes. Upon completion the reaction was diluted with water (15 mL) and washed with diethyl ether. The organic layer was separated and the pH of the aqueous layer was adjusted to 12 with sodium hydroxide. The aqueous layer was washed with 5 volumes of ethyl acetate and the organic layer was separated, filtered over sodium sulfate and concentrated. The product was isolated by separation over silica eluting a gradient of ethyl acetate in hexanes containing 1% TEA to yield 0.434 g (64%).

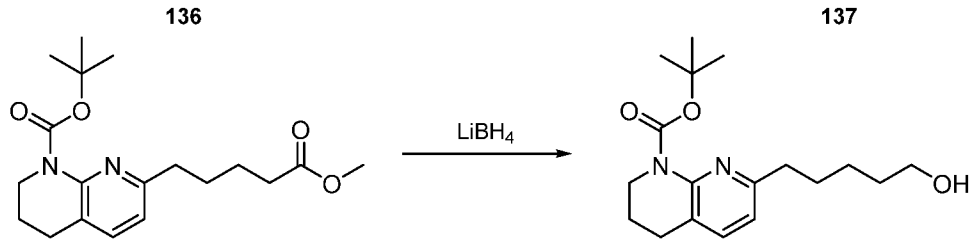


[0335] To a mixture of compound 133 (0.120 g, 0.497 mmol) and PEG (0.151 g, 0.696 mmol) in THF (2 mL) over 3Å molecular sieves was added STAB-H (0.253 g, 1.19 mmol) and the suspension was stirred for 16 hours at room temperature. Upon completion the reaction was quenched by addition of saturated sodium bicarbonate and the crude was extracted with three portions of ethyl acetate. The separated organic extracts were combined, dried over sodium sulfate, filtered and concentrated. The crude obtained was used subsequently without further purification.

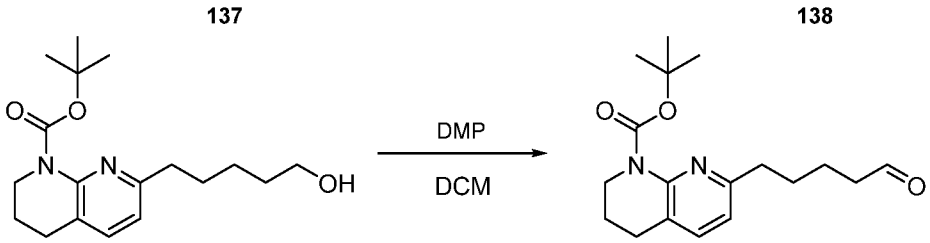


[0336] Compound 134 (0.200 g, 0.597 mmol) in DMF (2 mL) was treated with HATU (0.227 g, 0.597 mmol) and stirred for 5 minutes. To the activated ester was added DIEA (0.259 mL, 1.49 mmol) followed by compound 125 (0.220 g, 0.497 mmol) in DMF (1 mL) and the resulting mixture was stirred for 1 hour. All volatiles were removed and the resulting crude was treated with neat TFA (3.8 mL) and stirred for 3 hours at 40°C. Upon completion of BOC removal all volatiles were removed and the crude was suspended in a mixture of THF (4 mL), water (8 mL), and MeOH (8 mL). The resulting mixture was treated with LiOH (71.6 mg, 2.98 mmol) and heated to 40°C for 16 hours. Upon completion the pH was adjusted to 3 with TFA, and the product was isolated by separation over a Phenomenex® Gemini® c18 column (21.2x250mm, 5 micron) eluting a gradient of acetonitrile in water containing 0.1% TFA to yield 56.2 mg (18%, 3-Steps).

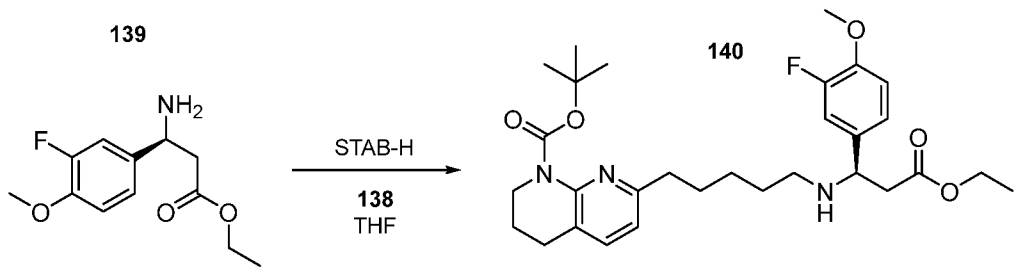
Synthesis of Structure 34c ((S)-1-azido-13-(3-fluoro-4-methoxyphenyl)-12-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentyl)-3,6,9-trioxa-12-azapentadecan-15-oic acid)



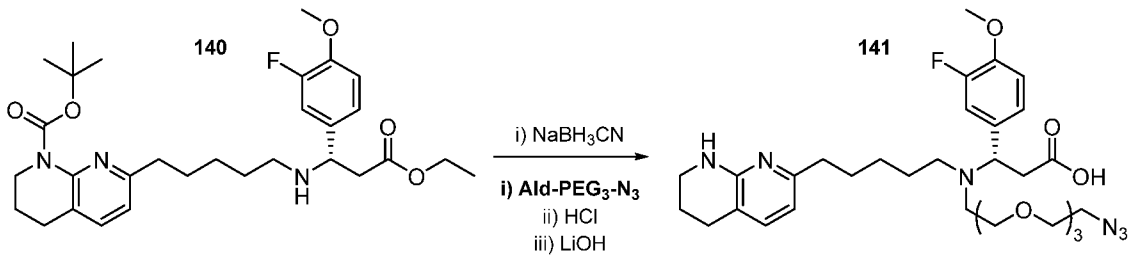
[0337] Compound 136 (0.500 g, 1.45 mmol) in a mixture of THF (9.0 mL) and MeOH (0.5 mL) at 0°C was treated with lithium borohydride (94.5 mg, 4.34 mmol). Cooling was removed and stirring was continued until gas evolution ceased. The reaction mixture was diluted with 5 volumes of EtOAc. The organic layer was washed with ammonium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The product was isolated by elution over silica using a gradient of ethyl acetate in hexanes to yield 309 mg (67%).



[0338] To a solution containing compound 137 (0.305 g, 0.952 mmol) in DCM (9 mL) at 0°C was added Martin's reagent in several portions. Several drops of water were added, cooling was removed, and the reaction was stirred for 3 hours. Upon completion the mixture was washed with saturated sodium bicarbonate then saturated sodium thiosulfate. The separated organic was dried over sodium sulfate, filtered and concentrated. The product 138 was separated over silica eluting a gradient of MeOH in DCM to yield 140 mg (46%).



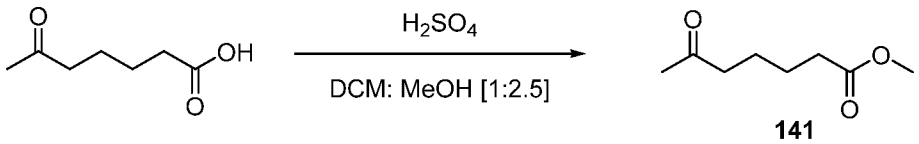
[0339] To a mixture containing compound 1 (85.2 mg, 0.353 mmol) and 138 (134.9 mg, 0.424 mmol) in THF (2.5 mL) over 3Å molecular sieves was added STAB-H (0.150 g, 0.706 mmol) and the resulting suspension was heated to 40°C for 16 hours. Upon completion the reaction was diluted with 5 volumes of ethyl acetate and treated with saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The product was isolated by separation over silica eluting a gradient of MeOH in DCM containing 1% TEA to yield 64 mg (33%).



[0340] To a mixture containing compound 140 (60 mg, 0.110 mmol), Ald-PEG_3-N_3 (71.9 mg, 0.331 mmol) and AcOH (3 µL, 0.0276 mmol) in MeOH (1 mL) over 3Å molecular sieves was added sodium cyanoborohydride (28.9 mg, 0.276 mmol) and the reaction was stirred at 40°C for 3 hours. Upon completion the mixture was cooled to 0°C, water was added (0.15 mL) and

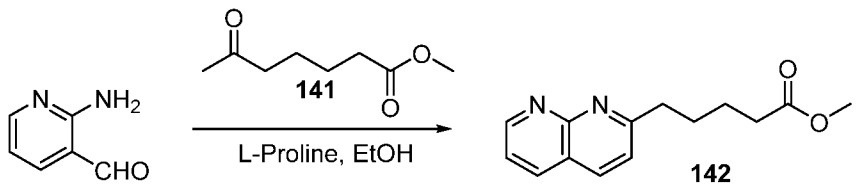
the solution was acidified to a pH of 7 using HCl (4M) in dioxane. All methanol was subsequently removed, 4M HCl (0.138 mL, 0.552 mmol) in dioxane was added and the mixture was stirred at 40°C for 2 hours. Upon completion of BOC removal all volatiles were removed and the crude was suspended in a mixture of THF (1 mL), water (2 mL) and MeOH (2 mL) and treated with lithium hydroxide (26.5 mg, 1.104 mmol). Upon completion of ester removal the pH was adjusted to 3 by addition of TFA and the product was isolated by separation on a Phenomenex® (21.2x250mm) C18 column eluting a gradient of acetonitrile in water containing 0.1% TFA to yield 16.4 mg (24%, 3-Steps).

Synthesis of Structure 36c ((S)-3-(4-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-3-fluorophenyl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid)



141

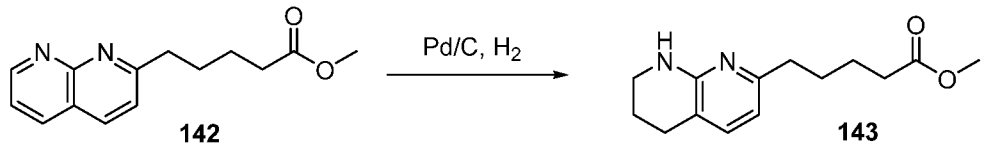
[0341] To a solution of 6-oxoheptanoic acid (9.74 g, 68 mmol) in DCM (30 mL) and MeOH (75 mL) was added conc. H_2SO_4 (0.18 mL, 3.4 mmol) at room temperature. The reaction mixture was refluxed overnight. The reaction mixture was then concentrated to an oil, redissolved in DCM (150 mL), and washed with sat. aq. $NaHCO_3$ (2 x 40 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was used in the next step without further purification. Yield of compound 141: 10.2 g (95%). ^1H NMR(400 MHz, DMSO-d6): δ 3.58 (s, 3H), 2.43 (t, 2H), 2.29 (t, 2H), 1.46 (m, 4H).



142

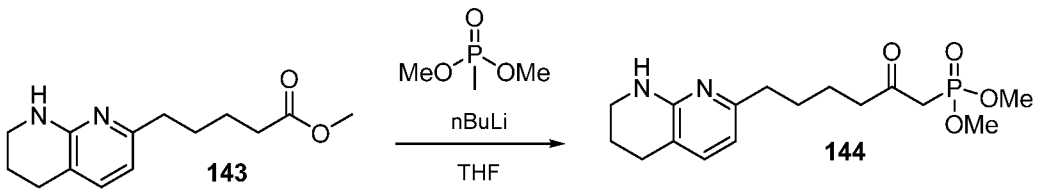
[0342] To a solution of compound 141 (10.2 g, 65 mmol) and 2-amino-3-formylpyridine (7.89 g, 65 mmol) in EtOH (80 mL) was added L-proline (3.72 g, 32 mmol). The reaction mixture was heated at reflux overnight. The reaction mixture was then concentrated, dissolved in EtOAc (50 mL), and washed with water (3 x 30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using

silica gel as the stationary phase and was eluted with a gradient of EtOAc in DCM (10-100%). Yield of compound 142: 6.08 g (39%). Mass calculated for $C_{14}H_{16}N_2O_2$ $[M+H]^+$: 245.13, found: 245.21.



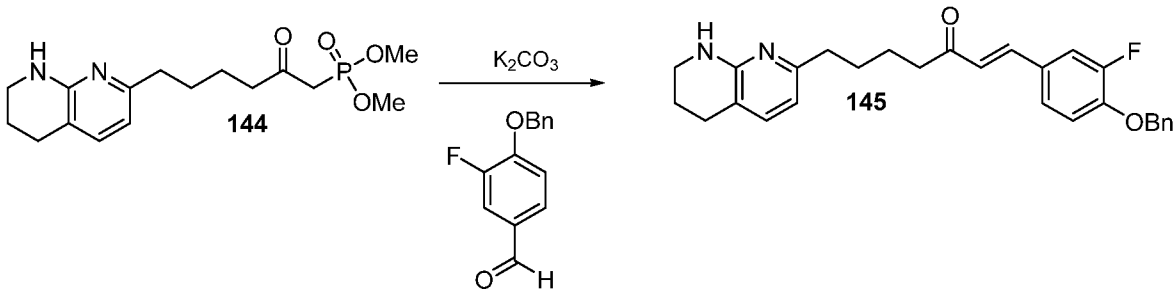
142 143

[0343] To a solution of compound 142 (6.08 g, 24.9 mmol) in MeOH (50 mL) was added Pd/C (10% loading, Degussa type, 1.99 g, 1.87 mmol). The reaction flask was charged with nitrogen, evacuated, and backfilled with nitrogen three times. This process was repeated with hydrogen, and the reaction vessel was finally charged with hydrogen (1 atm) and stirred overnight at room temperature. The reaction mixture was filtered over Celite®, the pad rinsed with MeOH, and the filtrate concentrated. The product, compound 143, was used in the next step without further purification assuming 100% yield. Mass calculated for $C_{14}H_{20}N_2O_2$ $[M+H]^+$: 249.16, found: 249.08.

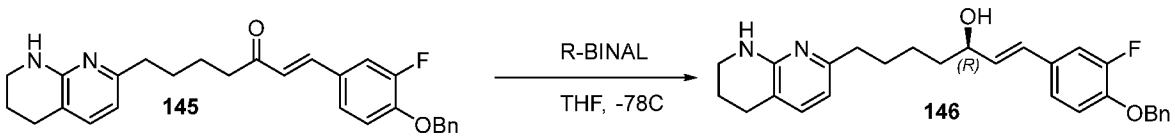


143 144

[0344] To a solution of dimethyl methylphosphonate (12.3 g, 100 mmol) in anhydrous THF (120 mL) was added n-BuLi solution (2.5 M in hexanes, 40 mL, 100 mmol) via syringe pump over 1 h at -78 °C. A solution of compound 143 (6.175 g, 24.9 mmol) in THF (40 mL) was added to the reaction mixture over 45 m at -78 °C. After stirring for 20 m at -78 °C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (200 mL), warmed to rt, and extracted with EtOAc (400 mL). The organic layer was washed with water (200 mL) and brine (200 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The product was used in the next step without further purification. Yield of compound 144: 7.86 g (93%). Mass calculated for $C_{16}H_{25}N_2O_4P$ $[M+H]^+$: 341.17, found: 341.17.



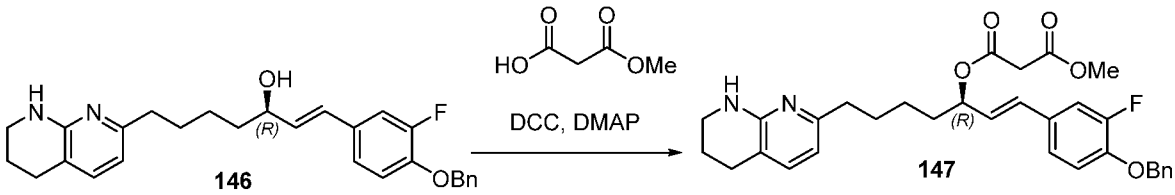
[0345] A suspension of 3-fluoro-4-(phenylmethoxy)-benzaldehyde (0.38 g, 1.65 mmol), compound 144 (0.67 g, 1.98 mmol), and anhydrous potassium carbonate (0.547 g, 3.96 mmol) in THF (13.5 mL) was heated at reflux overnight. Additional 3-fluoro-4-(phenylmethoxy)-benzaldehyde (0.19 g, 0.83 mmol) and potassium carbonate (0.23 g, 1.65 mmol) were added and the reaction mixture was refluxed for an additional 4 h. The mixture was diluted with EtOAc (100 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of MeOH in DCM (0-10%). Yield of compound 145: 446 mg (61%). Mass calculated for $C_{28}H_{29}FN_2O_2$ $[M+H]^+$: 445.23, found: 445.41.



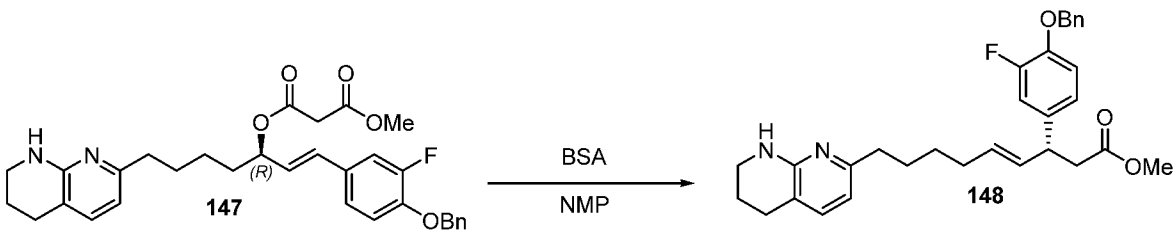
[0346] Preparation of R-BINAL: To a slurry of LAH (0.396 g, 10.4 mmol, 0.98 eq) dry THF (34 mL) was added EtOH (0.492 g, 10.65 mmol, 1.00 eq) as a solution in THF (3.2 mL) over 10 m while maintaining an internal temperature < 35 °C. After aging for 30 m, R-BINOL (3.05 g, 10.65 mmol, 1.00 eq) was added as a solution in THF (10 mL), maintaining an internal temperature < 35 °C (ca 10 minutes). After stirring for 2 h at room temperature, the reaction mixture was cooled on a dry ice/acetone bath to -78 °C.

[0347] Compound 145 (1.18 g, 2.65 mmol) was dried azeotropically with anhydrous toluene (50 mL) and was dissolved in anhydrous THF (12 mL). The solution of compound 145 was added dropwise to the solution of R-BINAL via syringe pump over 45 m at -78 °C. After 1.5 h, the reaction vessel was transferred to a very large dewer, filled with dry ice/acetone, and covered with aluminum foil. The reaction mixture was stirred ON at -78 °C. The majority of the reduction occurred within the first 1.5 h with only a small amount additional conversion overnight. The reaction was quenched by addition of sat. aq. NH_4Cl (150 mL) and warmed to

room temperature. The mixture was further acidified to pH = 7 using 6 N HCl then extracted with EtOAc (2 x 250 mL). The combined organic phase was washed with water (125 mL) and brine (125 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of MeOH in DCM (0-5%). Yield of compound 146: 634 mg (53%). Chiral purity was determined by analytical chiral HPLC, Chiralpak AD-H column 4.6 x 250 mm, 5 micron, EtOH 0.1% diethylamine isocratic, 1.75 mL/min. The first eluting R isomer was 86 area% pure, corresponding to 72% ee. Compound 146 was further purified by chiral semi-preparative HPLC (Chiralpak AD-H 21.2 x 250 mm, 5 micron, EtOH 0.1% diethylamine, 20 mL/min). Final yield of compound 146: 445 mg (98% ee). Mass calculated for $C_{28}H_{31}FN_2O_2$ $[M+H]^+$: 447.25, found: 447.30.

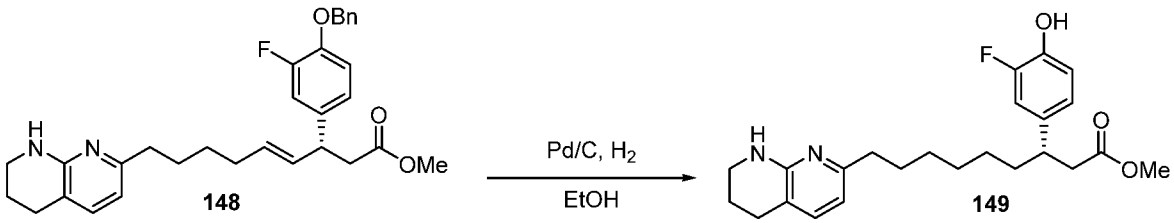


[0348] To a solution of compound 146 (0.325 g, 0.73 mmol) and malonic acid monomethyl ester (0.103 g, 0.87 mmol) in DCM (3 mL) was added a solution of DMAP (9 mg, 0.073 mmol) in DCM. The mixture was cooled to 0 °C and DCC (0.180 g, 0.87 mmol) was added. The cooling bath was removed, and the reaction was stirred at rt ON. The reaction mixture was then diluted with DCM (10 mL) and filtered. The filtrate was concentrated and purified by CombiFlash using silica gel as the stationary phase, eluting with a gradient of MeOH (0-5%) in DCM. Yield of compound 147: 142 mg (37%). Mass calculated for $C_{32}H_{35}FN_2O_5$ $[M+H]^+$: 547.26, found: 547.58.

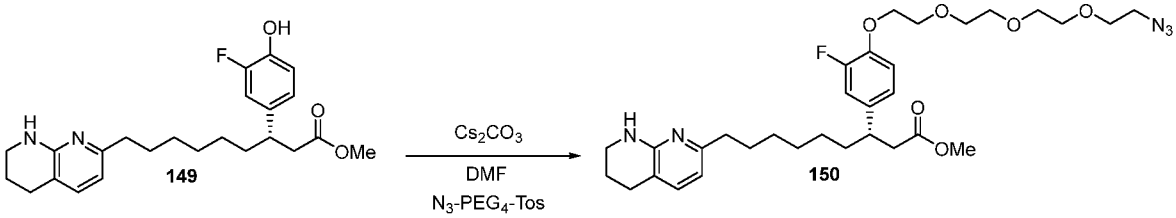


[0349] To a solution of compound 147 (0.232 g, 0.42 mmol) in NMP (0.5 mL) was added *N,O*-bis(trimethylsilyl)acetamide (0.229 g, 1.12 mmol) at room temperature. The mixture was heated at 60 °C for 30 m. Brine (58 μL) was added in two portions over 5 m. The reaction

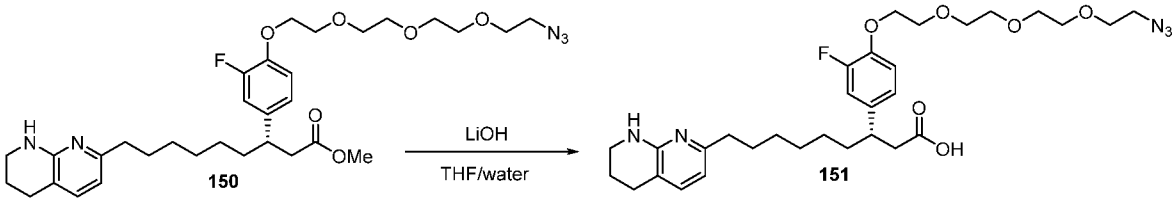
mixture was then heated at 90 °C for 3 h then room temperature overnight. The reaction mixture was diluted with EtOAc (12 mL) and washed with water (3 mL). The aqueous layer was back extracted with EtOAc (12 mL). The combined organic layer was concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of MeOH in DCM. Yield of compound 148: 140 mg (66%). Mass calculated for $C_{31}H_{35}FN_2O_3$ $[M+H]^+$: 503.27, found: 503.29.



[0350] To a solution of compound 148 (0.169 g, 0.34 mmol) in EtOH (3 mL) was added a slurry of Pd/C (10% loading, 36 mg, 0.034 mmol) in EtOH (1 mL). The reaction vessel was pressurized and vented with hydrogen three times. The reaction vessel was repressurized to 55 psi for 3 h. The reaction mixture was diluted with MeOH (5 mL) and filtered. The filtrate was concentrated and the product, compound 149, was used in the next step without further purification assuming 100% yield. Mass calculated for $C_{24}H_{31}FN_2O_3$ $[M+H]^+$: 415.24, found: 415.07.

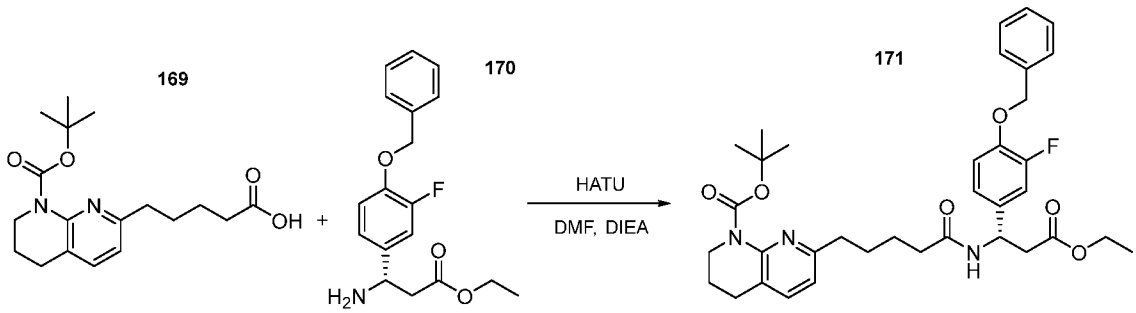


[0351] To a solution of compound 149 (139 mg, 0.34 mmol) and azido-PEG_4-tosylate (0.188 mg, 0.50 mmol) in DMF (2.5 mL) was added cesium carbonate (164 mg, 0.50 mmol). The reaction mixture was heated at 40 °C for 1 h then quenched with sat. aq. $NaHCO_3$ (3 mL). The mixture was extracted with EtOAc, (3 x 10 mL). The combined organic phase was washed with water (2 x 5 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated, and used in the next step without further purification. Mass calculated for $C_{32}H_{46}FN_5O_6$ $[M+H]^+$: 616.35, found: 616.90.

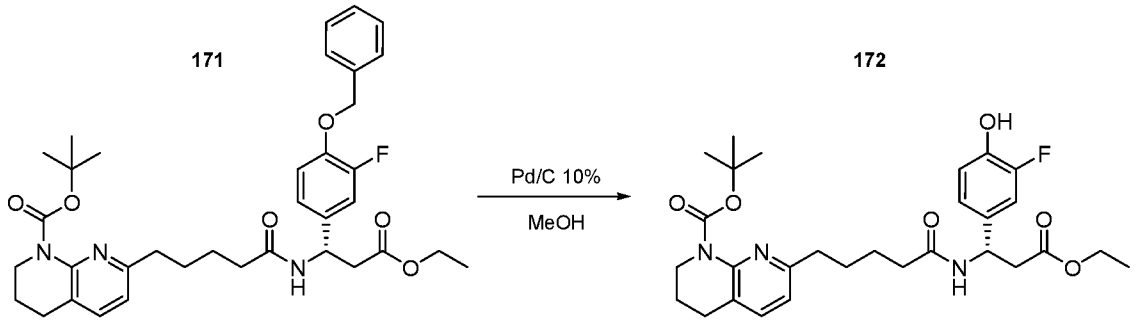


[0352] To a solution of compound 150 (0.207 mg, 0.34 mmol) in THF (1.5 mL) and water (1.5 mL) was added lithium hydroxide (0.040 g, 1.68 mmol). The reaction mixture was heated to 40 °C overnight. The next morning the reaction mixture was acidified with 6 N HCl to pH = 7 and concentrated under reduced pressure. The residue was dissolved in 35% ACN in H_2O, 0.1% TFA, and purified by RP-HPLC (Thermo Aquasil C18, 250 x 21 mm, 5 µm, 20 mL/min, gradient of ACN in H_2O containing 0.1% TFA). Yield of compound 151 (SM 36): 125 mg (52% over 3 steps). Mass calculated for $C_{31}H_{44}FN_5O_6$ $[M+H]^+$: 602.34, found: 602.85.

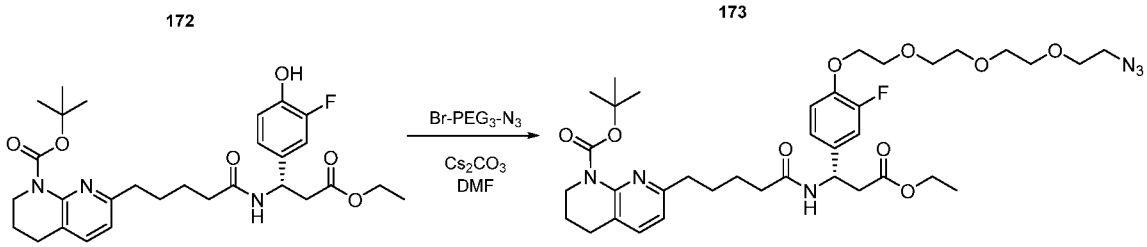
Synthesis of Structure 37c ((S)-3-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-3-fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid)



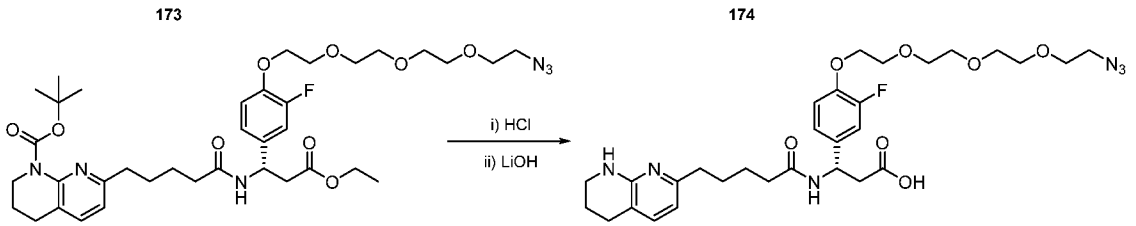
[0353] Compound 169 (90 mg, 0.268 mmol) in DMF (1.5 mL) was treated with HATU (112 mg, 0.295 mmol) and stirred for 5 minutes. A mixture containing compound 170 (94 mg, 0.295 mmol) and DIEA (0.154 mL, 0.884 mmol) in DMF (0.5) was subsequently added and stirring was continued for 1 hour. Upon completion all volatiles were removed and compound 171 was isolated by separation over silica eluting a gradient of MeOH in DCM yielding 123 mg (72%).



[0354] A suspension containing 10 % palladium on carbon (21 mg, 0.0194 mmol) and compound 171 (123 mg, 0.194 mmol) in MeOH (2 mL) was charged with 60 PSI hydrogen and stirred for 1 hour. Upon completion the suspension was filtered over Celite® and concentrated to yield 88 mg (83%) of crude that was used subsequently without further purification.



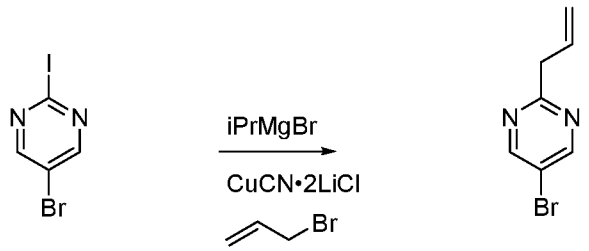
[0355] A suspension containing compound 172 (87 mg, 0.160 mmol), Br-PEG_3-N_3 (50 mg, 0.176 mmol) and cesium carbonate (115 mg, 0.352 mmol) in DMF (1 mL) was heated to 60°C and stirred for 2 hours. Upon completion all volatiles were removed and compound 173 was isolated by separation over silica eluting a gradient of MeOH in DCM yielding 91 mg (76%).



[0356] Compound 173 (50 mg, 0.067 mmol) in dioxane (0.5 mL) was treated with a 4M HCl (0.671 mmol, 0.168 mL) solution in dioxane and stirred at 40°C for 3 hours. Upon completion all volatiles were removed. The crude was dissolved in a mixture of H_2O (0.4 mL), THF (0.2 mL) and MeOH (0.4 mL), treated with LiOH (8 mg, 0.356 mmol), and stirred at 40°C for 16 hours. Upon completion the pH was adjusted to 3 with TFA and the product was isolated by separation over a Phenomenx Gemini C18 column (21.2x250mm, 5 micron)

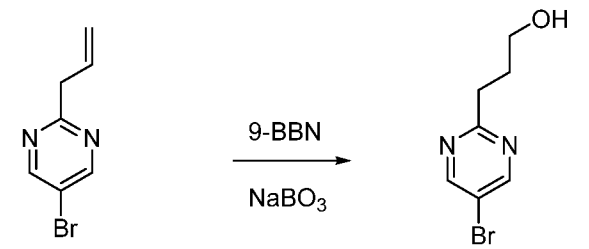
eluting a gradient of acetonitrile in water containing 0.1% TFA to yield 25 mg (60%, 2-Steps).

Synthesis of Structure 38c ((S)-3-(2-(3-((2-(2-(2-azidoethoxy)ethoxy)ethyl)amino)-3-oxopropyl)pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid) and Structure 39c ((S)-3-(2-(1-azido-12-oxo-3,6,9-trioxa-13-azahexadecan-16-yl)pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid)



152

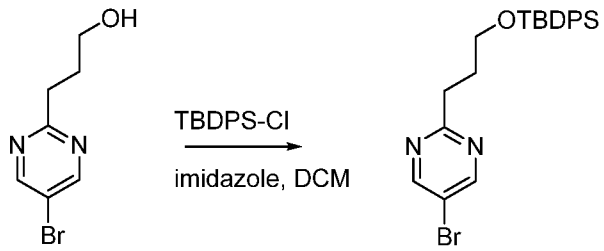
[0357] To a solution of 5-bromo-2-iodo-pyrimidine (8.00 g, 28.1 mmol) in anhydrous THF (95 mL) was added a solution of i-PrMgBr in THF (0.75 M, 56 mL, 42.0 mmol) at -78 °C while maintaining an internal temperature < -70 °C (ca. 15 m). The resulting solution was then stirred for 15 minutes before adding CuCN•2LiCl solution in THF (1 M, 31 mL, 31.0 mmol) and then allyl bromide (5.10 g, 42 mmol) as a solution in THF (10 mL). The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with MeOH (40 mL) and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc in hexanes (0-20%). Yield of compound 152: 4.13 g (74%). Mass calculated for $C_7H_7BrN_2$ $[M+H]^+$: 198.99, found: 199.05.



152 153

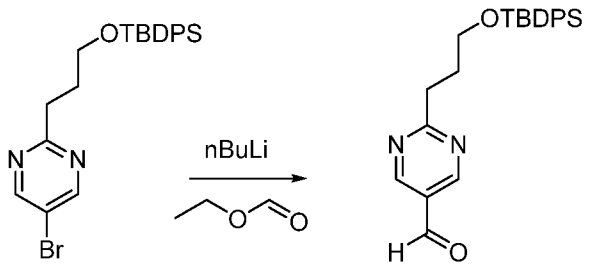
[0358] To a solution of compound 152 (7.70 g, 38.7 mmol) in THF (115 mL) was added a solution of 9-BBN in THF (0.5 M, 131 mL, 65.8 mmol) at 0 °C over 30 m. The reaction mixture was warmed to room temperature and stirred overnight. To the reaction mixture was

added a slurry of $NaHCO_3$ (48.7 g, 580 mmol) in water (100 mL) followed by a slurry of $NaBO_3$ monohydrate (46.3 g, 464 mmol) in water (100 mL) at 0 °C. The cooling bath was removed, and the mixture was stirred vigorously for 1 h. The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (200 mL). The organic phases were combined and washed with brine (100 mL). The brine layer was back extracted with EtOAc (100 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to yield ~15 g crude, yellow oil. The crude was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc in hexanes (50-100%). Yield of compound 153: 3.44 g (41%). Mass calculated for $C_7H_9BrN_2O$ $[M+H]^+$: 217.00, found: 216.97.



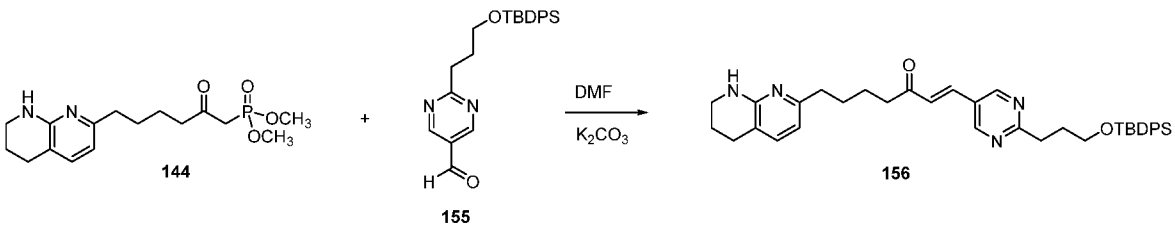
153 **154**

[0359] To a solution of compound 153 (3.44 g, 15.8 mmol) in DCM (40 mL) was added imidazole (1.73 g, 25.4 mmol) and a solution of TBDPSCl (5.23 g, 19.0 mmol) in DCM (12 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was diluted with DCM (75 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc (0-8%) in hexanes. Yield of compound 154: 5.56 g (77%). Mass calculated for $C_{23}H_{27}BrN_2OSi$ $[M+H]^+$: 455.12, found: 455.44.

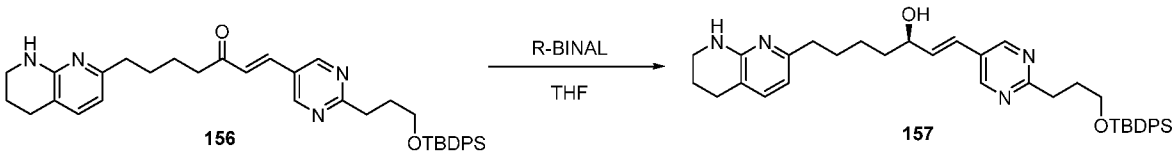


154 155

[0360] To a solution of compound 154 (6.07 g, 13.3 mmol) in THF (150 mL) at -75 °C was added a solution of nBuLi in THF (2.5 M, 5.6 mL, 14.0 mmol) dropwise, maintaining an internal temperature < -70 °C (ca. 10 m). After 3 m, a solution of ethyl formate (1.04 g, 1.13 mL, 14.0 mmol) in THF (5 mL) was added dropwise, maintaining an internal temperature < -70 °C. The mixture was stirred at -78 °C for 20 m then quenched with HCl in dioxane (4 M, 3.67 mL, 14.7 mmol) that was further diluted with THF (5 mL), maintaining an internal temperature < -65 °C. The cooling bath was removed, and the reaction was warmed to ambient temperature and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc in hexanes (0-20%). Yield of compound 155: 1.79 g (33%). ^{1}H NMR(400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 9.06 (s, 2H), 7.64 (m, 4H), 7.38 (m, 6H), 3.77 (t, 2H), 3.20 (t, 2H), 2.17 (q, 2H), 1.03 (s, 9H).



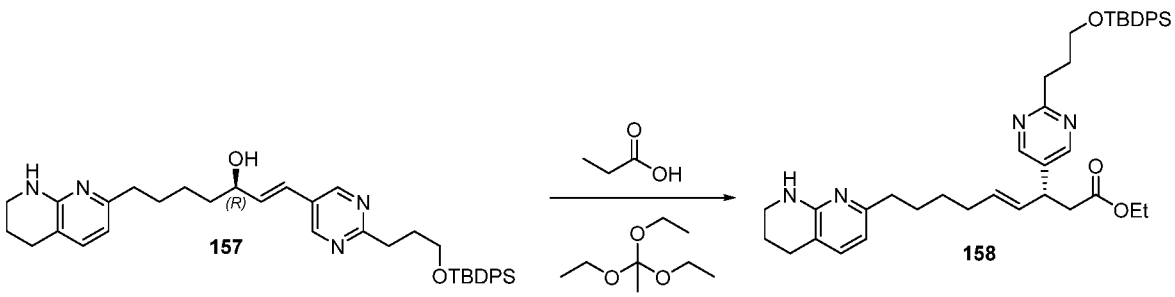
[0361] To a solution of compound 144 (1.68 g, 4.15 mmol) and compound 155 (1.70 g, 4.98 mmol) in THF (25 mL) was added K_2CO_3 (0.861 g, 6.23 mmol). The reaction mixture was heated to 40 °C for 2.5 h then 50 °C for 12 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc (0-100%) in hexanes containing 1% triethylamine. Yield of compound 156: 2.04 g (79%). Mass calculated for $C_{38}H_{46}N_4O_2Si$ $[M+H]^+$: 619.35, found: 619.69.



156 157

[0362] Preparation of R-BINAL: LAH (1.169 g, 30.8 mmol) was slurried in dry THF (90 mL). To the slurry was added EtOH as a solution in THF (6 M, 5.2 mL, 31.4 mmol) keeping T_{int} < 40 °C. The mixture was aged at 35 °C for 40 m then cooled to 30 °C. A solution of R-(BINOL) (9.00 g, 31.4 mmol) in THF (45 mL) was added, keeping T_{int} < 40 °C. The mixture was aged at 50 °C for 1 h, cooled to ambient temperature, then heated to 50 °C and TMEDA (14.1 mL, 11.0 g, 94.3 mmol) was added. The mixture was aged at 50 °C for 1 h, cooled to ambient temperature, and then used with compound 156.

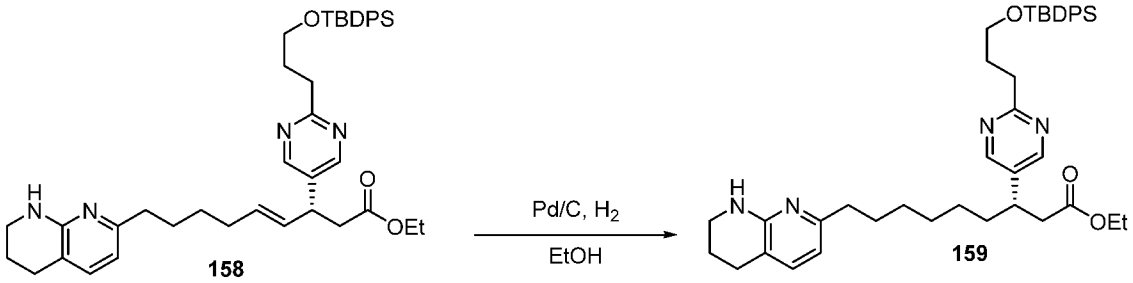
[0363] To a solution of R-BINAL (~0.2 M, 110 mL, 22.0 mmol) in THF was added a solution of compound 16 (1.16 g, 1.88 mmol) in THF (12 mL) at -78 °C over 5 m. After 30 m, the reaction mixture was quenched with sat. aq. NH_4Cl, warmed to rt, and the product was extracted with EtOAc (3 x 125 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of MeOH (0-5%) in EtOAc containing 1% triethylamine. Yield of compound 157: 0.96 g (82%). Chiral purity was determined by analytical chiral HPLC, Chiralpak AD-H column 4.6 x 250 mm, 5 micron, 25% EtOH, 75% hexanes, 0.1% diethylamine isocratic, 2 mL/min). The second eluting R isomer was ~95 area% pure, corresponding to ~90% ee. Mass calculated for $C_{38}H_{48}N_4O_2Si$ $[M+H]^+$: 621.36, found: 621.71.



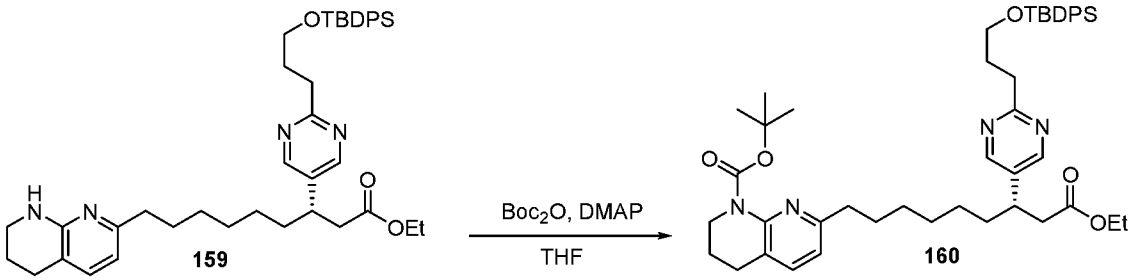
157 158

[0364] To a solution of compound 157 (0.925 g, 1.49 mmol) in triethylorthoacetate (9.25 mL) was added a solution of propionic acid in trimethylorthoacetate (0.15 M, 0.55 mL, 0.08 mmol). The reaction mixture was heated at 140 °C in a sealed vial for 1.5 h. The reaction mixture was concentrated, and the residue was purified by CombiFlash using silica gel as the

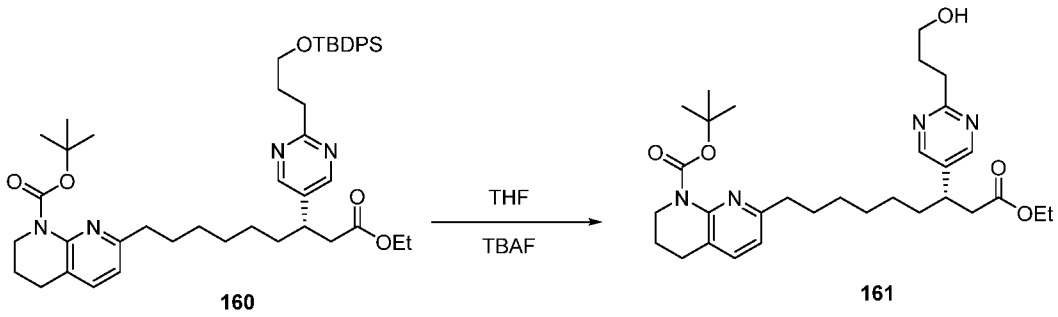
stationary phase, eluting with a gradient of EtOAc (0-50%) in hexanes containing 1% triethylamine. Yield of compound 158: 0.898 g (87%). Mass calculated for $C_{42}H_{54}N_4O_3Si$ $[M+H]^+$: 691.41, found: 691.93.



[0365] To a solution of compound 158 (0.893 g, 1.30 mmol) in EtOH (10 mL) was added a slurry of Pd/C (extent of loading: 10 wt%, 0.138 g, 0.13 mmol) in EtOH (4 mL). The reaction mixture was charged 50 psi H_2 and stirred for 4.5 h. The reaction mixture was filtered, concentrated, and used in the next step without further purification. Yield of compound 159: 0.885 g (99%). Mass calculated for $C_{42}H_{56}N_4O_3Si$ $[M+H]^+$: 693.42, found: 693.82.

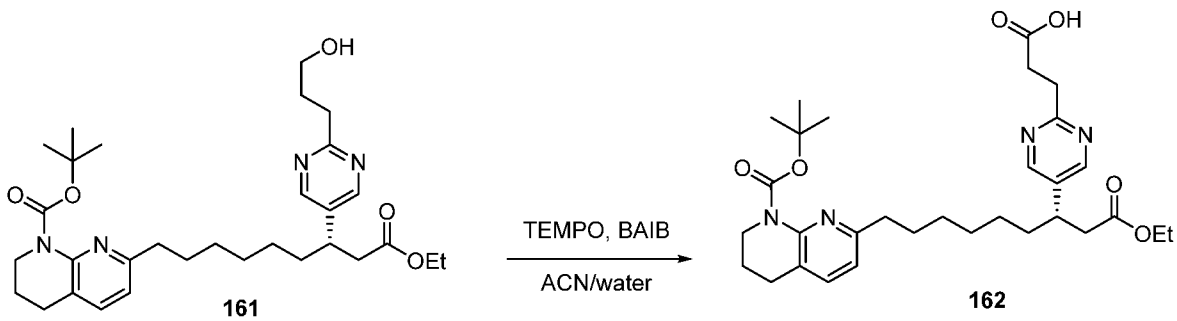


[0366] A solution of Boc anhydride (0.836 g, 3.83 mmol) in THF (2.5 mL) was added to compound 159 (0.885 g, 1.28 mmol) followed by a solution of DMAP (20 mg/mL in THF, 155 uL, 0.0031 g, 0.026 mmol). The mixture was heated to 60 °C for 6 h. The reaction mixture was concentrated and the residue was purified by CombiFlash using silica gel as the stationary phase, eluting with a gradient of EtOAc (0-50%) in hexanes. Yield of compound 160: 0.721 g (71%). Mass calculated for $C_{47}H_{64}N_4O_5Si$ $[M+H]^+$: 793.47, found: 794.28.



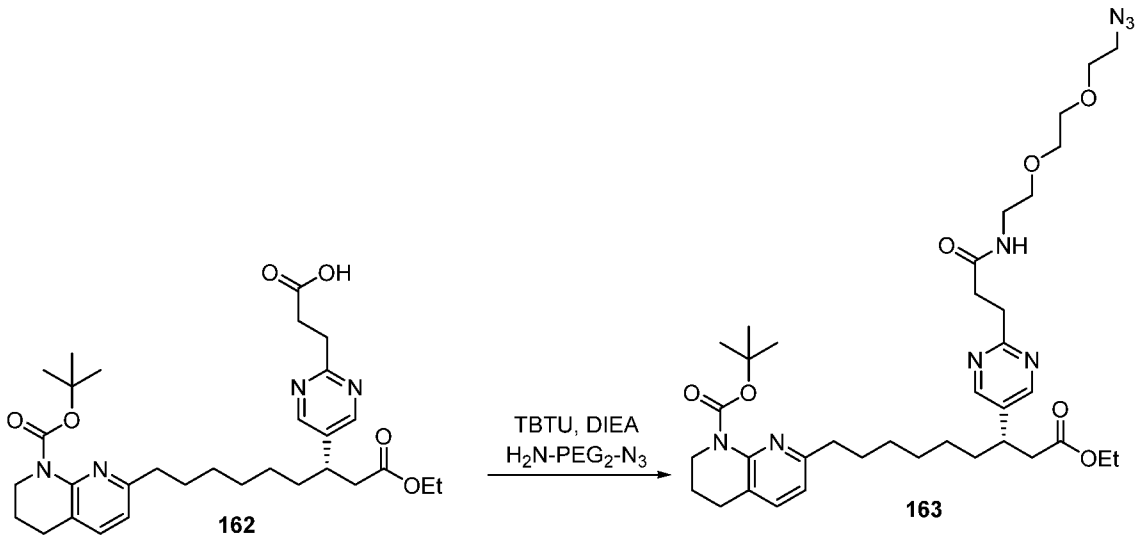
160 161

[0367] To a solution of compound 160 (0.621 g, 0.783 mmol) in THF (6 mL) was added a solution of TBAF in THF (1 M, 1.2 mL, 1.2 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with sat. aq. NH_4Cl (2 x 10 mL). The organic layer was concentrated. The residue was purified by CombiFlash using silica gel as the stationary phase and was eluted with a gradient of EtOAc (50-100%) in hexanes. Yield of compound 21: 0.362 g (83%). Chiral purity was determined by analytical chiral HPLC, Chiralpak AD-H column 4.6 x 250 mm, 5 micron, 20% EtOH, 80% hexanes, 0.1% diethylamine, isocratic, 1.5 mL/min. The second eluting R isomer was 93% pure, corresponding to 86% ee. was Compound 161 was further purified by chiral semi-preparative HPLC (Chiralpak AD-H 21.2 x 250 mm, 5 micron, 20% EtOH, 80% hexanes, 0.1% diethylamine, 60 mL/min). Final yield of compound 161: 308 mg (99% ee). Mass calculated for $C_{31}H_{46}N_4O_5$ $[M+H]^+$: 555.36, found: 555.72.

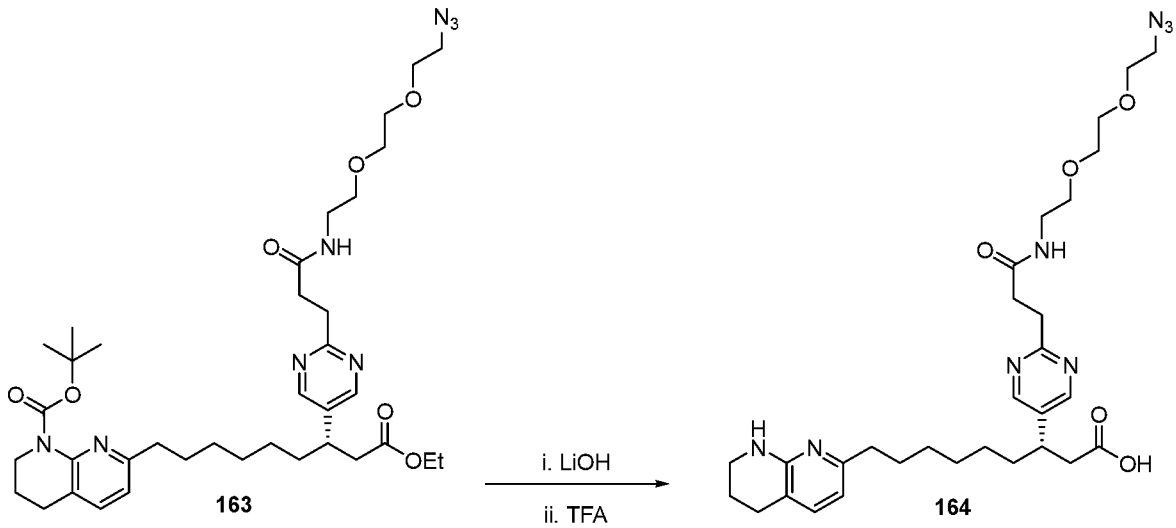


161 162

[0368] To a solution of compound 161 (0.030 g, 0.054 mmol) in ACN (0.30 mL) was added BAIB (0.042 g, 0.130 mmol) and TEMPO (2.5 mg, 0.016 mmol) followed by water (0.30 mL) at room temperature. After 2 hr, the reaction mixture was concentrated. The residue was purified by RP-HPLC (Phenomenex Gemini C18 21.2 x 250 mm, 5 micron, 0.1% TFA water/ACN, 30-80% ACN gradient). Yield of compound 162: 0.030 g (97%). Mass calculated for $C_{31}H_{44}N_4O_6$ $[M+H]^+$: 569.34, found: 569.68.

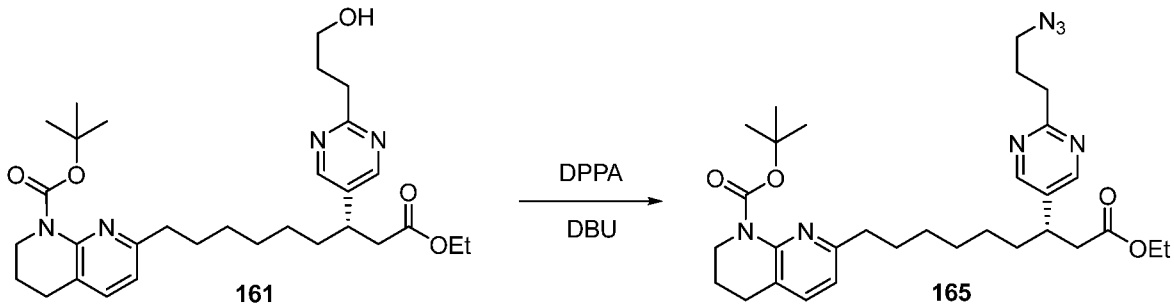


[0369] To a solution of compound 162 (33 mg, 0.058 mmol) and amino-PEG_2-azide (15 mg, 0.087 mmol) in DMF (0.5 mL) was added TBTU (32 mg, 0.099 mmol) then DIEA (35 µL, 26 mg, 0.203 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 m. The reaction mixture was concentrated, and the product, compound 163, was used in the next step without purification. Mass calculated for $C_{37}H_{56}N_8O_7$ $[M+H]^+$: 725.44, found: 725.77.

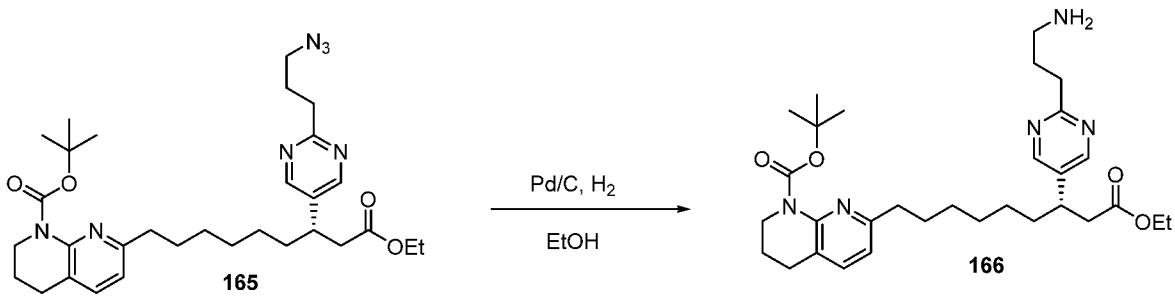


[0370] To a solution of compound 163 (42 mg, 0.058 mmol) in THF (0.30 mL) was added a 1 M solution of LiOH (0.174 mL, 0.174 mmol). The reaction mixture was heated at 40 °C for 1 hr. An additional portion of LiOH was added (0.174 mL, 0.174 mmol). After 3 h, the reaction stalled, and an additional portion of LiOH was added (0.174 mL, 0.174 mmol). The

reaction was stirred for an additional 2 hr (9 eq LiOH, 5 hr total). The reaction mixture was neutralized to pH = 5 using 3 N HCl and concentrated. The residue was dissolved in TFA:water [95:5] and stirred for 2 hours at room temperature. The reaction mixture was concentrated, and the residue was purified by RP-HPLC (Phenomenex Gemini C18 21.2 x 250 mm, 5 micron, water/ACN containing 0.1% TFA, 20-50% ACN gradient). Yield of compound 164 (**Structure 38c**): 23 mg (66%). Mass calculated for $C_{30}H_{44}N_8O_5$ $[M+H]^+$: 597.35, found: 597.85.

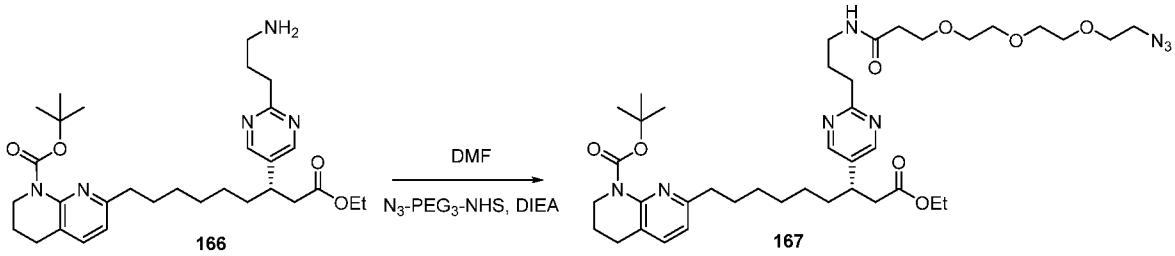


[0371] To a solution of compound 161 (30 mg, 0.054 mmol) in THF (150 µL) was added diphenyl phosphoryl azide (35 µL, 45 mg, 0.162 mmol) followed by DBU (12 µL, 12 mg, 0.081 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The next morning, the reaction mixture was heated at 60 °C for 7 h. The reaction mixture was concentrated and purified by RP-HPLC (Phenomenex Gemini C18 21.2 x 250 mm, 5 micron, 0.1% TFA water/ACN, 32-60% ACN gradient). Yield of compound 165: 14 mg (44%). Mass calculated for $C_{31}H_{45}N_7O_4$ $[M+H]^+$: 580.36, found: 580.66.

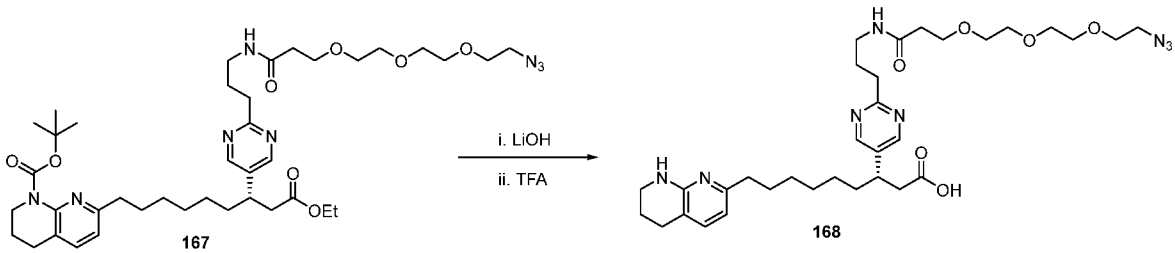


[0372] To a solution of compound 165 (18 mg, 0.031 mmol) in EtOH (100 µL) was added a slurry of Pd/C (10% loading, 3.3 mg, 0.003 mmol) in EtOH (170 µL). The reaction vessel was charged with H_2 then evacuated three times and then charged with H_2 (1 atm). After 30

m, the reaction mixture was filtered, concentrated, and used in the next step without further purification. Yield of compound 166: 17 mg (99%). Mass calculated for $C_{31}H_{47}N_5O_4$ $[M+H]^+$: 554.37, found: 554.73.



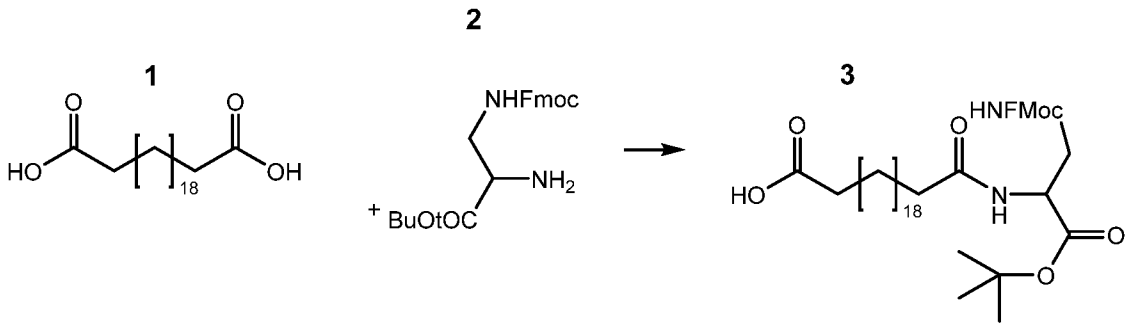
[0373] To a solution of compound 166 (17 mg, 0.031 mmol) and azido-PEG_3-NHS ester (14 mg, 0.040 mmol) in DMF (170 µL) was added DIEA (16 µL, 12 mg, 0.092 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, concentrated, and then used in the next step without purification. Mass calculated for $C_{40}H_{62}N_8O_8$ $[M+H]^+$: 783.48, found: 783.84.



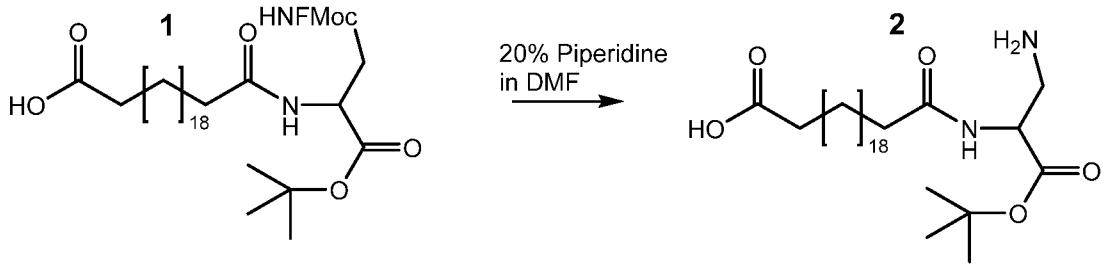
[0374] To a solution of compound 167 (24 mg, 0.031 mmol) in THF (180 µL) was added a 1 M solution of LiOH (153 µL, 0.153 mmol). The reaction mixture was heated at 40 °C. After 1 hr, an additional portion of LiOH was added (153 uL, 0.153 mmol, 5 eq). The reaction mixture was stirred for 3 h at 40 °C then room temperature overnight. The reaction mixture was neutralized to pH = 5 using 3 N HCl and concentrated. The residue was dissolved in TFA:water [95:5] and stirred for 3 hours at room temperature. The reaction mixture was concentrated, and the residue was purified by RP-HPLC (Phenomenex Gemini C18 21.2 x 250 mm, 5 micron, water/ACN containing 0.1% TFA, 15-45% ACN gradient). Yield of compound 168 (**Structure 39c**): 9.8 mg (49%). Mass calculated for $C_{33}H_{50}N_8O_6$ $[M+H]^+$: 655.40, found: 656.01.

Synthesis of Pharmacokinetic Enhancers

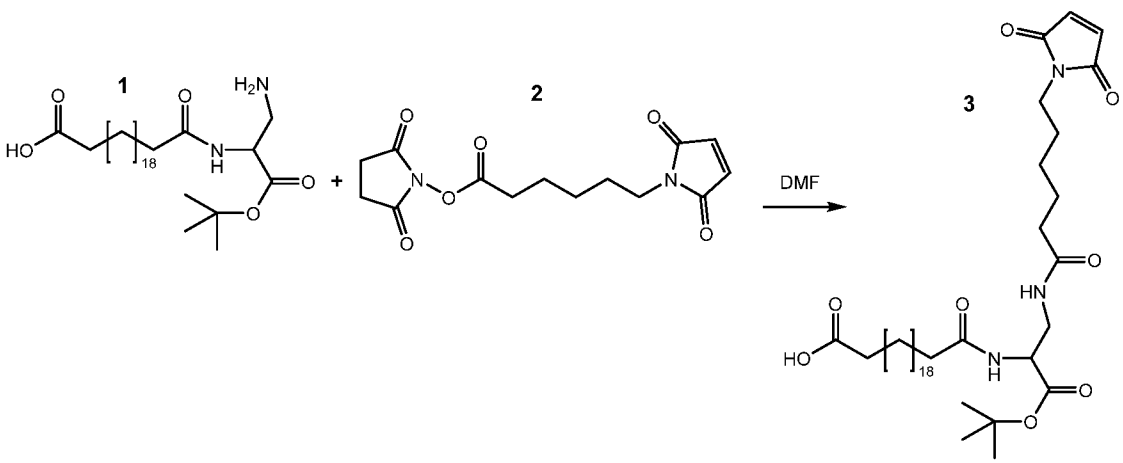
[0375] Mal-C22-diacid



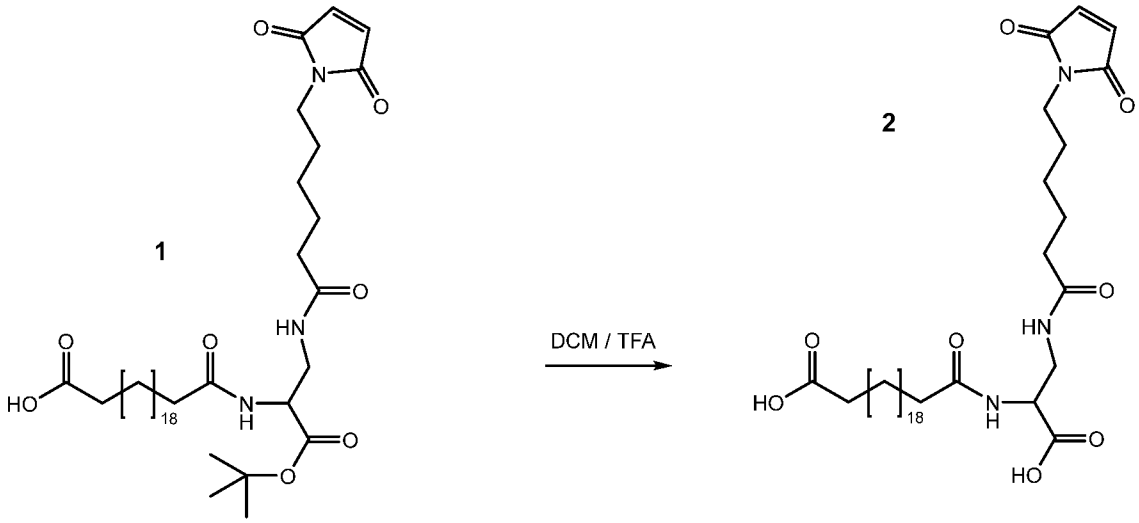
[0376] Compound **1** (0.200 g) was mixed with TBTU (0.182 g) in 2 mL of DMF. DIPEA (0.207 mL) was added dropwise. Then Compound **2** (0.227 g) was added after 5 minutes. The mixture was stirred for 1 hour. The mixture was then diluted with 40 mL of DCM and washed with 5% citric acid (4x30mL) and dried over Na_2SO_4, filtered and concentrated. The product was dried on rotary evaporator and high vacuum. The resulting solid was dry-loaded onto 12 G Redi-Sep® Rf column on CombiFlash® in Hex:EtOAc 0=>80% over 30 minutes. Yield: 53 mg (39.2%.)



[0377] Compound 1 was azeotropically distilled with toluene, 20% piperidine in DMF, and Et_3N mixture twice. The yield was 50 mg.

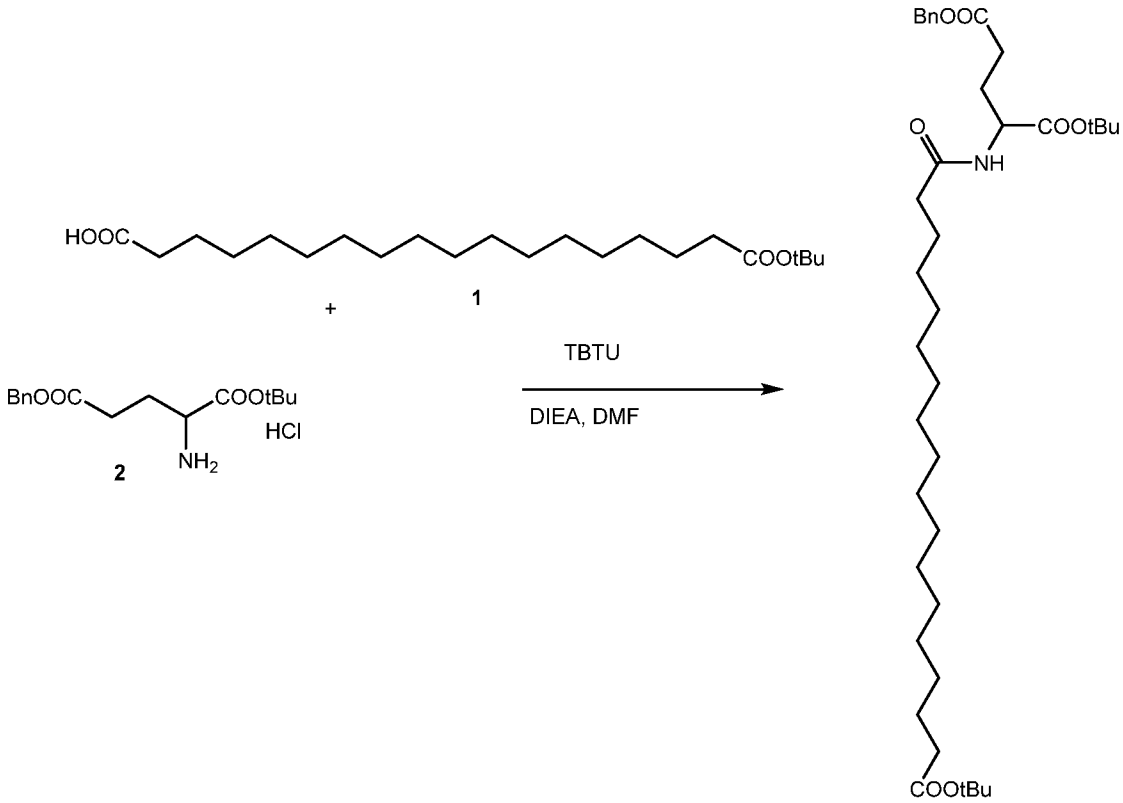


[0378] Compounds 1 (0.0350 g) and 2 (0.105 g) were combined in DMF and Et_3N (0.095 mL) was added. The reaction was complete after one hour. The mixture was then diluted with DCM and washed with 5% citric acid (3x8mL) and dried with Na_2SO_4, filtered and concentrated. The product was brought up in 1 mL of toluene and loaded onto a 4G Redi-Sep Rf column on CombiFlash®, with Hex:EtOAc 0=>100% EtOAc over 15 minutes. Then the mobile phase was switched to DCM:DCM with 20% MeOH 0=>100% over 20 minutes. Yield: 12 mg (24.9%.)

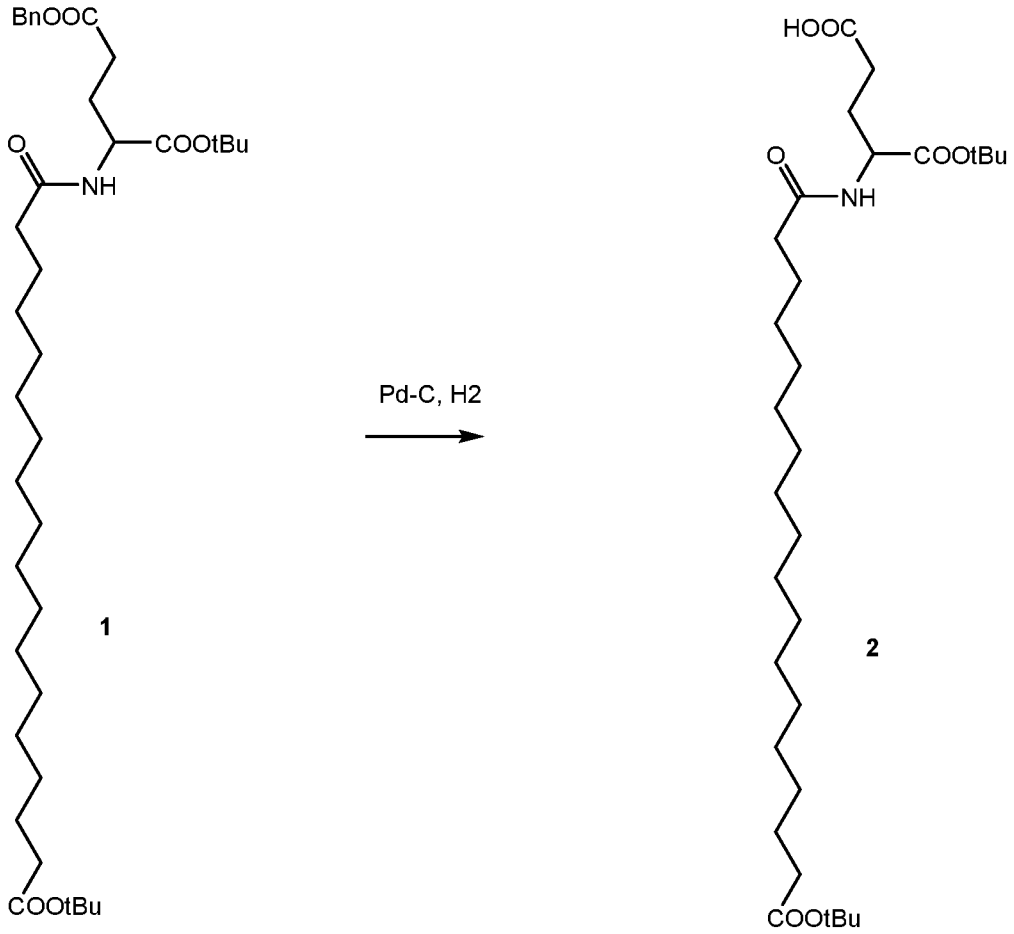


[0379] Compound 1 (0.012 g) was dissolved in 1 mL of a 1:1 mixture of DCM/TFA. The reaction was allowed to stir for 3 hours. The product was dried on rotary evaporator and high vacuum. Yield: 0.0110 g (99.6%.)

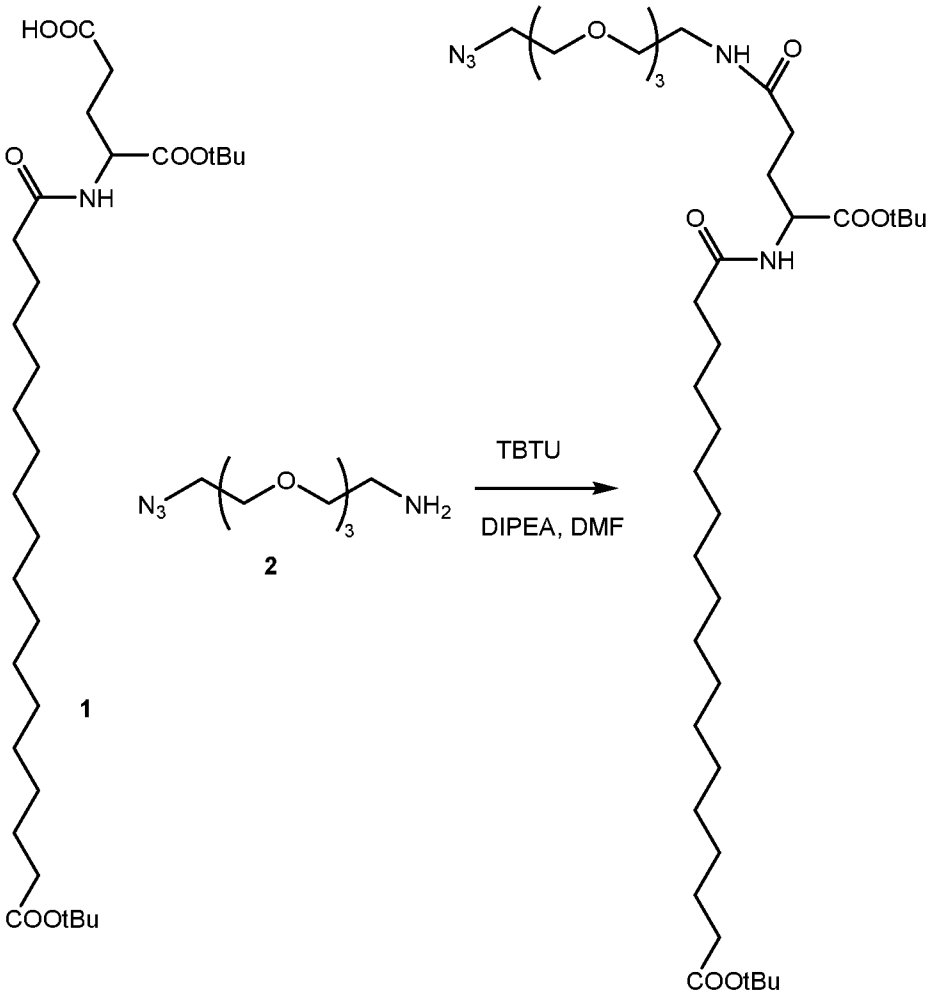
[0380] C18-diacid-N3



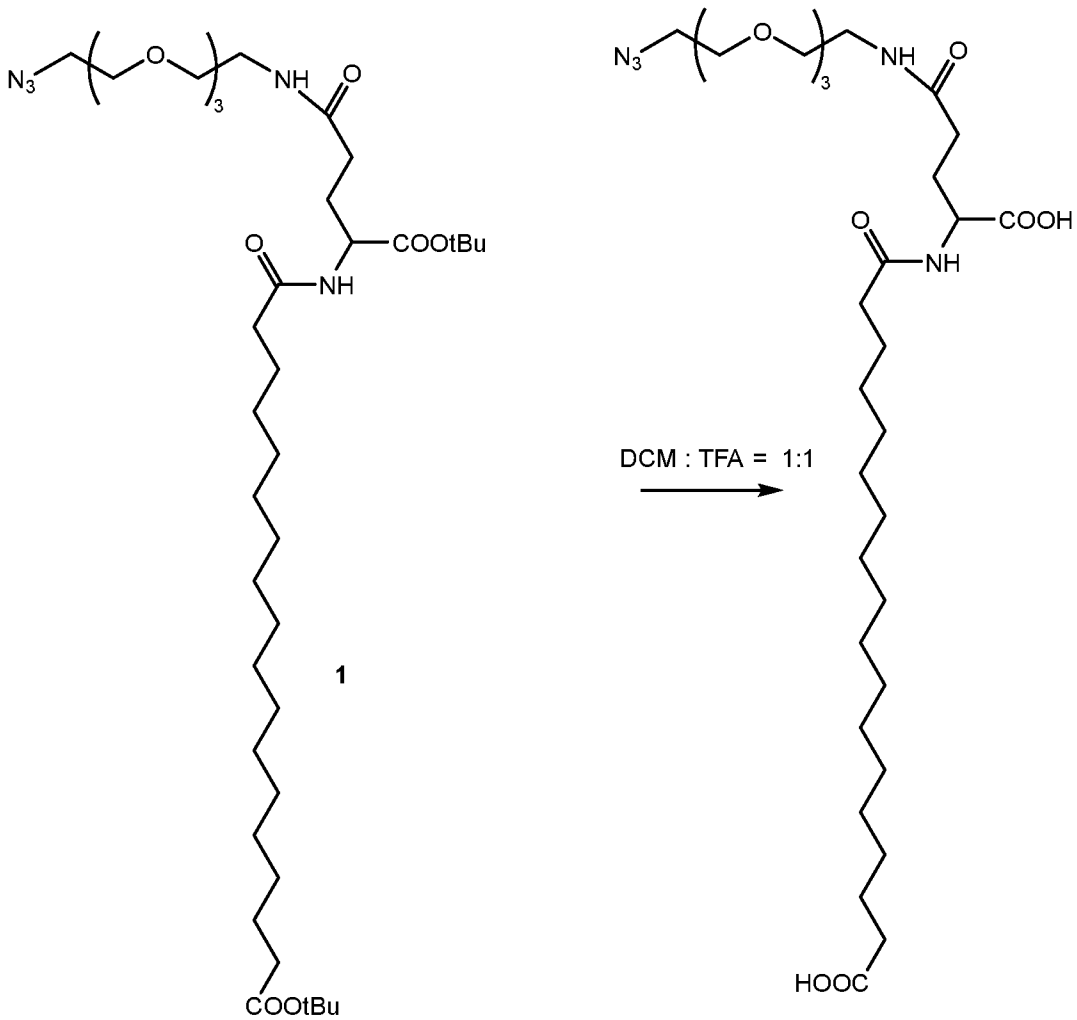
[0381] Compound 1 (0.500 g, Asta Tech. ® #64704) and compound 2 (0.454 g, Chem-Impex #16167) were dissolved in DMF and TBTU (0.442 g) and DIPEA (0.586 mL) were added. The mixture was allowed to stir for two hours. The mixture was then diluted with DCM (40 mL) and washed with H_2O (4x40mL), dried over Na_2SO_4, filtered and concentrated. The product was brought up in 2 mL of DCM and loaded onto Redi-Sep Rf column on CombiFlash® (Mobile phase DCM:DCM with 20% MeOH 0=>20% over 25 minutes.) The product was concentrated on high vacuum. Yield: 740 mg (85%.)



[0382] Compound 1 (0.720 g) was dissolved in 5 mL of MeOH in a flask. A septum was put on the flask and the atmosphere was evacuated and replaced with nitrogen two times. Then Pd/C 30% (0.200 g) was added via weighing papers. The septum was replaced, then the atmosphere was evacuated and replaced with hydrogen two times. The reaction was allowed to stir at room temperature for one hour. The mixture was filtered, and the filtrate dried on rotary evaporator and high vacuum. Yield: 665 mg.

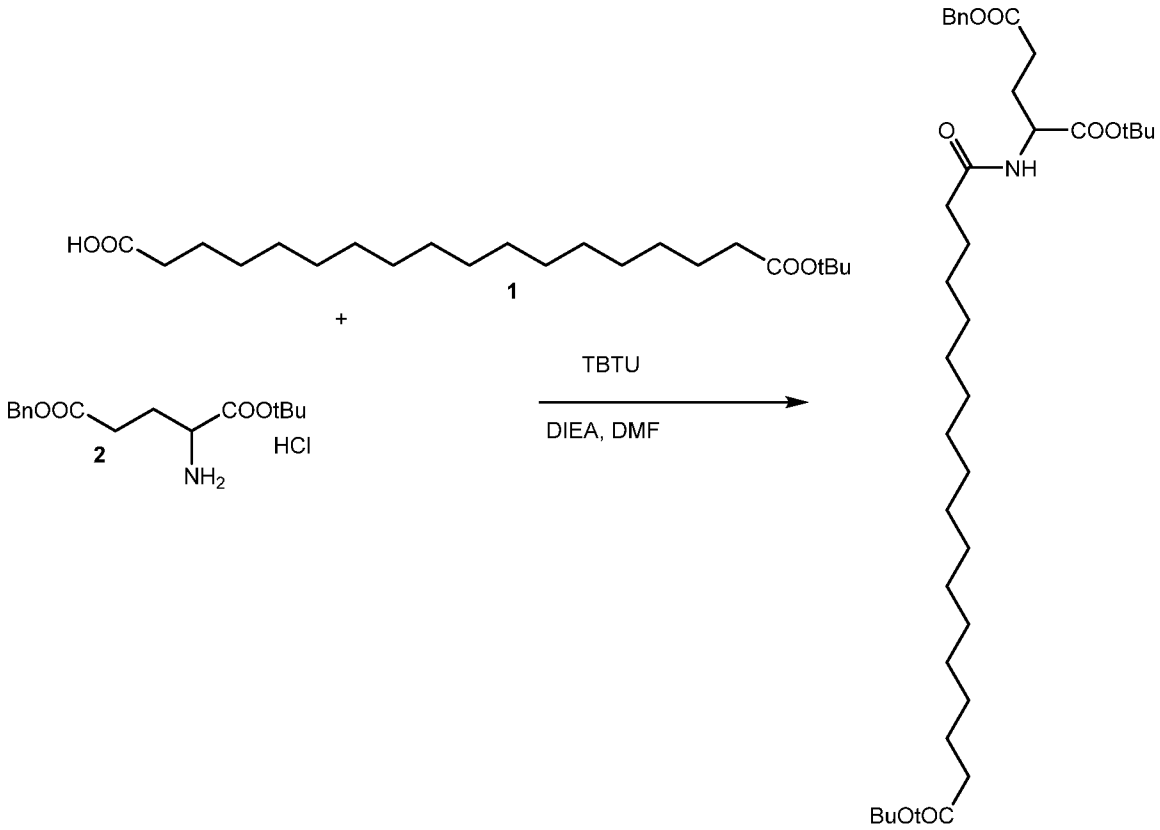


[0383] Compound 1 (0.150 g) and Compound 2 (0.0618 g) were dissolved in DMF and TBTU (0.0884 g) and DIPEA (0.117 mL) were added to the mixture. The reaction was allowed to stir at room temperature for one hour. The mixture was then diluted with DCM (12 mL), washed with water (4 x 8 mL), dried over Na_2SO_4, filtered and concentrated on high vacuum. The product was brought up in DCM (1 mL) and loaded onto 4G Redi-Sep Rf column on CombiFlash® (mobile phase DCM:DCM with 20% methanol 0=>50% over 25 minutes.) Yield: 162 mg (79%.)

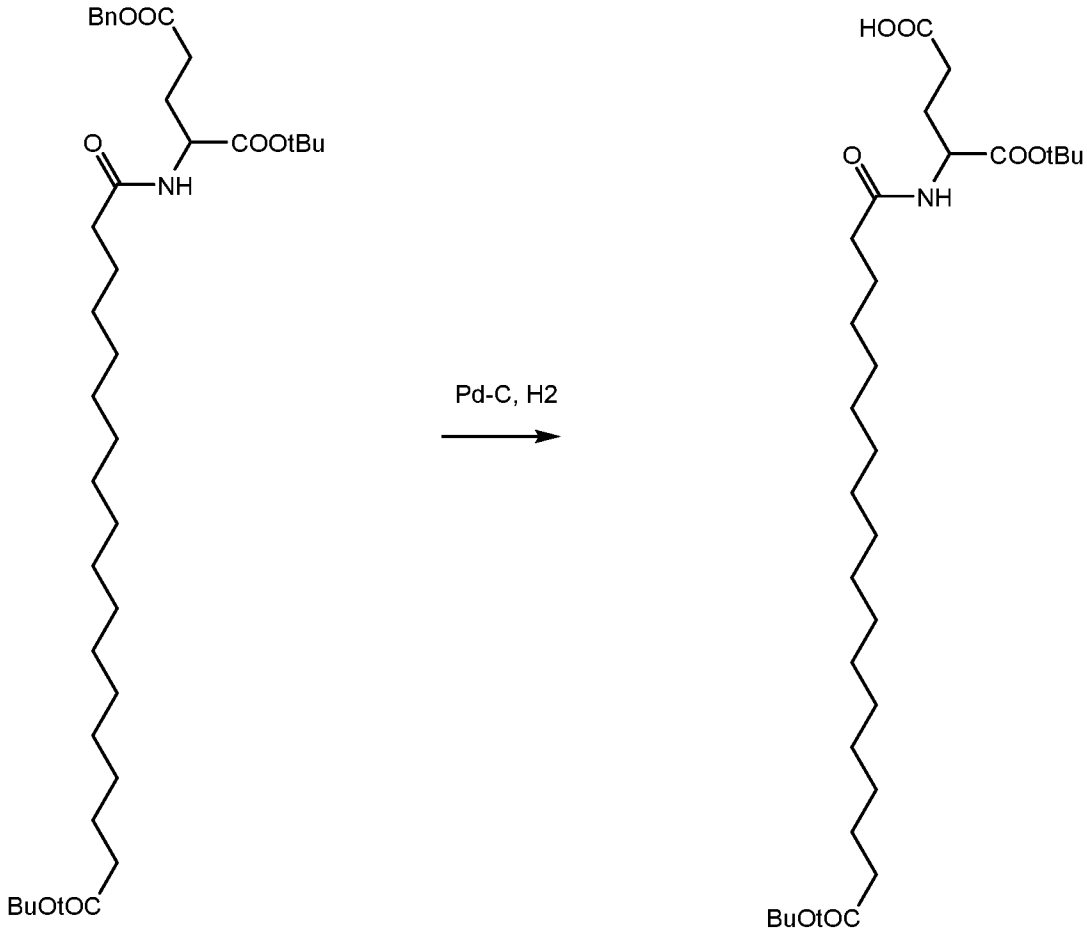


[0384] Compound 1 (0.155 g) was dissolved in a 1:1 mixture of DCM:TFA. The reaction was allowed to stir at room temperature for two hours. The product was concentrated on rotary evaporator and placed on high vacuum. Yield: 129 mg (97%.)

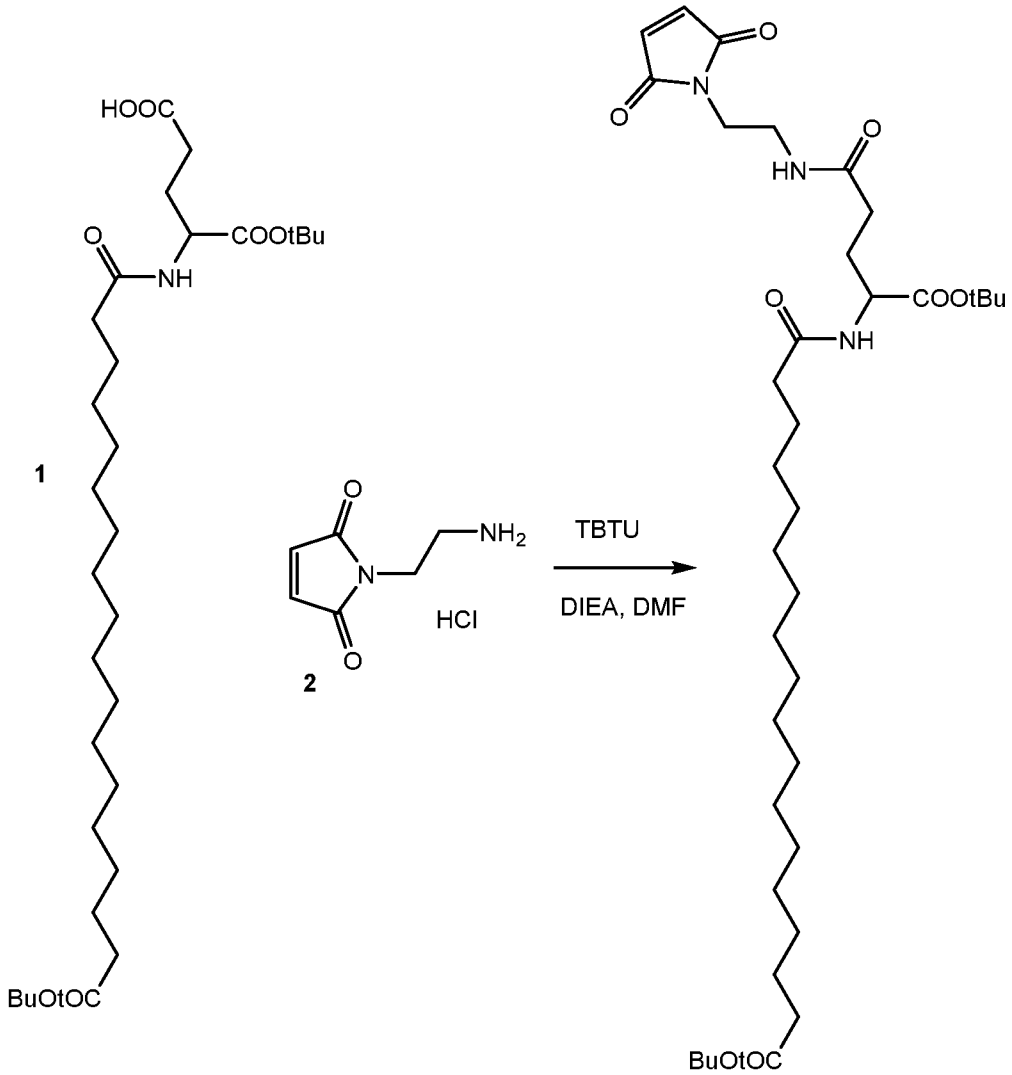
[0385] Mal-C18-Diacid (D-version)



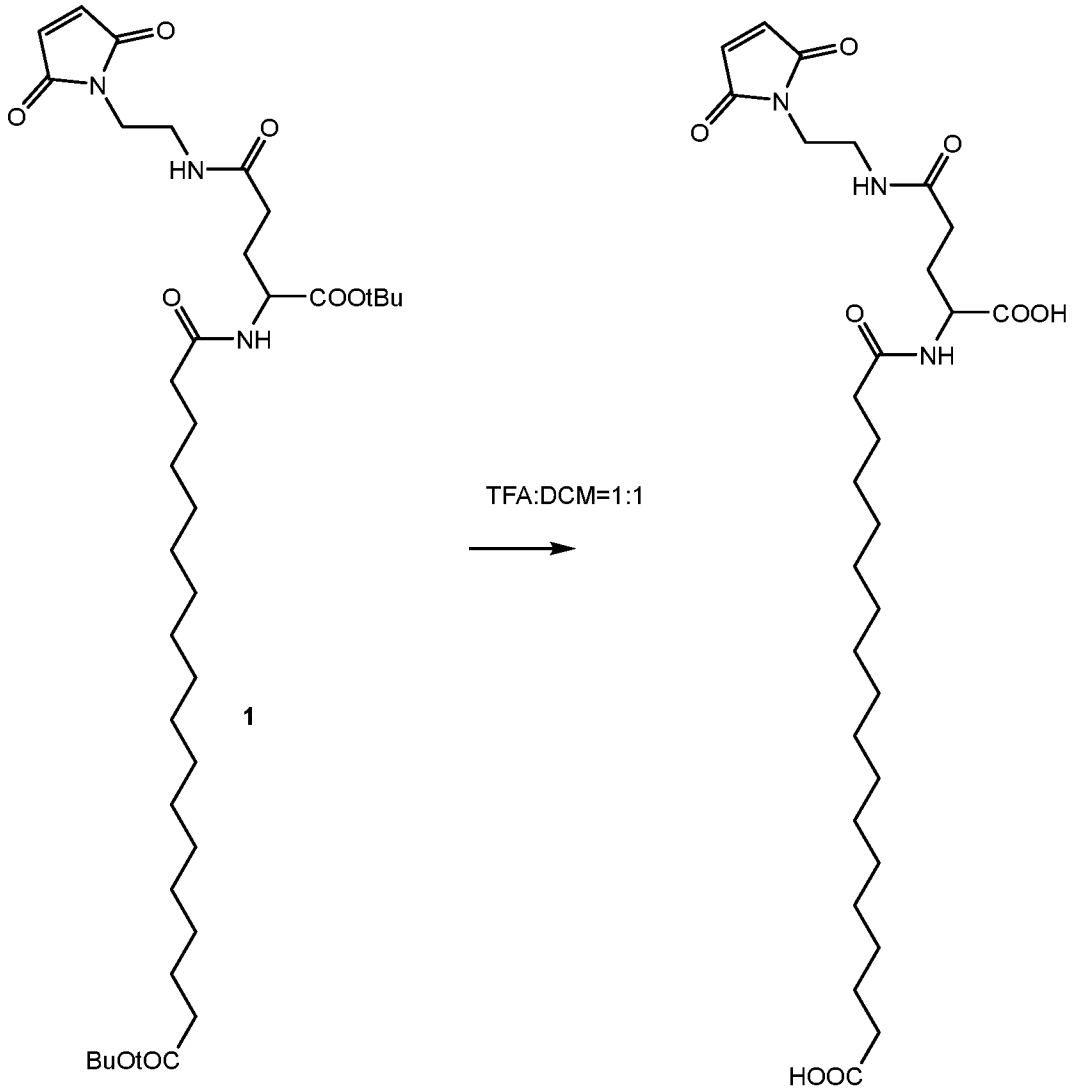
[0386] Compound **1** (0.500 g) and Compound **2** (0.4539 g) were dissolved in DMF and TBTU (0.4418 g) and DIPEA (0.586 mL) were added to the mixture. The reaction was allowed to stir at room temperature for two hours. The mixture was then diluted with DCM (40 mL), washed with water (4 x 40 mL), dried over Na_2SO_4, filtered and concentrated on high vacuum. The product was brought up in DCM (2 mL) and loaded onto 4G Redi-Sep Rf column on CombiFlash® (mobile phase DCM:DCM with 20% methanol 0=>50% over 25 minutes.) Yield: 740 mg (85%.)



[0387] Compound **1** (0.720 g) was dissolved in 5 mL of MeOH, then a septum was placed on the flask and N_2 was applied two times. Then, Pd/C (0.200 g) was added via weighing papers, then the septum was replaced and vacuum followed by H_2 was applied two times. The reaction was allowed to stir at room temperature for 1 hour. The product was filtered and the filtrate was dried on rotavap and high vacuum. Yield: 655 mg.

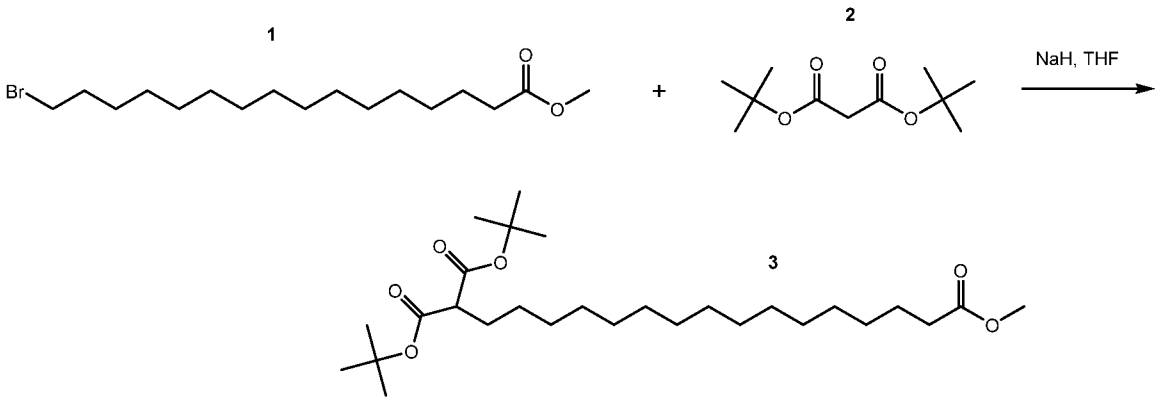


[0388] Compound **1** (0.100 g) and Compound **2** (0.0318 g) were dissolved in DMF and TBTU (0.0589 g) and DIPEA (0.078 mL) were added to the mixture. The reaction was allowed to stir at room temperature for one hour. The mixture was then diluted with DCM (10 mL), washed with water (4 x 7 mL), dried over Na_2SO_4, filtered and concentrated on high vacuum. The product was brought up in DCM (0.5 mL) and loaded onto 4G Redi-Sep Rf column on CombiFlash® (mobile phase DCM:DCM with 20% methanol 0=>50% over 25 minutes.) Yield: 100 mg (82%.)

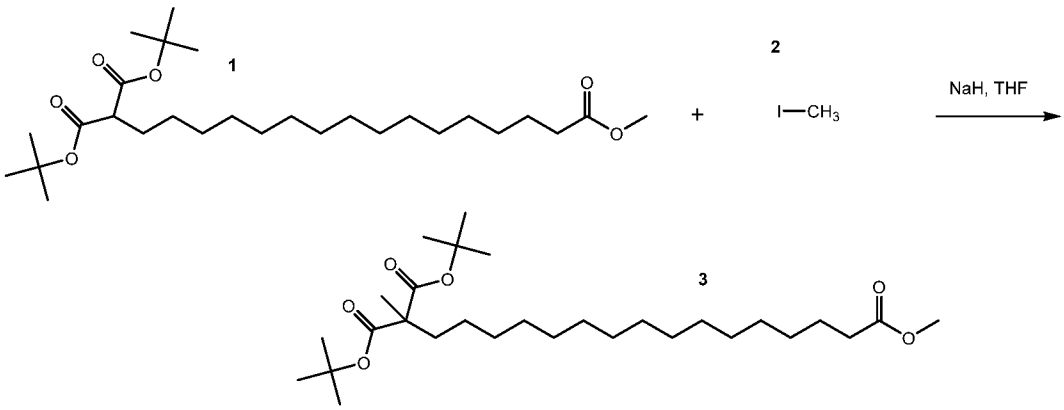


[0389] Compound **1** (96 mg) was dissolved in a 1:1 mixture of TFA:DCM. The reaction was allowed to stir at room temperature for two hours. The product was concentrated and placed on high vacuum. Yield 80 mg (99%.)

[0390] Mal-C18-methyl-triacid

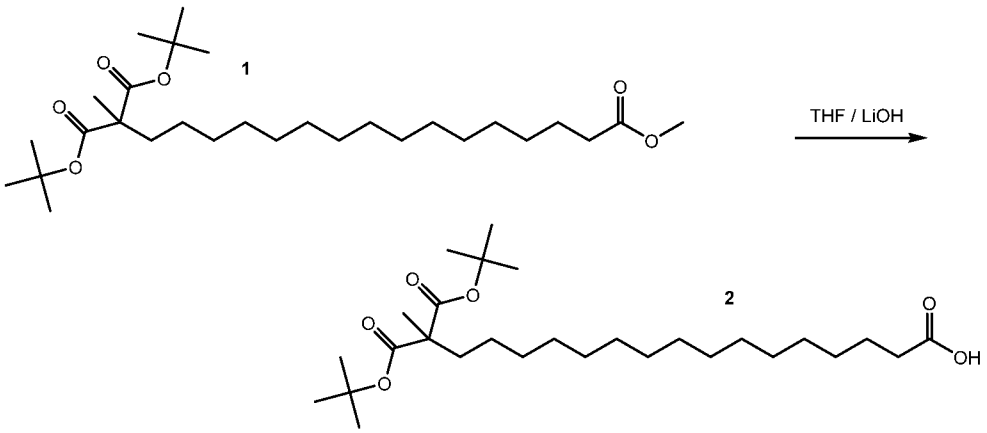


[0391] Compound **2** (Sigma® #254487, 0.405 g) in 1 mL of THF was added to a suspension of NaH in THF (3.5 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 20 minutes. The reaction was mixed until it became clear. Then compound **1** (Sigma® #684511, 0.436 g) in 2 mL THF was added dropwise at 0 °C and stirred for 0.5 h. Then the ice bath was removed and the reaction was allowed to stir at room temperature overnight. The reaction was then diluted with DCM (35 mL,) and washed with NH_4Cl solution (1 x 8 mL.) The organics was back-extracted with DCM (1 x 8 mL.) The organics were combined and washed with H_2O (2 x 8 mL.) The organic phase was dried over Na_2SO_4, filtered and concentrated. The product was purified via chromatography (wet-loaded in toluene (1 mL) onto a CombiFlash® 12 G RediSep Rf Gold, mobile phase Hexane:Hexane with 10% EA => 0=>50% over 25 minutes.) Yield: 390 mg (64.5%.)

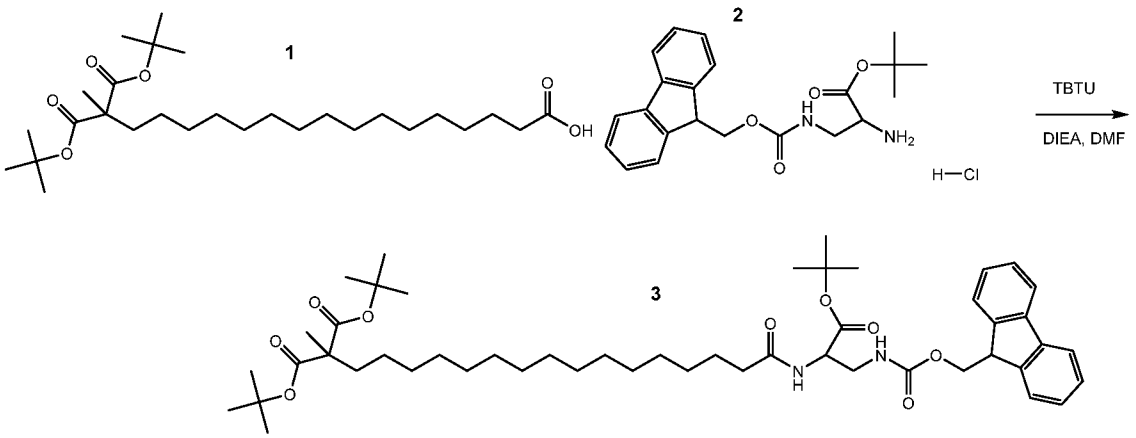


[0392] Compound **1** (0.100 g in 0.5 mL THF) was added to a suspension of NaH in 0.75 mL THF at 0 °C. The reaction was warmed to room temperature and stirred for 20 minutes. The reaction mixture became clear. Then compound **2** (Sigma® 67692, 0.016 mL in 0.5 mL THF) was added dropwise at 0 °C and stirred for 0.5 h. The ice bath was removed and the reaction was allowed to stir at room temperature overnight. The reaction was diluted with DCM (20 mL) and washed with NH_4Cl (1 x 5 mL.) The organic layer was back-extracted with DCM (1

x 5 mL). The organics were combined and washed with H_2O (2 x 5 mL.) The organic phase was dried over Na_2SO_4, filtered and concentrated. The product was purified via chromatography (wet-loaded in toluene (1 mL) onto a CombiFlash® 12 G RediSep Rf Gold, mobile phase Hexane:Hexane with 10% EA 0=>50% over 25 minutes.) Yield: 30 mg (29.2%.)

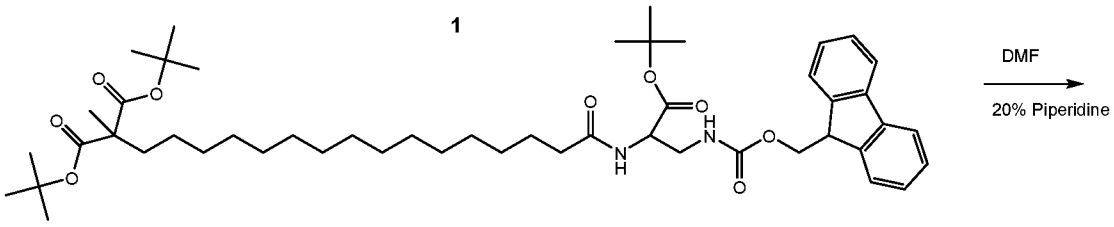


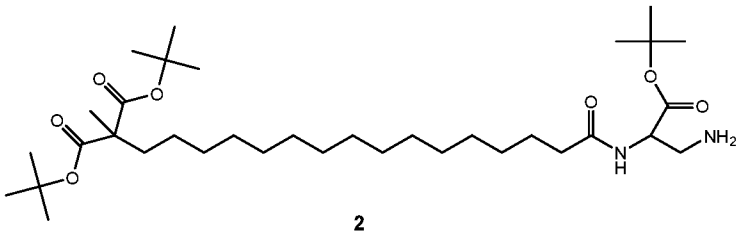
[0393] Compound **1** (0.0300 g) was dissolved in 0.4 mL of THF. Then LiOH (480 mg in 10 mL of THF) was added. The reaction was allowed to stir for 16 hours. The reaction was acidified to pH=3 with citric acid. The organic layer was extracted with 2 x 6 mL of DCM, and the organics were combined and dried over Na_2SO_4, filtered and concentrated. Yield: 25 mg (85.7%.)



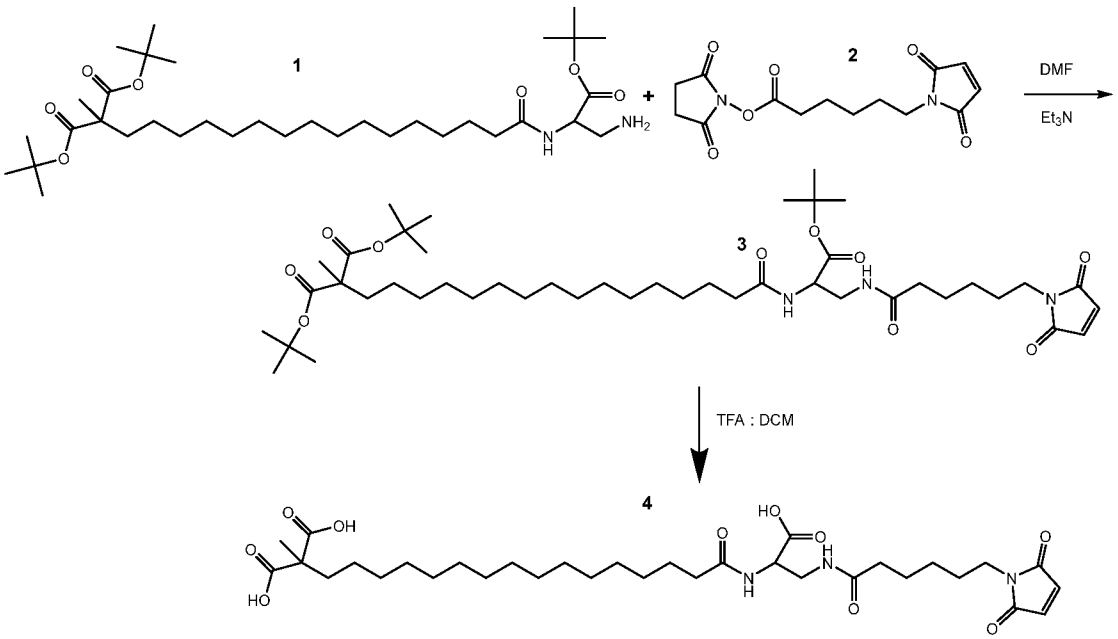
[0394] Compound **1** (0.0250 g) and Compound **2** (Chem Impex® # 30487, 0.0238 g) were dissolved in DMF and TBTU (0.0190 g) and DIPEA (0.022 mL) were added to the mixture. The reaction was allowed to stir at room temperature for one hour. The mixture was then diluted to 9 mL with DCM, washed with water (3 x 7 mL), dried over Na_2SO_4, filtered and concentrated on high vacuum. The product was brought up in DCM (0.5 mL) and loaded onto

4G Redi-Sep Rf column on CombiFlash® (mobile phase DCM:DCM with 20% methanol 0=>25% over 15 minutes.) Yield: 37.1 mg (84.7%.)





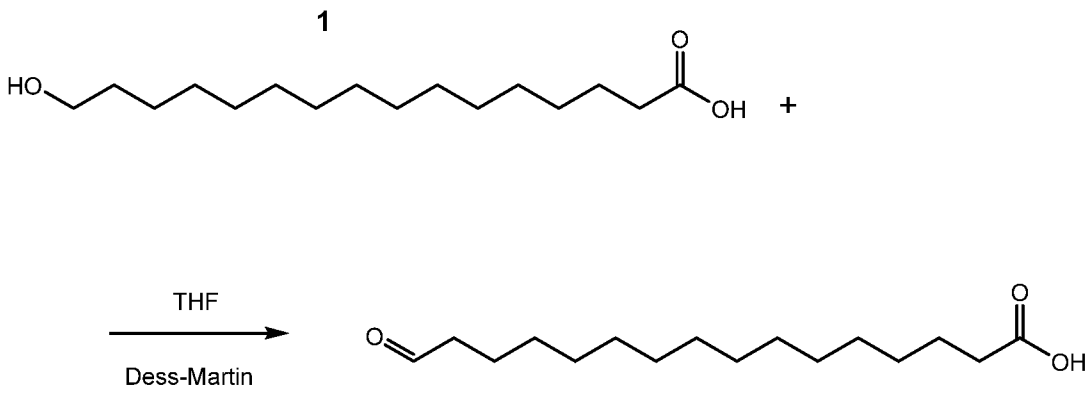
[0395] Compound 1 (0.0320 g) was dissolved in 0.5 mL of 20% piperidine in DMF. The reaction was allowed to stir at room temperature for one hour. The product was concentrated on high vacuum, then dissolved in toluene and concentrated on high vacuum. The product was brought up in 0.5 mL of DCM with 2 x 0.25 mL rinses and wet-loaded onto pre-equilibrated 4g RediSep Gold Rf column on CombiFlash®, mobile phase DCM=>DCM with 20% MeOH 0=>50% over 20 minutes. Yield: 0.020 g (84.7%.)



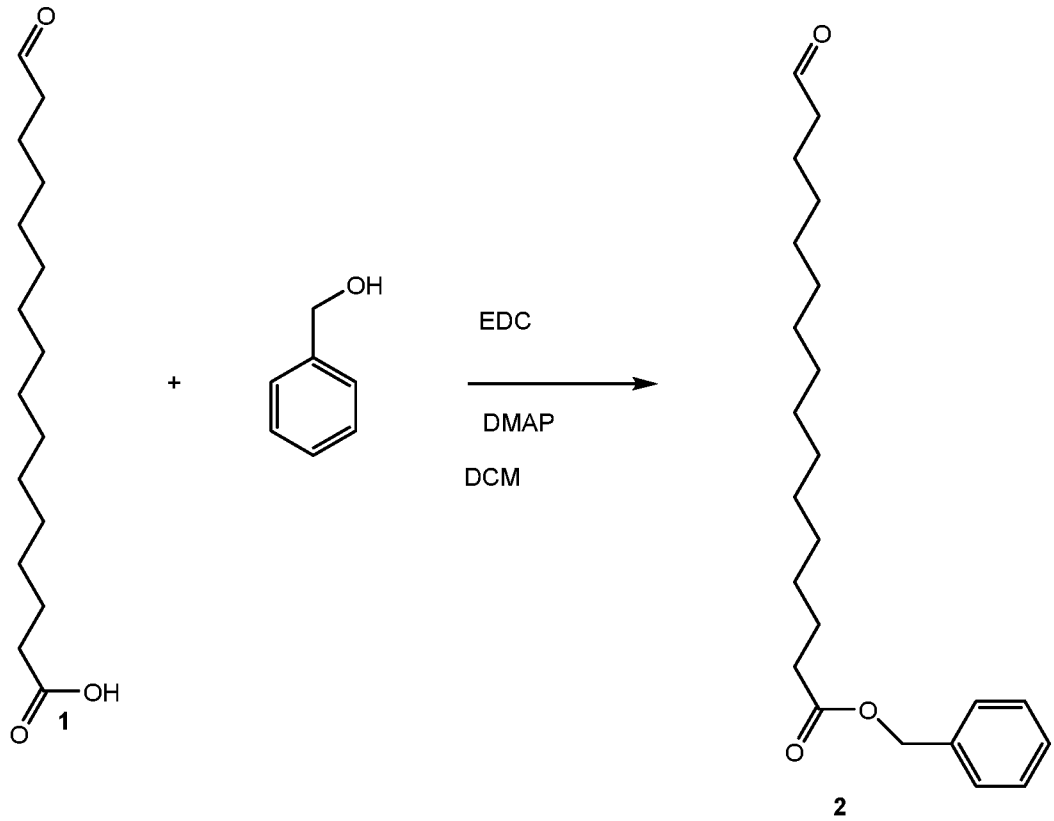
[0396] Compound **1** (0.0200 g) was added to a solution of Et3N (0.022 mL) in DMF (0.4 mL.) Then compound **2** (Asta Tech® #24961, 0.0246 g) was added. The Reaction was allowed to stir at room temperature for one hour. The reaction was diluted to 10 mL with DCM and washed with 5% citric acid in water (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated on high vacuum. The product was wet-loaded in 0.5 mL DCM with 2 x 0.3 mL rinses onto pre-equilibrated 4g Redi Sep Gold Rf Column, mobile phase DCM => 20% MeOH in DCM 0 => 30% over 20 minutes. Yield: 20 mg.

[0397] The product was then brought up in 2 mL of a 1:1 mixture of TFA:DCM and allowed to stir for two hours. The product was concentrated on rotary evaporator and high vacuum. Yield: 13 mg.

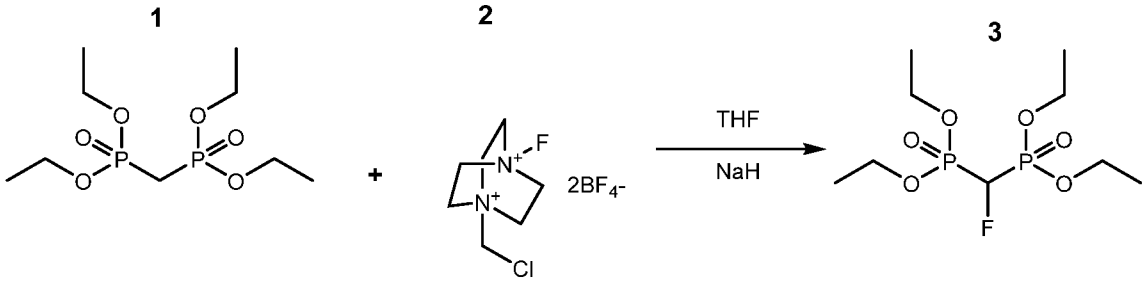
[0398] Mal-C_{17}-Fluoro-PO_3 Monoacid



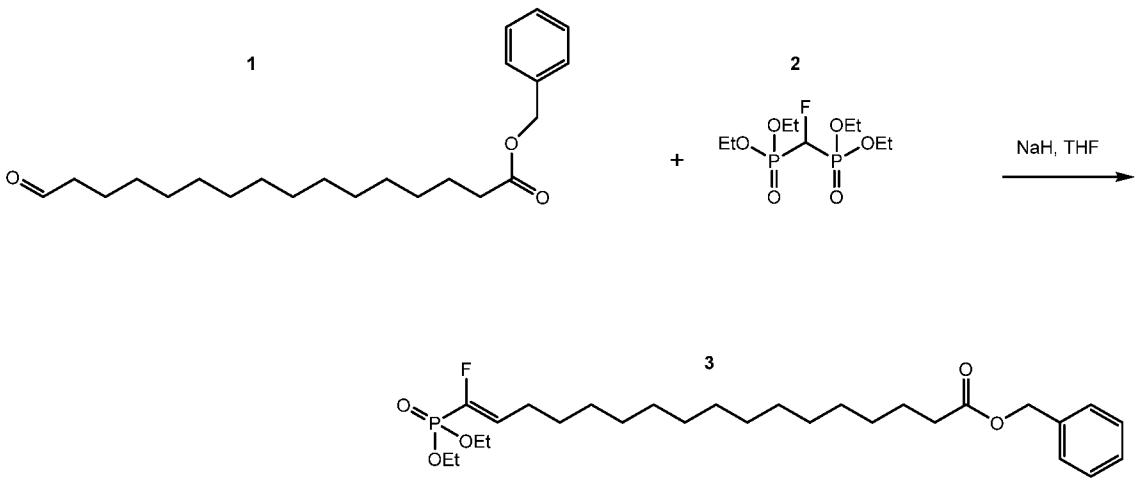
[0399] Compound **1** (Sigma® #177490, 5.00 g) was dissolved in a mixture of 70 mL THF and 20 mL of DMF. Then Dess-Martin Periodinane (Sigma® #274623, 11.7 g) was added. The reaction was allowed to stir for three hours. The mixture was concentrated on rotary evaporator and high vacuum, then dry-loaded onto 120g Redi-Sep Gold Rf column on CombiFlash®, mobile phase hexane with 10% DCM : EtOAc, 0=>30% over 30 minutes. Yield: 2.86 g.



[0400] Compound **1** (2.85 g) and benzyl alcohol (1.36 mL) were mixed in 50 mL of DCM, and cooled to 0 °C. Then EDC (2.53 g) and DMAP (0.257 g) were added sequentially. The reaction was allowed to warm to room temperature, then stirred for two hours while monitored by TLC. The mixture was extracted with NH_4Cl (1 x 50 mL) solution and DCM. The organic phase was dried over Na_2SO_4, concentrated and dry-loaded on 80g RediSep Gold Rf column, mobile phase Ethyl Acetate : Hexane, 0=>15% over 30 minutes. Yield: 2.31 g (61.0%.)

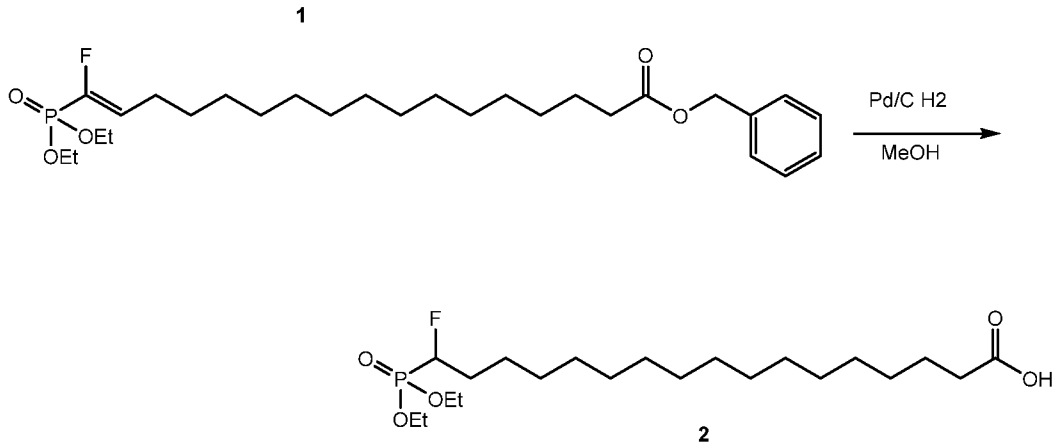


[0401] NaH (60% in oil, 0.047 mL) was added to a flask and the flask was charged with 15 mL THF. The flask was cooled to 0 °C, and compound **1** (AK Scientific #J91196, 0.500 g) in 2 mL THF was added dropwise. The reaction was stirred for five minutes, then the ice was removed and the reaction was allowed to stir for 15 minutes at room temperature. The reaction was cooled to 0 °C, and compound 2 (Tokyo Chemical Industry Co. #f0358, 0.768 g) was added as one solid portion. Then 0.3 mL of anhydrous DMF was added, followed by removal of the ice bath. The reaction was allowed to stir at room temperature overnight. The reaction was then diluted with DCM (50 mL) and washed with saturated NH_4Cl (1 x 12 mL.) The aqueous layer was washed with DCM (1 x 10 mL.) The organics were combined and washed with H_2O (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated on rotary evaporator and high vacuum. The product was loaded in 1.5 mL DCM onto 4G Redi-Sep Gold Rf column on CombiFlash, mobile phase DCM : DCM with 20% MeOH, 0=>30% over 20 minutes. Yield 157 mg (36.2%.)

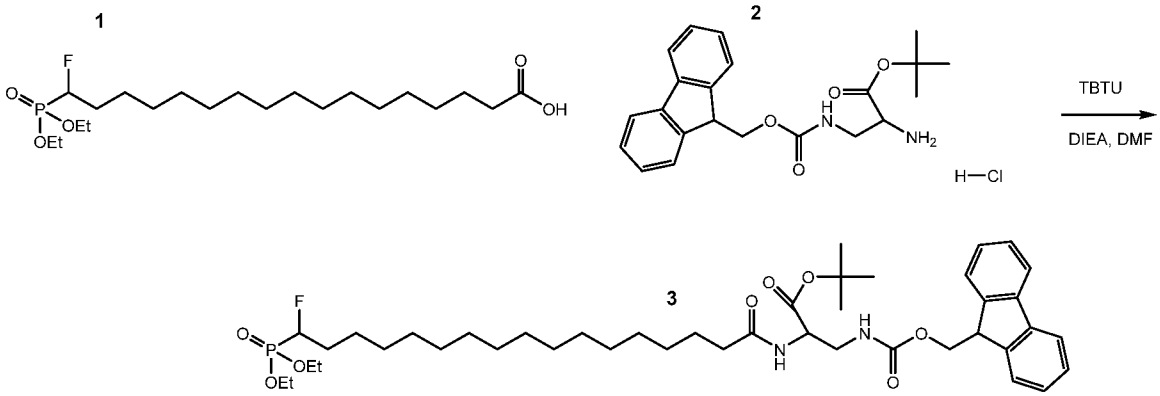


[0402] Compound **2** (0.149 g in 0.5 mL THF) was added to a suspension of NaH in THF (0.75 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 20 minutes. A solution of compound **1** (0.140 g) in 1.25 mL THF was added gradually at 0 °C and stirred for 0.5 h. The reaction was then diluted with DCM (20 mL) and washed with sat. NH_4Cl (1 x

5 mL). The product was back-extracted with DCM (1 x 5 mL.) The combined organic layers were washed with H_2O (2 x 5 mL.) The organic phase was dried over Na_2SO_4, filtered and concentrated. The product was dry loaded onto 1 g silica, 4G RediSep Rf Gold, mobile phase Hexane:EtOAc 0=>50%. Yield 67 mg (33.7%.)

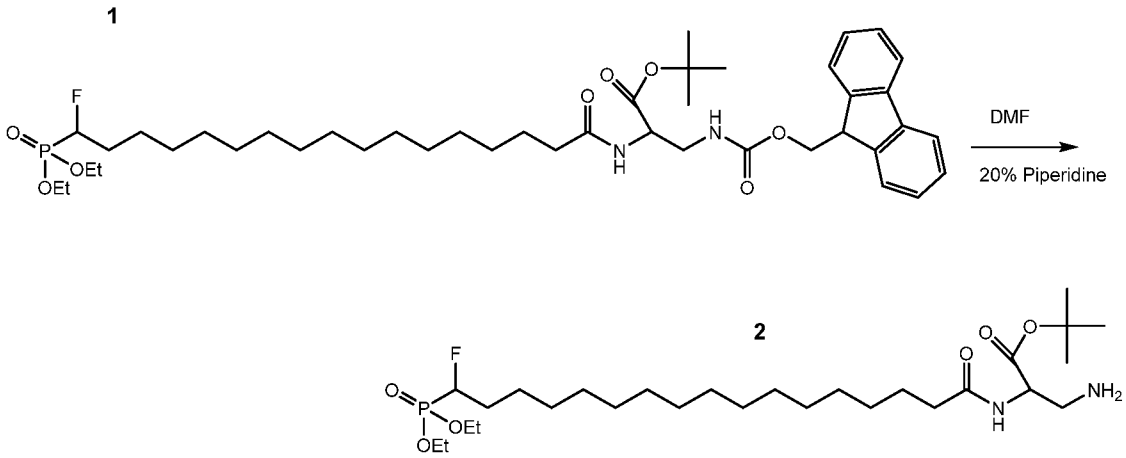


[0403] Compound **1** (0.0530 g) was dissolved in 2 mL MeOH, then a septum was placed on the flask and N_2 was applied two times. Then, Pd/C (0.0250 g) was added via weighing papers, then the septum was replaced and vacuum followed by H_2 was applied two times. The reaction was allowed to stir at room temperature for 2 hours. The product was filtered with a syringe filter and the filtrate was dried on rotavap and high vacuum. Yield: 36 mg (82.0%.)

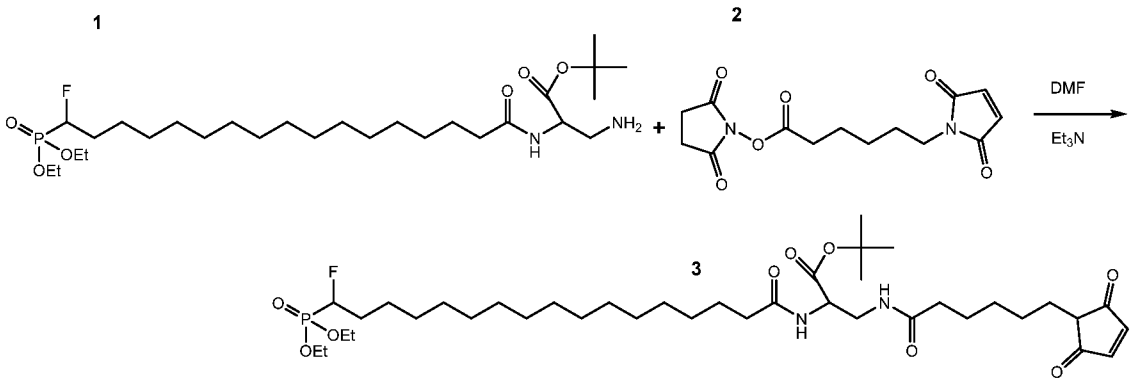


[0404] Compound 1 (0.0200 g) was dissolved in 0.3 mL of DMF, then TBTU (0.0174 g) followed by DIPEA 0.021 mL were added. The mixture was allowed to stir for 5 minutes, and then compound 2 (Chem Impex® #30487, 0.0217 g) was added. The reaction was allowed to stir at room temperature for one hour. Then the mixture was diluted with 6 mL DCM and washed with H_2O (3 x 3 mL), and dried over Na_2SO_4, filtered and concentrated on rotary evaporator and high vacuum. The product was loaded in 1 mL DCM onto RediSep 4G

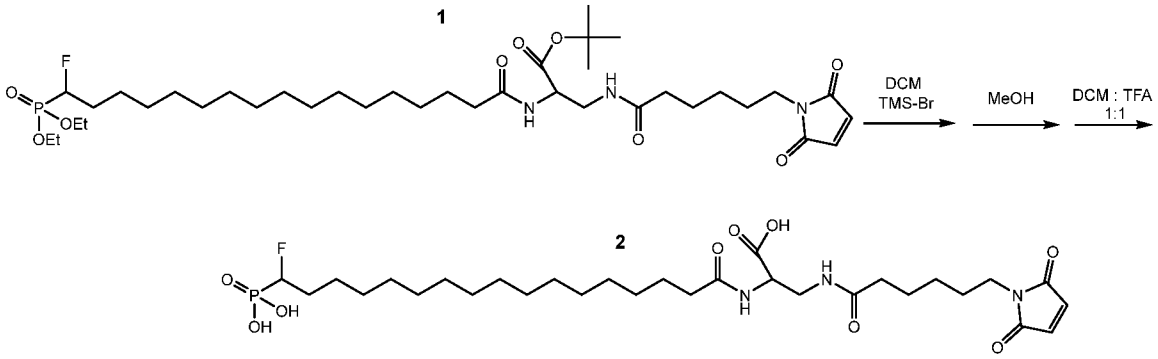
Gold Rf column on CombiFlash®, mobile phase DCM : DCM with 20% MeOH, 0=>30% over 15 minutes. Yield 10 mg (88.8%.)



[0405] Compound 1 (0.0330 g) was dissolved in 0.5 mL DMF with 20% piperidine. The reaction was allowed to stir at room temperature for one hour. The reaction was concentrated on rotary evaporator and high vacuum. The product was loaded in 1 mL DCM onto 4G RediSep Gold Rf column on CombiFlash, mobile phase DCM : DCM with 20% MeOH, 0=>50% over 20 minutes. Yield: 11.5 mg (48.5%.)

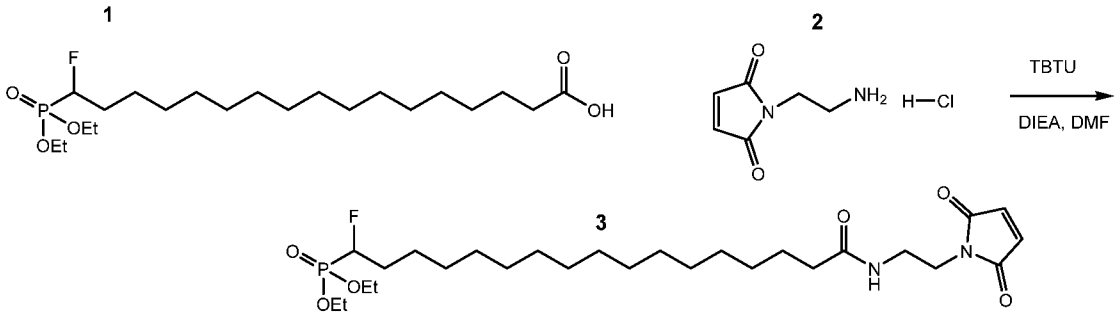


[0406] Compound 1 (0.0115 g) was dissolved in 0.3 mL DMF, and Compound 2 (Asta Tech® #24961, 0.0156 g) and Et_3N (0.014 mL) were added. The reaction was allowed to stir at room temperature overnight. The reaction was then diluted with DCM (6 mL) and washed with 5% citric acid (3 x 3 mL), dried over Na_2SO_4, filtered and concentrated. The product was loaded in 1 mL DCM onto 4G RediSep Gold Rf column on CombiFlash, mobile phase DCM : DCM with 20% MeOH from 0 => 35% over 20 minutes. Yield: 10 mg (64.9%.)

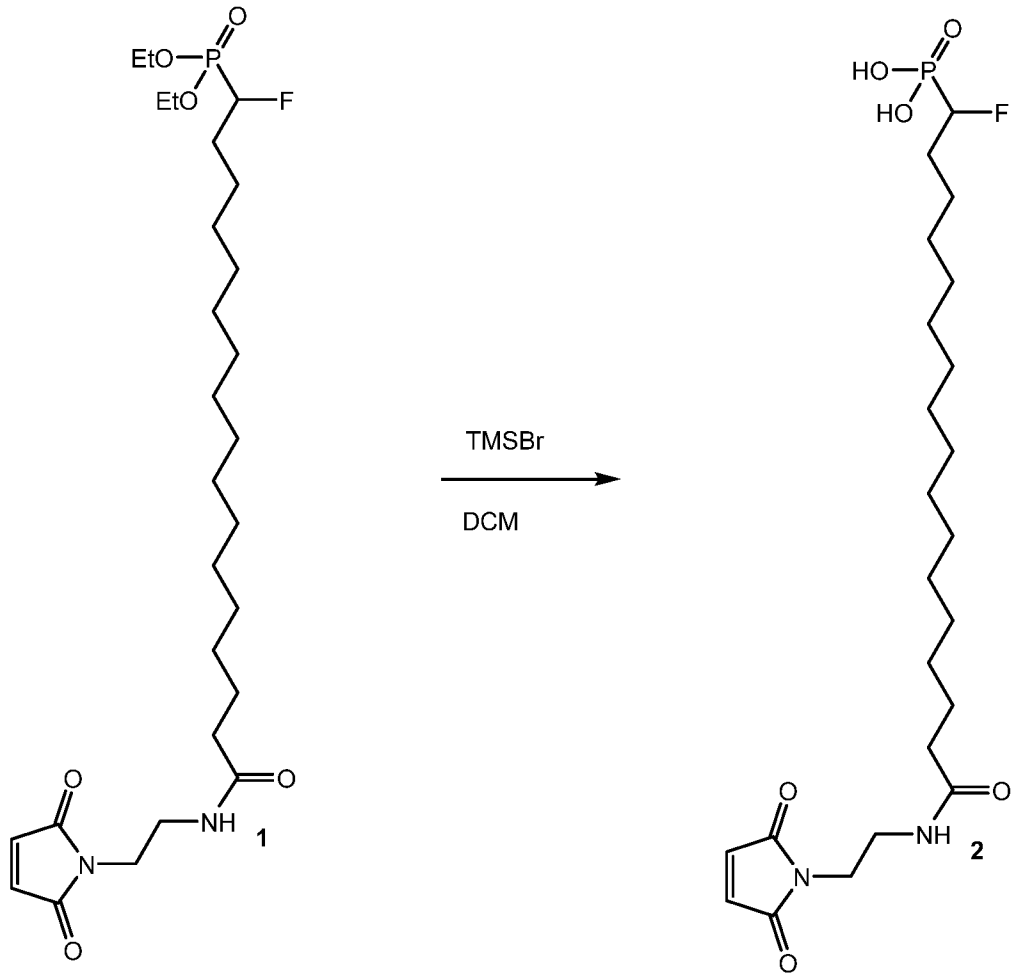


[0407] Compound 1 (0.0100 g) was dissolved in 0.3 mL of DCM and the mixture was cooled to 0 °C. Then 0.051 mL of TMS-Br was added and the reaction was allowed to stir at 0 °C for 4 hours, followed by 3 hours at room temperature. The reaction was dried and 1 mL of MeOH was added. The reaction was allowed to stir overnight. The product was dried on rotary evaporator and high vacuum with toluene azeotroping (3 x 1 mL.) The reaction was then brought up in DCM : TFA 1:1 (1 mL) and set stirring at room temperature. After 1.5 h, the reaction was concentrated on rotary evaporator and high vacuum. Yield: 8.5 mg (99%.)

[0408] Mal-C_{17}-Fluoro-PO_3

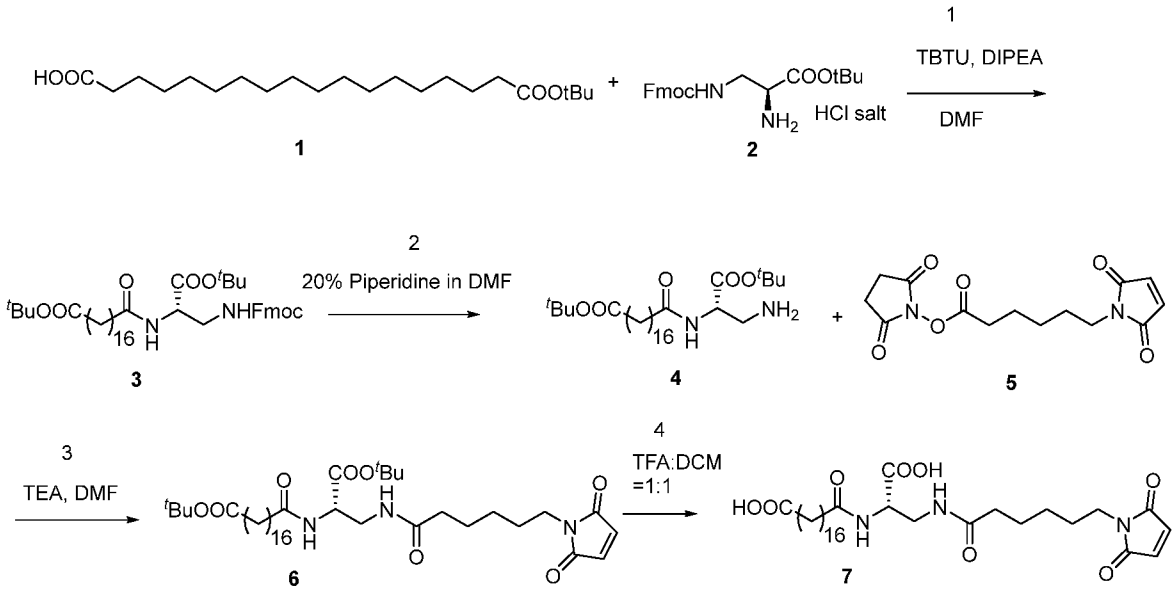


[0409] Compound 1 (0.0150 g) was dissolved in 0.25 mL of DMF. Then TBTU (0.0125) was added to the mixture, followed by DIEA (0.015 mL), and the mixture was allowed to stir for 5 minutes. Then, compound 2 (0.0062 g) was added to the mixture, and the reaction was stirred at room temperature for one hour. Then the reaction was diluted with DCM (6 mL) and washed with H_2O (3 x 3 mL), dried over Na_2SO_4, filtered and concentrated on rotary evaporator and high vacuum. The product was loaded in 1 mL DCM onto 4G RediSep Gold Rf column on CombiFlash, mobile phase DCM : DCM with 20% MeOH from 0 => 30% over 15 minutes. Yield: 12.5 mg (64.7%.)



[0410] A solution of compound 1 (0.0125 g) in 0.4 mL DCM was cooled to 0 °C and TMSBr was added dropwise. The reaction was stirred at 0 °C for three hours. The volatiles were completely removed by rotary evaporator and high vacuum. The residue was stirred with MeOH for 2 hours to remove TMS. The mixture was dried on rotary evaporator and high vacuum. Yield: 11.5 mg (98.8%.)

[0411] Synthesis of Mal-C18-Diacid and related compounds



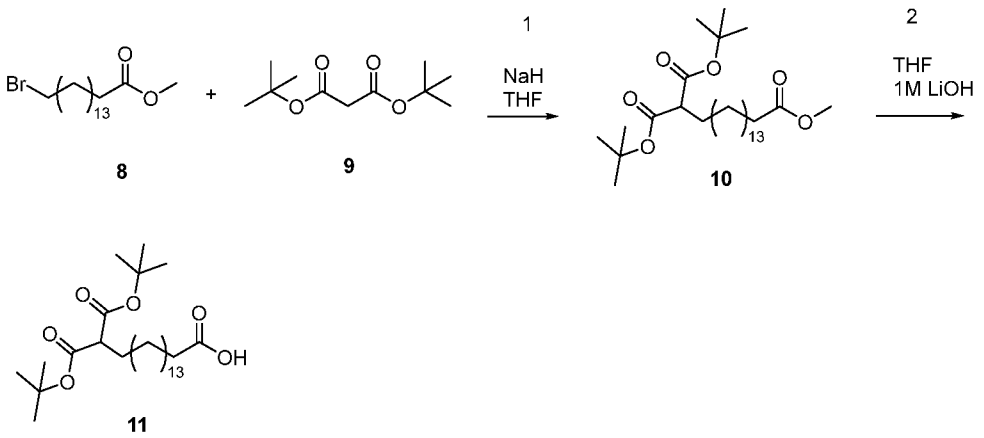
[0412] Step 1: Compound **1** (MW=370.57, 0.741g, 2mmol) was dissolved in 10mL DMF. TBTU (Mw=321, 0.642g, 2mmol) and DIPEA (Mw=129, 0.87ml, 5mmol) were sequentially added and the mixture was stirred for 5 minutes. Compound **2** was added (Mw=418.9, 0.838g, 2mmol). The solution was stirred for 1 hour. The solution was diluted by 40 ml DCM and washed with water 3 times (40mL each time). The organic phase was evaporated and purified using column chromatography (EA:HEX=0%-100%) to provide compound **3** (80% yield). (Mass Observed, M + 1 = 736).

[0413] Step 2: Compound **3** was treated with 20% Piperidine in DMF for half an hour. The solvent was evaporated and the residue was purified through chromatography (MeOH:DCM=0%-10%). (Mass Observed, M + 1 = 514). (Mass Observed, M + 1 = 707).

[0414] Step 3: Compound **4** (Mw=513, 50mg, 0.0975mmol) was dissolved in 1 ml DMF. Compound **5** (Mw=308, 36mg, 1.2 equiv) and TEA (0.041ml, 3 equiv) were added. The reaction was stirred for 2 hours. The solution was diluted by DCM and washed with water 3 times. The organic phase was evaporated and purified by chromatography (EA:HEX=0%-100%) to provide compound **6**. (Mass Observed, M + 1 = 594).

[0415] Step 4: Compound **6** was treated with 50% TFA in DCM for 2 hours. The solvent was evaporated to provide compound **7** (Mal-C18-diacid) (Mass Observed, M+1 = 594.)

[0416] Mal-C18-triacid

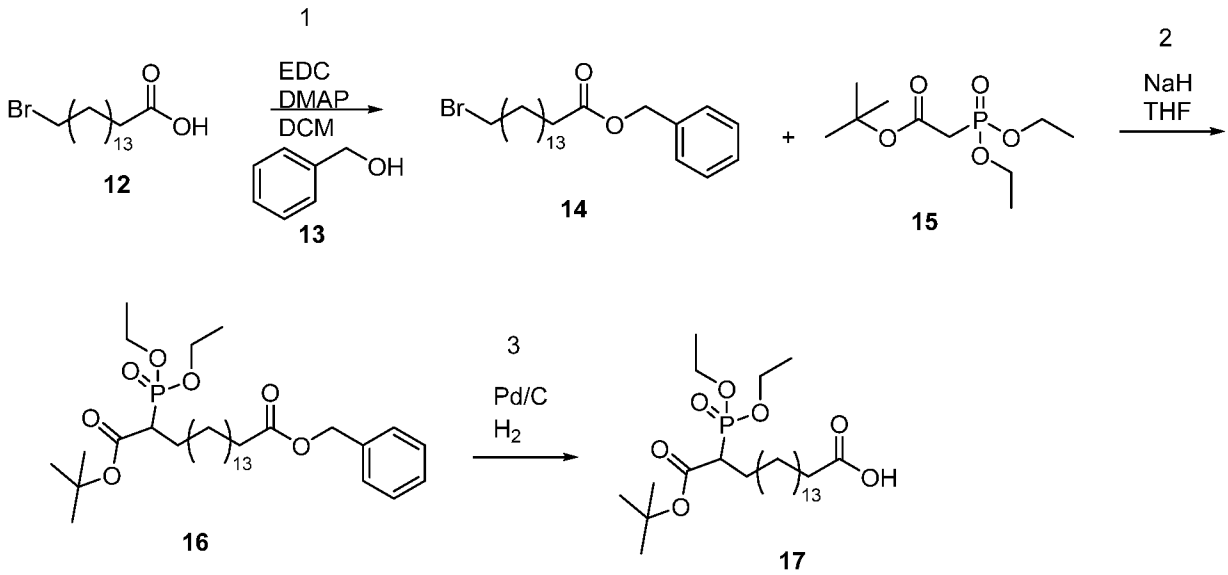


[0417] Step 1: Compound **9** (1.2 eq) was added to a solution of NaH (1.2 eq) in 3 ml of THF at 0°C, stir at room temperature for 0.5 hr. Compound **8** (1 mmol, 1 eq) in 1 ml of THF was then added to the mixture dropwise at 0°C. The mixture was stirred at 0°C for 0.5h, until the solution was clear. The solution was then raised to room temperature, and the solution slowly became a slurry. After 5h, the reaction was quenched with NH_4Cl, and extracted with DCM. The product was purified on column (Hex : 10% EtOAc in Hexanes), peaks come out around 0%-3% of EtOAc. (42% Yield, 200 mg) (Mass Observed, M + 1 = 486).

[0418] Step 2: Compound **10** was dissolved in THF (3 mL) and 1M LiOH (3 mL) was added. The reaction was stirred 16 hr at 25°C. Then, the solution was acidified to pH =3 with Citric Acid, and extracted with DCM (3 x 10 mL). The organic phases were combined and concentrated *in vacuo*, no further purification. (Mass Observed, M + 1 = 472).

[0419] Mal-C18-Triacid was synthesized by using Compound 11 in place of compound 1 in the same synthesis as described for Mal-C18-diacid. (Mass Observed, M+1 = 638).

[0420] Mal-C_{18}-diacid-PO_3



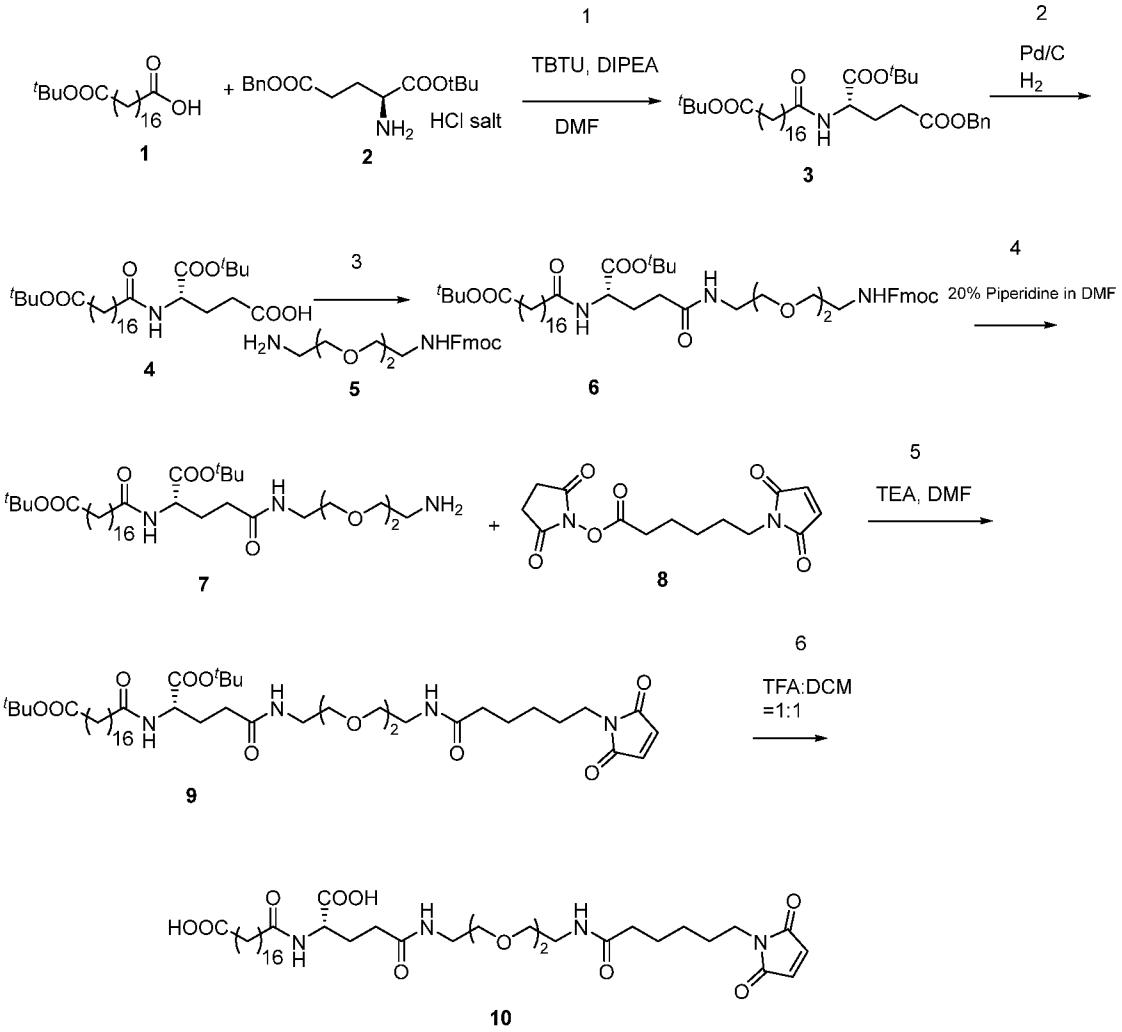
[0421] Step 1: Compound 12 (2.64 mmol, 1 eq) and Compound 13 (2.909 mmol, 1.1 eq) were mixed together in DCM, and the mixture was cooled to 0 °C. EDC (1.1 eq) and DMAP (0.2 eq) were added sequentially. The reaction was warmed to room temperature. The reaction was stirred for 2 hours and was monitored by TLC Hexane : EtOAc 8:2. The organics were extracted with NH_4Cl solution and DCM. The organic phase was dried over Na_2SO_4, concentrated, and purified using chromatography (EA: HEX = 0% to 10%). The product spot comes out around 2% of EA. (Mass Observed, M + 1 = 426).

[0422] Step 2: Compound **15** (1.2 eq) was added to a solution of NaH (1.2 eq) in 3 mL of THF at 0°C, and stirred at room temperature for 0.5 hr. Compound **14** (0.470 mmol, 1 eq) in 1 ml of THF was added to the mixture dropwise at 0°C. The reaction was stirred at 0°C for 0.5h, and the solution was clear. Then the mixture was raised to room temperature, and the solution slowly became a slurry. After 5h, the reaction was quenched with NH_4Cl, and extracted with DCM. Column (Hex : 10% EtOAc in Hexanes), peaks come out around 3% of EtOAc. (16% Yield, 45 mg) (Mass Observed, M + 1 = 598).

[0423] Step 3: Compound 16 (0.0519 mmol, 1 eq) was dissolved in MeOH. Then Pd/C (60 mg) was added to the reaction and several purge and refill cycles were performed with H_2. The reaction was stirred at 25°C for 12 hrs. The mixture was filtered through silica and concentrated *in vacuo* to provide product. (24 mg, 92% Yield) (Mass Observed, M + 1 = 508).

[0424] Mal-C_{18}-diacid-PO_3 was synthesized in the same manner as Mal-C18-diacid by substituting Compound 17 for compound 1 in the synthesis of Mal-C18-diacid. (Mass Observed, M+1 = 674).

[0425] Mal-C6-PEG2-C18-diacid



[0426] Step 1: Compound **1** (1 eq, 2mmol) was dissolved in 10mL DMF. TBTU (1 eq, 2mmol) and DIPEA (2.5 eq, 5mmol) were sequentially added and the mixture was stirred for 5 minutes. Compound **2** was added (1 eq, 2mmol). The solution was stirred for 1 hour. The solution was diluted by 40 mL DCM and washed with water 3 times (40mL each time). The organic phase was evaporated and purified by chromatography (DCM : DCM with 20% MeOH =0%-25%) to provide compound **3** (80% yield). (Mass Observed, M + 1 = 647). (Mass Observed, M+1 = 767.)

[0427] Step 2: Compound **3** (1.6 mmol, 1 eq) was dissolved in MeOH. Pd/C (150 mg) was added to the reaction and several purge and refill cycles were performed with H_2. The reaction was stirred at 25°C for 12 hrs. The reaction was filtered through silica and concentrated *in vacuo* to provide product. (1.5 mmol, 94% Yield) (Mass Observed, M + 1 = 557).

[0428] Step 3: Compound **4** (1 eq, 1.5 mmol) was dissolved in 10 ml DMF. TBTU (1 eq) and DIPEA (2.5 eq) were sequentially added and the mixture was stirred for 5 minutes. Compound 5 (1 eq, 1.5 mmol) was added. The solution was stirred for 1 hour. The solution was diluted with 40 mL DCM and washed with water 3 times (40 mL each time). The organic phase was evaporated and chromatography (DCM : DCM with 20% MeOH =0%-25%) to provide compound **6** (80% yield). (Mass Observed, M + 1 = 909).

[0429] Step 4: Compound **6** (1 eq, 1.2 mmol) was treated with 20% Piperidine in DMF for 30 mins. The solvent was evaporated and the residue was purified through chromatography (DCM : DCM with 20% MeOH =0%-30%) to provide Compound **7** (0.984 mmol, 82% yield) (Mass Observed, M + 1 = 687).

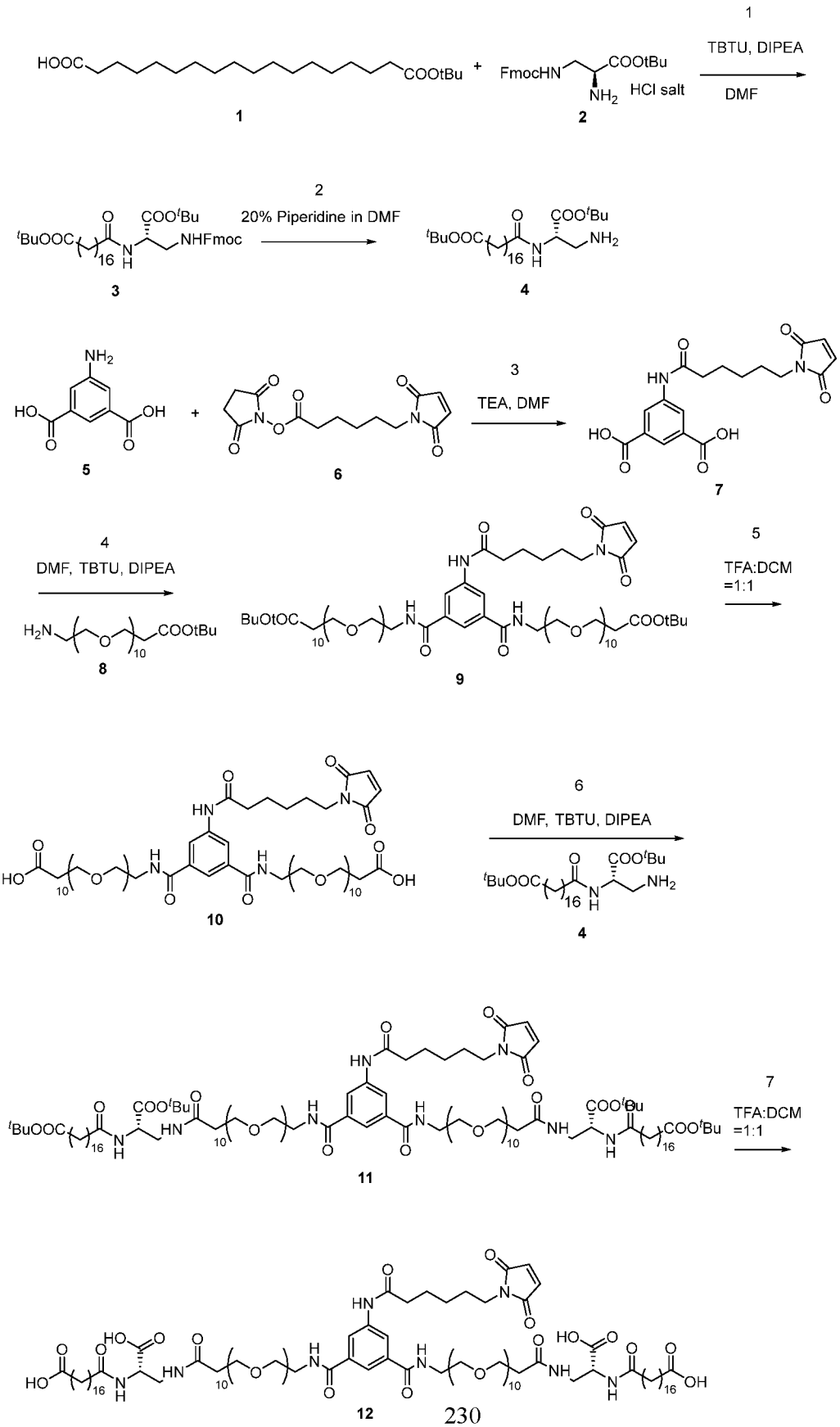
[0430] Step 5: Compound **7** (1 eq, 0.984 mmol) was dissolved in 1 mL DMF. Compound **8** (1.2 eq, 1.18 mmol) and TEA (3 eq, 2.952 mmol) were added. The reaction was stirred for 2 hours. The solution was diluted by DCM (30 mL) and washed with water 3 times (15 mL each time). The organic phase was evaporated and chromatography (DCM : DCM with 20% MeoH =0%-30%) to provide compound **9** (0.738 mmol, 75% yield). (Mass Observed, M + 1 = 880).

[0431] Step 6: Compound **9** was treated with 50% TFA in DCM for 2 hours. The mixture was concentrated *in vacuo* to provide compound **10**. (Mass Observed, M + 1 = 768).

[0432] Mal-C6-PEG4-C18-diacid

[0433] Mal-C6-PEG4-C18-diacid was synthesized in the same manner as Mal-C18-diacid, but compound 7 was subjected to treatment with NHFmoc-PEG_2-NH_2. The Fmoc protecting group was removed with 20% piperidine deprotection as described in Step 4, then the steps 5 and 6 were repeated as described above (Mass Observed, M+1 = 912.)

[0434] Mal-Bis C18-diacid


1
TBTU, DIPEA
DMF
HCl salt
2
20% Piperidine in DMF
3
TEA, DMF
4
DMF, TBTU, DIPEA
5
TFA:DCM
=1:1
6
DMF, TBTU, DIPEA
7
TFA:DCM
=1:1

[0435] Steps 1 & 2: Compound **4** was synthesized as described in the synthesis of Mal-C18-Diacid, above.

[0436] Step 3: Compound **5** (1.0 mmol, 1 eq), compound **6** (1.3 eq) and TEA (5.0 eq) were well mixed in 3 mL DMF. The reaction was stirred overnight. The mixture was concentrated on rotary evaporator and purified via column chromatography. The product elutes around 4%MeOH in 1%HOAc in DCM. LC-MS shows desired peak with impurities. The final product was 170 mg with 45% yield.

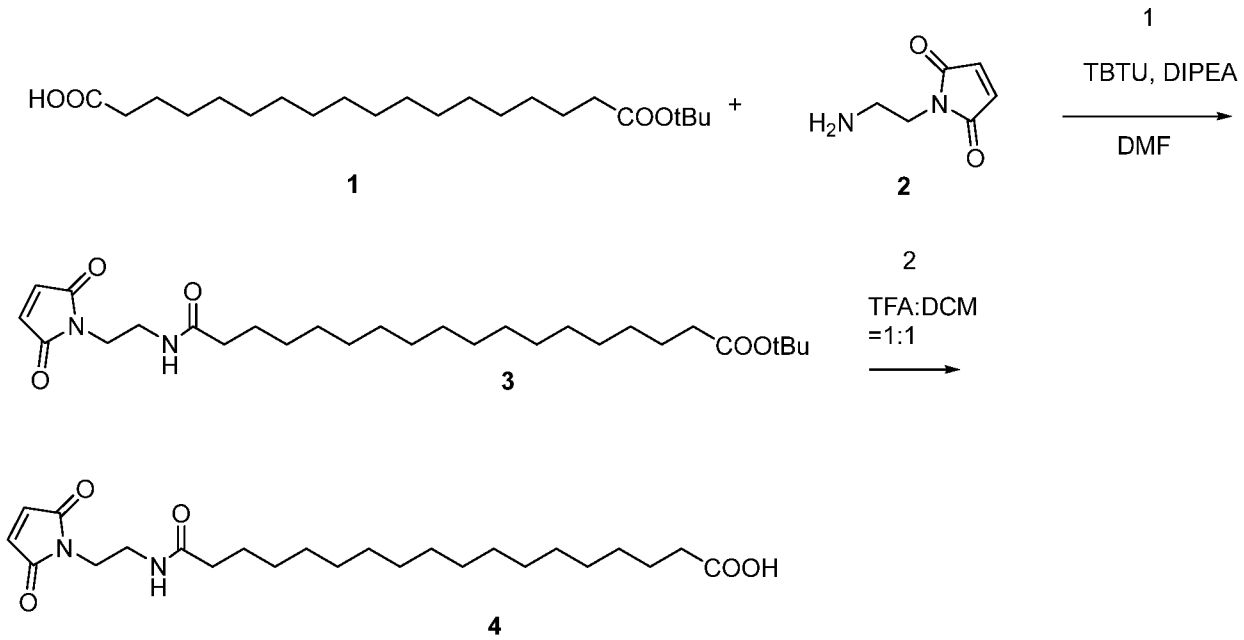
[0437] Step 4: Compound **7** (0.12 mmol, 1eq), compound **8** (2.4 eq), TBTU (2.4 eq) and DIPEA (5.0 eq) were well mixed in 1 mL DMF. The reaction was stirred overnight. LC-MS shows product as well as one major side product (more than product) and three small impurities. The mixture was concentrated by rotary evaporator and purified on column by DCM/MeOH. The product elutes around 6-12% of MeOH. The final product was obtained as 78 mg (oil) with 42% yield.

[0438] Step 5: Compound **9** (0.05 mmol) was dissolved in 2mL DCM/TFA (1/1, v/v). The reaction was stirred for 1 hr. The solvents were evaporated to obtain compound **10** 72 mg with 99% yield.

[0439] Step 6: Compound **10** (0.05 mmol, 1 eq), compound **4** (2.2 eq), TBTU (2.2 eq) and DIPEA (8.0 eq) were well mixed in 0.5 mL DMF. The reaction was stirred for 1h. LC-MS shows product as well as one major side product (nonpolar TFA method). The mixture was concentrated by rotary evaporator and purified on column by DCM/MeOH. The product elutes around 8-12% of MeOH. Compound **11** was obtained as 60 mg with 49% yield.

[0440] Step 7: Compound **11** (0.025 mmol) was dissolved in 0.5 mL DCM/TFA (1/1, v/v). The reaction was stirred for 1 hr. The solvents were evaporated to obtain compound **12**, 53 mg with 97% yield.

[0441] Synthesis of Mal-C18-acid and related compounds



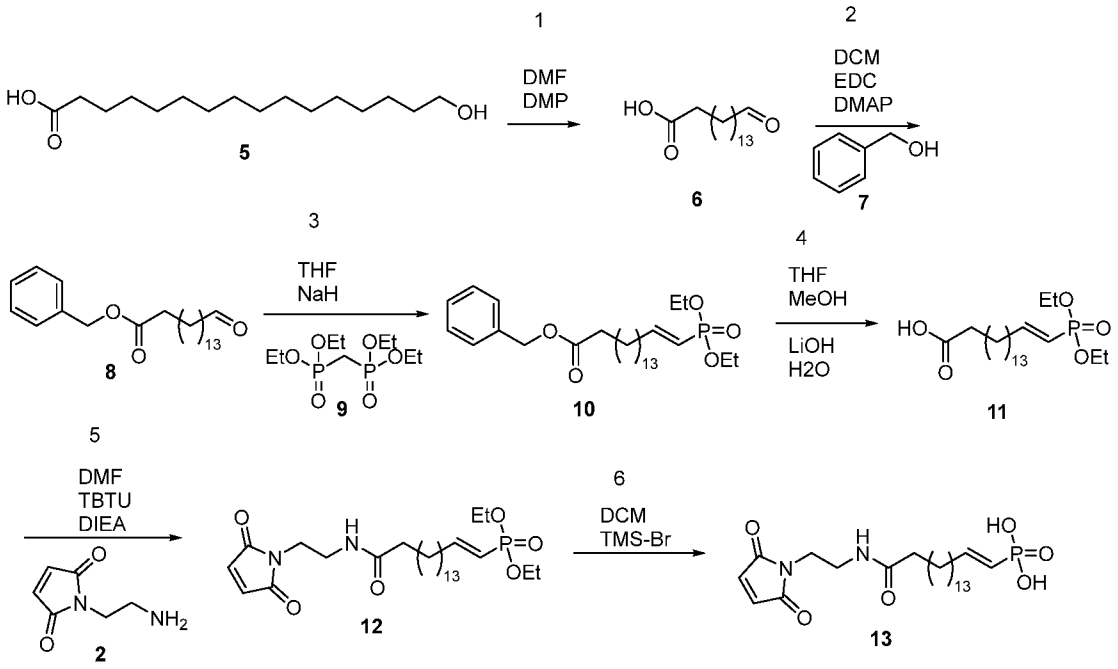
[0442] Step 1: Compound **1** (0.27 mmol, 1 eq) was dissolved in 1 mL DMF. TBTU (1 eq) and DIPEA (2.5 eq) were sequentially added and the mixture was stirred for 5 minutes. Compound **2** was added (1 eq). The solution was stirred for 1 hour. The solution was diluted with 40 ml DCM and washed with water 3 times (40mL each time). The organic phase was concentrated using rotary evaporator and purified using column chromatography (EA:HEX=0%-100%) to provide compound **3**. (Mass Observed, M + 1 = 494).

[0443] Step 2: Compound **3** was treated with 50% TFA in DCM for 2 hours. The product was concentrated using rotary evaporator to provide compound **4**. (Mass Observed, M+1 = 437).

[0444] Mal-C_{20}-acid

[0445] Mal-C_{20}-acid was synthesized in the same manner as Mal-C18-acid using commercially available C_{20} starting material in place of compound **1** (Mass Observed, M+1 = 465).

[0446] Mal-C_{17}-PO_3



[0447] Step 1: DMP (1.3 eq, 4.78 mmol) and compound **5** (1 eq, 3.68 mmol) were mixed in DMF (15 mL). After 2 hours, the reaction was finished as shown by TLC. Some solid precipitate formed. Workup: filtration to get rid of solids, rinse with DCM. The product was concentrated *in vacuo* and purified using chromatography (Hex with 10% DCM : EtOAC => 0% -20%), product elutes at 5%-10%. (0.8136 mmol, 22% Yield) (Mass Observed, M + 1 = 271).

[0448] Step 2: Compound **6** (1 eq, 0.8136 mmol) and Compound **7** (1.1 eq, 0.8949 mmol) were mixed in DCM (5 mL), cool to 0°C. EDC (1.1 eq) and DMAP (0.2 eq) were added sequentially. The reaction was warmed to room temperature. The reaction was stirred for 2 hours and was monitored by TLC Hexane : EtOAc 8:2. The product was extracted with NH_4Cl solution and DCM. The organic phase was dried over Na_2SO_4, concentrated, and purified through chromatography (Hex : EtOAC = 0% to 10%). The product spot comes out at 4% of EtOAc (0.4438 mmol, 54.5 % Yield). (Mass Observed, M + 1 = 361).

[0449] Step 3: Compound **9** (1.4 eq) was added to a solution of NaH (1.2 eq) in 1.5 ml of THF at 0°C and stirred at room temperature for 0.5 hr. Compound **8** (1 eq, 0.4438 mmol) in 1 ml of THF was added to the mixture dropwise at 0°C. The reaction was stirred at 0°C for 0.5h, and the solution was clear. The mixture was warmed to room temperature, and the solution slowly became a slurry. After 5h, the reaction was quenched with NH_4Cl, and

extracted with DCM. Column (Hex : EtOAc => 0% to 50%), product comes out at 35% of EtOAc. (0.2020 mmol, 45.5% Yield) (Mass Observed, M + 1 = 496).

[0450] Step 4: Compound **10** (1 eq, 0.2020 mmol) was dissolved in a mixture of 1:1:1 of MeOH, THF, and 1M LiOH (3 mL total solution). The mixture was stirred for 2 hr at 25°C. The reaction was acidified to pH =3 with Citric Acid, and extracted with DCM (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. No further purification was necessary. (Mass Observed, M + 1 = 405).

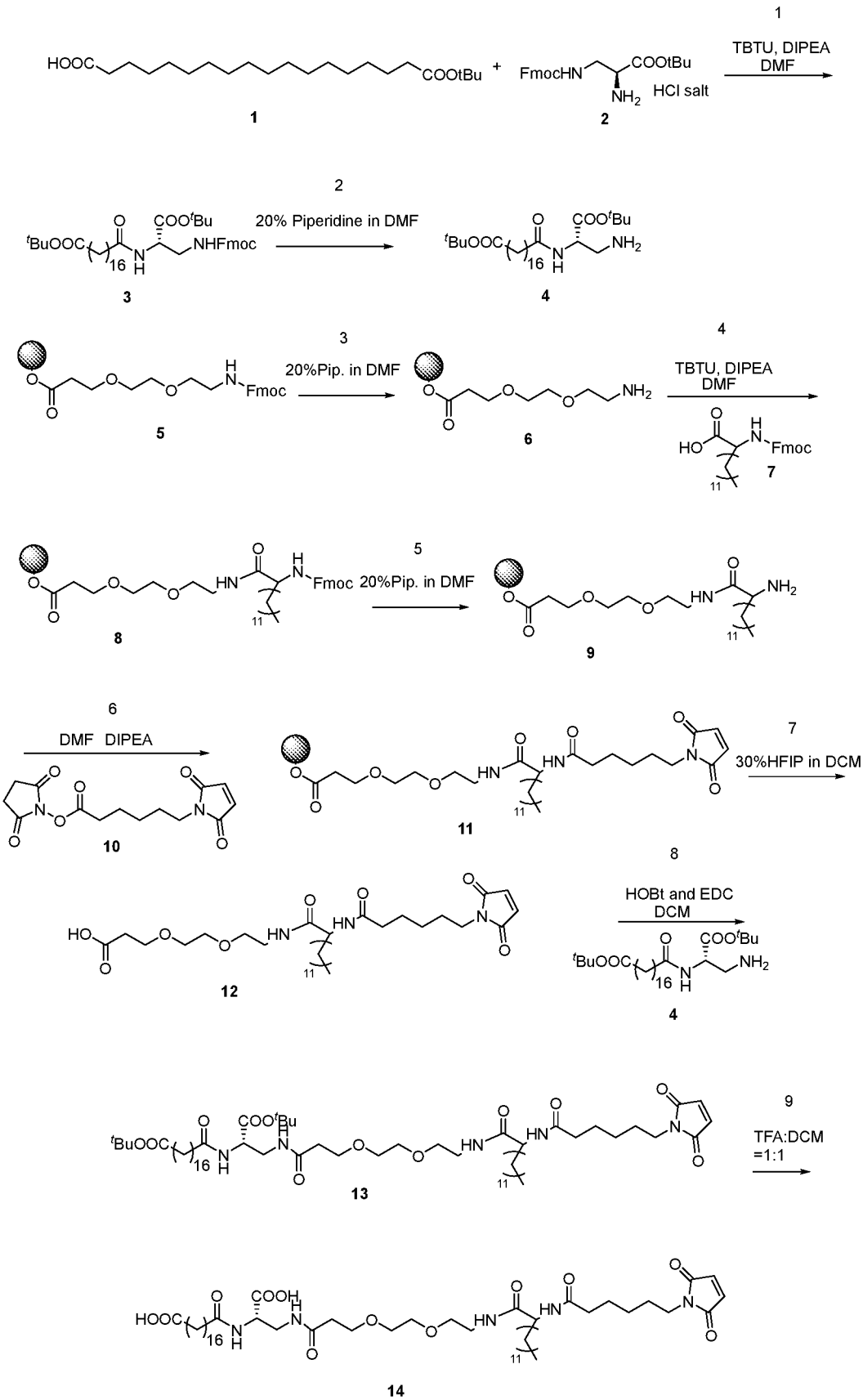
[0451] Step 5: Compound **11** (1 eq, 0.0938 mmol) was dissolved in 1 mL DMF. TBTU (1 eq) and DIPEA (2.5 eq) were sequentially added and the mixture was stirred for 5 minutes. Compound 2 was added (1 eq). The solution was stirred for 1 hour. The solution was diluted by 10 mL with DCM and washed with water 3 times (5 mL each time). The organic phase was evaporated and purified by chromatography (DCM : DCM with 20% MeOH =0%-30%) to provide compound **12** (0.0683, 73% Yield) (Mass Observed, M + 1 = 528).

[0452] Step 6: A solution of compound **12** in DCM was cooled to 0 °C and TMS-Br was added dropwise. The reaction was stirred at 0°C and monitored by LC-MS. The reaction was complete within 2.5 hours. The volatiles were completely removed by rotary evaporator and high vacuum (to completely remove acid). The residue was stirred with MeOH for 2 hours to remove TMS. The product was concentrated *in vacuo* to provide desired product. (Assume 100% Yield) (Mass Observed, M + 1 = 471).

[0453] Mal-C_{18}-diacid (L-version)

[0454] Mal-C18-diacid (L-version) was synthesized in the same manner as Mal-C18-acid Mal-C18-Glu (L)-Diacid, but Glu(D) was used in place of Glu(L) (Mass Observed, M+1 = 567)

[0455] Synthesis of Mal-C6-C12-PEG2-C18 diacid and related compounds


1
TBTU, DIPEA
DMF
HCl salt
2
20% Piperidine in DMF
3
4
5
20%Pip. in DMF
6
7
8
9
DMF DIPEA
10
11
30%HFIP in DCM
12
HOBt and EDC
DCM
13
TFA:DCM
=1:1
14

[0456] Steps 1 & 2: Compound **4** was synthesized as described in the synthesis of Mal-C18-Diacid, above.

[0457] Step 3: Compound **5** (1 mmol, 1 eq) was treated with 3 mL 20% piperidine in DMF for 20 mins. Then the resin was rinsed 3 times with DMF and used in the next step without further purification.

[0458] Step 4: To compound **6** was added a mixture of TBTU (2 eq), compound 7 (2 eq), DIPEA (6 eq) in 3 mL of DMF, and stirred for 1 hr. The solvents were removed under vacuum and the resin was rinsed 3 times with 3 mL of DMF.

[0459] Step 5: Compound **8** was treated with 3 ml 20% piperidine in DMF for 20 mins. Then the resin was rinsed 3 times with DMF and used in the next step without further purification.

[0460] Step 6: To compound **9** was added a mixture of compound **10** (2 eq) and DIPEA (6 eq) in 3 mL of DMF and stirred overnight. The solvents were removed under vacuum and the resin was rinsed 3 times with 3 mL of DMF.

[0461] Step 7: Compound **11** was treated with 3 ml 30% HFIP in DCM for 30 mins. The solution was filtered, and the filtrate was collected and evaporated to provide compound **12**.

[0462] Step 8: To compound **10** (1 eq) in DCM was added EDC (1 eq), followed by HOBt (1 eq) and stirred for 15 mins. Compound **4** was then added, and the reaction was further stirred for another 4 hrs. The solvent was evaporated, and the crude material was purified through chromatogram in DCM and MeOH.

[0463] Step 9: Compound **13** was treated with 3 ml 50% TFA in DCM for 1 hr. The solvents evaporated to provide compound **14**. Mal-C6-C12-Peg2-C18 Diacid (Mass Observed, M+1 = 979).

[0464] Mal-C6-C12-C12-PEG2-C18-Diacid

[0465] Mal-C6-C12-C12-PEG2-C18-Diacid was synthesized using the same procedure as Mal-C6-C12-PEG2-C18 diacid, though compound **9** was subjected to the reactions of steps 4 and 5 before continuing to further steps. (Mass Observed, M+1 = 1204).

[0466] Mal-C6-C12-C12-C12-PEG2-C18 Diacid

[0467] Mal-C6-C12-C12-C12-PEG2-C18 Diacid was synthesized using the same procedure as Mal-C6-C12-PEG2-C18 diacid, though compound **9** was subjected to the reactions of steps 4 and 5 twice before continuing to further steps. (Mass Observed, M+1 = 1429.)

[0468] Mal-C6-C12-C12-C12-PEG2-C12 acid

[0469] Mal-C6-C12-C12-C12-PEG2-C12 acid was synthesized using the same procedure as Mal-C6-C12-PEG2-C18 diacid, though compound **9** was subjected to the reactions of steps 4

and 5 twice before continuing to further steps, followed by use of a commercially available C12 analog of compound 4. (Mass Observed, M+1 = 1245).

Example 2. Orthotopic Clear Cell Renal Cell Carcinoma (ccRCC) Tumor-Bearing Mouse Model Using Human A-498 Cells.

[0470] *Creation of SEAP-expressing clear cell renal cell carcinoma (ccRCC) A498 cells.* A pCR3.1 expression vector expressing the reporter gene secreted alkaline phosphatase (SEAP) under the CMV promoter was prepared by directional cloning of the SEAP coding sequence PCR amplified from Clontech's pSEAP2-basic vector. Convenient restriction sites were added onto primers used to amplify the SEAP coding sequence for cloning into the pCR3.1 vector (Invitrogen). The resultant construct pCR3-SEAP was used to create a SEAP-expressing A498 ccRCC cell line. Briefly, pCR3-SEAP plasmid was transfected into A498 ccRCC cells by electroporation following manufacturer's recommendation. Stable transfectants were selected by G418 resistance. Selected A498-SEAP clones were evaluated for SEAP expression and integration stability.

[0471] *Implantation of of SEAP-expressing clear cell renal cell carcinoma (ccRCC) A498 cells.* Female athymic (immuno-deficient) nude mice were anesthetized with ~3% isoflourane and placed in the right lateral decubitus position. A small, 0.5-1cm, longitudinally abdominal incision in the left flank was made. Using a moist cotton swab, the left kidney was lifted out of the peritoneum and gently stabilized. Just before injection, a 1.0 ml syringe was filled with the cell/Matrigel mixture and a 27 gauge needle catheter was attached to the syringe tip. The filled syringe was then attached to a syringe pump (Harvard Apparatus, model PHD2000) and primed to remove air. The tip of a 27-gauge needle catheter attached to a syringe was inserted just below the renal capsule near the caudal pole and the tip of the needle was then carefully advanced cranially along the capsule 3-4 mm. A 10 µl aliquot of 2:1 (vol:vol) cell/matrigel mixture containing about 300,000 cells was slowly injected into the kidney parenchyma using a syringe pump. The needle was left in the kidney for 15-20 seconds to ensure the injection was complete. The needle was then removed from the kidney and a cotton swab was placed over the injection site for 30 seconds to prevent leakage of the cells or bleeding. The kidney was then gently placed back into the abdomen and the abdominal wall was closed. Serum was collected every 7-14 days after implantation to monitor tumor growth using a commercial SEAP assay kit. For most studies, tumor mice were used 5-6 weeks after implantation, when tumor measurements were typically around 4-8 mm.

[0472] *Determination of HIF2 mRNA Expression.* For the studies reported in the Examples herein, mice were euthanized the identified day after injection and total RNA was isolated from kidney tumor using Trizol reagent following manufacturer's recommendation. Relative HiF2α mRNA levels were determined by RT-qPCR as described below and compared to mice treated with delivery buffer (isotonic glucose) only. In preparation for quantitative PCR, total RNA was isolated from tissue samples homogenized in TriReagent (Molecular Research Center, Cincinnati, OH) following the manufacturer's protocol. Approximately 500 ng RNA was reverse-transcribed using the High Capacity cDNA Reverse Transcription Kit (Life Technologies). For human (tumor) Hif2α (EPAS1) expression, pre-manufactured TaqMan gene expression assays for human Hif2α (Catalog # 4331182) and CycA (PPIA) Catalog #: 4326316E) were used in biplex reactions in triplicate using TaqMan Gene Expression Master Mix (Life Technologies) or VeriQuest Probe Master Mix (Affymetrix). Quantitative PCR was performed by using a 7500 Fast or StepOnePlus Real-Time PCR system (Life Technologies). The $\Delta\Delta C_T$ method was used to calculate relative gene expression.

Example 3. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

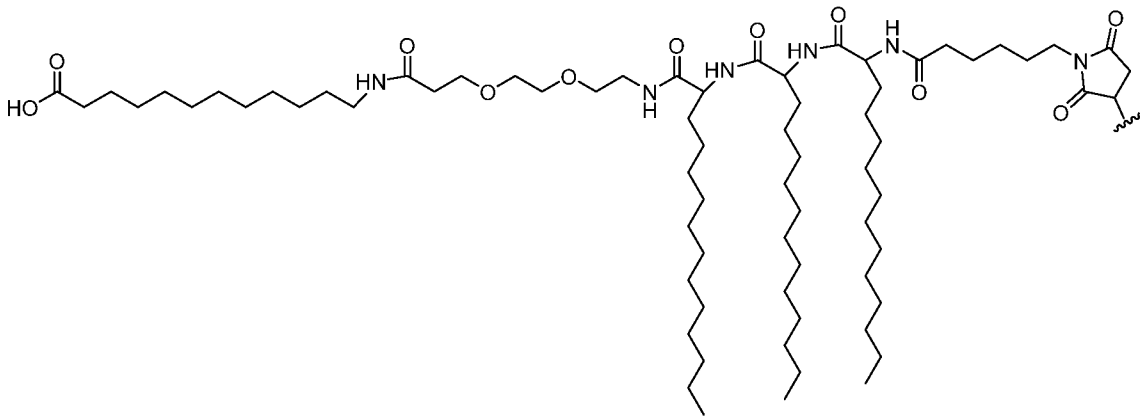
[0473] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according dosing Groups that included the following:

Table 8. Dosing Groups of Tumor-Bearing Mice in Example 3.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD04545 (without any targeting ligand), formulated in isotonic glucose.	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 3' terminal end of the sense strand to a branched (4 arm) 40 kilodalton (kD) polyethylene glycol (PEG) PK enhancer, formulated in isotonic glucose.	Single IV injection on day 1

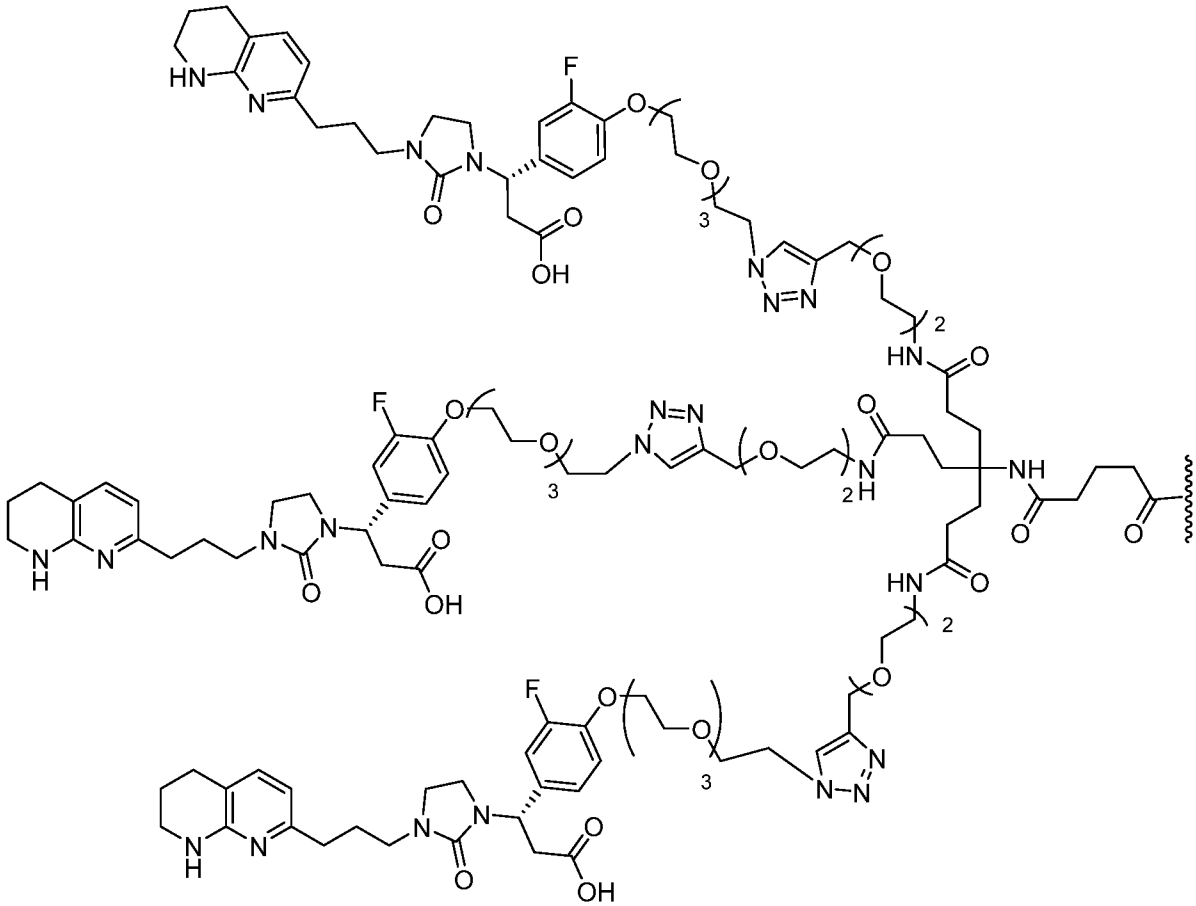
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to a branched (4 arm) 40 kilodalton (kDa) polyethylene glycol (PEG) PK enhancer, formulated in isotonic glucose.	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-C12-C12-PEG2-C12 acid, formulated in isotonic glucose.	Single IV injection on day 1
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-C12-C12-PEG2-C12 acid, formulated in isotonic glucose.	Single IV injection on day 1

[0474] In Groups 5 and 6, the PK enhancer having the following structure was linked to the 3' terminal end of the sense strand by reducing the disulfide and undertaking a Michael Addition reaction to link the maleimide reactive group of the PK enhancer compound:



, wherein ≷ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3 (See also Example 1).

[0475] In Groups 4 and 6, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) was linked to the 5' terminal end of the sense strand by coupling to the functionalized amine linker (NH2-C6):



[0476] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 9. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 3.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.162	0.193
Group 2 (7.5 mg/kg AD04545 (no ligand))	3	1.030	0.058	0.061

Group 3 (7.5 mg/kg AD04546-40kDa PEG)	3	0.638	0.083	0.095
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-40-kDa PEG)	3	0.308	0.028	0.030
Group 5 (7.5 mg/kg AD04546-Mal-C6-C12-C12-C12-PEG2-C12 acid)	3	0.630	0.049	0.053
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C6-C12-C12-C12-PEG2-C12 acid)	3	0.456	0.068	0.079

[0477] As shown in Table 9 above, only minimal knockdown was observed for Group 2 (AD04545, showing approximately 0% knockdown (1.030) compared to vehicle control), which was a HIF-2 alpha RNAi agent that was not linked to a targeting ligand or to a PK enhancer. Groups 4 and 6, which each included tridentate targeting groups, showed greater activity compared to constructs without a targeting ligand present indicating a targeting ligand dependence. Further, additional inhibitory activity was observed in the Groups that included both a targeting ligand and a PK enhancer. (*See, for example*, Group 4 (showing approximately 70% knockdown (0.308) and Group 6 (showing approximately 55% knockdown (0.456)).

Example 4. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0478] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to dosing Groups that included the following:

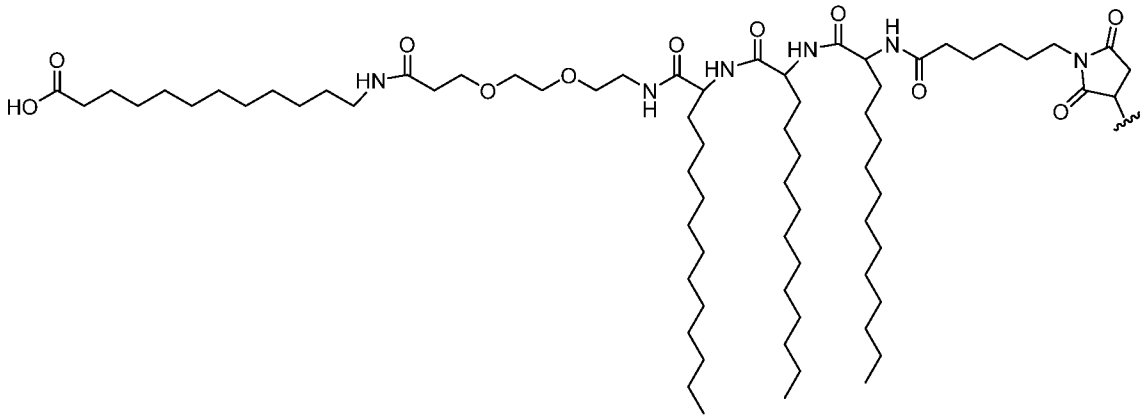
Table 10. Dosing Groups of Tumor-Bearing Mice in Example 4.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to a branched (4 arm) 40 kilodalton (kDa) polyethylene glycol (PEG) PK enhancer, formulated in isotonic glucose.	Single IV injection on day 1

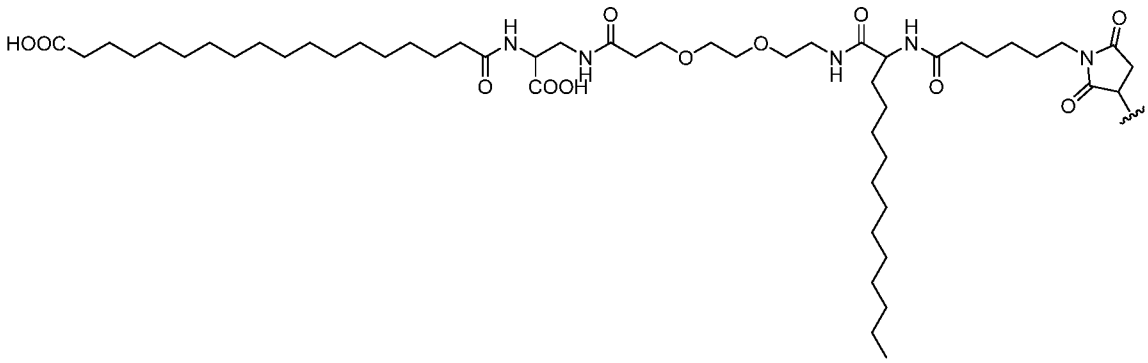
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-C12-C12-PEG2-C12 acid, formulated in isotonic glucose.	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-PEG2-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-C12-PEG2-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C6-C12-C12-C12-PEG2-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
8	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-acid, formulated in isotonic glucose.	Single IV injection on day 1
9	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C20-acid, formulated in isotonic glucose.	Single IV injection on day 1

[0479] In Groups 3-9, the respective PK enhancers having the following structures were linked to the 3' terminal end of the sense strand:

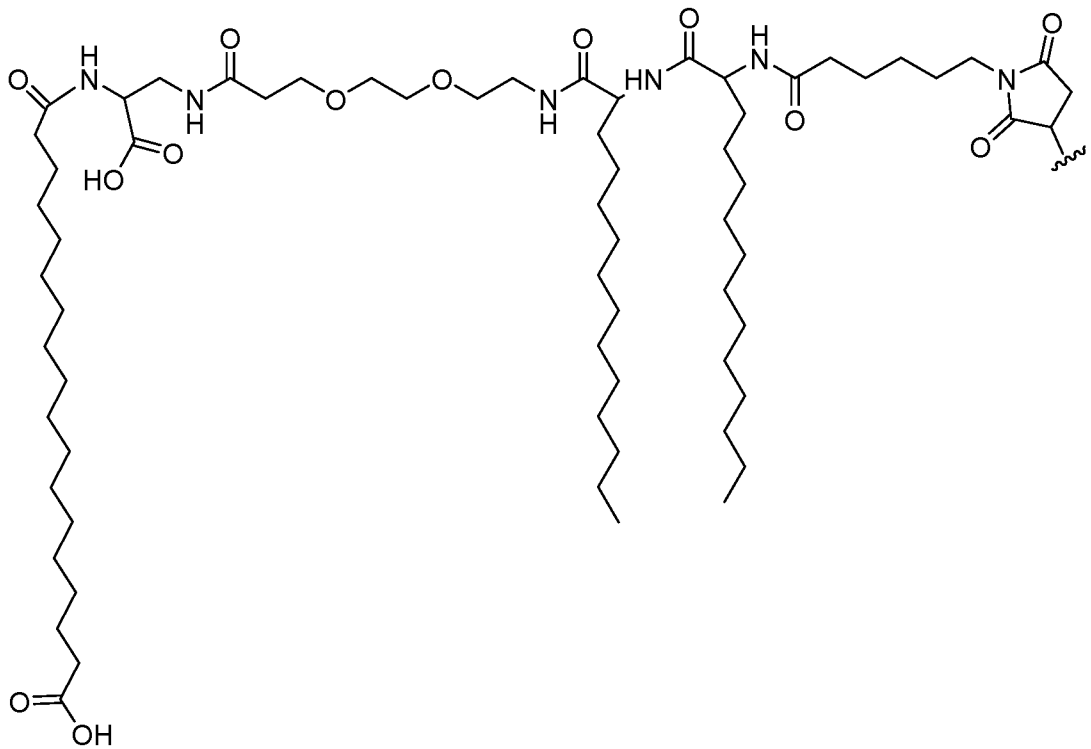
Group 3:



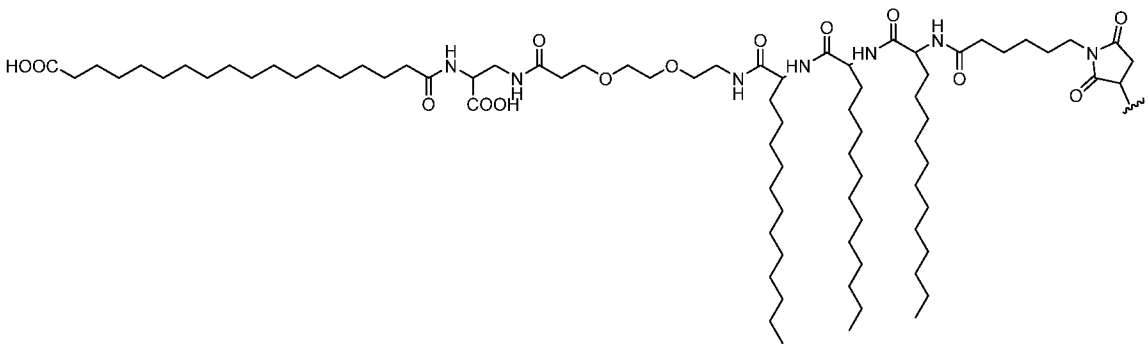
Group 4:



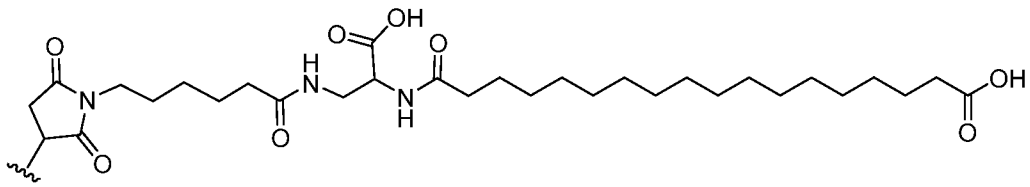
Group 5:



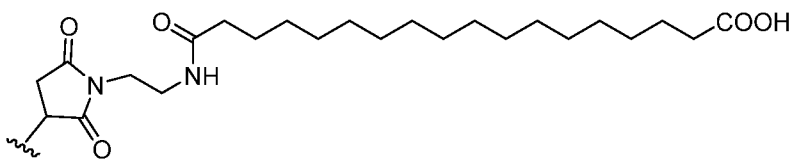
Group 6:



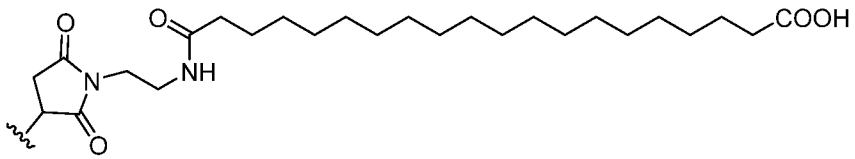
Group 7:



Group 8:



Group 9:



, wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0480] In Groups 2-9, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0481] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 11. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 4.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.130	0.150
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-40kDa PEG)	3	0.206	0.018	0.020
Group 3 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C6-C12-C12-C12-PEG2-C12 acid)	3	0.381	0.052	0.060
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C6-C12-PEG2-C18 diacid)	3	0.343	0.028	0.030
Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C6-C12-C12-PEG2-C18 diacid)	3	0.279	0.034	0.039

Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C6-C12-C12-C12-PEG2-C18 Diacid)	3	0.454	0.122	0.167
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C_{18}-diacid)	3	0.306	0.041	0.048
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C_{18}-acid)	3	0.363	0.053	0.062
Group 9 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C_{20}-acid)	3	0.354	0.036	0.039

As shown in Table 11 above, each of the HIF-2 alpha RNAi agents linked to tridentate targeting groups (Groups 2 through 9) showed substantial inhibitory activity compared to control.

Example 5. ***In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.***

[0482] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice in Groups 1 through 6 listed herein were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups in Table 12, below. Additionally, mice in Group 7 listed herein were dosed via subcutaneous (SQ) injection between the skin and muscle into the loose skin over the neck and shoulder area. The Groups dosed included the following:

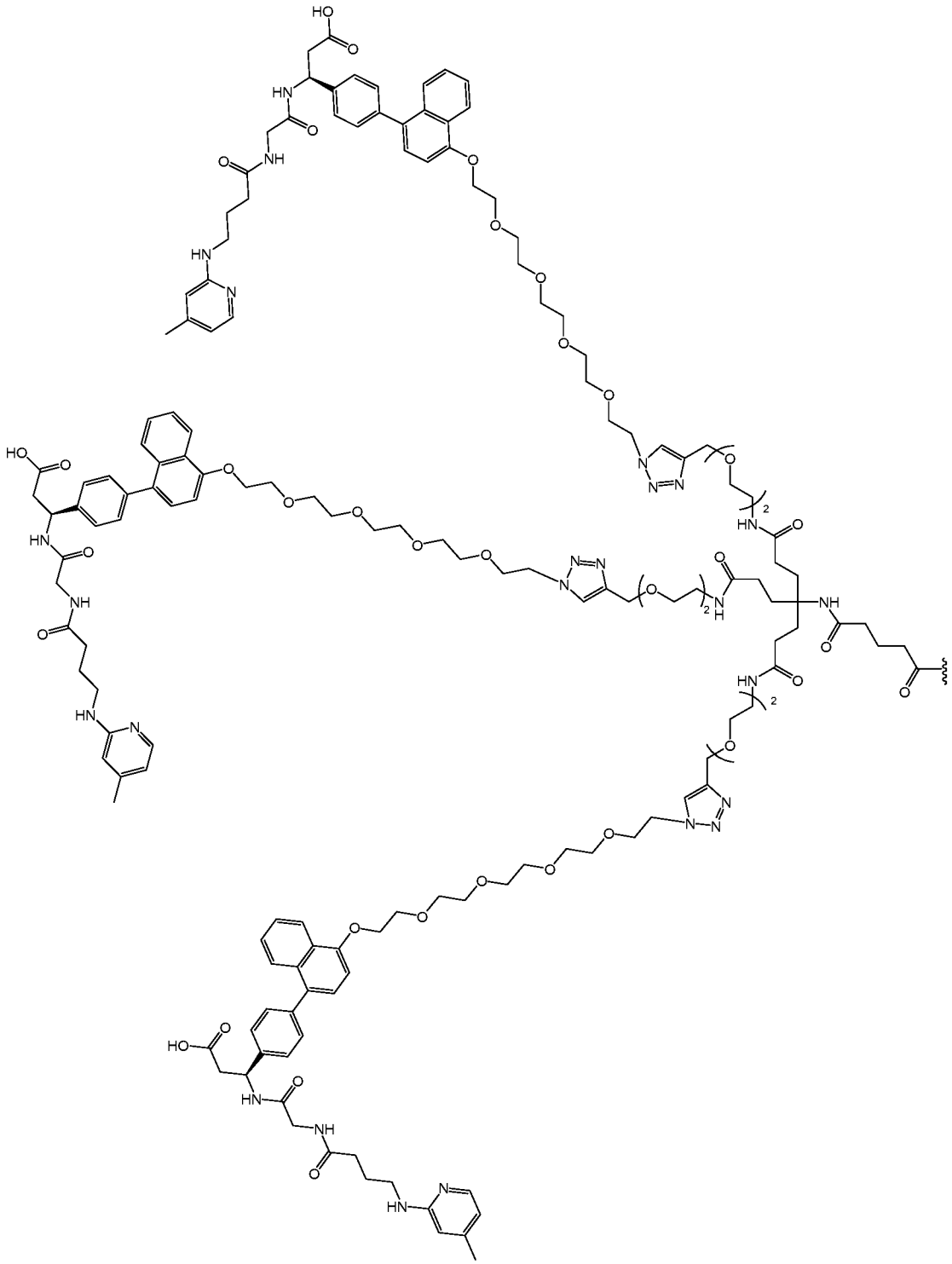
Table 12. Dosing Groups of Tumor-Bearing Mice in Example 5.

Group	**RNAi Agent and Dose**	**Dosing Regimen**
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C_{18}-diacid, formulated in isotonic glucose	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 6.1-avb6, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose	Single IV injection on day 1

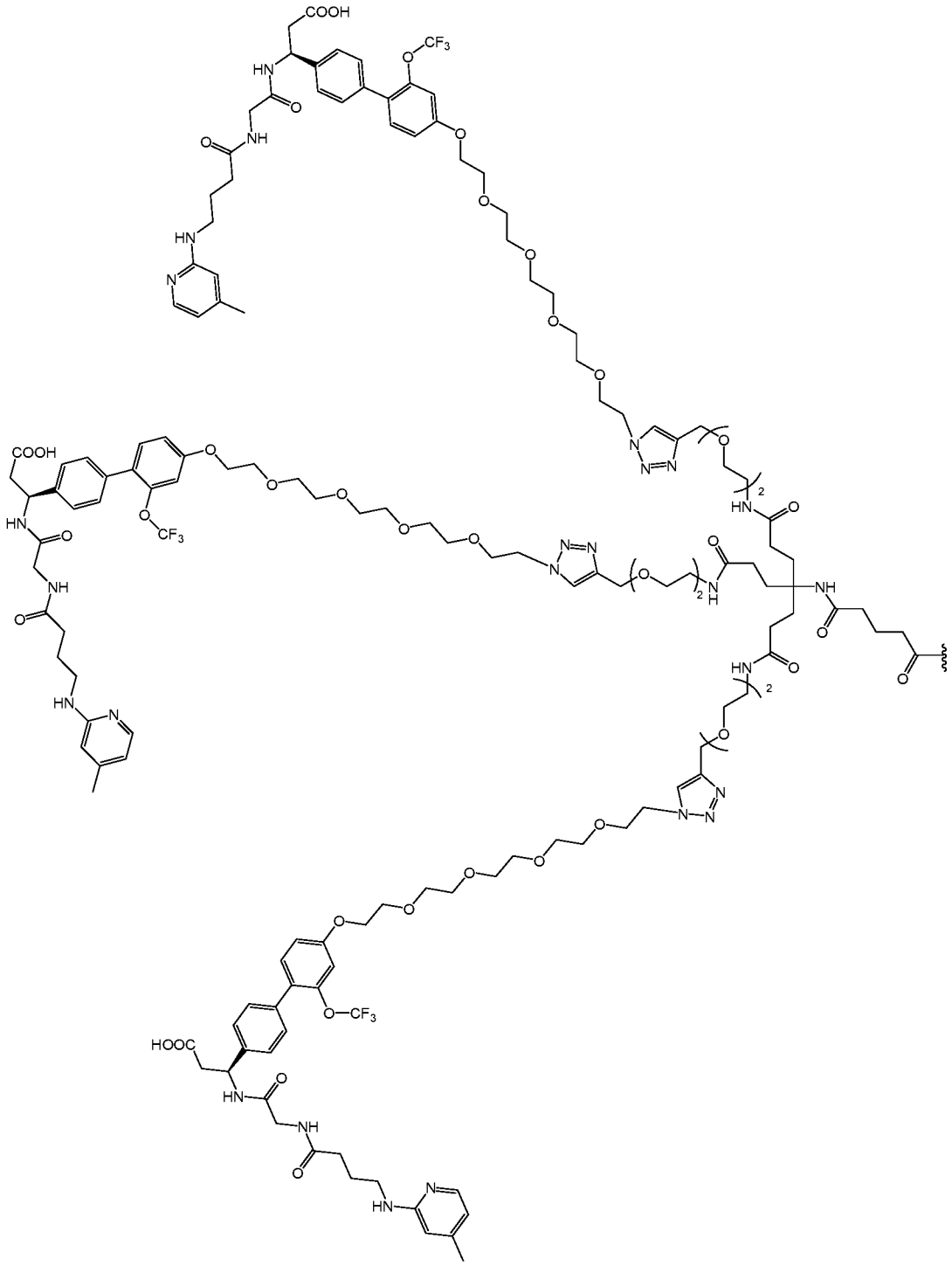
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 14-avb6, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose	Single IV injection on day 1
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD04545, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, formulated in isotonic glucose.	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose	Single SQ injection on day 1

[0483] In Groups 2-5 and 7, the PK enhancer having the structures indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand.

[0484] In Groups 2 and 5-7, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above. In Group 3, a tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-6 of the structure of Structure 6.1-avb6) was linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6), and in Group 4, a tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-6 of the structure of Structure 14-avb6) was linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6). The structures for the tridentate targeting groups that include the integrin targeting ligands Structure 6.1-avb6 and Structure 14-avb6 are shown below:



Targeting group for Structure 6.1-avb6,



Targeting group for Structure 14-avb6,

wherein ≈ indicates the point of connection to the functionalized amine linker.

[0485] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 13. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 5.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.108	0.122
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18 diacid) (IV)	3	0.437	0.054	0.062
Group 3 (7.5 mg/kg Tri-Structure 6.1-avb6-AD04546-Mal-C18 diacid)	3	0.691	0.056	0.060
Group 4 (7.5 mg/kg Tri-Structure 14-avb6-AD04546-Mal-C18 diacid)	3	0.582	0.170	0.241
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD04545)	3	0.751	0.125	0.150
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18 diacid) (SQ)	3	0.427	0.035	0.038

[0486] As shown in Table 13 above, the preference for linking one or more targeting ligands and a PK enhancer showed improved potency in silencing HIF-2 alpha expression. (*See, for example*, Group 6 (without PK enhancer) achieving only approximately 25% knockdown (0.751). Further, the data shows a preference for targeting groups that include targeting ligands that have affinity for integrin alpha-v-beta-3, compared to targeting ligands having affinity for alpha-v-beta-6. (Compare Group 3 (approximately 31% knockdown (0.691) using alpha-v-beta-6 ligand) and Group 4 (approximately 42% knockdown (0.582) using alpha-v-beta-6 ligand) with Group 2 (approximately 56% knockdown (0.437) using alpha-v-beta-3 ligand) and Group 5 (approximately 58% knockdown (0.413) using alpha-v-beta-3 ligand). Additionally, as shown in Groups 7 and 2, comparable efficacy can be achieved for dosing both IV and SQ using the PK enhancer of C18-diacid (C18diacid).

Example 6. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

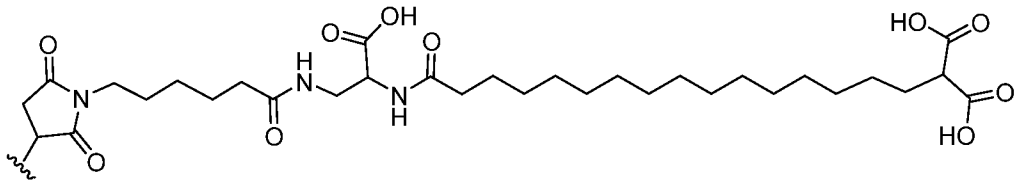
[0487] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 14. Dosing Groups of Tumor-Bearing Mice in Example 6.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-triacid, formulated in isotonic glucose.	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD05786, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] When viewing 5' → 3' on the sense strand of AD05786, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, 16, and 20 of the sense strand).	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD05915, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, having a Azide-C18-Diacid PK enhancer linked internally at the 2' position of nucleotide 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

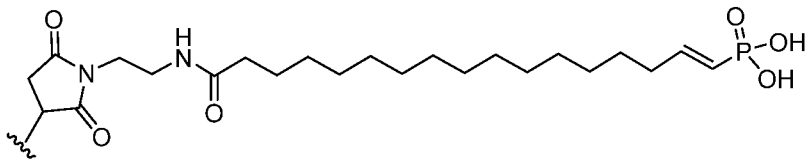
	(ii) When viewing 5' → 3' on the sense strand of AD05915, the C18-diacid PK enhancer is linked to the 2'-O-propargyl nucleotide (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence is at nucleotide 16 of the sense strand).	
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD05916, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, having a Azide-C18-Diacid PK enhancer linked internally at the 2' position of nucleotide 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(iii), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (iii) When viewing 5' → 3' on the sense strand of AD05916, the C18-diacid PK enhancer is linked to the 2'-O-propargyl nucleotide (represented by aAlk in the modified sense strand sequence for AD005916), which when viewed 5' → 3' on the sense strand sequence is at nucleotide 7 of the sense strand).	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD05917, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, having a Azide-C18-Diacid PK enhancer linked internally at the 2' position of each of nucleotides 6 and 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(iv), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (iv) When viewing 5' → 3' on the sense strand of AD05917, the C18-diacid PK enhancers are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 7 and 16 of the sense strand).	Single IV injection on day 1
10	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C17-vinyl-PO3, formulated in isotonic glucose.	Single IV injection on day 1
11	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal-C17-fluoro-PO3, formulated in isotonic glucose.	Single IV injection on day 1

[0488] In Groups 2, 4-7, the PK enhancer having the structures indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand. Group 3 included the PK enhancer linked to 3' terminal end of the sense strand of the following structure:



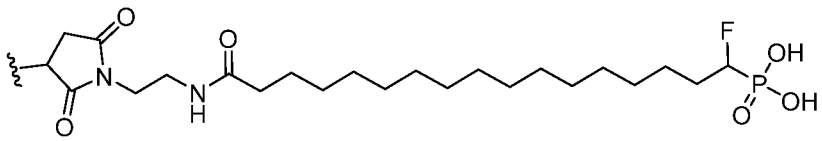
, wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0489] Group 10 included the PK enhancer linked to 3' terminal end of the sense strand of the following structure:



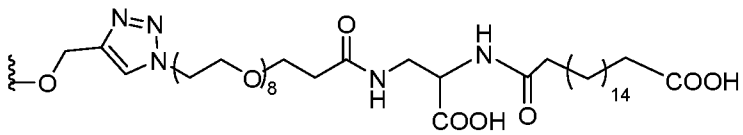
, wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0490] Group 11 included the PK enhancer linked to 3' terminal end of the sense strand of the following structure:



, wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0491] In Groups 5-7, PK enhancers were conjugated to internal nucleotides. Nucleotides as indicated included a 2'-O-propargyl group, and azide-containing PK enhancers (C18-diacid-N_3) were added to form a triazole. Groups 5-7 included a PK enhancer of the structure:



wherein ≈ indicates the point of attachment to the RNAi agent at the 2' position of the indicated nucleotide.

[0492] In Groups 2-11, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0493] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 15. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 6.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.148	0.173
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-C18 diacid))	3	0.345	0.056	0.067
Group 3 (7.5 mg/kg Tri-Structure 2a-avb3- AD04546-C18 triacid)	3	0.302	0.085	0.118
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD05786 (Int Structure 2a-avb3)$_4$-C18-diacid)	3	0.228	0.050	0.065
Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD05915 (Int C18-diacid)-C18-diacid)	3	0.414	0.120	0.169
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD05916 (Int C18-diacid)-C18-diacid)	3	0.524	0.091	0.111
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD05917 (Int C18-diacid)-C18-diacid)	3	0.391	0.124	0.182
Group 10 (7.5 mg/kg Tri-Structure 11-avb3-AD04546-C17-vinyl-PO3)	3	0.318	0.082	0.111
Group 11 (7.5 mg/kg Tri-Structure 11-avb3-AD04546-C17-fluoro-PO3)	3	0.388	0.087	0.112

[0494] As shown in Table 15 above, each of the HIF-2 alpha RNAi agents linked to tridentate targeting groups (Groups 2 through 11) showed substantial inhibitory activity compared to control.

Example 7. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0495] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, which included the following dosing Groups:

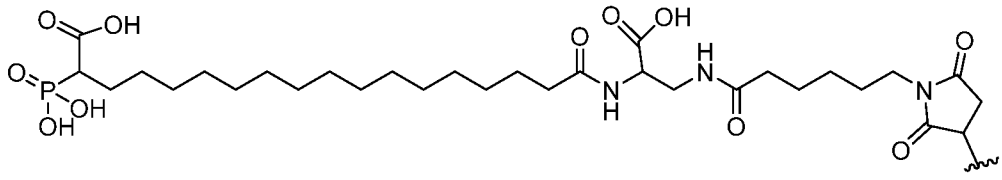
Table 16. Dosing Groups of Tumor-Bearing Mice in Example 7.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD05786, having a Structure 2a-avb3 targeting ligand linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD05786, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] *See* Example 6.	Single IV injection on day 1
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid-PO3, formulated in isotonic glucose.	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C22-diacid, formulated in isotonic glucose.	Single IV injection on day 1

8	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-triacid, formulated in isotonic glucose.	Single IV injection on day 1
9	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 10-avb6, and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
10	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 26-avb6, and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

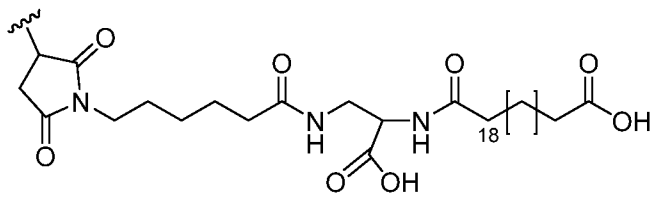
[0496] In Groups 2-4, 9 and 10, the PK enhancer having the structures indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand.

[0497] Group 6 includes a PK enhancer on the 3' end of the sense strand having the structure:



wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0498] Group 7 includes a PK enhancer on the 3' end of the sense strand having the structure:

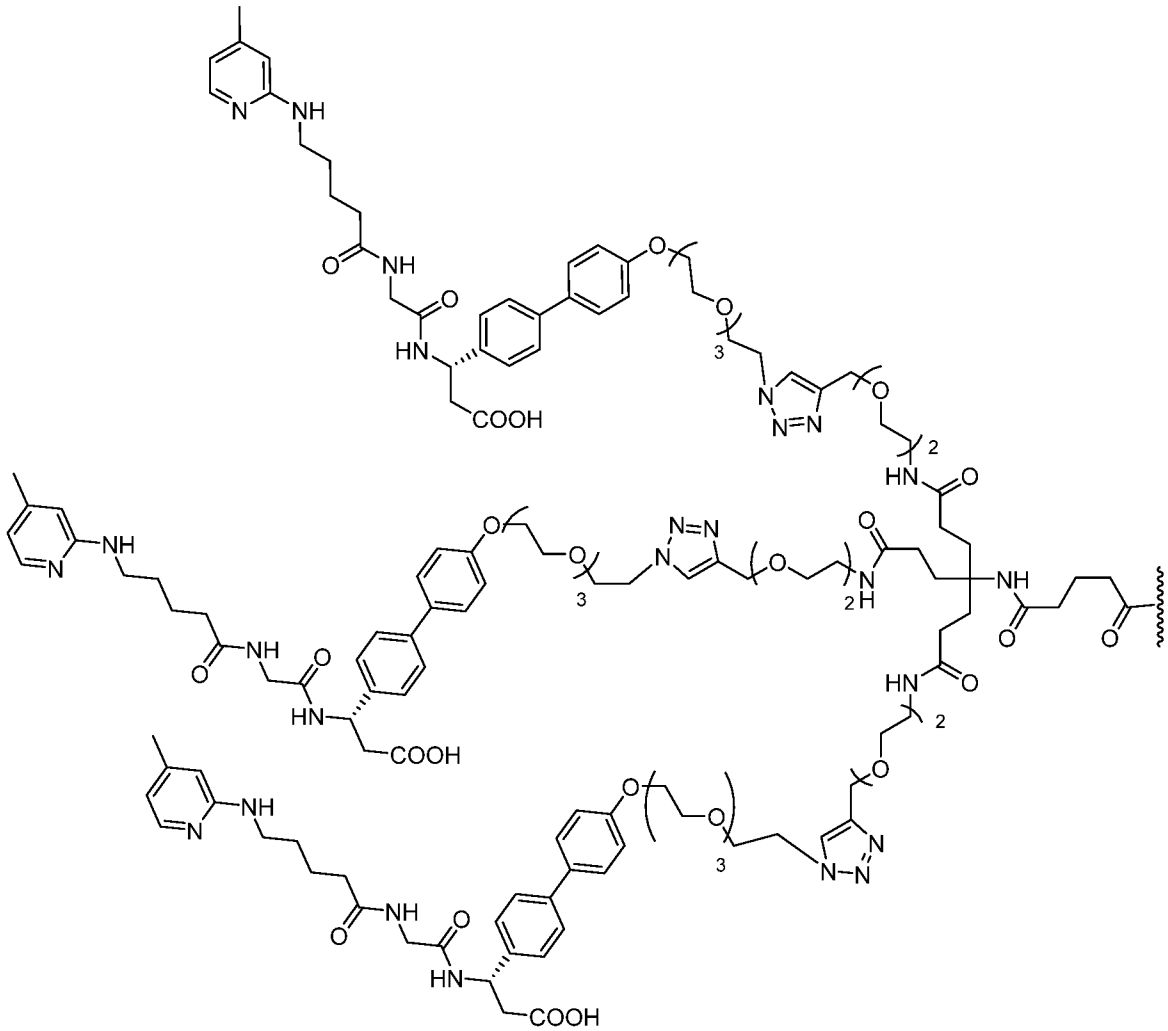


wherein ≈ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

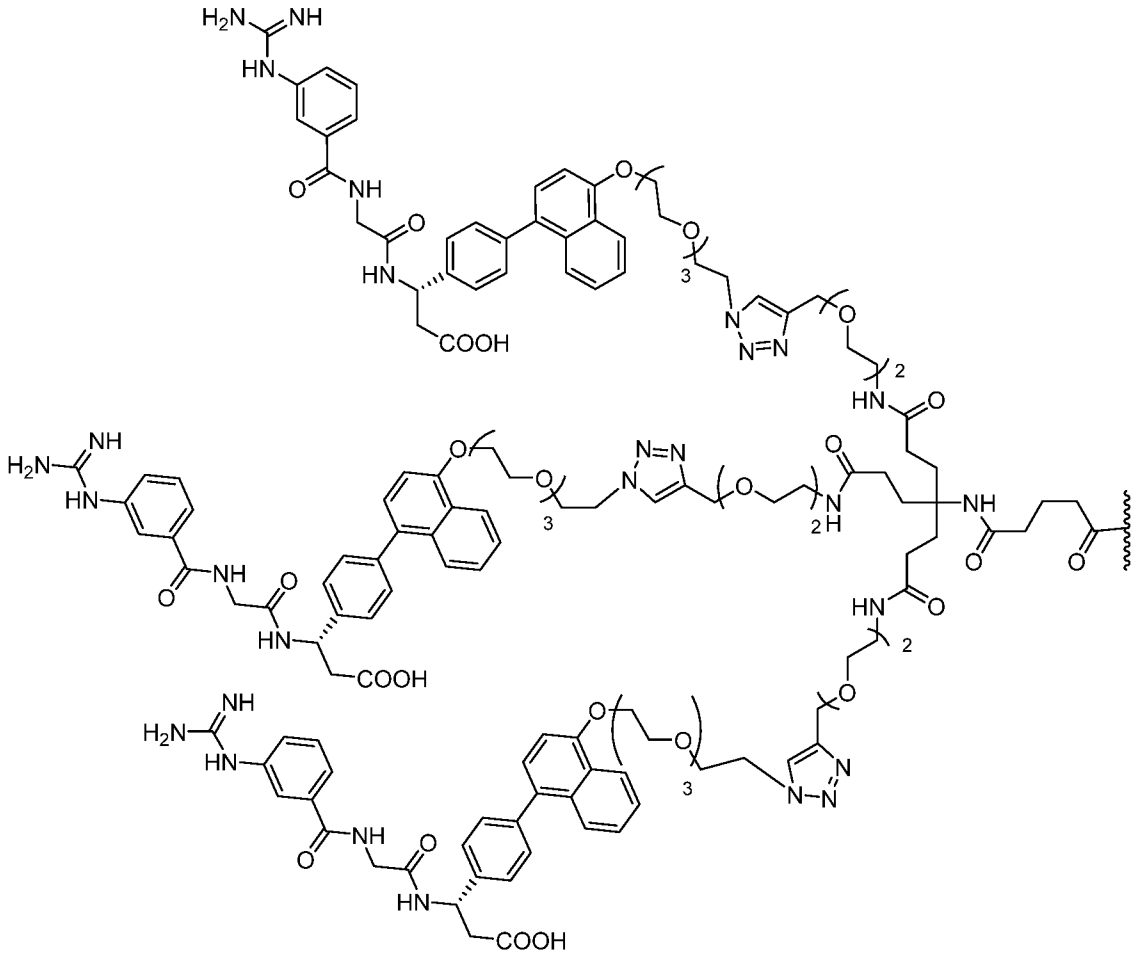
[0499] Group 8 includes a PK enhancer formed by the Michael addition of Mal-C_{18}-triacid to the 3' end of the sense strand comprising a disulfide, as shown in Example 6.

[0500] In Groups 2, 4-8, and 10, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine

reactive group linker (NH2-C6) has the structure set forth in Example 3, above. Group 9 included the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-6 of the structure of Structure 10-avb6) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6), the structure of which is shown below:



[0501] Group 10 included the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-6 of the structure of Structure 26-avb6) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6), the structure of which is shown below:



[0502] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 17. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 7.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.119	0.135
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-C18 diacid)	3	0.433	0.085	0.106

Group 3 (7.5 mg/kg AD05786 (Int-Structure 2a-avb3)4-C18 diacid)	3	0.336	0.059	0.072
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD05786 (Int-Structure 2a-avb3)4-C18 diacid)	3	0.224	0.028	0.032
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18 diacid-PO_3)	3	0.412	0.085	0.107
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C22-diacid)	3	0.595	0.067	0.075
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18-triacid)	3	0.300	0.041	0.048
Group 9 (7.5 mg/kg Tri-Structure 10-avb6-AD04546-Mal-C18-diacid)	3	0.607	0.072	0.082
Group 10 (7.5 mg/kg Tri-Structure 26-avb6-AD04546-Mal-C18-diacid)	3	0.819	0.179	0.229

As shown in Table 17 above, Group 4, which included four (4) internally placed Structure 2a-avb3 ligands on the sense strand of the HIF-2 alpha RNAi agent, exhibited approximately 78% knockdown of huHIF-2 alpha mRNA (0.228).

Example 8. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0503] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

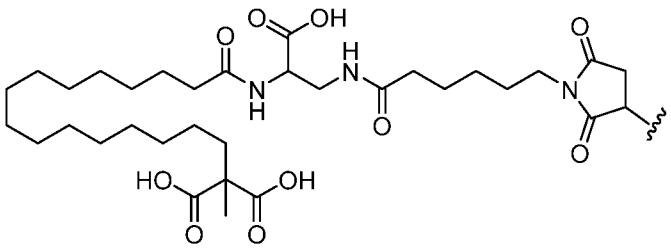
Table 18. Dosing Groups of Tumor-Bearing Mice in Example 8.

Group	**RNAi Agent and Dose**	**Dosing Regimen**
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD05930, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)],	Single IV injection on day 1

	and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (i) When viewing 5' → 3' on the sense strand of AD05930, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, 16, and 20 of the sense strand).	
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD05930, linked at the 5' terminal end of the sense strand to a single integrin targeting ligand having the structure of Structure 2a-avb3 and also with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(i), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (i) When viewing 5' → 3' on the sense strand of AD05930, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, 16, and 20 of the sense strand).	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD05930, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(i), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-triacid, formulated in isotonic glucose. (i) When viewing 5' → 3' on the sense strand of AD05930, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, 16, and 20 of the sense strand).	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD05932, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 3, 5, 6, 15, 16, 19, and 20 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(ii), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (ii) When viewing 5' → 3' on the sense strand of AD05932, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 2, 3, 6, 7, 16, 17, 19, and 20 of the sense strand).	Single IV injection on day 1

6	7.5 mg/kg of HIF-2 alpha RNAi agent AD05786, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] See Example 6.	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD05934, linked at the 5' terminal end of the sense strand to PK enhancer Mal-C18-diacid, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of AD05934, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, 16, and 20 of the sense strand).	Single IV injection on day 1
8	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1
9	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-triacid, formulated in isotonic glucose.	Single IV injection on day 1
10	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-diacid-PO_3, formulated in isotonic glucose.	Single IV injection on day 1
11	7.5 mg/kg of HIF-2 alpha RNAi agent AD04546, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, and also linked at the 3' terminal end of the sense strand to PK enhancer Mal- C18-methyl-triacid, formulated in isotonic glucose.	Single IV injection on day 1

[0504] In Groups 2, 3 and 5-8, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction. Groups 4 and 9 included a PK enhancer having the structure indicated in Example 6. Group 10 included a PK enhancer having the structure indicated in Example 7. Group 11 includes a PK enhancer on the 3' end of the sense strand having the structure:



wherein ≀ indicates the point of attachment to the RNAi agent at the C6-S group as indicated in Table 4.3.

[0505] In Groups 2, 4-5, and 8-11, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above. In Group 2, a single Structure 2a-avb3 targeting ligand was linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6). In Group 7, PK enhancer C18-diacid was linked to the (C6-SS-C6) disulfide linker located on the 5' terminal end of the sense strand as well as the to the 3' terminal end of the sense strand.

[0506] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 19. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 8.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.208	0.263
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD05930-(Int Structure 2a-avb3)$_4$-Mal-C18 diacid)	3	0.183	0.023	0.026
Group 3 (7.5 mg/kg Structure 2a-avb3-AD05930-(Int Structure 2a-avb3)$_4$-Mal-C18-diacid)	3	0.311	0.042	0.049

Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD05930-(Int Structure 2a-avb3)$_4$-Mal-C18-triacid)	3	0.209	0.043	0.054
Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD05932-(Int Structure 2a-avb3)$_8$-Mal-C18-diacid)	3	0.136	0.014	0.016
Group 6 (7.5 mg/kg AD05786 (Int Structure 2a-avb3)-Mal-C18-diacid)	3	0.488	0.055	0.062
Group 7 (7.5 mg/kg C18-diacid-AD05934 (Int Structure 2a-avb3)$_4$-Mal-C18-diacid)	3	0.314	0.028	0.031
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18-diacid)	3	0.516	0.060	0.068
Group 9 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18-triacid)	3	0.541	0.120	0.155
Group 10 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18-diacid-PO3)	3	0.477	0.058	0.067
Group 11 (7.5 mg/kg Tri-Structure 2a-avb3-AD04546-Mal-C18-methyl-triacid)	3	0.495	0.042	0.046

[0507] As shown in Table 19 above, inclusion of internal targeting ligand located on the sense strand of the HIF-2 alpha RNAi agents shows additional improvement in knockdown. (*See, for example*, Group 2 (four (4) internally positioned targeting ligands showing approximately 82% knockdown (0.183), and Group 8 (with no internally positioned targeting ligands showing approximately 49% knockdown (0.516).

Example 9. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0508] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 20. Dosing Groups of Tumor-Bearing Mice in Example 9.

Group	**RNAi Agent and Dose**	**Dosing Regimen**

1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD05930, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 8.	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD05954, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, and 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] When viewing 5' → 3' on the sense strand of AD05954, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, and 16 of the sense strand).	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD05955, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of AD05955, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 7, and 20 of the sense strand).	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD05956, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iv)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iv)] When viewing 5' → 3' on the sense strand of AD05956, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand	Single IV injection on day 1

	sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3, 16, and 20 of the sense strand).	
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD05957, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(v)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(v)] When viewing 5' → 3' on the sense strand of AD05957, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 7, 16, and 20 of the sense strand).	Single IV injection on day 1
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD05958, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 15 and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(vi)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(vii)] When viewing 5' → 3' on the sense strand of AD05958, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 16 and 20 of the sense strand).	Single IV injection on day 1
8	7.5 mg/kg of HIF-2 alpha RNAi agent AD05959, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(vii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(vii)] When viewing 5' → 3' on the sense strand of AD05959, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3 and 7 of the sense strand).	Single IV injection on day 1
9	7.5 mg/kg of HIF-2 alpha RNAi agent AD05960, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(viii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	(viii) When viewing 5' → 3' on the sense strand of AD05960, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3 and 20 of the sense strand).	
10	7.5 mg/kg of HIF-2 alpha RNAi agent AD05961, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 6 and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(ix), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (ix) When viewing 5' → 3' on the sense strand of AD05961, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 7 and 20 of the sense strand).	Single IV injection on day 1
11	7.5 mg/kg of HIF-2 alpha RNAi agent AD05962, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(x), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (x) When viewing 5' → 3' on the sense strand of AD05962, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 3 and 16 of the sense strand).	Single IV injection on day 1
12	7.5 mg/kg of HIF-2 alpha RNAi agent AD05917, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, having a C18-diacid PK enhancer linked internally at the 2' position of each of nucleotides 6 and 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(xi), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (xi) See Example 6.	Single IV injection on day 1
13	7.5 mg/kg of HIF-2 alpha RNAi agent AD05932, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 3, 5, 6, 15, 16, 19, and 20 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand(xii), and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	(xii) See Example 8.	

[0509] In Groups 2-13, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction

[0510] In Groups 2-13, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0511] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 21. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 9.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.197	0.246
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD05930-(Int Structure 2a-avb3)$_4$-Mal-C18-diacid)	3	0.265	0.031	0.036
Group 3 (7.5 mg/kg Structure 2a-avb3-AD05954-(Int Structure 2a-avb3)$_3$-Mal-C18-diacid)	3	0.337	0.095	0.133
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD05955-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.401	0.049	0.056
Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD05956-(Int Structure 2a-avb3)$_3$-Mal-C18-diacid)	3	0.315	0.100	0.146
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD05957-(Int Structure 2a-avb3)$_3$-Mal-C18-diacid)	3	0.313	0.050	0.060

Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD05958-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.426	0.126	0.179
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD05959-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.330	0.080	0.105
Group 9 (7.5 mg/kg Tri-Structure 2a-avb3-AD05960-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.359	0.063	0.076
Group 10 (7.5 mg/kg Tri-Structure 2a-avb3-AD05961-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.515	0.082	0.098
Group 11 (7.5 mg/kg Tri-Structure 2a-avb3-AD05962-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.433	0.142	0.212
Group 12 (7.5 mg/kg Tri-Structure 2a-avb3-AD05917-(Int Structure 2a-avb3)$_2$-Mal-C18-diacid)	3	0.460	0.100	0.128
Group 13 (7.5 mg/kg Tri-Structure 2a-avb3-AD05932-(Int Structure 2a-avb3)$_8$-Mal-C18-diacid)	3	0.135	0.029	0.037

Each of the HIF-2 alpha RNAi agents examined in Example 9 included at least 2 internal nucleotides that included an avb3 integrin targeting ligand attached at the 2' position of the nucleotide, and as shown in Table 21 above, each of the HIF-2 alpha RNAi agents tested exhibited nearly 50% or greater knockdown of HIF-2 alpha compared to vehicle control. Groups 2 (having 4 internal ligands, approximately 74% knockdown) and 13 (having 8 internal ligands, approximately 86% knockdown) showed particularly high reductions of huHIF-2 alpha mRNA expression.

Example 10. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0512] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 22. Dosing Groups of Tumor-Bearing Mice in Example 10.

Group	**RNAi Agent and Dose**	**Dosing Regimen**

1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	7.5 mg/kg of HIF-2 alpha RNAi agent AD05930, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, 15, and 19 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 8.	Single IV injection on day 1
3	7.5 mg/kg of HIF-2 alpha RNAi agent AD05963, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of nucleotide 2 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] When viewing 5' → 3' on the sense strand of AD05963, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotide 20 of the sense strand.	Single IV injection on day 1
4	7.5 mg/kg of HIF-2 alpha RNAi agent AD05915, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of nucleotide 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] See Example 6.	Single IV injection on day 1
5	7.5 mg/kg of HIF-2 alpha RNAi agent AD05916, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of nucleotide 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iv)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iv)] See Example 6.	Single IV injection on day 1
6	7.5 mg/kg of HIF-2 alpha RNAi agent AD05964, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of nucleotide 19 (3'→ 5') from the first nucleotide	Single IV injection on day 1

	that forms a base pair with the antisense strand[v], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [v] When viewing 5' → 3' on the sense strand of AD05964, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotide 3 of the sense strand.	
7	7.5 mg/kg of HIF-2 alpha RNAi agent AD05966, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4, 8, 14, and 18 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vi], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vi] When viewing 5' → 3' on the sense strand of AD05966, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 4, 8, 14, and 18 of the sense strand.	Single IV injection on day 1
8	7.5 mg/kg of HIF-2 alpha RNAi agent AD05967, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 7, 10, 14, and 17 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vii] When viewing 5' → 3' on the sense strand of AD05967, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, cAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 5, 8, 12, and 15 of the sense strand.	Single IV injection on day 1
9	7.5 mg/kg of HIF-2 alpha RNAi agent AD05968, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 9, 10, 14, and 15 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[viii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vii] When viewing 5' → 3' on the sense strand of AD05968, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense	Single IV injection on day 1

	strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 7, 8, 12, and 13 of the sense strand.	
10	7.5 mg/kg of HIF-2 alpha RNAi agent AD05969, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 14, 16, 18, and 20 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ix)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ix)] When viewing 5' → 3' on the sense strand of AD05969, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 2, 4, 6, and 8 of the sense strand.	Single IV injection on day 1
11	7.5 mg/kg of HIF-2 alpha RNAi agent AD05970, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 17, 18, 19, and 20 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(x)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(x)] When viewing 5' → 3' on the sense strand of AD05970, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, and gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 2, 3, 4, and 5 of the sense strand.	Single IV injection on day 1
12	7.5 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(xi)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(xi)] When viewing 5' → 3' on the sense strand of AD05971, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1
13	7.5 mg/kg of HIF-2 alpha RNAi agent AD05972, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 3, 4, and 5 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(xii)], and further linked at the 3' terminal end of the sense	Single IV injection on day 1

	strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. (xii) When viewing 5' → 3' on the sense strand of AD05972, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 17, 18, 19, and 20 of the sense strand.	

[0513] In Groups 2-13, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction

[0514] In Groups 2-13, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0515] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 23. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 10.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.204	0.256
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD05930-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.267	0.046	0.055
Group 3 (7.5 mg/kg Structure 2a-avb3-AD05963-(Int Structure 2a-avb3)- Mal-C18-diacid)	3	0.405	0.065	0.077
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD05915-(Int Structure 2a-avb3)- Mal-C18-diacid)	3	0.455	0.014	0.015

Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD05916-(Int Structure 2a-avb3)- Mal-C18-diacid)	3	0.392	0.032	0.034
Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD05964-(Int Structure 2a-avb3)- Mal-C18-diacid)	3	0.445	0.070	0.084
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD05966-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.166	0.020	0.023
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD05967-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.211	0.037	0.045
Group 9 (7.5 mg/kg Tri-Structure 2a-avb3-AD05968-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.505	0.065	0.075
Group 10 (7.5 mg/kg Tri-Structure 2a-avb3-AD05969-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.416	0.090	0.116
Group 11 (7.5 mg/kg Tri-Structure 2a-avb3-AD05970-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.469	0.028	0.030
Group 12 (7.5 mg/kg Tri-Structure 2a-avb3-AD05971-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.161	0.018	0.020
Group 13 (7.5 mg/kg Tri-Structure 2a-avb3-AD05972-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.193	0.025	0.029

Example 11. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0516] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 24. Dosing Groups of Tumor-Bearing Mice in Example 11.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1

2	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] When viewing 5' → 3' on the sense strand of AD06294, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1
3	2.0 mg/kg of HIF-2 alpha RNAi agent AD06058, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of nucleotide 4 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] When viewing 5' → 3' on the sense strand of AD06058, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotide 18 of the sense strand.	Single IV injection on day 1
4	2.0 mg/kg of HIF-2 alpha RNAi agent AD06146, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4 and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of AD06146, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by gAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14 and 18 of the sense strand.	Single IV injection on day 1
5	2.0 mg/kg of HIF-2 alpha RNAi agent AD06160, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 4 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iv)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	[iv] When viewing 5' → 3' on the sense strand of AD06160, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 18 and 20 of the sense strand.	
6	2.0 mg/kg of HIF-2 alpha RNAi agent AD06161, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4 and 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[v], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [v] When viewing 5' → 3' on the sense strand of AD06161, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 16 and 18 of the sense strand.	Single IV injection on day 1
7	2.0 mg/kg of HIF-2 alpha RNAi agent AD06162, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 6 and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vi], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vi] When viewing 5' → 3' on the sense strand of AD06162, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14 and 16 of the sense strand.	Single IV injection on day 1
8	2.0 mg/kg of HIF-2 alpha RNAi agent AD06163, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vii] When viewing 5' → 3' on the sense strand of AD06163, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14 and 20 of the sense strand.	Single IV injection on day 1
9	2.0 mg/kg of HIF-2 alpha RNAi agent AD05959, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 6 (3'→ 5') from the first	Single IV injection on day 1

	nucleotide that forms a base pair with the antisense strand[viii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [viii] See Example 9.	

[0517] In Groups 2-9, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction

[0518] In Groups 2-9, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0519] Three (3) mice were dosed in each Group, except for Group 2 in which only two (2) mice were dosed. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 25. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 11.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.094	0.104
Group 2 (7.5 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	2	0.313	0.029	0.032
Group 3 (7.5 mg/kg Structure 2a-avb3-AD06058-(Int Structure 2a-avb3)- Mal-C18-diacid)	3	0.548	0.049	0.054
Group 4 (7.5 mg/kg Tri-Structure 2a-avb3-AD06146-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.485	0.043	0.047
Group 5 (7.5 mg/kg Tri-Structure 2a-avb3-AD06160-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.508	0.060	0.068

Group 6 (7.5 mg/kg Tri-Structure 2a-avb3-AD06161-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.464	0.054	0.061
Group 7 (7.5 mg/kg Tri-Structure 2a-avb3-AD06162-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.455	0.031	0.033
Group 8 (7.5 mg/kg Tri-Structure 2a-avb3-AD06163-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.516	0.065	0.074
Group 9 (7.5 mg/kg Tri-Structure 2a-avb3-AD05959-(Int Structure 2a-avb3)$_2$- Mal-C18-diacid)	3	0.642	0.063	0.070

Example 12. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0520] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 26. Dosing Groups of Tumor-Bearing Mice in Example 12.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on day 1
3	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	[i] See Example 11.	
4	2.0 mg/kg of HIF-2 alpha RNAi agent AD06065, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 and 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[ii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [ii] When viewing 5' → 3' on the sense strand of AD06065, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk and gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 16, 18, and 20 of the sense strand.	Single IV injection on day 1
5	4.0 mg/kg of HIF-2 alpha RNAi agent AD06065, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 and 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[ii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [ii] When viewing 5' → 3' on the sense strand of AD06065, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk and gAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 16, 18, and 20 of the sense strand.	Single IV injection on day 1
6	2.0 mg/kg of HIF-2 alpha RNAi agent AD06066, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[iii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [iii] When viewing 5' → 3' on the sense strand of AD06066, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 18, and 20 of the sense strand.	Single IV injection on day 1
7	4.0 mg/kg of HIF-2 alpha RNAi agent AD06066, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[iv], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	[iv] When viewing 5' → 3' on the sense strand of AD06066, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 18, and 20 of the sense strand.	
8	2.0 mg/kg of HIF-2 alpha RNAi agent AD06067, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[v], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [v] When viewing 5' → 3' on the sense strand of AD06067, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, and 20 of the sense strand.	Single IV injection on day 1
9	4.0 mg/kg of HIF-2 alpha RNAi agent AD06067, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[v], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [v] When viewing 5' → 3' on the sense strand of AD06067, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, and 20 of the sense strand.	Single IV injection on day 1
10	2.0 mg/kg of HIF-2 alpha RNAi agent AD06068, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vi], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vi] When viewing 5' → 3' on the sense strand of AD06068, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, and 18 of the sense strand.	Single IV injection on day 1
11	4.0 mg/kg of HIF-2 alpha RNAi agent AD06068, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4, 6, and 8 (3'→ 5') from the	Single IV injection on day 1

	first nucleotide that forms a base pair with the antisense strand[(vi)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(vi)] When viewing 5' → 3' on the sense strand of AD06068, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, and 18 of the sense strand.	

[0521] In Groups 2-11, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction.

[0522] In Groups 2-11, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0523] Three (3) mice were dosed in each Group, except for Group 6 in which only two (2) mice were dosed. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 27. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 12.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.114	0.128
Group 2 (2.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.245	0.026	0.029
Group 3 (4.0 mg/kg Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.188	0.049	0.066

Group 4 (2.0 mg/kg Tri-Structure 2a-avb3-AD06065-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.357	0.066	0.080
Group 5 (4.0 mg/kg Tri-Structure 2a-avb3-AD06065-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.331	0.045	0.052
Group 6 (2.0 mg/kg Tri-Structure 2a-avb3-AD06066-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	2	0.291	0.035	0.040
Group 7 (4.0 mg/kg Tri-Structure 2a-avb3-AD06066-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.222	0.068	0.098
Group 8 (2.0 mg/kg Tri-Structure 2a-avb3-AD06067-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.320	0.028	0.031
Group 9 (4.0 mg/kg Tri-Structure 2a-avb3-AD06067-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.243	0.048	0.060
Group 10 (2.0 mg/kg Tri-Structure 2a-avb3-AD06068-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.327	0.018	0.019
Group 11 (4.0 mg/kg Tri-Structure 2a-avb3-AD06068-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.266	0.070	0.095

Example 13. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0524] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 28. Dosing Groups of Tumor-Bearing Mice in Example 13.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from	Single IV injection on day 1

	the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	
3	2.0 mg/kg of HIF-2 alpha RNAi agent AD05972, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 3, 4, and 5 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] See Example 10.	Single IV injection on day 1
4	2.0 mg/kg of HIF-2 alpha RNAi agent AD06071, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, and 5 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of AD06071, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 17, 18, and 20 of the sense strand.	Single IV injection on day 1
5	4.0 mg/kg of HIF-2 alpha RNAi agent AD06072, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 3, 4, and 5 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iv)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iv)] When viewing 5' → 3' on the sense strand of AD06072, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 17, 18, and 19 of the sense strand.	Single IV injection on day 1
6	2.0 mg/kg of HIF-2 alpha RNAi agent AD06059, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 3, 4, 5, and 6 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(v)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(v)] When viewing 5' → 3' on the sense strand of AD06059, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl	Single IV injection on day 1

	nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 16, 17, 18, and 19 of the sense strand.	
7	4.0 mg/kg of HIF-2 alpha RNAi agent AD06060, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 4, 5, 6, and 7 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vi], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vi] When viewing 5' → 3' on the sense strand of AD06060, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 15, 16, 17, and 18 of the sense strand.	Single IV injection on day 1
8	2.0 mg/kg of HIF-2 alpha RNAi agent AD06061, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 5, 6, 7, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[vii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [vii] When viewing 5' → 3' on the sense strand of AD06061, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 15, 16, and 17 of the sense strand.	Single IV injection on day 1
9	4.0 mg/kg of HIF-2 alpha RNAi agent AD06062, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 6, 7, 8, and 9 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[viii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [viii] When viewing 5' → 3' on the sense strand of AD06062, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 13, 14, 15, and 16 of the sense strand.	Single IV injection on day 1

10	2.0 mg/kg of HIF-2 alpha RNAi agent AD06068, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 7, 8, 9, and 10 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ix)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ix)] When viewing 5' → 3' on the sense strand of AD06063, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 12, 13, 14, and 15 of the sense strand.	Single IV injection on day 1

[0525] In Groups 2-10, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction.

[0526] In Groups 2-10, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0527] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 29. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 13.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	3	1.000	0.087	0.096
Group 2 (2.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.341	0.047	0.054

Group 3 (2.0 mg/kg Structure 2a-avb3-AD05972-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.422	0.056	0.065
Group 4 (2.0 mg/kg Tri-Structure 2a-avb3-AD06071-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.481	0.089	0.109
Group 5 (2.0 mg/kg Tri-Structure 2a-avb3-AD06072-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.440	0.020	0.021
Group 6 (2.0 mg/kg Tri-Structure 2a-avb3-AD06059-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.438	0.062	0.073
Group 7 (2.0 mg/kg Tri-Structure 2a-avb3-AD06060-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.413	0.042	0.047
Group 8 (2.0 mg/kg Tri-Structure 2a-avb3-AD06061-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.459	0.069	0.081
Group 9 (2.0 mg/kg Tri-Structure 2a-avb3-AD06062-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.513	0.138	0.189
Group 10 (2.0 mg/kg Tri-Structure 2a-avb3-AD06063-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.602	0.049	0.053

Example 14. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0528] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, according to the following dosing Groups:

Table 30. Dosing Groups of Tumor-Bearing Mice in Example 14.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from	Single IV injection on day 1

	the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	
3	5.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] See Example 11.	Single IV injection on day 1
4	2.0 mg/kg of HIF-2 alpha RNAi agent AD06296, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of each of AD06296, AD06297, and AD06299, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1
5	5.0 mg/kg of HIF-2 alpha RNAi agent AD06296, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of each of AD06296, AD06297, and AD06299, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1
6	2.0 mg/kg of HIF-2 alpha RNAi agent AD06297, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose.	Single IV injection on day 1

	[iii] When viewing 5' → 3' on the sense strand of each of AD06296, AD06297, and AD06299, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14, 16, 18, and 20 of the sense strand.	
7	2.0 mg/kg of HIF-2 alpha RNAi agent AD06299, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[iii], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [iii] When viewing 5' → 3' on the sense strand of each of AD06296, AD06297, and AD06299, the Structure 2a-avb3 targeting ligands is linked to the 2'-O-propargyl nucleotide (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1

[0529] In Groups 2-7, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction.

[0530] In Groups 2-7, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0531] Three (3) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 31. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 14.

Group ID	Number of animals	Average Relative HIF-2 alpha	Low (error)	High (error)

	(n=)	mRNA expression		
Group 1 (isotonic glucose vehicle)	3	1.000	0.167	0.201
Group 2 (2.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.382	0.080	0.101
Group 3 (5.0 mg/kg Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.194	0.044	0.057
Group 4 (2.0 mg/kg Tri-Structure 2a-avb3-AD06296-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.512	0.170	0.255
Group 5 (5.0 mg/kg Tri-Structure 2a-avb3-AD06296-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.212	0.025	0.028
Group 6 (2.0 mg/kg Tri-Structure 2a-avb3-AD06297-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.404	0.081	0.102
Group 7 (2.0 mg/kg Tri-Structure 2a-avb3-AD06299-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.282	0.057	0.072

[0532] Each of the HIF-2 alpha RNAi agents in Example 14 included a sense strand that comprised (i) a tridentate targeting group located at the 5' terminal end of the sense strand that comprised three targeting ligands; (ii) a total of four additional internal targeting ligands linked at the 2' position to each of the nucleotides located at positions 2, 4, 6, and 8 from the first nucleotide that forms a base pair with the antisense strand; and (iii) a PK enhancer linked to the 3' terminal end of the sense strand. As shown in Table 31 above, each of the RNAi agents, dosed at both 2.0 mg/kg and 5.0 mg/kg exhibited substantial reductions of huHIF-2 alpha mRNA compared to vehicle control.

Example 15. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0533] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study day 1, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection, which included the following dosing Groups:

Table 32. Dosing Groups of Tumor-Bearing Mice in Example 15.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1
2	2.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on day 1
3	5.0 mg/kg of HIF-2 alpha RNAi agent AD06153, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2 and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(ii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(ii)] When viewing 5' → 3' on the sense strand of AD06153 the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14 and 20 of the sense strand.	Single IV injection on day 1
4	2.0 mg/kg of HIF-2 alpha RNAi agent AD06157, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(iii)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(iii)] When viewing 5' → 3' on the sense strand of each of AD06157, the Structure 2a-avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, cAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence at nucleotides 14, 16, 18, and 20 of the sense strand.	Single IV injection on day 1

[0534] In Groups 2-4, the PK enhancer having the structure indicated in previous examples for Mal-C_{18}-diacid was linked to the 3' terminal end of the sense strand by linking the maleimide reactive group by reducing the disulfide and undertaking a Michael Addition reaction.

[0535] In Groups 2-4, the tridentate integrin targeting group (which included three integrin ligands having affinity for alpha-v-beta-3 of the structure of Structure 2a-avb3) linked to the 5' terminal end of the sense strand by coupling to the functionalized amine reactive group linker (NH2-C6) has the structure set forth in Example 3, above.

[0536] Three (3) mice were dosed in each Group, except for the vehicle control group (Group 1), which only had 2 mice. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 33. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice (Day 8) in Example 15.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose vehicle)	2	1.000	0.057	0.061
Group 2 (2.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.397	0.044	0.049
Group 3 (5.0 mg/kg Structure 2a-avb3-AD06153-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid)	3	0.470	0.076	0.091
Group 4 (2.0 mg/kg Tri-Structure 2a-avb3-AD06157-(Int Structure 2a-avb3)$_3$- Mal-C18-diacid)	3	0.451	0.105	0.137

Example 16. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0537] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. On study days 1, 2, 8, 9, 15, 22, and 29, mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection of either 5.0

mg/kg of Tri-Structure 2a-avb3-AD05971-(Int Structure 2a-avb3)$_4$-C18-diacid, or isotonic glucose with no RNAi agent.

[0538] Six (6) mice were dosed in each Group. Mice were sacrificed on study day 36, kidney tumors were harvested. Figure 4A shows the kidneys from a mouse in the untreated control group, with the tumor kidney shown on the right side of the image, and the contralateral kidney shown on the left. Figure 4B shows the kidneys from a mouse in the group treated with RNAi agent, also with the tumor kidney shown on the right side of that image and the contralateral kidney shown on the left. As is evident from the images and confirmed by tumor weigts, the HIF-2 alpha RNAi agent group inhibited tumor growth. Additionally, as shown in Figure 5A, immunohistochemistry (IHC) staining of cells from a tumor-bearing mouse in the control group confirms the presence of HIF-2 alpha protein as is visible by the darkened spots, while no such darkened spots are evident on the image of Figure 5B showing the cells of a tumor-bearing mouse treated with HIF-2 alpha RNAi agent.

Example 17. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0539] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. Mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection according to the following dosing Groups:

Table 34. Dosing Groups of Tumor-Bearing Mice in Example 17.

Group	RNAi Agent and Dose	Dosing/Sacrifice Regimen
1	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on days 1 and 8; day 22 harvest
2	5.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on days 1 and 8; day 15 harvest

3	5.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on days 1 and 8; day 22 harvest
4	Isotonic glucose (D5W) (no RNAi agent)	Single IV injection on day 1 and 15; day 29 harvest
5	5.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on day 1 and 15; day 22 harvest
6	5.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on day 1 and 15; day 29 harvest

[0540] Four (4) mice were dosed in each Group. At the scheduled date of sacrifice as noted in Table 34, above, kidney tumors were harvested and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 35. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice in Example 17.

Group ID	Number of animals (n=)	Average Relative HIF-2 alpha mRNA expression	Low (error)	High (error)
Group 1 (isotonic glucose vehicle, Day 1 and 8 dosing; day 22 harvest)	4	1.000	0.267	0.364
Group 2 (5.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, day 1 and 8 dosing; day 15 harvest)	4	0.192	0.041	0.053
Group 2 (5.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, day 1 and 8 dosing; day 22 harvest)	4	0.334	0.095	0.132
Group 4 (isotonic glucose vehicle, Day 1 and 15 dosing; day 29 harvest)	4	1.000	0.260	0.352
Group 5 (5.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, day 1 and 15 dosing; day 22 harvest)	4	0.168	0.029	0.035
Group 6 (5.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, day 1 and 15 dosing; day 29 harvest)	4	0.282	0.066	0.086

Example 18. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0541] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. Mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection according to the following dosing Groups:

Table 36. Dosing Groups of Tumor-Bearing Mice in Example 18.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single IV injection on day 1
2	20.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the	Single IV injection on day 1

	antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	
3	10.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	An initial IV injection on day 1, and a second IV injection four hours later on day 1 [2 x 10 mg/kg injections on day 1]
4	10.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection on day 1

[0542] Four (4) mice were dosed in each Group. Mice were sacrificed on study day 8, kidney tumors were harvested, and total human HIF-2 mRNA in the kidney tumors was isolated following collection and homogenization. HIF-2 alpha (huHIF-2 alpha) mRNA expression was quantitated by probe-based quantitative PCR, normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

Table 37. Average Relative huHIF-2 alpha mRNA Expression at Sacrifice in Example 18.

Group ID	**Number of animals (n=)**	**Average Relative HIF-2 alpha mRNA expression**	**Low (error)**	**High (error)**
Group 1 (saline vehicle)	4	1.000	0.065	0.069
Group 2 (20.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, single injection on day 1)	4	0.191	0.040	0.050

Group 3 (2 x 10.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, two injections on day 1 (4 hours apart))	4	0.148	0.027	0.033
Group 4 (10.0 mg/kg Tri-Structure 2a-avb3-AD06294-(Int Structure 2a-avb3)$_4$- Mal-C18-diacid, single injection on day 1)	4	0.220	0.056	0.075

Example 19. In Vivo Administration of HIF-2 Alpha RNAi Agents In ccRCC Tumor-Bearing Mice.

[0543] The tumor-bearing mouse model of Example 2 was used to evaluate HIF-2 alpha RNAi agents *in vivo*. Mice were dosed via tail vein intravenous (IV) injection with approximately 300 microliters volume of injection according to the following dosing Groups:

Table 38. Dosing Groups of Tumor-Bearing Mice in Example 19.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single IV injection weekly
2	20.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	Single IV injection weekly
3	10.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	An initial IV injection followed by a second IV injection four hours later on day one [2 x 10 mg/kg injections], starting on day 1 and administered weekly

4	10.0 mg/kg of HIF-2 alpha RNAi agent AD06294, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] See Example 11.	An initial IV injection followed by a second IV injection four hours later on day one [2 x 10 mg/kg injections], starting on day 1 and administered biweekly (every other week).

[0544] Fifteen (15) mice were dosed in each Group and body weight and tumor growth were monitored by palpation and caliper estimates weekly. One animal in Group 4 was found dead on day 21. Figure 6 shows the effects on tumor growth up to study Day 34. As reported in Figure 6, the data show an overall improvement in tumor size reduction when administered with a HIF-2 alpha RNAi agent compared to the saline vehicle control.

Example 20. In Vivo Administration of Integrin Targeting Ligands Conjugated to RNAi Agents Targeting HIF-2 alpha in Kidney Tumor Bearing Mice.

[0545] RNAi agents that included a sense strand and an antisense strand were synthesized according to phosphoramidite technology on solid phase in accordance with general procedures known in the art and commonly used in oligonucleotide synthesis as set forth in Example 1 herein. The RNAi agents had the respective modified nucleotide sequences set forth in Example 2 herein and were designed to target Hif2α (*EPAS1*).

[0546] On study day 1, kidney tumor bearing mice were dosed via tail vein injection according to the following dosing Groups:

Table 39. Dosing Groups of Mice in Example 20.

Group	**RNAi Agent and Dose**	**Dosing Regimen**
1	Isotonic glucose (d5w (5% dextrose in water)) (no RNAi agent)	Single injection on day 1

4	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
5	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 32a-avb3, with an integrin targeting ligand of Structure 32a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
6	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 33a-avb3, with an integrin targeting ligand of Structure 33a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

7	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 34a-avb3, with an integrin targeting ligand of Structure 34a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

[0547] Three (3) tumor bearing mice were dosed in each Group (n=3). Mice were sacrificed on study day 8 after injection, and total RNA was isolated from kidney tumor. Relative Human HIF2α mRNA expression was then quantitated by probe-based quantitative PCR (RT-qPCR), normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (isotonic glucose) (geometric mean, +/- 95% confidence interval).

Table 40. Average Relative Hif2α mRNA Expression at Sacrifice in Example 20.

Group ID	**Average Relative huHIF2α mRNA Expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose)	1.000	0.077	0.083
Group 4 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid pk extender)	0.245	0.048	0.059
Group 5 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 32a, three internal ligands of Structure 32a, and Mal-C18-diacid)	0.213	0.065	0.094
Group 6 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 33a, three internal ligands of Structure 33a, and Mal-C18-diacid)	0.603	0.117	0.146

Group ID	Average Relative huHIF2α mRNA Expression	Low (error)	High (error)
Group 7 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 34a, three internal ligands of Structure 34a, and Mal-C18-diacid)	0.528	0.067	0.077

[0548] As shown in Table 40 above, each of the Hif2α RNAi agent-integrin targeting ligand conjugates showed a reduction in mRNA expression in mice compared to control.

Example 21. In Vivo Administration of Integrin Targeting Ligands Conjugated to RNAi Agents Targeting HIF-2 alpha in Kidney Tumor Bearing Mice.

[0549] RNAi agents that included a sense strand and an antisense strand were synthesized according to phosphoramidite technology on solid phase in accordance with general procedures known in the art and commonly used in oligonucleotide synthesis as set forth in Example 1 herein. The RNAi agents had the respective modified nucleotide sequences set forth herein and were designed to target Hif2α (*EPAS1*).

[0550] On study day 1, kidney tumor bearing mice (see Example 4) were dosed via tail vein injection according to the following dosing Groups:

Table 41. Dosing Groups of Mice in Example 21.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (d5w (5% dextrose in water)) (no RNAi agent)	Single injection on day 1

2	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11-avb3, with an integrin targeting ligand of Structure 2.11a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
5	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 36-avb3, with an integrin targeting ligand of Structure 36a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
6	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 37-avb3, with an integrin targeting ligand of Structure 37a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

[0551] Three (3) tumor bearing mice were dosed in each Group (n=3). Mice were sacrificed on study day 8 after injection, and total RNA was isolated from kidney tumor. Relative

Human HIF2α mRNA expression was then quantitated by probe-based quantitative PCR (RT-qPCR), normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (isotonic glucose) (geometric mean, +/- 95% confidence interval).

Table 42. Average Relative Hif2α mRNA Expression at Sacrifice in Example 21.

Group ID	**Average Relative huHIF2α mRNA Expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose)	1.000	0.090	0.099
Group 2 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.362	0.021	0.022
Group 5 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 36a, three internal ligands of Structure 36a, and Mal-C18-diacid)	0.617	0.028	0.029
Group 6 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 37a, three internal ligands of Structure 37a, and Mal-C18-diacid)	0.375	0.081	0.103

[0552] As shown in Table 42 above, each of the Hif2α RNAi agent-integrin targeting ligand conjugates showed a reduction in mRNA expression in mice compared to control.

Example 22. In Vivo Administration of Integrin Targeting Ligands Conjugated to RNAi Agents Targeting HIF-2 alpha in Kidney Tumor Bearing Mice.

[0553] RNAi agents that included a sense strand and an antisense strand were synthesized according to phosphoramidite technology on solid phase in accordance with general procedures known in the art and commonly used in oligonucleotide synthesis as set forth in Example 1 herein. The RNAi agents had the respective modified nucleotide sequences set forth herein and were designed to target Hif2α (*EPAS1*).

[0554] On study day 1, kidney tumor bearing mice were dosed via tail vein injection according to the following dosing Groups:

Table 43. Dosing Groups of Mice in Example 22.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (d5w (5% dextrose in water)) (no RNAi agent)	Single injection on day 1
2	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
3	4.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a-avb3, with an integrin targeting ligand of Structure 2a-avb3 targeting ligand linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

6	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 38-avb3, with an integrin targeting ligand of Structure 38a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
7	4.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 38-avb3, with an integrin targeting ligand of Structure 38a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
8	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 39-avb3, with an integrin targeting ligand of Structure 39a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

9	4.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 39-avb3, with an integrin targeting ligand of Structure 39a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
10	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 40-avb3, with an integrin targeting ligand of Structure 40a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
11	4.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 40-avb3, with an integrin targeting ligand of Structure 40a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

12	2.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 41-avb3, with an integrin targeting ligand of Structure 41a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
13	4.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having the structure of integrin targeting ligand Structure 41-avb3, having a Structure 41a-avb3 linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PK enhancer Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

[0555] Three (3) tumor bearing mice were dosed in each Group (n=3). Mice were sacrificed on study day 8 after injection, and total RNA was isolated from kidney tumor according to the procedure set forth in Example 4. Relative Human HIF2α mRNA expression was then quantitated by probe-based quantitative PCR (RT-qPCR), normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (isotonic glucose) (geometric mean, +/- 95% confidence interval).

Table 44. Average Relative Hif2α mRNA Expression at Sacrifice in Example 22.

Group ID	**Average Relative huHIF2α mRNA Expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose)	1.000	0.247	0.327
Group 2 (2.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid)	0.286	0.037	0.043
Group 3 (4.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid)	0.263	0.035	0.040
Group 6 (2.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 38a, three internal ligands of Structure 38a, and Mal-C18-diacid)	0.655	0.050	0.054
Group 7 (4.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 38a, three internal ligands of Structure 38a, and Mal-C18-diacid)	0.488	0.042	0.046
Group 8 (2.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 39a, three internal ligands of Structure 39a, and Mal-C18-diacid)	0.609	0.065	0.073
Group 9 (4.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 39a, three internal ligands of Structure 39a, and Mal-C18-diacid)	0.518	0.050	0.055
Group 10 (2.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 40a, three internal ligands of Structure 40a, and Mal-C18-diacid)	0.805	0.113	0.132
Group 11 (4.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 40a, three internal ligands of Structure 40a, and Mal-C18-diacid)	0.738	0.091	0.104
Group 12 (2.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 41a, three internal ligands of Structure 41a, and Mal-C18-diacid)	0.978	0.082	0.090
Group 13 (4.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 41a, three internal ligands of Structure 41a, and Mal-C18-diacid)	0.779	0.106	0.123

[0556] As shown in Table 44 above, each of the Hif2α RNAi agent-integrin targeting ligand conjugates showed a reduction in mRNA expression in mice compared to control.

Example 23. In Vivo Administration of Integrin Targeting Ligands Conjugated to RNAi Agents Targeting HIF-2 alpha in Kidney Tumor Bearing Mice.

[0557] RNAi agents that included a sense strand and an antisense strand were synthesized according to phosphoramidite technology on solid phase in accordance with general procedures known in the art and commonly used in oligonucleotide synthesis as set forth in Example 1 herein. The RNAi agents had the respective modified nucleotide sequences set forth in Example 2 herein and were designed to target Hif2α (*EPAS1*).

[0558] On study day 1, kidney tumor bearing mice were dosed via tail vein injection according to the following dosing Groups:

Table 45. Dosing Groups of Mice in Example 23.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (0.9%) (no RNAi agent)	Single injection on day 1
2	2.5 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

3	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
4	10.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
5	2.5 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

6	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
7	10.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2.11a, with an integrin targeting ligand of Structure 2.11a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
8	2.5 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a, with an integrin targeting ligand of Structure 2a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

9	5.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a, with an integrin targeting ligand of Structure 2a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1
10	10.0 mg/kg of HIF-2 alpha RNAi agent AD05971, linked at the 5' terminal end of the sense strand to a tridentate targeting group having three integrin targeting ligands of Structure 2a, with an integrin targeting ligand of Structure 2a linked internally at the 2' position of each of nucleotides 2, 4, 6, and 8 (3'→ 5') from the first nucleotide that forms a base pair with the antisense strand[(i)], and further linked at the 3' terminal end of the sense strand to PD modulator Mal-C18-diacid, formulated in isotonic glucose. [(i)] The avb3 targeting ligands are linked to the 2'-O-propargyl nucleotides (represented by aAlk, gAlk, and uAlk in the modified sense strand sequence), which when viewed 5' → 3' on the sense strand sequence are at nucleotides 14, 16, 18, and 20 of the sense strand.	Single injection on day 1

[0559] Four (4) tumor bearing mice were dosed in each Group (n=4), except for Group 4 which only had three (3) mice as one mouse was deemed to have a faulty injection. Mice were sacrificed on study day 8 after injection, and total RNA was isolated from kidney tumor according to the procedure set forth in Example 4. Relative Human HIF2α mRNA expression was then quantitated by probe-based quantitative PCR (RT-qPCR), normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (isotonic glucose) (geometric mean, +/- 95% confidence interval).

Table 46. Average Relative Hif2α mRNA Expression at Sacrifice in Example 23.

Group ID	Average Relative huHIF2α mRNA Expression	Low (error)	High (error)
Group 1 (isotonic glucose)	1.000	0.180	0.220
Group 2 (2.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.278	0.068	0.091
Group 3 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.229	0.062	0.086
Group 4 (10.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.202	0.014	0.015
Group 5 (2.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.324	0.035	0.040
Group 6 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.308	0.018	0.019
Group 7 (10.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2.11a, three internal ligands of Structure 2.11a, and Mal-C18-diacid)	0.197	0.041	0.052
Group 8 (2.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid)	0.218	0.048	0.062
Group 9 (5.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid)	0.160	0.065	0.109
Group 10 (10.0 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, three internal ligands of Structure 2a, and Mal-C18-diacid)	0.276	0.053	0.066

[0560] As shown in Table 46 above, each of the Hif2α RNAi agent-integrin targeting ligand conjugates showed a reduction in mRNA expression in mice compared to control.

Example 24. In Vivo Administration of Integrin Targeting Ligands Conjugated to RNAi Agents Targeting HIF-2 alpha in Kidney Tumor Bearing Mice.

[0561] RNAi agents that included a sense strand and an antisense strand were synthesized according to phosphoramidite technology on solid phase in accordance with general procedures known in the art and commonly used in oligonucleotide synthesis as set forth in Example 2 herein. The RNAi agents had the respective modified nucleotide sequences set forth in Example 2 herein and were designed to target Hif2α (*EPAS1*).

[0562] On study day 1, kidney tumor bearing mice were dosed via tail vein injection according to the following dosing Groups:

Table 47. Dosing Groups of Mice in Example 24.

Group	RNAi Agent and Dose	Dosing Regimen
1	Isotonic glucose (d5w (5% dextrose in water)) (no RNAi agent)	Single injection on day 1
2	7.5 mg/kg of Hif2α RNAi agent (AD04546) conjugated to a tridentate integrin targeting ligand of Structure 2a, and further including a C18-diacid moiety linked to the construct, formulated in isotonic glucose.	Single injection on day 1
6	7.5 mg/kg of Hif2α RNAi agent (AD04546) conjugated to a tridentate integrin targeting ligand of Structure 28a, and further including a Mal-C18-diacid moiety linked to the construct, formulated in isotonic glucose.	Single injection on day 1
7	7.5 mg/kg of Hif2α RNAi agent (AD04546) conjugated to a tridentate integrin targeting ligand of Structure 29a, and further including a Mal-C18-diacid moiety linked to the construct, formulated in isotonic glucose.	Single injection on day 1
8	7.5 mg/kg of Hif2α RNAi agent (AD04546) conjugated to a tridentate integrin targeting ligand of Structure 30a, and further including a Mal-C18-diacid moiety linked to the construct, formulated in isotonic glucose.	Single injection on day 1
9	7.5 mg/kg of Hif2α RNAi agent (AD04546) conjugated to a tridentate integrin targeting ligand of Structure 31a, and further including a Mal-C18-diacid moiety linked to the construct, formulated in isotonic glucose.	Single injection on day 1

[0563] The RNAi agents were synthesized having nucleotide sequences directed to target the human Hif2α gene, and included a functionalized amine reactive group (NH_2-C_6) at the 5′ terminal end of the sense strand to facilitate conjugation to the integrin targeting ligands.

[0564] Three (3) tumor bearing mice were dosed in each Group (n=3). Mice were sacrificed on study day 8 after injection, and total RNA was isolated from kidney tumor according to

the procedure set forth in Example 4. Relative Human HIF2α mRNA expression was then quantitated by probe-based quantitative PCR (RT-qPCR), normalized to human Cyclophilin A (PPIA) expression and expressed as fraction of vehicle control group (isotonic glucose) (geometric mean, +/- 95% confidence interval), as explained in Example 4.

Table 48. Average Relative Hif2α mRNA Expression at Sacrifice in Example 24.

Group ID	**Average Relative huHIF2α mRNA Expression**	**Low (error)**	**High (error)**
Group 1 (isotonic glucose)	1.000	0.077	0.083
Group 2 (7.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 2a, Mal-C18-diacid)	0.456	0.113	0.150
Group 6 (7.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 28a, Mal-C18-diacid)	0.649	0.072	0.081
Group 7 (7.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 29a, Mal-C18-diacid)	0.426	0.054	0.062
Group 8 (7.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 30a, Mal-C18-diacid)	0.699	0.064	0.070
Group 9 (7.5 mg/kg RNAi agent-tridentate integrin targeting ligand of Structure 31a, Mal-C18-diacid)	0.580	0.069	0.079

[0565] As shown in Table 48 above, each of the Hif2α RNAi agent-integrin targeting ligand conjugates showed a reduction in mRNA expression compared to control.

EMBODIMENTS

Embodiment 1. An RNAi agent for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene, comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3;

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand; and

(iii) one or more targeting ligands.

Embodiment 2. The RNAi agent of embodiment 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences provided in Table 3.

Embodiment 3. The RNAi agent of embodiment 1 or embodiment 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sense strand sequences provided in Table 4, 4.1, 4.2, or 4.3, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.

Embodiment 4. The RNAi agent of any one of embodiments 1-3, wherein all or substantially all of the nucleotides of the sense strand of the RNAi agent, the antisense strand of the RNAi agent, or both the sense strand and the antisense strand of the RNAi agent, are modified nucleotides.

Embodiment 5. The RNAi agent of embodiment 4, wherein at least one modified nucleotide is selected from the group consisting of: 2′-O-methyl nucleotide, 2′-fluoro nucleotide, 2′-deoxy nucleotide, 2′,3′-seco nucleotide mimic, locked nucleotide, 2'-F-arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted 2′-O-methyl nucleotide, inverted 2′-deoxy nucleotide, 2′-amino-modified nucleotide, 2′-alkyl-modified nucleotide, morpholino nucleotide, vinyl phosphonate deoxyribonucleotide, 2′-O-propargyl-modified nucleotide, 2′-O-triazole-modified nucleotides, and 3′-O-methyl nucleotide.

Embodiment 6. The RNAi agent of embodiment 5, wherein each modified nucleotide is independently selected from the group consisting of: 2′-O-methyl nucleotides, 2′-fluoro nucleotides, and 2′-O-triazole-modified nucleotides.

Embodiment 7. The RNAi agent of any one of embodiments 1-6, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3.

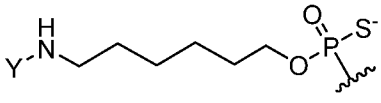
Embodiment 8. The RNAi agent of any one of embodiments 1-7, wherein the sense strand comprises the nucleotide sequence of any of the modified sense strand sequences provided in Table 4.

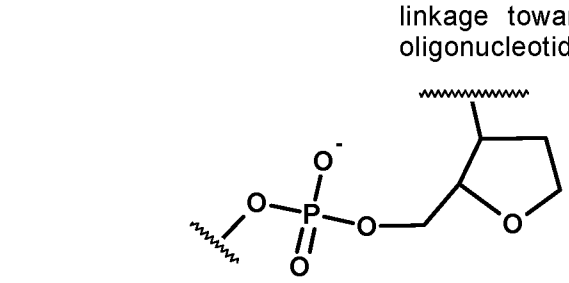
Embodiment 9. The RNAi agent of any one of embodiments 1-8, wherein the antisense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 3 and the sense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 4, Table 4.1, Table 4.2, or Table 4.3.

Embodiment 10. The RNAi agent of any one of embodiments 1-9, wherein the antisense strand comprises nucleotides 2-18 of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively.

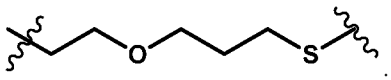
Embodiment 11. The RNAi agent of embodiment 10, wherein the antisense strand comprises the sequence of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively.

Embodiment 12. The RNAi agent of embodiment 1, wherein the sense strand comprises nucleotides 2-18 of the sequence of CAACGUAACGAUUUCAUGAAA (SEQ ID NO: 428).

Embodiment 13. The RNAi agent of embodiment 1, wherein the sense strand comprises the sequence of Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, and each *Z* independently represents a pharmacological moiety, Y-(NH-C6)s represents:  (invAb) represents:

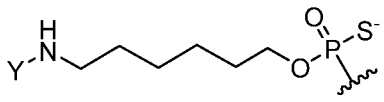


and (6-S) represents:

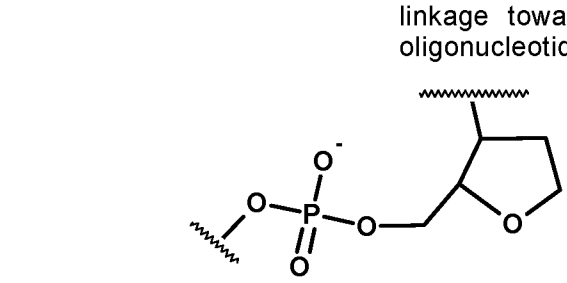


Embodiment 14. The RNAi agent of any one of embodiments 12 or 13, wherein the antisense strand is at least substantially complementary to the sense strand.

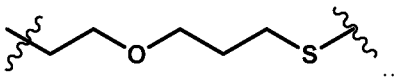
Embodiment 15. The RNAi agent of any of embodiments 1-14, wherein the nucleotides of the sense strand consist of the sequence of Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, and each *Z* independently represents a pharmacological moiety, Y-(NH-C6)s represents:



(invAb) represents:



and (6-S) represents:



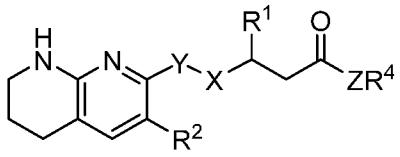
Embodiment 16. The RNAi agent of embodiment 15 wherein the nucleotides of the antisense strand consist of the sequence of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively.

Embodiment 17. The RNAi agent of any one of embodiments 1-16, wherein the sense strand of the RNAi agent is linked to at least one targeting ligand.

Embodiment 18. The RNAi agent of embodiment 17, wherein the targeting ligand comprises a compound having affinity for an integrin.

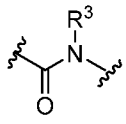
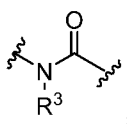
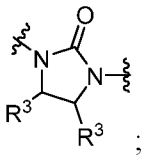
Embodiment 19. The RNAi agent of embodiment 18, wherein the targeting ligand comprises a compound that has affinity for integrin alpha-v-beta-3, alpha-v-beta-5, or both alpha-v-beta-3 and alpha-v-beta-5.

Embodiment 20. The RNAi agent of embodiment 19, wherein the targeting ligand is a compound of the formula:



(Formula I),

wherein,

X is -C(R^3)$_2$-, -NR^3-, , , or ;

Y is optionally substituted alkylene with 1 to 8 carbon atoms in the alkylene chain;

Z is O, NR^3, or S;

R^1 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl or R^1 comprises the RNAi agent;

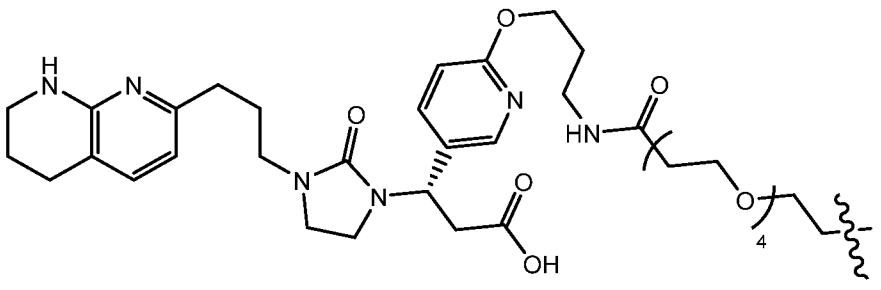
R^2 is H, optionally substituted alkyl, or R^2 comprises the RNAi agent;

each instance of R^3 is independently selected from the group consisting of H and optionally substituted alkyl, or R^3 comprises the RNAi agent;

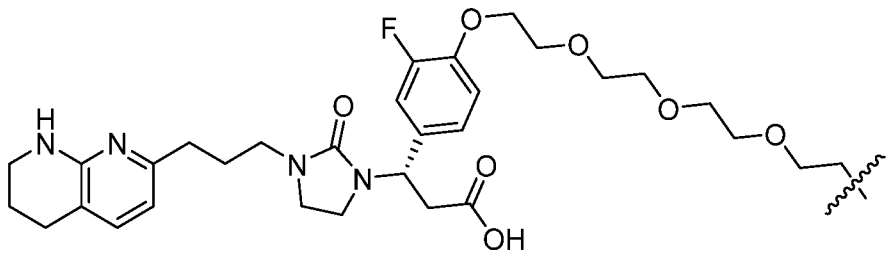
R^4 is H or optionally substituted alkyl; and

wherein at least one of Y, R^1, R^2, any instance of R^3, and R^4 comprises the RNAi agent.

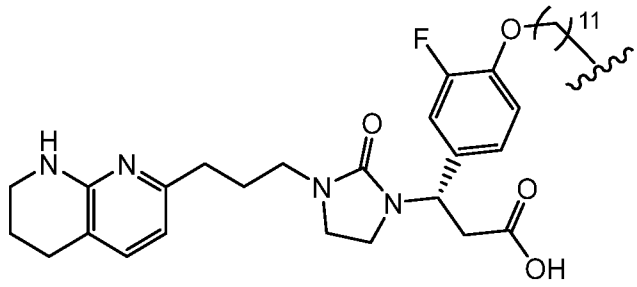
Embodiment 21. The RNAi agent of embodiment 20, wherein the targeting ligand is selected from:



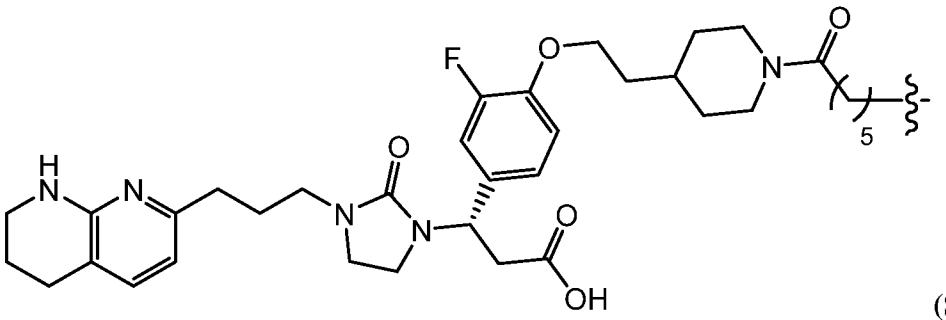
(Structure 1a);



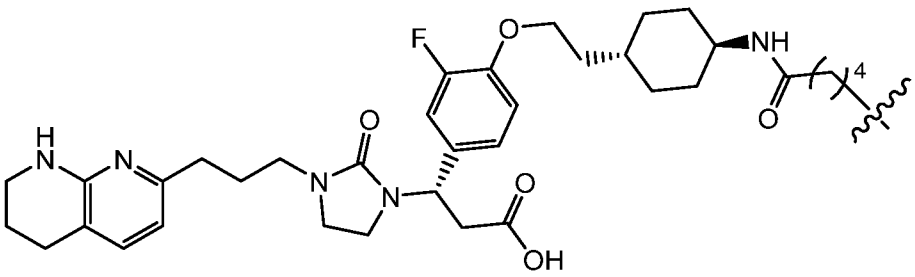
(Structure 2a);



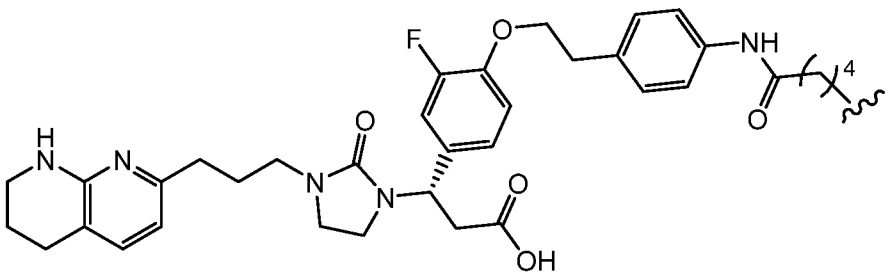
(Structure 2.1a);



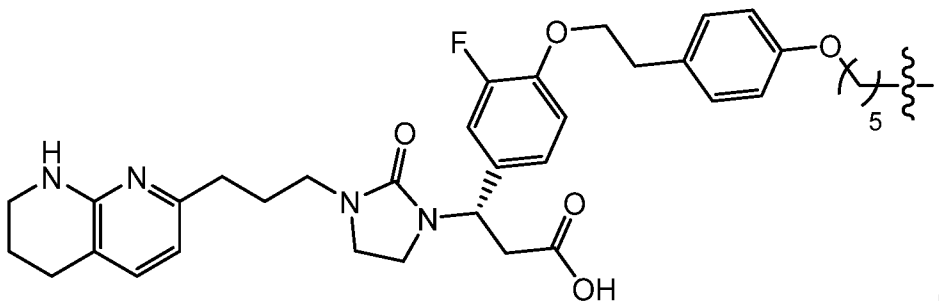
(Structure 2.2a);



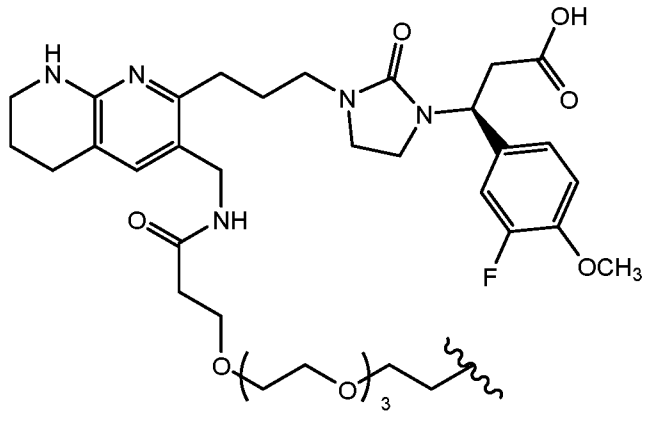
(Structure 2.3a);



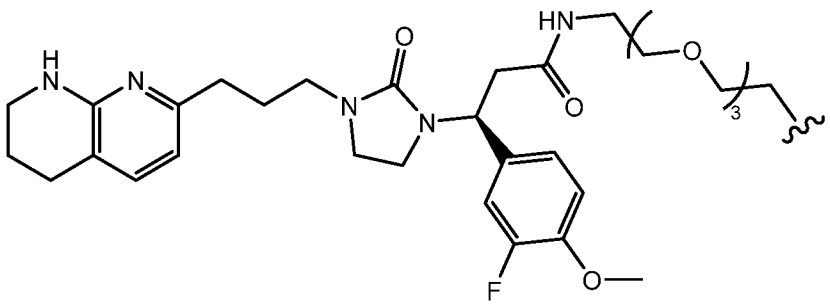
(Structure 2.4a);



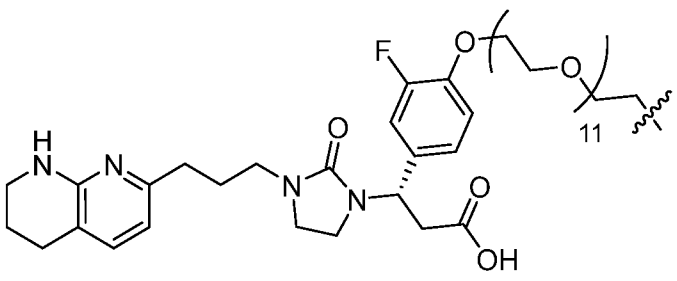
(Structure 2.5a);



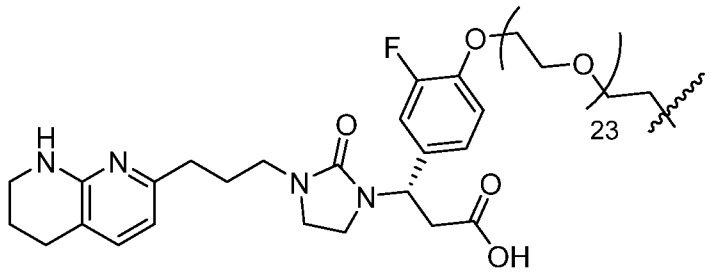
(Structure 2.6a);



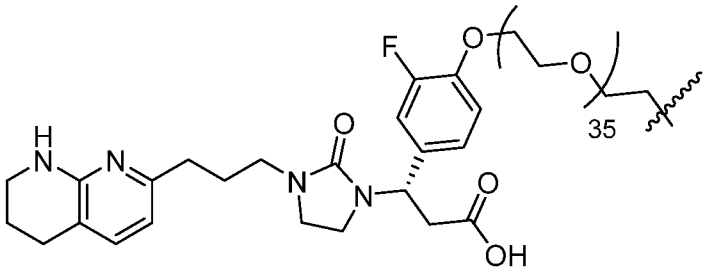
(Structure 2.7a);



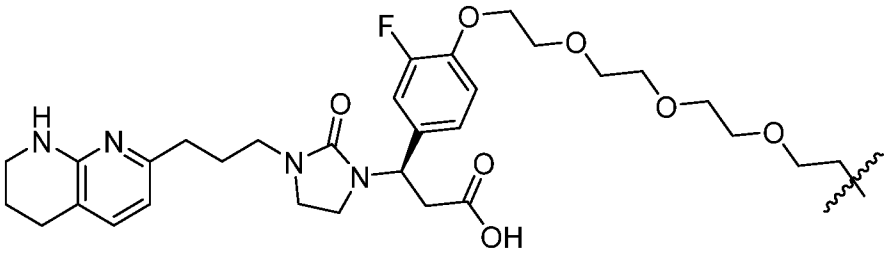
(Structure 2.8a);



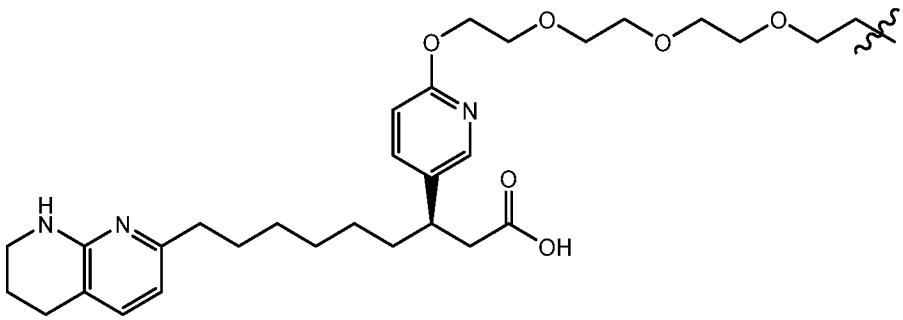
(Structure 2.9a);



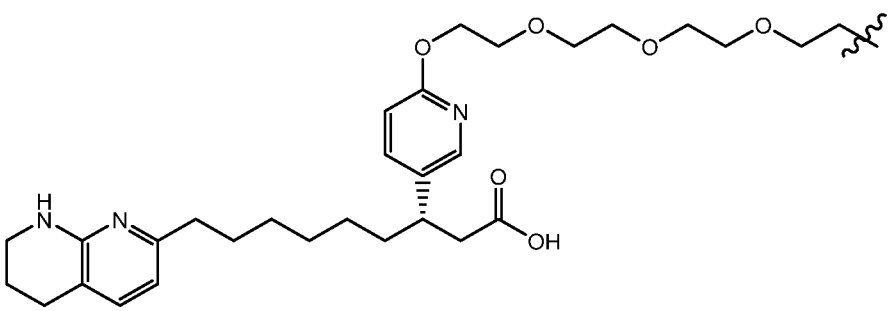
(Structure 2.10a);



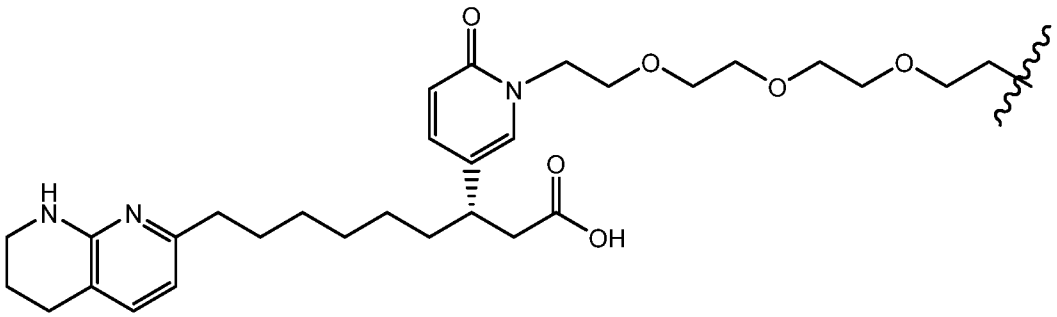
(Structure 2.11a);



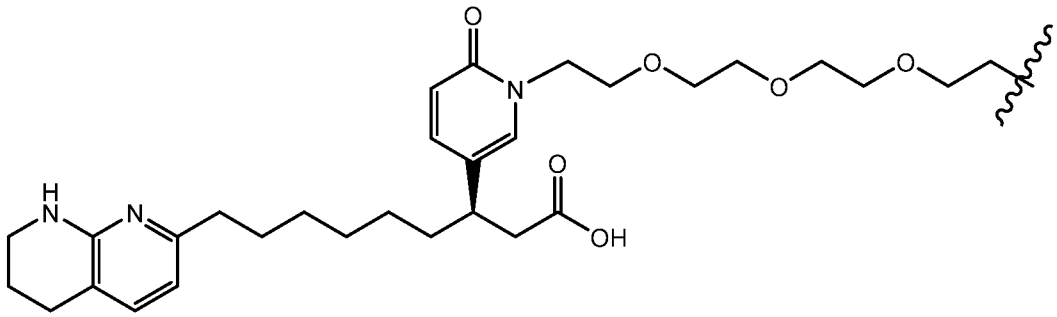
(Structure 28a);



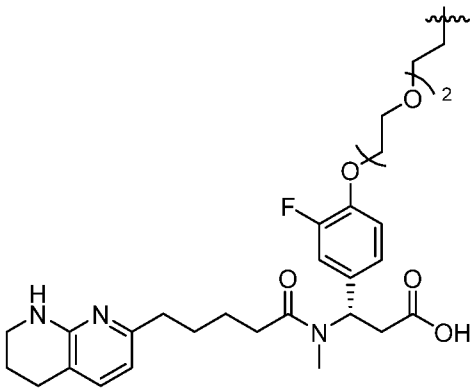
(Structure 29a);



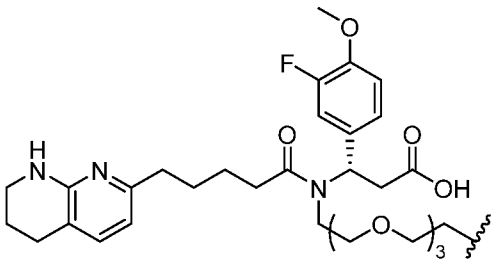
(Structure 30a);



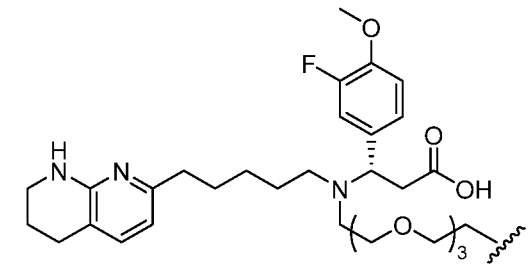
(Structure 31a);



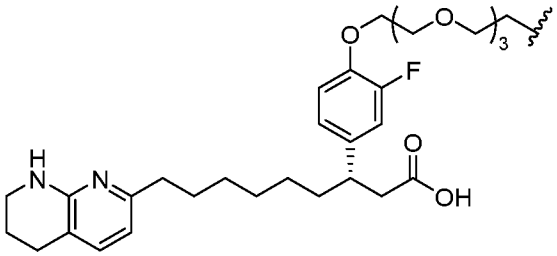
(Structure 32a);



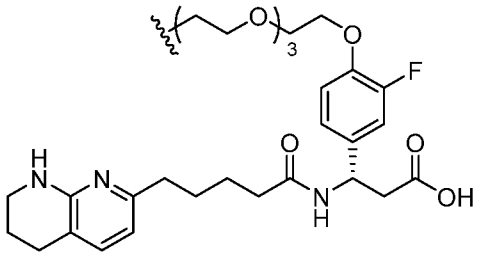
(Structure 33a);



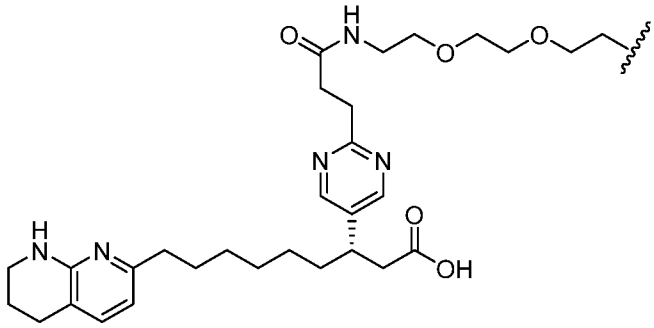
(Structure 34a);



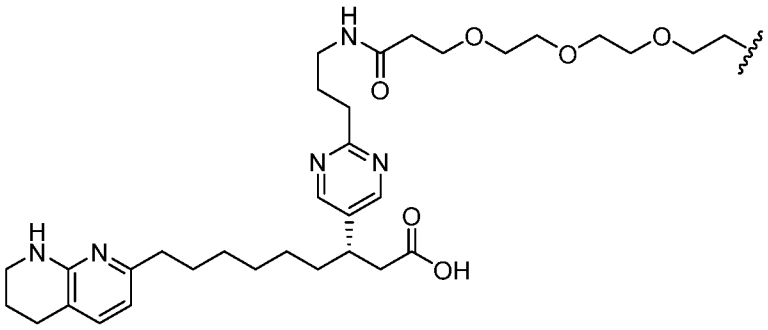
(Structure 36a);



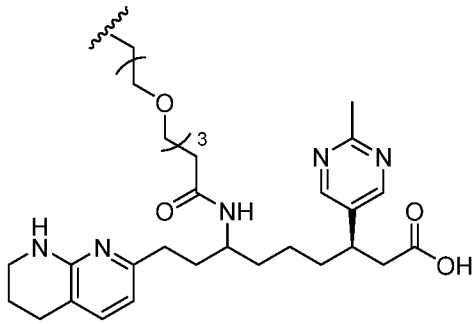
(Structure 37a);



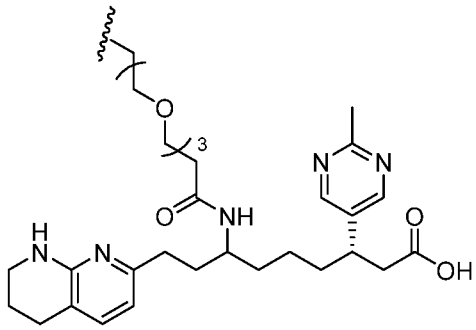
(Structure 38a);



(Structure 39a);



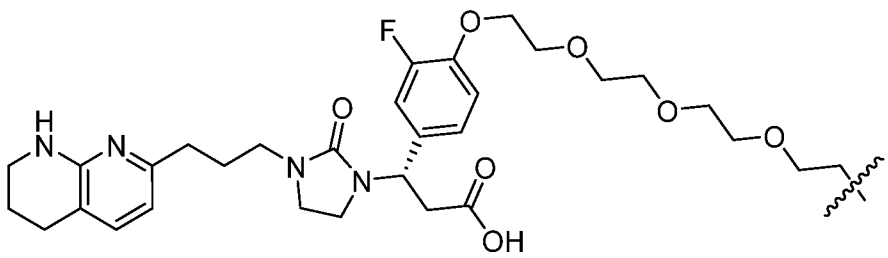
(Structure 40a); and



(Structure 41a)

wherein ≈ indicates the point of connection to the HIF-2 alpha RNAi agent.

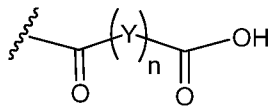
Embodiment 22. The RNAi agent of any one of embodiments 1-21, wherein the targeting ligand is of the structure



(Structure 2a).

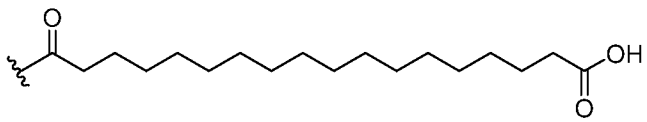
Embodiment 23. The RNAi agent of any one of embodiments 1-22, further comprising a pharmacokinetic (PK) enhancer.

Embodiment 24. The RNAi agent of embodiment 23, wherein the PK enhancer comprises the formula:



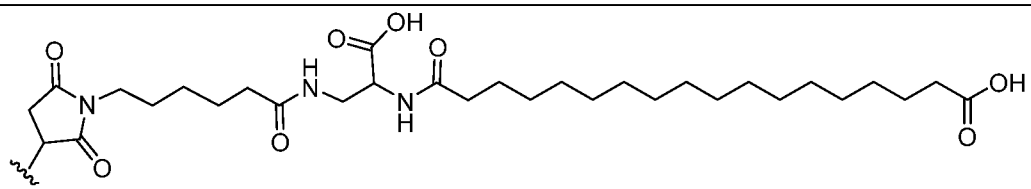
, wherein Y is an optionally substituted saturated or unsaturated aliphatic chain and n is an integer from 5-25.

Embodiment 25. The RNAi agent of embodiment 24, wherein the PK enhancer comprises

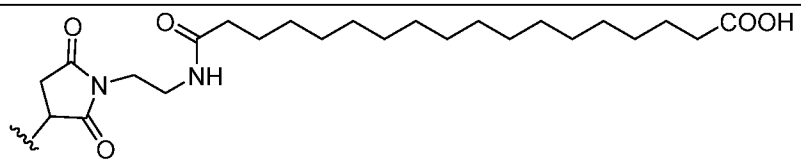


.

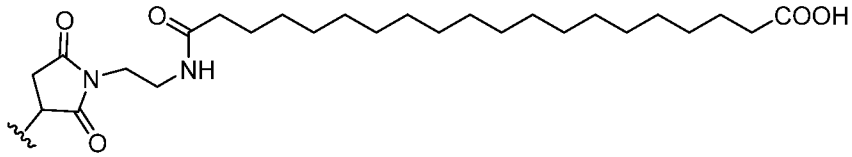
Embodiment 26. The RNAi agent of embodiment 23, wherein the PK enhancer is selected from the group consisting of:



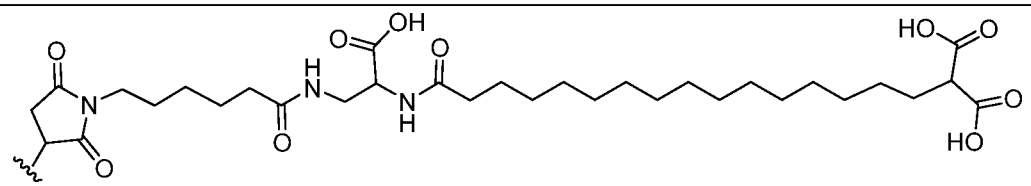
Mal-C_{18}-diacid

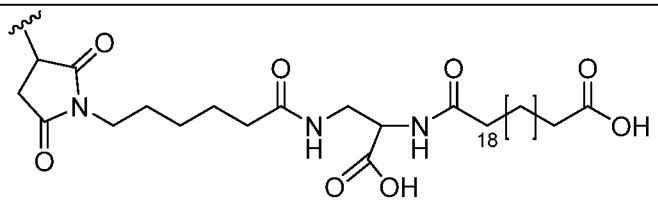
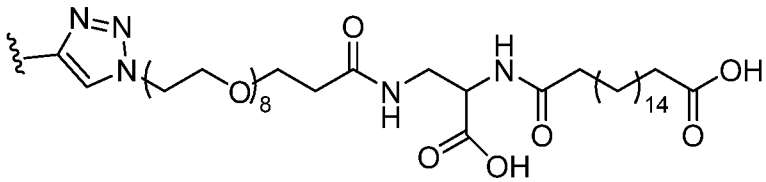
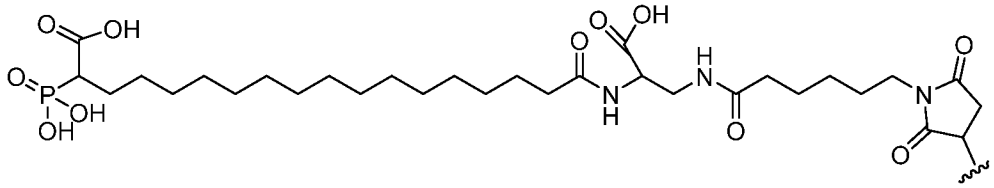
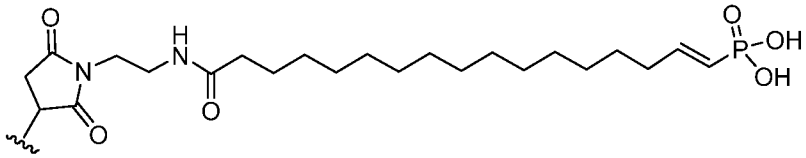
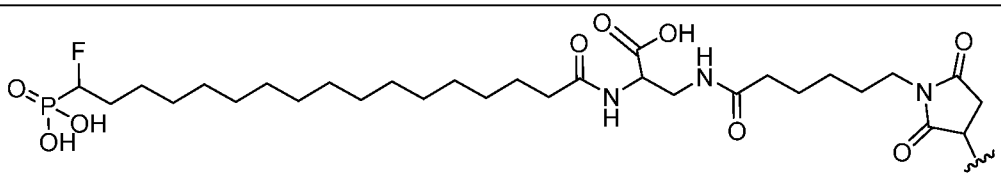


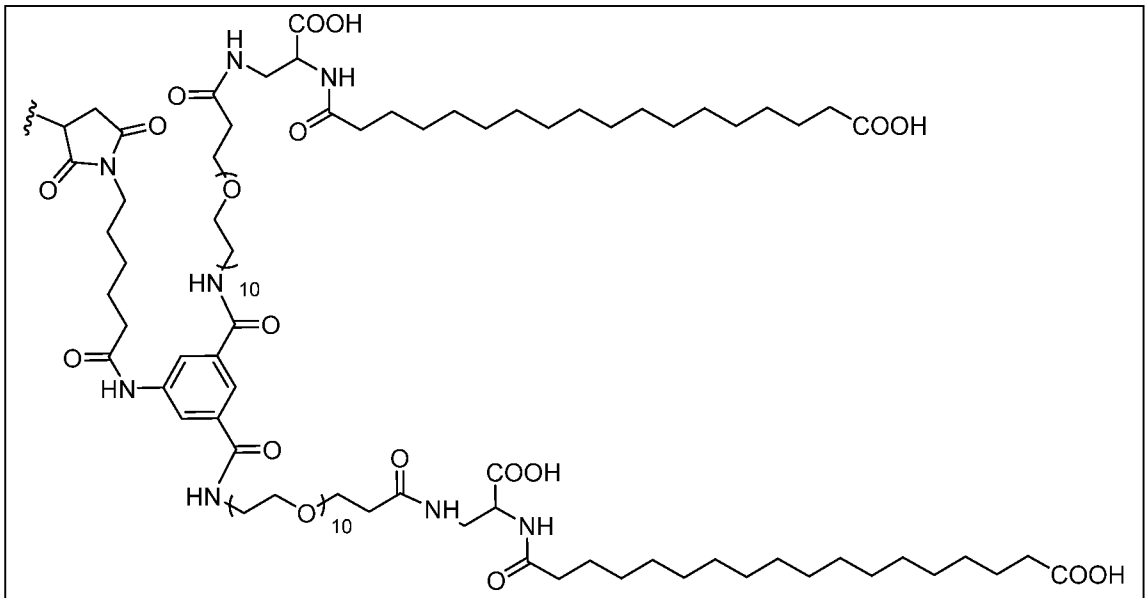
Mal-C_{18}-acid



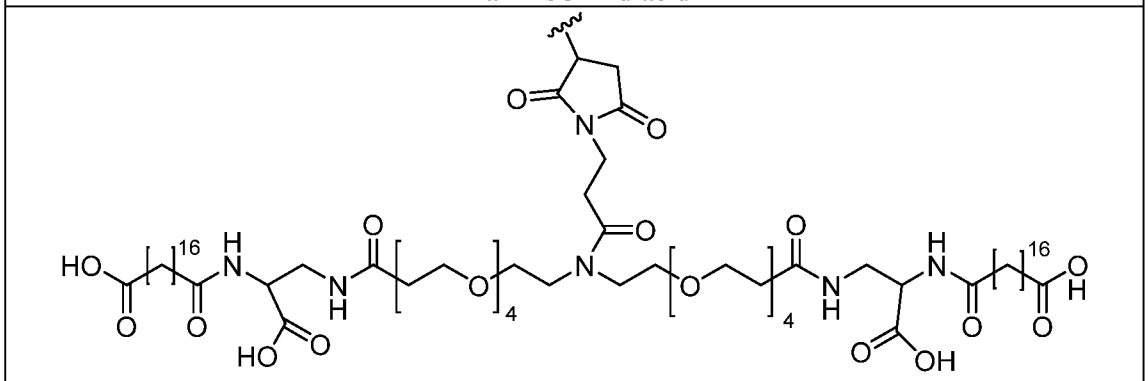
Mal-C_{20}-acid



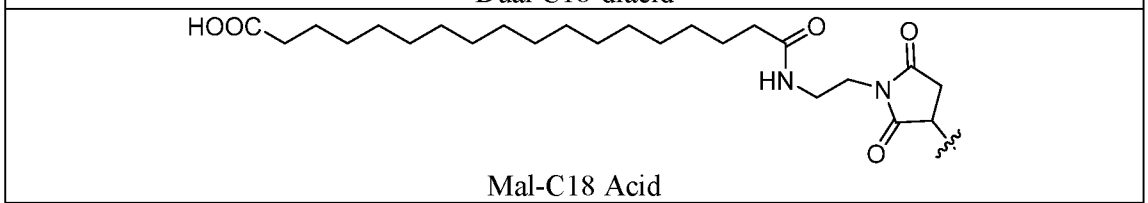
Mal-C_{18}-triacid
 Mal-C_{22}-diacid
 C_{18}-diacid-N_3
 Mal-C_{18}-diacid-PO_3
 Mal-C_{17}-PO_3
 Mal-C_{17}-Fluoro-PO_3 Monoacid



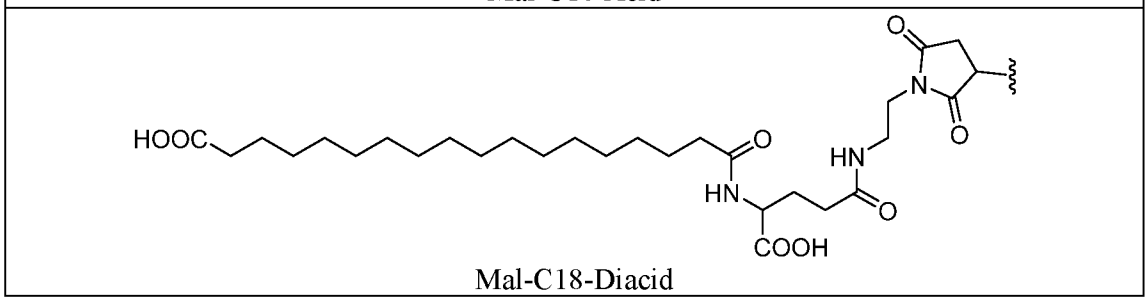
Mal-BisC18-diacid



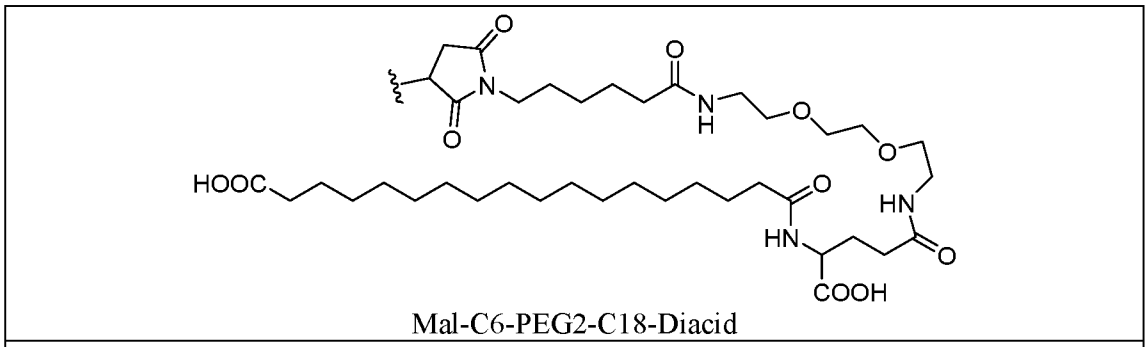
Dual C18-diacid



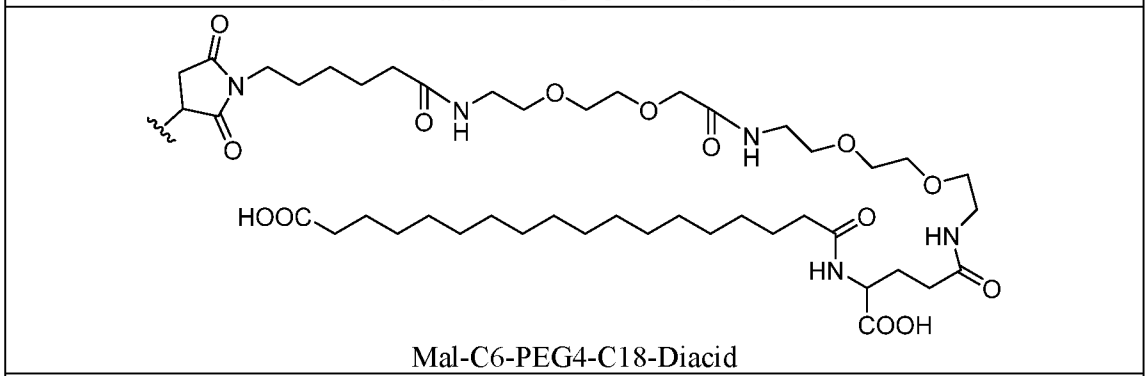
Mal-C18 Acid



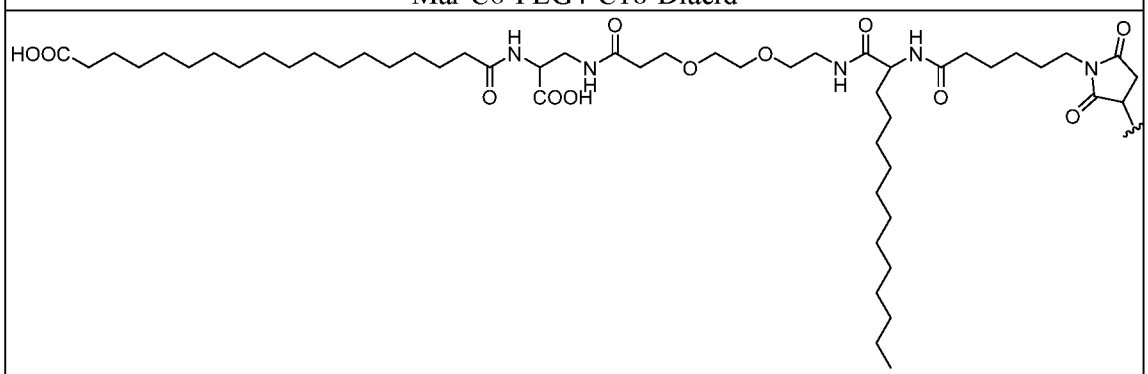
Mal-C18-Diacid



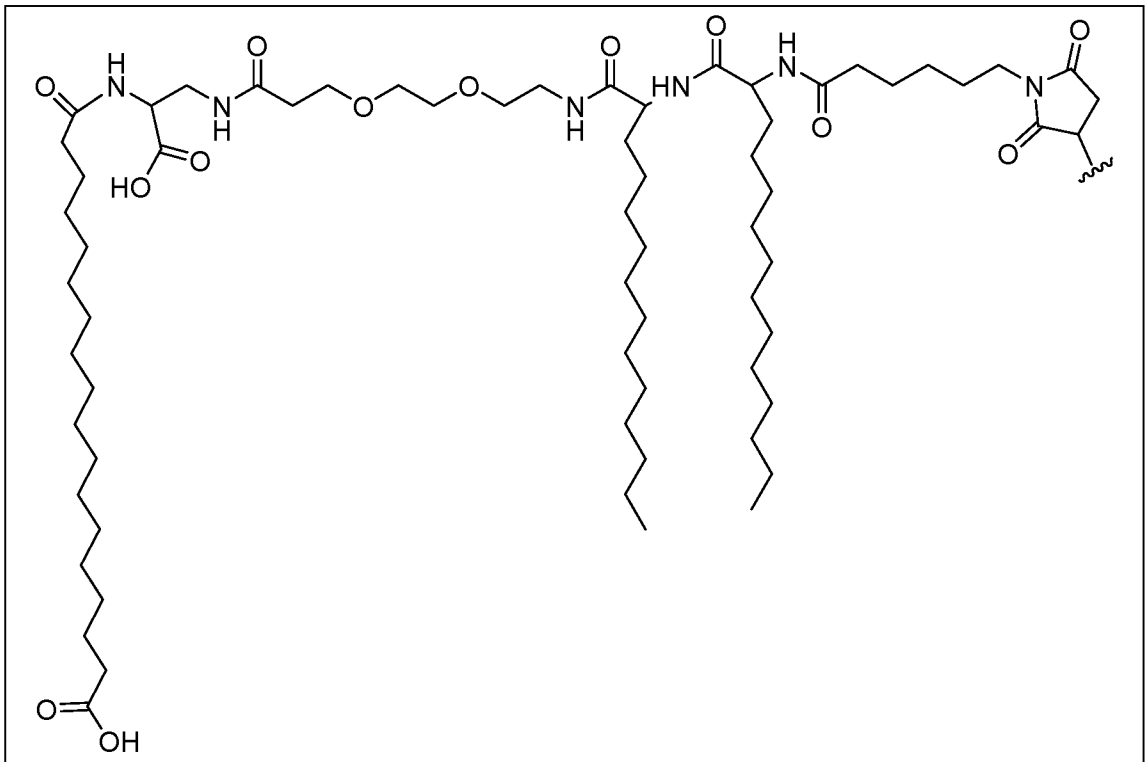
Mal-C6-PEG2-C18-Diacid



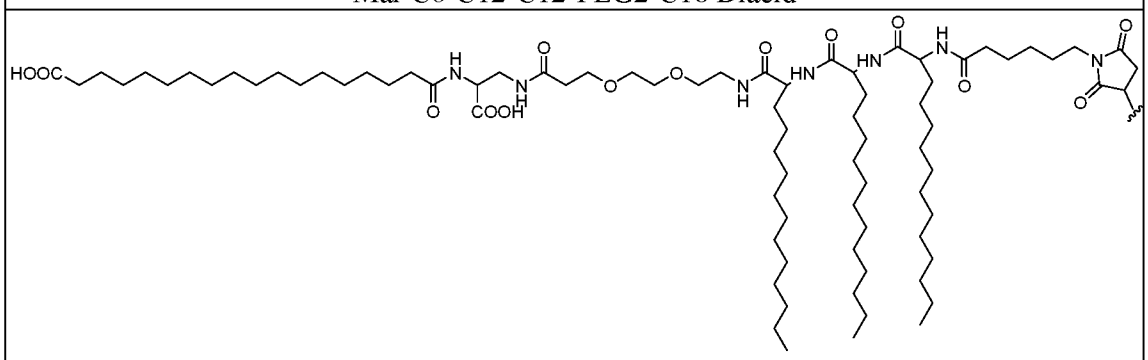
Mal-C6-PEG4-C18-Diacid



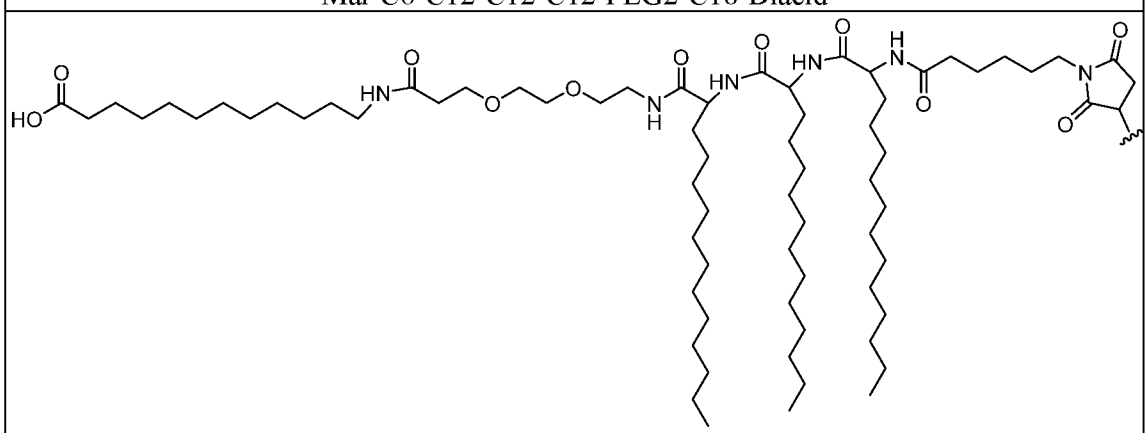
Mal-C6-C12-PEG2-C18 Diacid



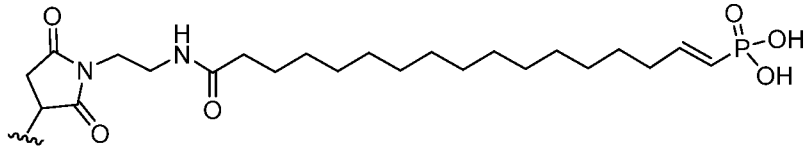
Mal-C6-C12-C12-PEG2-C18 Diacid



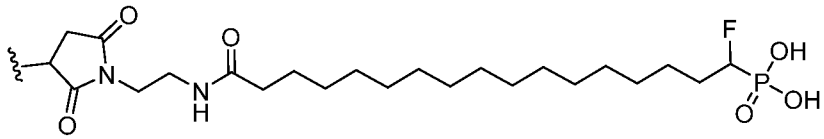
Mal-C6-C12-C12-C12-PEG2-C18-Diacid



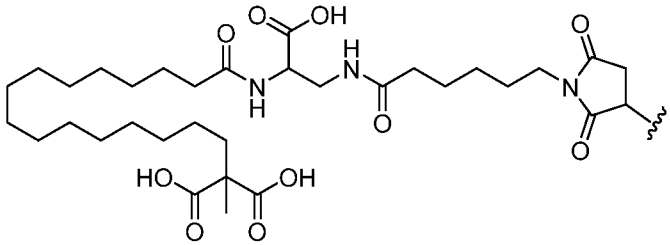
Mal-C6-C12-C12-C12-PEG2-C12 Diacid



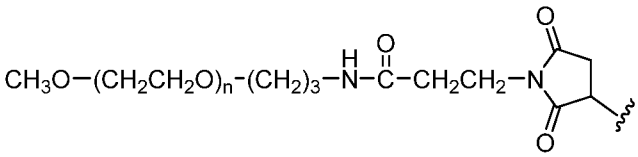
Mal-C_{17}-vinyl-PO_3



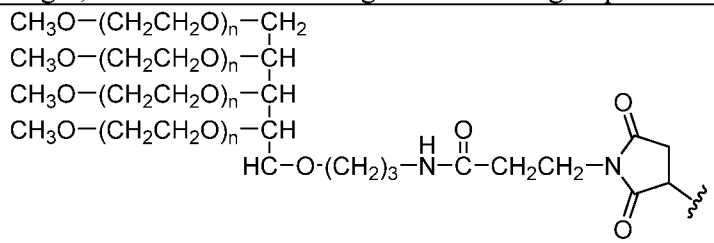
Mal-C_{17}-Fluoro-PO_3



Mal-C_{18}-methyl-triacid



PEG40K,
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



PEG40K (4-arm),
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons

wherein ≀ indicates the point of attachment to the RNAi agent.

Embodiment 27. The RNAi agent of any one of embodiments 1-26, wherein the targeting ligand is linked to the sense strand.

Embodiment 28. The RNAi agent of any one of embodiments 23-27, wherein the PK enhancer is linked to the sense strand.

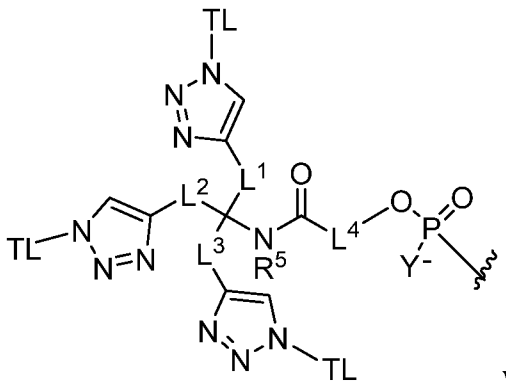
Embodiment 29. The RNAi agent of any one of embodiments 1-28, wherein the RNAi agent is linked to 2 to 10 targeting ligands.

Embodiment 30. The RNAi agent of any one of embodiments 1-29, wherein the RNAi agent is linked to a targeting group comprising two or more targeting ligands at the 5' terminal end of the sense strand.

Embodiment 31. The RNAi agent of any one of embodiments 1-30, wherein at least one targeting ligand is linked to the 5' terminal end of the sense strand, and at least one targeting ligand is linked to a non-terminal nucleotide of the sense strand.

Embodiment 32. The RNAi agent of any one of embodiments 1-31, linked to two or more targeting ligands, wherein the two or more targeting ligands are linked at a branch point to form a targeting group.

Embodiment 33. The RNAi agent of embodiment 32, wherein the targeting group comprises three targeting ligands and the targeting group is of the formula:



wherein,

L^1, L^2 and L^3 are each independently linkers comprising an optionally substituted alkylene;

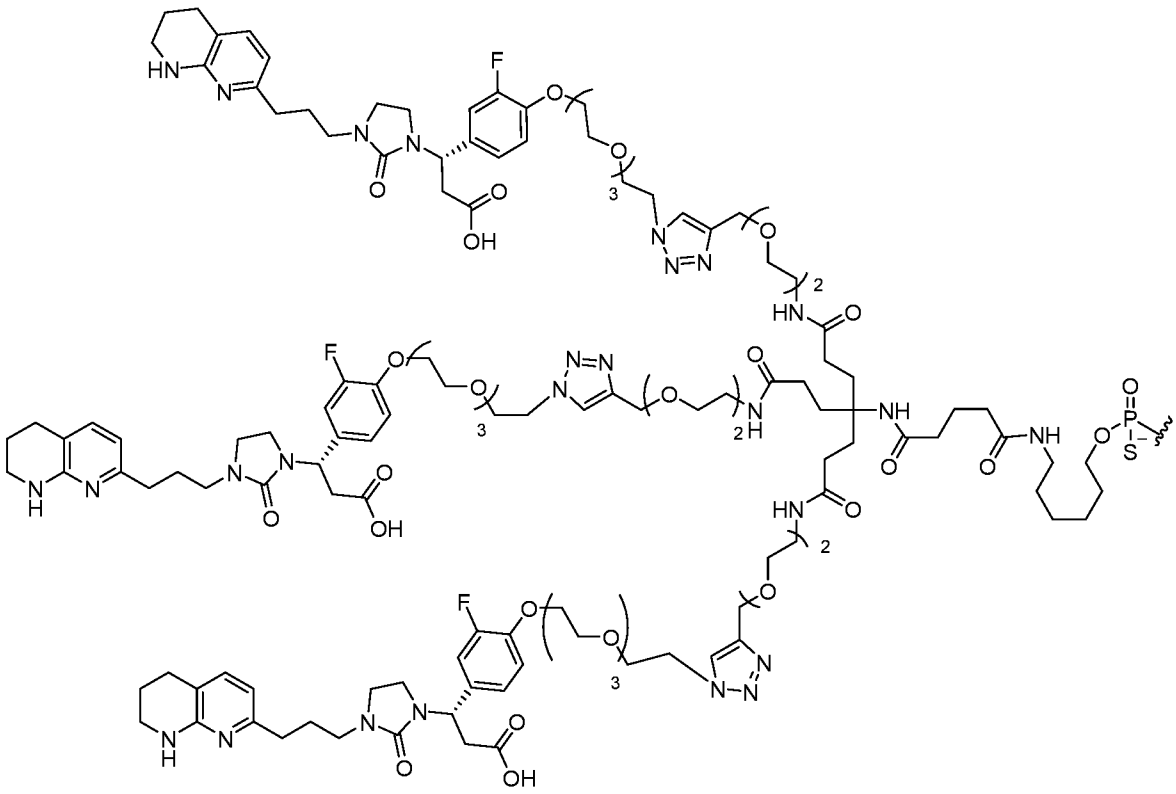
L^4 is a linker comprising an optionally substituted alkylene, optionally substituted aryl, or optionally substituted cycloalkyl;

R^5 is H or optionally substituted alkyl;

TL is a targeting ligand; and

Y is O or S.

Embodiment 34. The RNAi agent of embodiment 33, wherein the targeting group is of the formula:



.

Embodiment 35. The RNAi agent of any one of embodiments 1-34, wherein a tridentate targeting group is linked to the 5' terminal end of the sense strand, and wherein at least two additional targeting ligands are linked to one or more nucleotides of the sense strand.

Embodiment 36. The RNAi agent of embodiment 31 or 35, wherein at least 10 nucleotides are positioned between the targeting group located on the 5' end of the sense strand and the targeting ligand located on the sense strand.

Embodiment 37. The RNAi agent of any one of embodiments 1-36, wherein at least one targeting ligand is linked to the 2' position of a nucleotide of the sense strand of the RNAi agent.

Embodiment 38. The RNAi agent of any one of embodiments 23-37, wherein the PK enhancer is linked to the 3' terminal end of the sense strand.

Embodiment 39. The RNAi agent of any one of embodiments 1-38, wherein 5 to 8 targeting ligands are linked to the sense strand.

Embodiment 40. The RNAi agent of embodiment 39, wherein the sense strand of the RNAi agent is linked to at least one tridentate targeting group and at least two targeting ligands linked to one or more nucleotides of the sense strand.

Embodiment 41. The RNAi agent of embodiment 40, wherein the sense strand of the RNAi agent is linked to (i) a tridentate targeting group at the 5' terminal end of the sense strand, and (ii) 2 to 4 targeting ligands linked to nucleotides other than the 5' terminal nucleotide of the sense strand.

Embodiment 42. The RNAi agent of any one of embodiments 29-41, wherein the targeting ligands are linked to the sense strand as follows: (i) a tridentate targeting group comprising 3 individual targeting ligands is located at the 5' terminal end of the sense strand; and (ii) the additional targeting ligands are individual targeting ligands linked to individual nucleotides of the sense strand that are at least 10 nucleotides away from the 5' terminal end of the sense strand.

Embodiment 43. The RNAi agent of embodiment 42, wherein the targeting ligands are linked to the sense strand nucleotides located at positions 2, 4, 6, and 8 (3' → 5') from the 3' terminal nucleobase that forms a base pair with the 5' terminal nucleotide on the antisense strand.

Embodiment 44. The RNAi agent of embodiment 43, wherein at least one targeting ligand is linked to an individual nucleotide at the 2' position of the ribose ring, the 3' position of the

ribose ring, the 1' position of the ribose ring or to the nucleobase of the nucleotide, the 4' position of the ribose ring, or the 5' position of the nucleotide.

Embodiment 45. The RNAi agent of embodiment 44, wherein at least one targeting ligand is linked to the 2' position of the ribose ring of an individual nucleotide.

Embodiment 46. The RNAi agent of any one of embodiments 1-45, wherein the sense strand is between 18 and 49 nucleotides in length, and the antisense strand is between 18 and 49 nucleotides in length.

Embodiment 47. The RNAi agent of embodiment 46, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.

Embodiment 48. The RNAi agent of embodiment 47, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.

Embodiment 49. The RNAi agent of embodiment 48, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

Embodiment 50. The RNAi agent of any one of embodiments 46-49, wherein the RNAi agent has two blunt ends.

Embodiment 51. The RNAi agent of any one of embodiments 1-50, wherein the sense strand comprises one or two terminal caps.

Embodiment 52. The RNAi agent of any one of embodiments 1-51, wherein the sense strand comprises one or two inverted abasic residues.

Embodiment 53. The RNAi agent of any one of embodiments 1-52, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 5.

Embodiment 54. The RNAi agent of any one of embodiments 51-53, wherein the sense strand further includes inverted abasic residues at the 3' end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both the 3' end and the 5' end of the nucleotide sequence.

Embodiment 55. A HIF-2 alpha RNAi agent comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3; and

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

Embodiment 56. An RNAi agent capable of inhibiting expression of a HIF-2 alpha (*EPAS1*) gene comprising:

(i) an antisense strand that is between 18 and 49 nucleotides in length that is at least partially complementary to a HIF-2 alpha (*EPAS1*) gene (SEQ ID NO:1);

(ii) a sense strand that is at least partially complementary to the antisense strand;

(iii) a targeting ligand linked to the sense strand; and

(iv) a PK enhancer linked to the sense strand.

Embodiment 57. The RNAi agent of embodiment 56, wherein the targeting ligand is linked to the 5' terminal end of the sense strand.

Embodiment 58. The RNAi agent of embodiment 56 or 57, wherein the PK enhancer is linked to the 3' terminal end of the sense strand.

Embodiment 59. The RNAi agent of any one of embodiments 56-58, wherein one or more targeting ligands are linked to one or more nucleotides of the sense strand.

Embodiment 60. The RNAi agent of embodiment 59, wherein 2 to 12 targeting ligands are linked to nucleotides of the sense strand.

Embodiment 61. The RNAi agent of any one of embodiments 56-60, wherein a tridentate targeting group comprised of three targeting ligands is linked to the 5' terminal end of the sense strand; a PK enhancer is linked to the 3' terminal end of the sense strand; and between 2 to 12 targeting ligands are linked to individual nucleotides of the sense strand.

Embodiment 62. The RNAi agent of embodiment 61, wherein the targeting ligands that are linked to individual nucleotides of the sense strand are linked at the 2' position of each respective nucleotide.

Embodiment 63. The RNAi agent of any one of embodiments 56-62, wherein targeting ligands are linked to nucleotides located at positions 2, 6, 15, and 19 (3' → 5') from the first nucleotide that forms a base pair with the antisense strand.

Embodiment 64. The RNAi agent of any one of embodiments 56-62, wherein targeting ligands are linked to nucleotides located at positions 2, 4, 6, and 8 (3' → 5') from the first nucleotide that forms a base pair with the antisense strand.

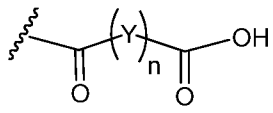
Embodiment 65. The RNAi agent of any one of embodiments 56-62, wherein targeting ligands are linked to nucleotides of the sense strand that are across from nucleotides 2, 4, 6, and 8 (5' → 3') of the antisense strand.

Embodiment 66. The RNAi agent of any one of embodiments 56-65, wherein a tridentate targeting group comprising three targeting ligands is located at the 5' terminal end of the sense strand, the sense strand further includes two to four targeting ligands that are linked to nucleotides of the sense strand, and there are at least 10 nucleotides separating the tridentate targeting group at the 5' terminal end of the sense strand and the next closest targeting ligand that is attached to nucleotide.

Embodiment 67. The RNAi agent of embodiment 66, wherein four targeting ligands are linked to individual nucleotides of the sense strand.

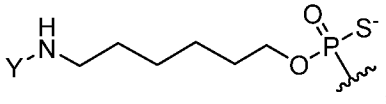
Embodiment 68. The RNAi agent of any one of embodiments 56-67, wherein the targeting ligand is an integrin targeting ligand that includes a compound that has affinity for integrin alpha-v-beta-3.

Embodiment 69. The RNAi agent of any one of embodiments 56-68, wherein the PK enhancer is of the formula:

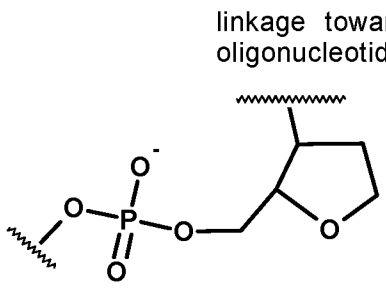


, wherein Y is an optionally substituted saturated or unsaturated aliphatic chain and n is an integer from 5-25.

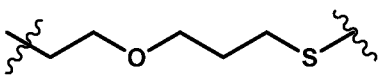
Embodiment 70. An RNAi agent comprising an antisense strand comprising the sequence usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), a sense strand comprising the sequence Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; u^{Z}, a^{Z}, g^{Z}, and c^{Z} represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety comprising *Z* linked at the 2′ position of the nucleotide; Y-(NH-C6)s represents:



; (invAb) represents:



; (6-S) represents:



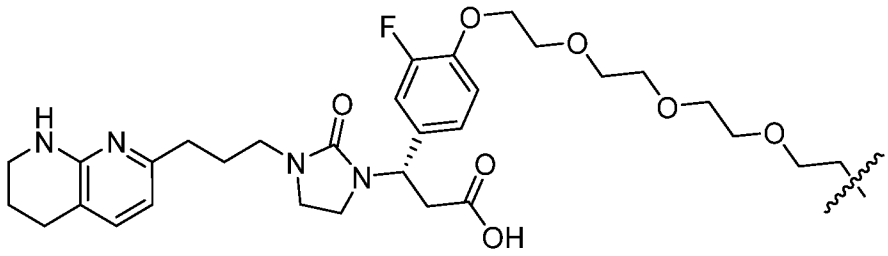
, and each X, Y and Z independently represents:

(i) a targeting group comprising one or more targeting ligands, wherein the targeting ligand is selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a;

(ii) a targeting ligand having a structure selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a; or

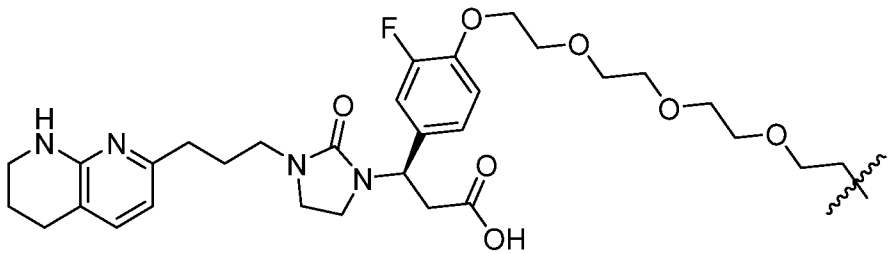
(iii) a PK enhancer having a structure selected from the group consisting of of C-18 diacid, C-18 triacid, Mal-C_{17}-vinyl-PO_3, and C20 acid.

Embodiment 71. The RNAi agent of embodiment 70, wherein each Z is a targeting ligand having a structure of Structure 2a:



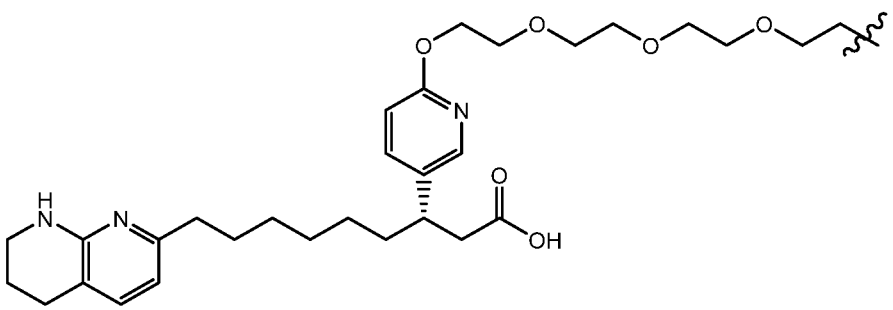
wherein ≀ indicates the point of attachment.

Embodiment 72. The RNAi agent of embodiment 70, wherein each Z is a targeting ligand having a structure of Structure 2.11a:



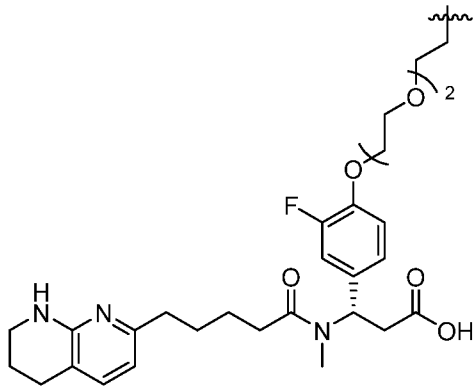
wherein ≀ indicates the point of attachment.

Embodiment 73. The RNAi agent of embodiment 70, wherein each Z is a targeting ligand having a structure of Structure 29a:



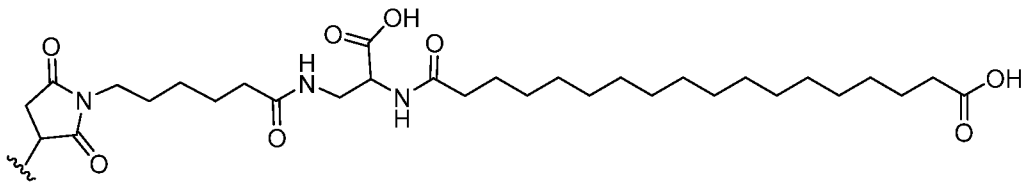
, wherein ≈ indicates the point of attachment.

Embodiment 74. The RNAi agent of embodiment 70, wherein each Z is a targeting ligand having a structure of Structure 32a:



, wherein ≈ indicates the point of attachment.

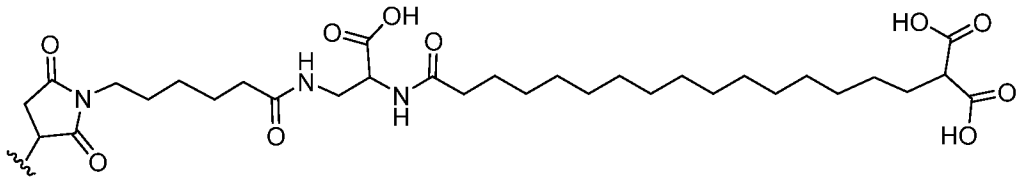
Embodiment 75. The RNAi agent of any one of embodiments 70-74, wherein X is a PK enhancer having a structure of C-18 diacid:



,

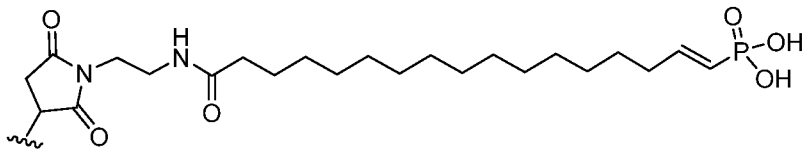
wherein ≈ indicates the point of attachment.

Embodiment 76. The RNAi agent of any one of embodiments 70-74, wherein X is a PK enhancer having a structure of Mal-C-18 triacid:



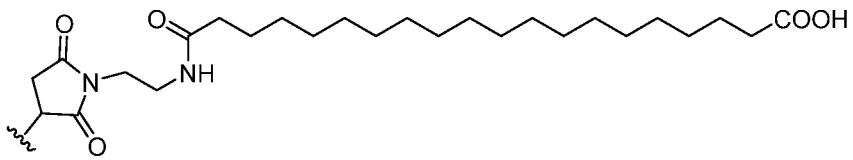
wherein ≋ indicates the point of attachment.

Embodiment 77. The RNAi agent of any one of embodiments 70-74, wherein X is a PK enhancer having a structure of Mal-C17-vinyl PO3:



, wherein ≋ indicates the point of attachment.

Embodiment 78. The RNAi agent of any one of embodiments 70-74, wherein X is a PK enhancer having a structure of Mal-C_{20} acid:

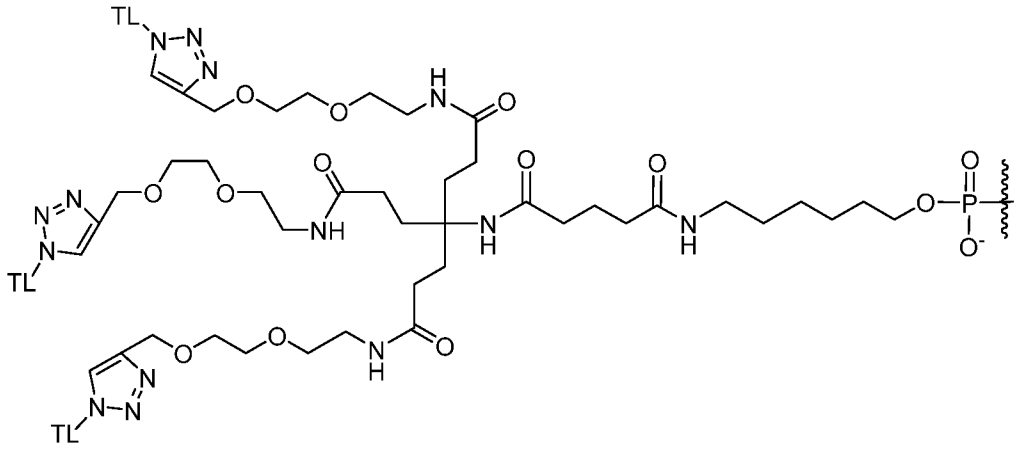


, wherein ≋ indicates the point of attachment.

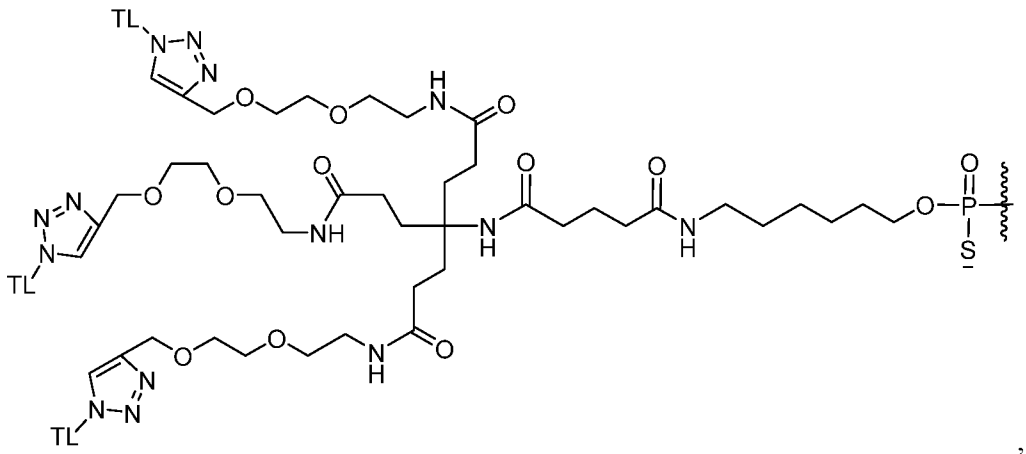
Embodiment 79. The RNAi agent of any one of embodiments 70-78, wherein the RNAi agent includes 2, 3, 4, 5, 6, 7, 8, 9, or 10 targeting ligands.

Embodiment 80. The RNAi agent of embodiment 79, wherein the RNAi agent includes 7 targeting ligands.

Embodiment 81. The RNAi agent of embodiment 80, wherein Y is a targeting group having the structure of TriAlk 14:



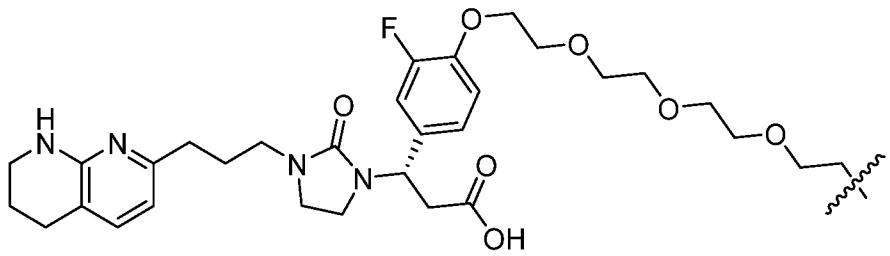
or TriAlk



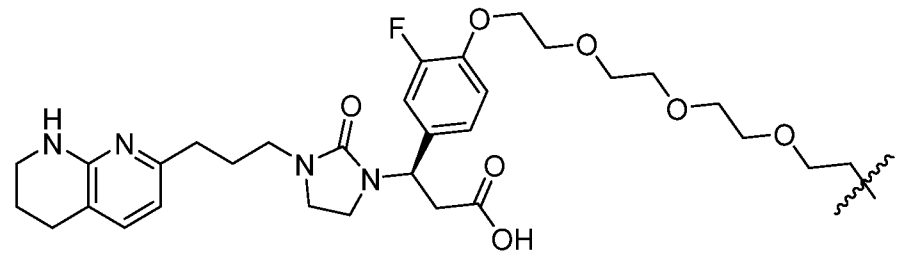
14s: ,

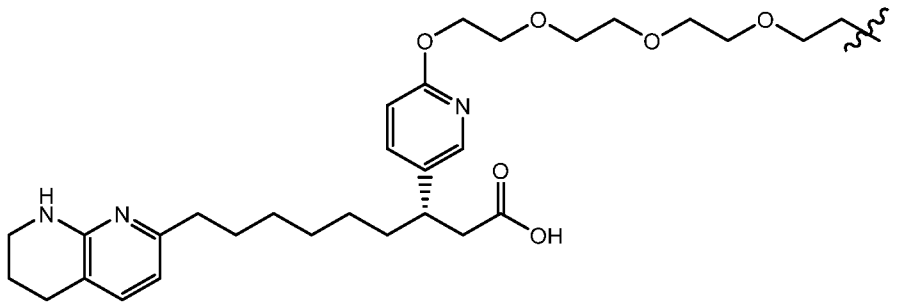
wherein TL comprises a targeting ligand selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a.

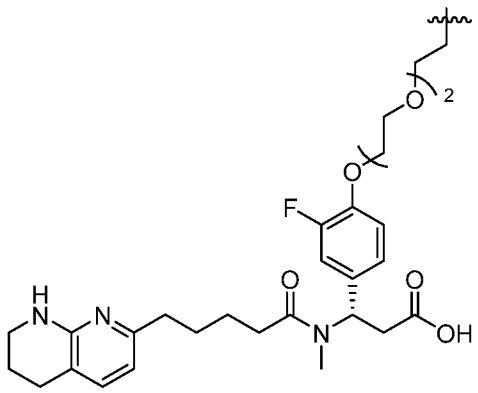
Embodiment 82. The RNAi agent of embodiment 81, wherein each TL comprises Structure



2a: wherein ≋ indicates the point of attachment.

Embodiment 83. The RNAi agent of embodiment 81, wherein each TL comprises Structure 2.11a:  wherein ≈ indicates the point of attachment.

Embodiment 84. The RNAi agent of embodiment 81, wherein each TL comprises Structure 29a:  , wherein ≈ indicates the point of attachment.

Embodiment 85. The RNAi agent of embodiment 81, wherein each TL comprises Structure 32a:  , wherein ≈ indicates the point of attachment.

Embodiment 86. The RNAi agent of any one of embodiments 70-81, wherein the nucleotides of the antisense strand consist of the nucleotides of SEQ ID NO: 30.

Embodiment 87. The RNAi agent of any one of embodiments 70-82, wherein the nucleotides of the sense strand consist of the nucleotides of SEQ ID NO: 761.

Embodiment 88. A composition comprising the RNAi agent of any one of embodiments 1-88, wherein the composition comprises a pharmaceutically acceptable excipient.

Embodiment 89. The composition of embodiment 88, further comprising a second RNAi agent for inhibiting the expression of HIF-2 alpha.

Embodiment 90. The composition of embodiment 88 or 89, further comprising one or more additional therapeutics.

Embodiment 91. A method for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene in a cell, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of embodiments 1-88 or the composition of any one of embodiments 88-90.

Embodiment 92. The method of embodiment 91, wherein the cell is within a subject.

Embodiment 93. The method of embodiment 92, wherein the subject is a human subject.

Embodiment 94. The method of any one of embodiments 91-94, wherein the HIF2-alpha gene expression is inhibited by at least about 30%.

Embodiment 95. A method of treating a HIF2-alpha-related disease or disorder, the method comprising administering to a human subject in need thereof a therapeutically effective amount of the composition of any one of embodiments 88-90.

Embodiment 96. The method of embodiment 95, wherein the disease or disorder is cancer, renal cancer, clear cell renal cell carcinoma, non-small cell lung cancer, astrocytoma (brain cancer), bladder cancer, breast cancer, chondrosarcoma, colorectal carcinoma, gastric carcinoma, glioblastoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, neuroblastoma, melanoma, multiple myeloma, ovarian cancer, rectal

cancer, metastases, gingivitis, psoriasis, Kaposi's sarcoma-associated herpesvirus, preeclampsia, inflammation, chronic inflammation, neovascular diseases, or rheumatoid arthritis

Embodiment 97. The method of embodiment 95 or 96, wherein the disease is clear cell renal cell carcinoma (ccRCC).

Embodiment 98. The method of any one of embodiments 91-97, wherein the RNAi agent is administered at a dose of about 3 mg/kg to about 80 mg/kg of body weight of the human subject.

Embodiment 99. The method of embodiment 98, wherein the RNAi agent is administered at a dose of about 5 mg/kg to about 20 mg/kg of body weight of the human subject.

Embodiment 100. The method of embodiment 98 or 99, wherein the RNAi agent is administered in a split dose, wherein about half of the desired daily amount is administered in an initial administration, and the remaining about half of the desired daily amount is administered approximately four hours after the initial administration.

Embodiment 101. The method of any one of embodiments 98-100, wherein the dose or doses of the RNAi agent is administered once a week.

Embodiment 102. The method of any one of embodiments 99-101, wherein the dose or split doses of the RNAi agent is administered biweekly (once every other week).

Embodiment 103. Use of the RNAi agent of any one of embodiments 1-88 or the composition according to any one of embodiments 88-90, for the treatment of a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression.

Embodiment 104. Use according to embodiment 103, wherein the disease is ccRCC.

Embodiment 105. Use of the RNAi agent of any one of embodiments 1-88 or the composition according to any one of embodiments 88-90, for the preparation of a pharmaceutical composition for treating a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression.

Embodiment 106. Use of embodiment 105, wherein the disease is ccRCC.

OTHER EMBODIMENTS

[0566] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS

1. An RNAi agent for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene, comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3;

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand; and

(iii) one or more targeting ligands.

2. The RNAi agent of claim 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences provided in Table 3.

3. The RNAi agent of claim 1 or claim 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sense strand sequences provided in Table 4, 4.1, 4.2, or 4.3, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.

4. The RNAi agent of any one of claims 1-3, wherein all or substantially all of the nucleotides of the sense strand of the RNAi agent, the antisense strand of the RNAi agent, or both the sense strand and the antisense strand of the RNAi agent, are modified nucleotides.

5. The RNAi agent of claim 4, wherein at least one modified nucleotide is selected from the group consisting of: 2′-O-methyl nucleotide, 2′-fluoro nucleotide, 2′-deoxy nucleotide, 2′,3′-seco nucleotide mimic, locked nucleotide, 2'-F-arabino nucleotide, 2′-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted 2′-O-methyl nucleotide, inverted 2′-deoxy nucleotide, 2′-amino-modified nucleotide, 2′-alkyl-modified nucleotide, morpholino nucleotide, vinyl phosphonate modified ribonucleotide, cyclopropyl phosphonate modified nucleotide, 2′-O-propargyl-modified nucleotide, 2′-O-triazole-modified nucleotide, and 3′-O-methyl nucleotide.

6. The RNAi agent of claim 5, wherein each modified nucleotide is independently selected from the group consisting of: 2′-O-methyl nucleotides, 2′-fluoro nucleotides, and 2′-O-triazole-modified nucleotides.

7. The RNAi agent of any one of claims 1-6, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3.

8. The RNAi agent of any one of claims 1-7, wherein the sense strand comprises the nucleotide sequence of any of the modified sense strand sequences provided in Table 4.

9. The RNAi agent of any one of claims 1-8, wherein the antisense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 3 and the sense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 4, Table 4.1, Table 4.2, or Table 4.3.

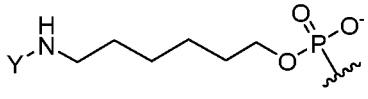
10. The RNAi agent of any one of claims 1-9, wherein the antisense strand comprises nucleotides 2-18 of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, and s represents a phosphorothioate linkage.

11. The RNAi agent of claim 10, wherein the antisense strand comprises the sequence of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively and s represents a phosphorothioate linkage.

12. The RNAi agent of claim 1, wherein the sense strand comprises nucleotides 2-18 of the sequence of CAACGUAACGAUUUCAUGAAA (SEQ ID NO: 428).

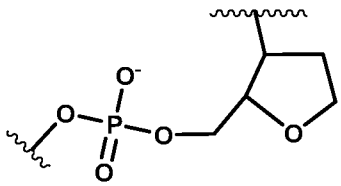
13. The RNAi agent of claim 1, wherein the sense strand comprises the sequence of Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761) wherein a, c,

g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, each X, Y and *Z* is independently a pharmacological moiety; u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety Z linked to the 2' position of a nucleotide, Y-(NH-C6) represents:



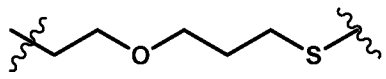
, (invAb) represents:

linkage towards 5' end



linkage towards 3' end

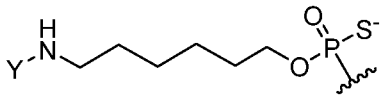
, (6-S) represents:



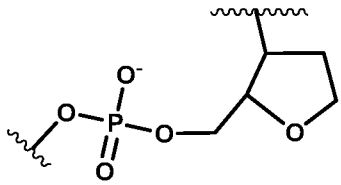
, and s represents a phosphorothioate linkage.

14. The RNAi agent of any one of claims 12 or 13, wherein the antisense strand is at least substantially complementary to the sense strand.

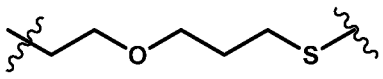
15. The RNAi agent of any of claims 1-14, wherein the nucleotides of the sense strand consist of the sequence of Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, and each X, Y and *Z* is independently a pharmacological moiety; u^Z, a^Z, g^Z, and c^Z represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety linked to the 2' position of a nucleotide (which for the HIF-2 alpha RNAi agents disclosed in the Examples herein was completed by coupling to a 2'-O-propargyl group), Y-(NH-C6)s represents:



linkage towards 5' end



(invAb) represents: linkage towards 3' end and (6-S) represents:



, and s represents a phosphorothioate linkage..

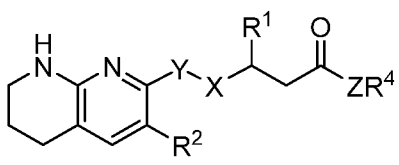
16. The RNAi agent of claim 15, wherein the nucleotides of the antisense strand consist of the sequence of usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30) wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively, and s represents a phosphorothioate linkage.

17. The RNAi agent of any one of claims 1-16, wherein the sense strand of the RNAi agent is linked to at least one targeting ligand.

18. The RNAi agent of claim 17, wherein the targeting ligand comprises a compound having affinity for an integrin.

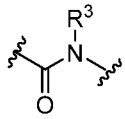
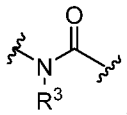
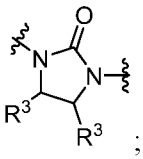
19. The RNAi agent of claim 18, wherein the targeting ligand comprises a compound that has affinity for integrin alpha-v-beta-3, alpha-v-beta-5, or both alpha-v-beta-3 and alpha-v-beta-5.

20. The RNAi agent of claim 19, wherein the targeting ligand is a compound of the formula:



(Formula I),

wherein,

X is -C(R^3)$_2$-, -NR^3-,  ,  , or  ;

Y is optionally substituted alkylene with 1 to 8 carbon atoms in the alkylene chain;

Z is O, NR^3, or S;

R^1 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl or R^1 comprises the RNAi agent;

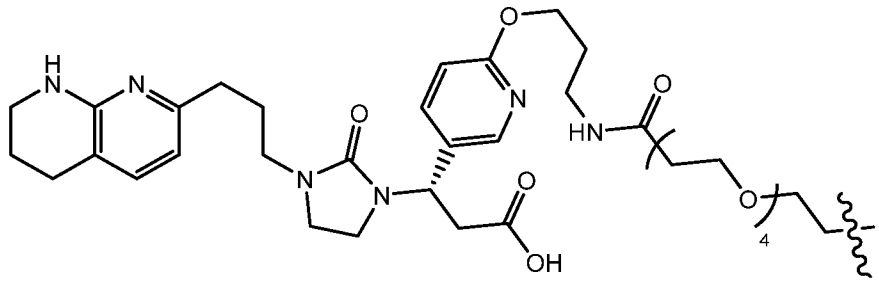
R^2 is H, optionally substituted alkyl, or R^2 comprises the RNAi agent;

each instance of R^3 is independently selected from the group consisting of H and optionally substituted alkyl, or R^3 comprises the RNAi agent;

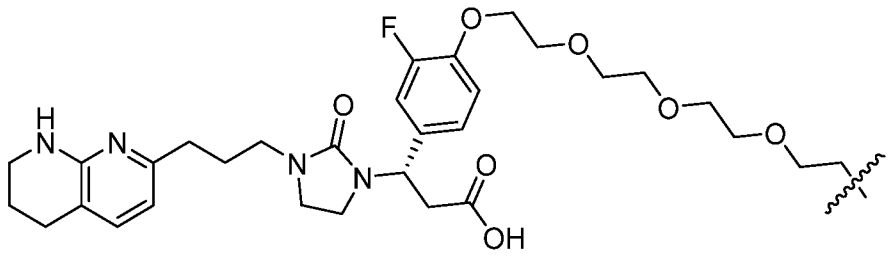
R^4 is H or optionally substituted alkyl; and

wherein at least one of Y, R^1, R^2, any instance of R^3, and R^4 comprises the RNAi agent.

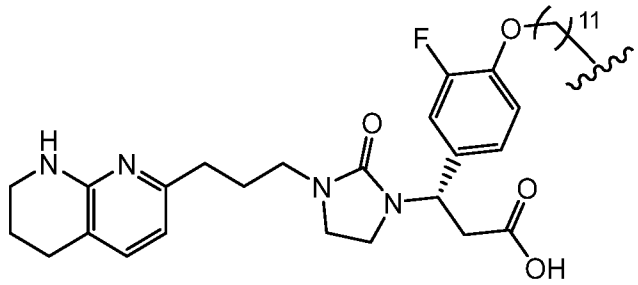
21. The RNAi agent of claim 20, wherein the targeting ligand is selected from:



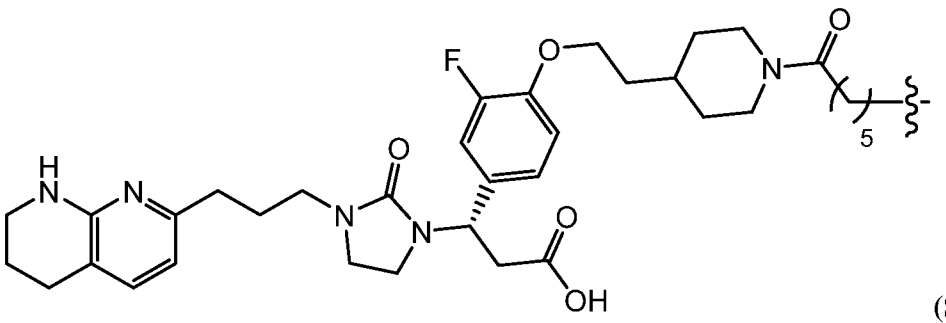
(Structure 1a);



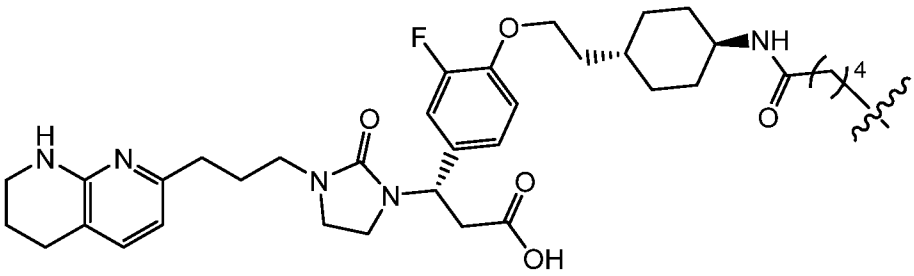
(Structure 2a);



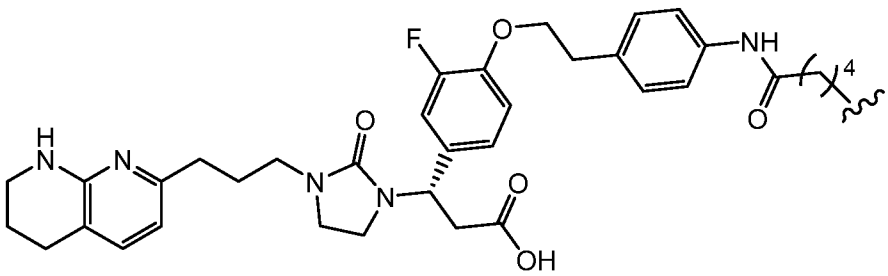
(Structure 2.1a);



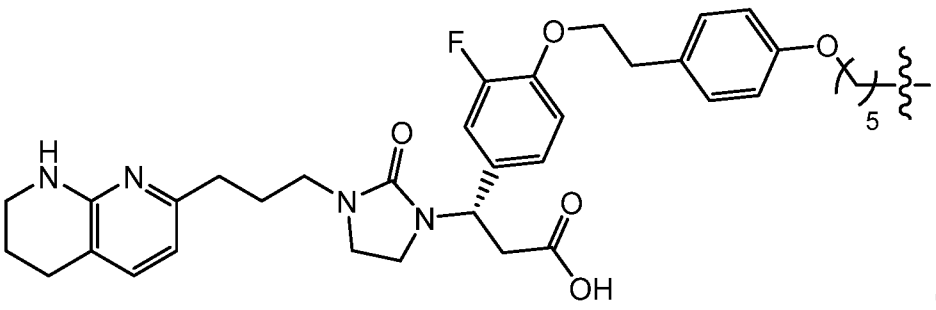
(Structure 2.2a);



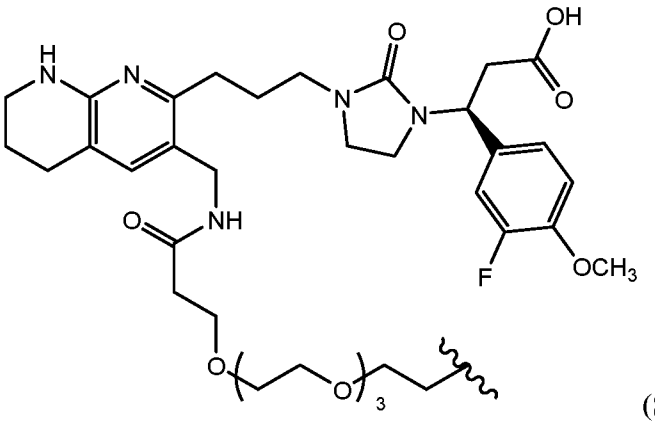
(Structure 2.3a);



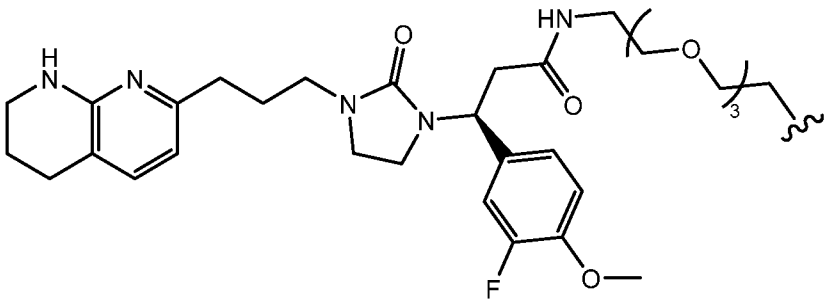
(Structure 2.4a);



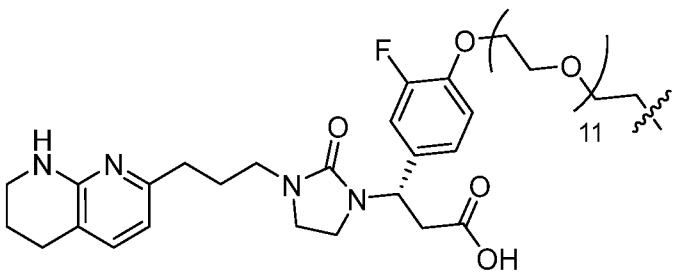
(Structure 2.5a);



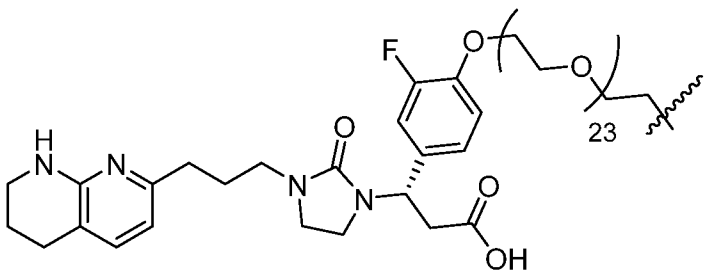
(Structure 2.6a);



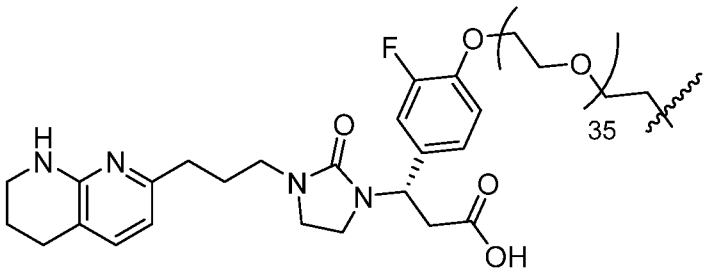
(Structure 2.7a);



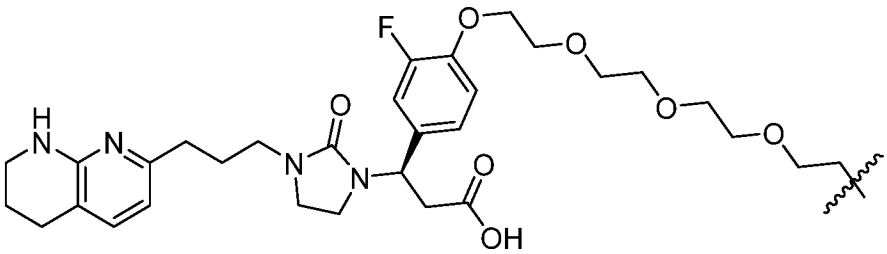
(Structure 2.8a);



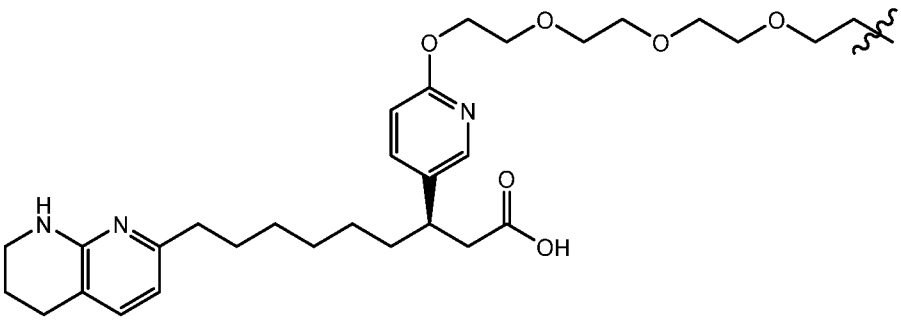
(Structure 2.9a);



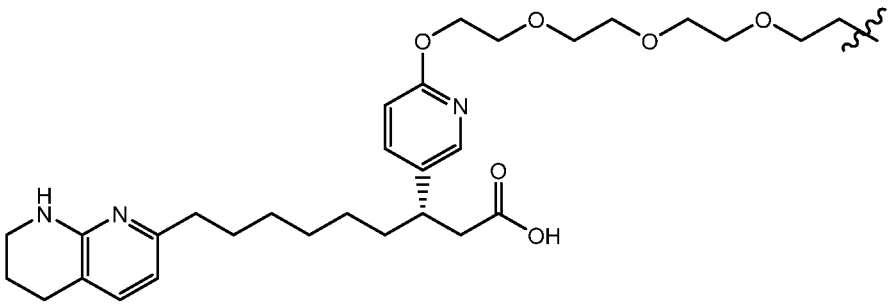
(Structure 2.10a);



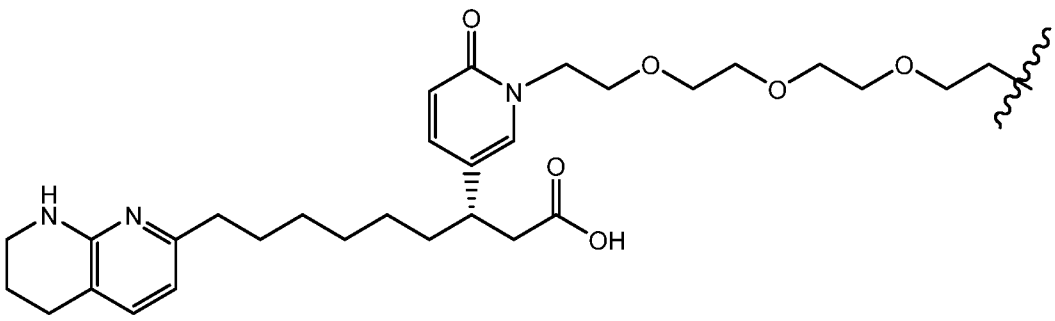
(Structure 2.11a);



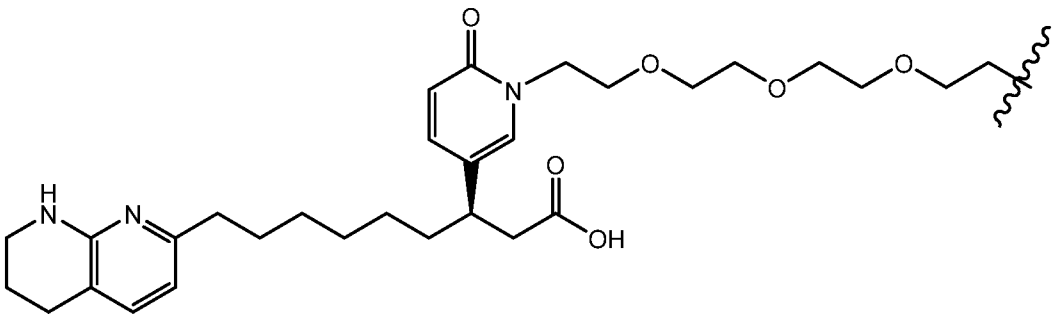
(Structure 28a);



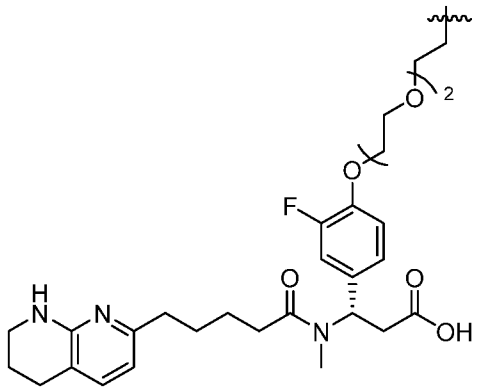
(Structure 29a);



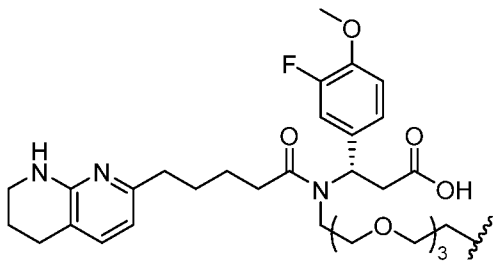
(Structure 30a);



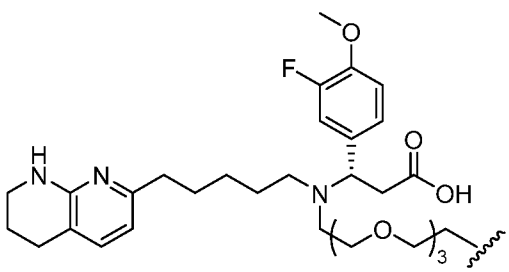
(Structure 31a);



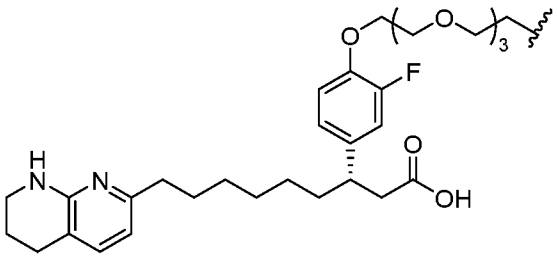
(Structure 32a);



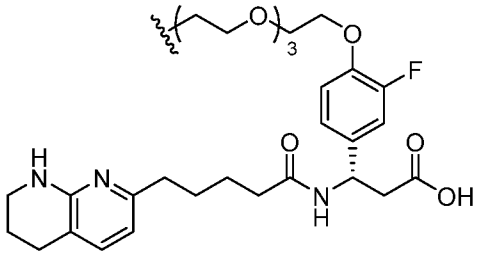
(Structure 33a);



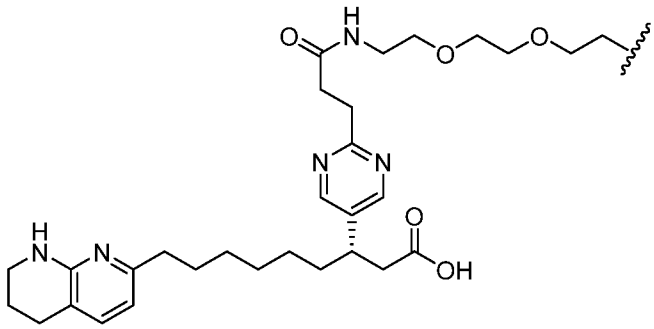
(Structure 34a);



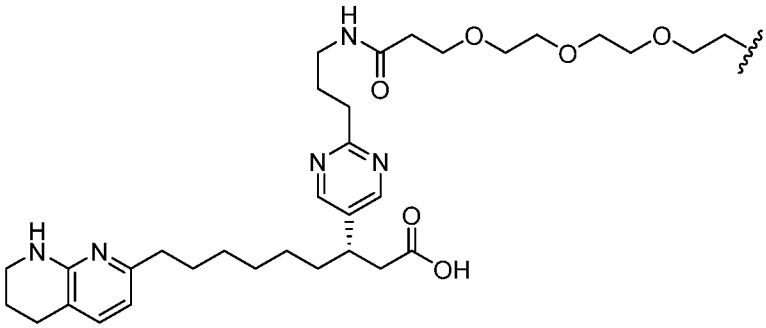
(Structure 36a);



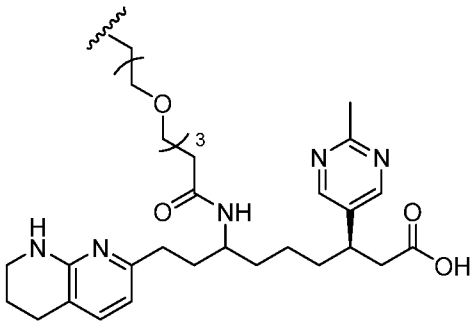
(Structure 37a);



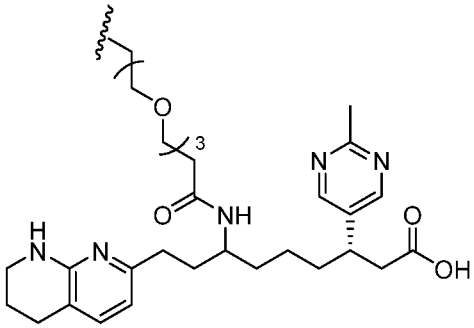
(Structure 38a);



(Structure 39a);

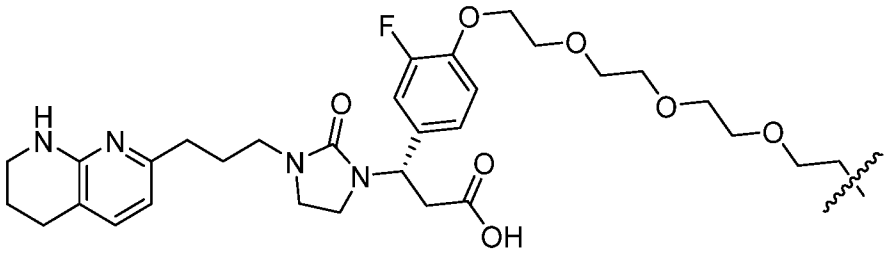


(Structure 40a); and



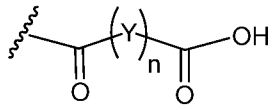
(Structure 41a)

wherein ≈ indicates the point of connection to the HIF-2 alpha RNAi agent.

22. The RNAi agent of any one of claims 1-21, wherein the targeting ligand is of the structure  (Structure 2a).

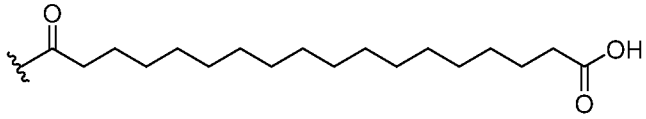
23. The RNAi agent of any one of claims 1-22, further comprising a pharmacokinetic (PK) enhancer.

24. The RNAi agent of claim 23, wherein the PK enhancer comprises the formula:



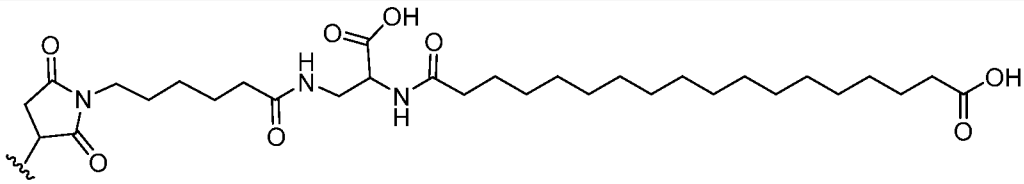
, wherein Y is an optionally substituted saturated or unsaturated aliphatic chain and n is an integer from 5-25.

25. The RNAi agent of claim 24, wherein the PK enhancer comprises

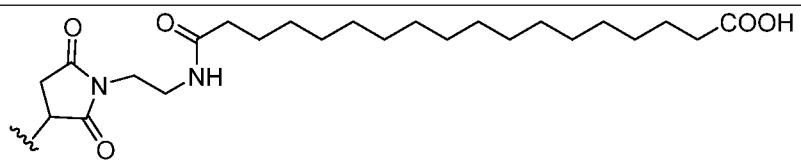


.

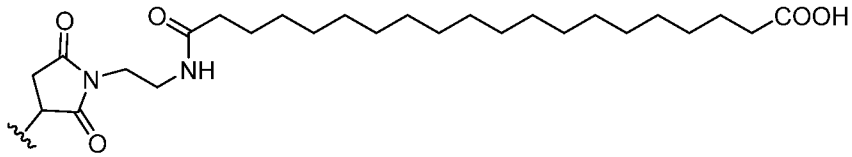
26. The RNAi agent of claim 23, wherein the PK enhancer is selected from the group consisting of:



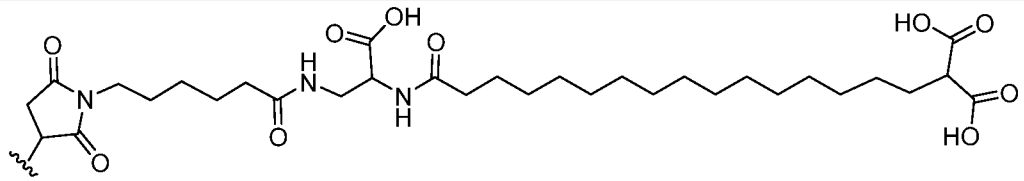
Mal-C_{18}-diacid



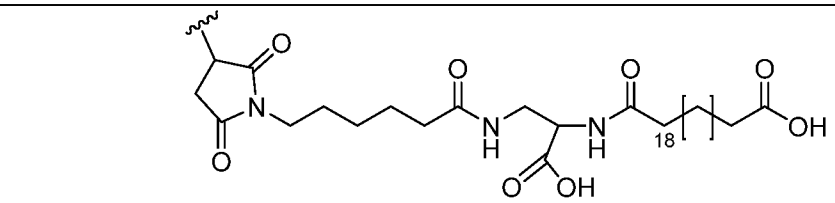
Mal-C_{18}-acid



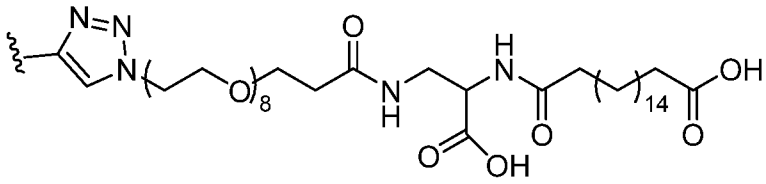
Mal-C_{20}-acid



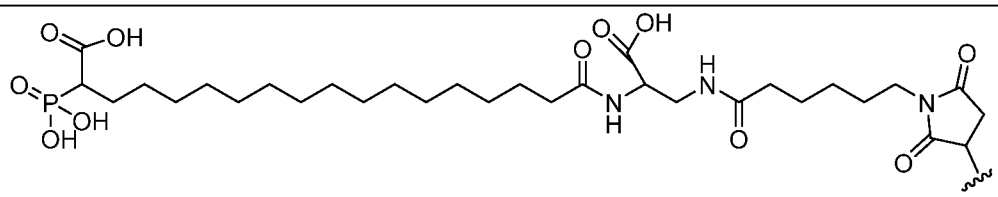
Mal-C_{18}-triacid



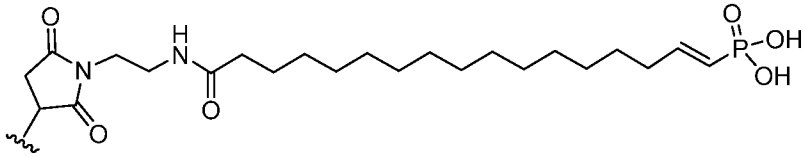
Mal-C_{22}-diacid



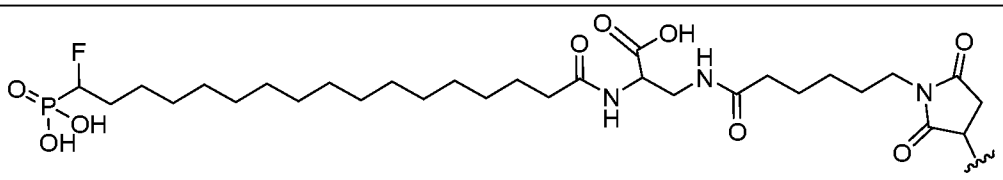
C_{18}-diacid-N_3



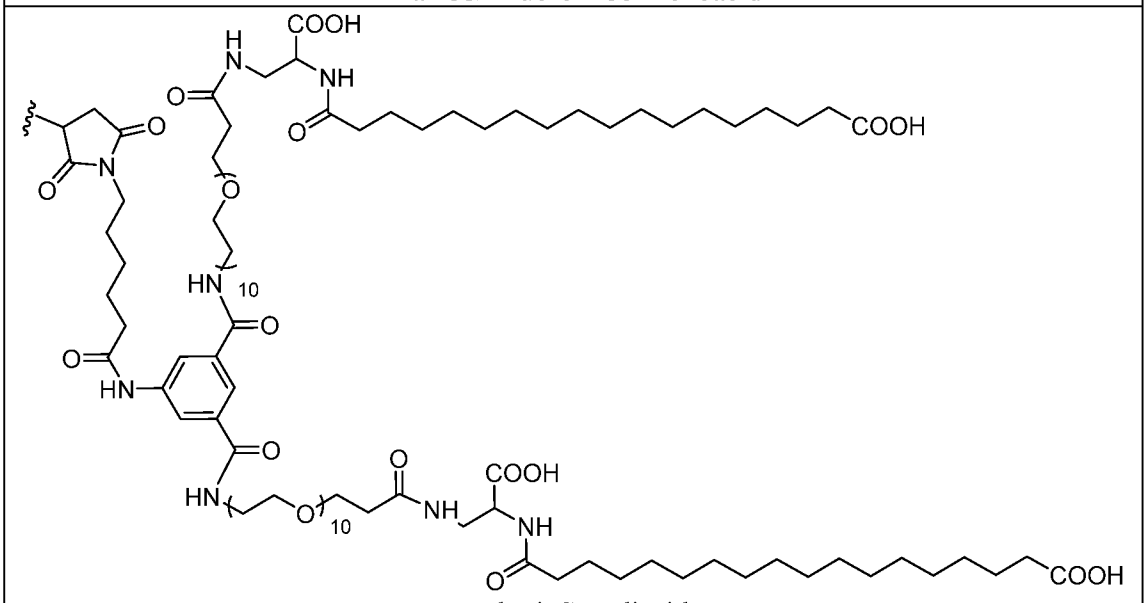
Mal-C_{18}-diacid-PO_3



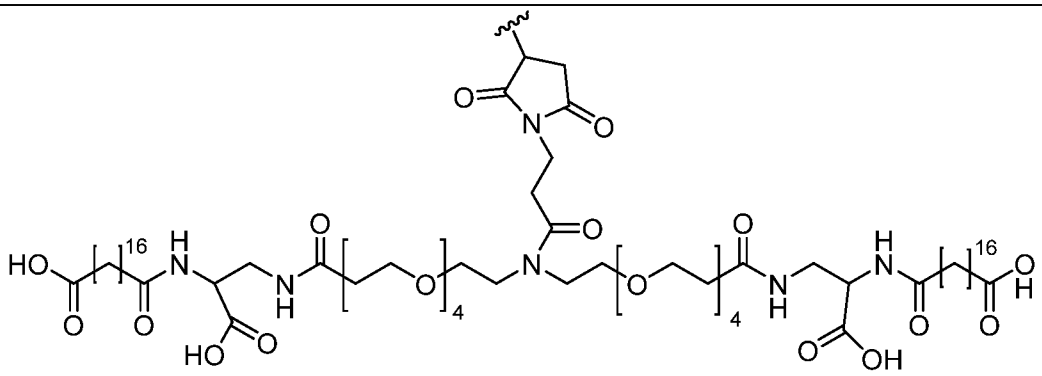
Mal-C_{17}-PO_3



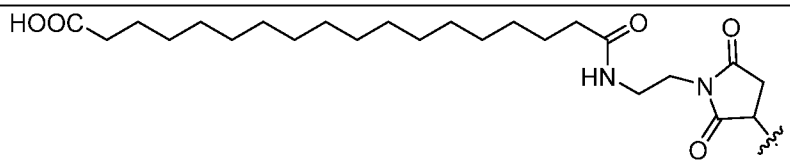
Mal-C_{17}-Fluoro-PO_3 Monoacid



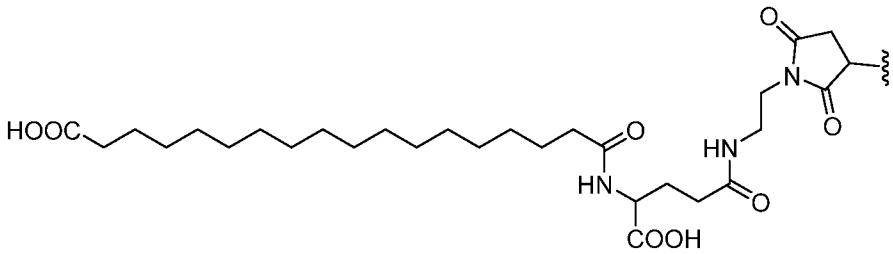
Mal-BisC18-diacid



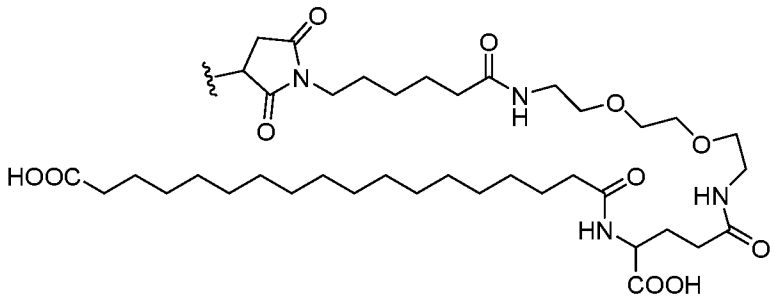
Dual C18-diacid



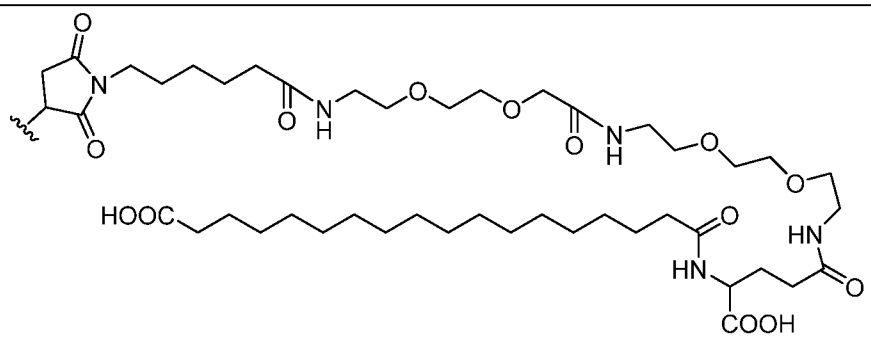
Mal-C18 Acid



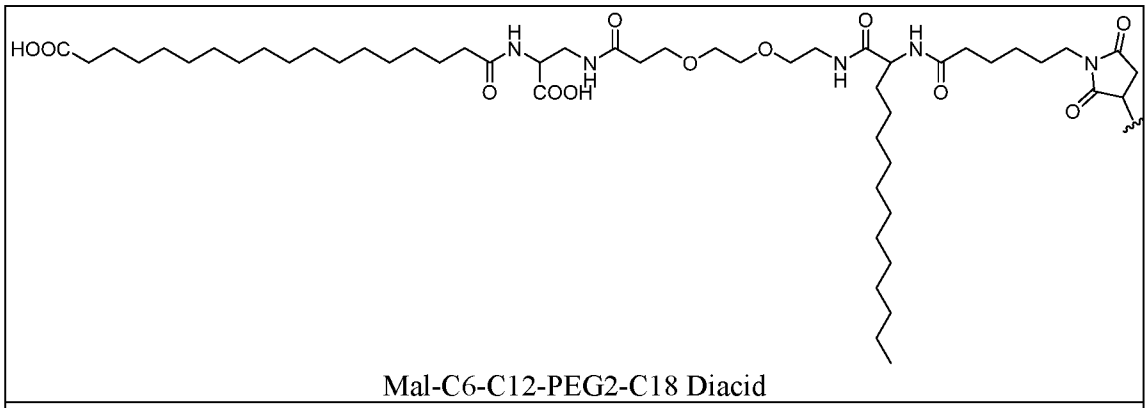
Mal-C18-Diacid



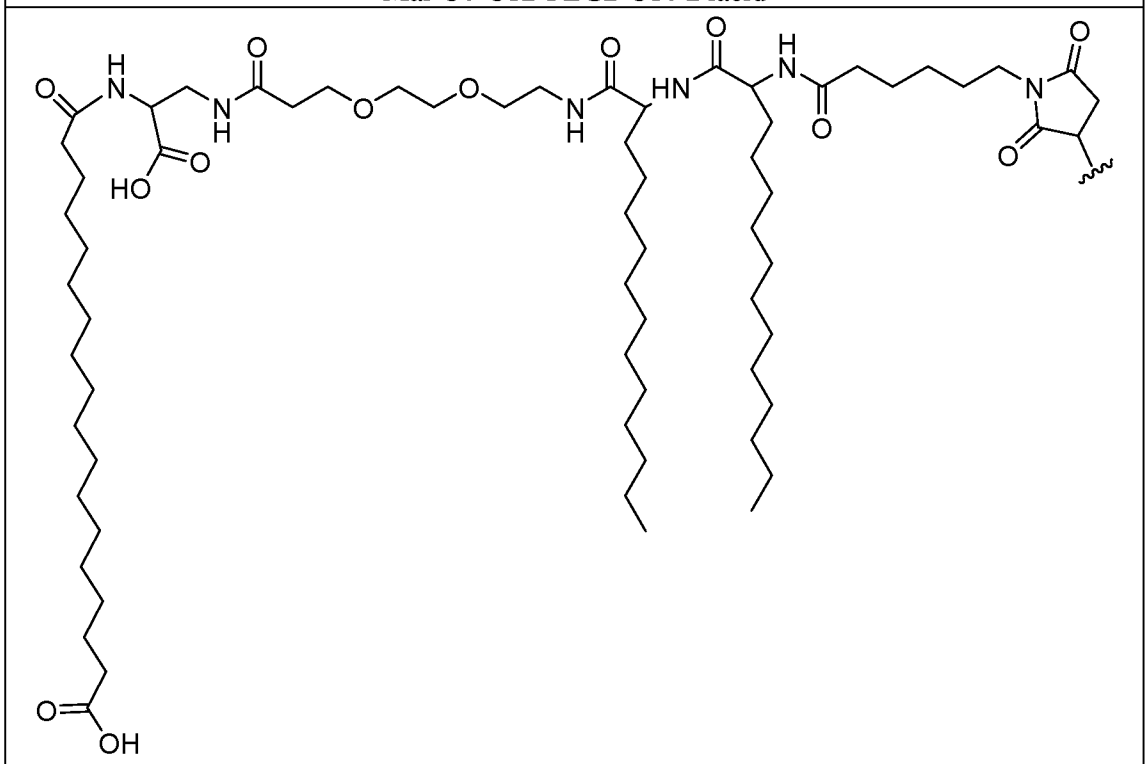
Mal-C6-PEG2-C18-Diacid



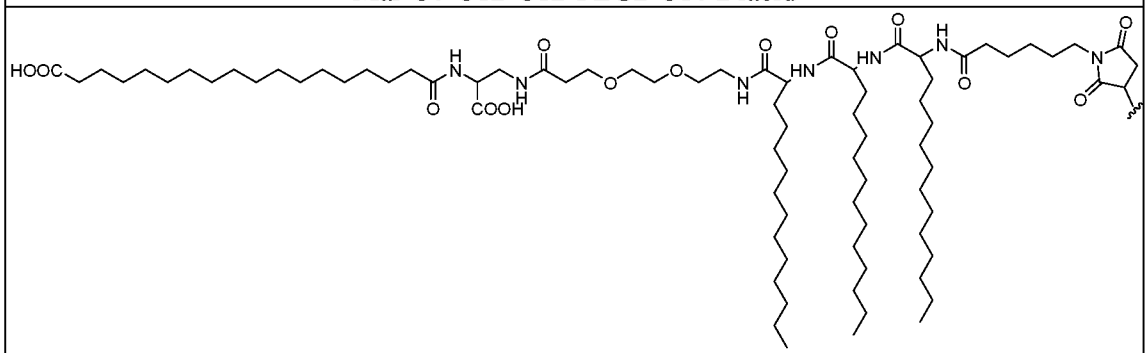
Mal-C6-PEG4-C18-Diacid



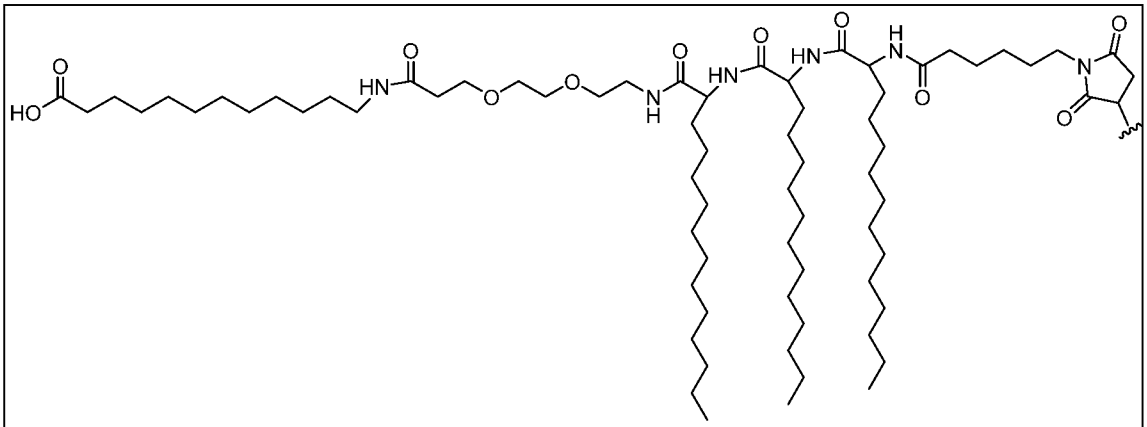
Mal-C6-C12-PEG2-C18 Diacid



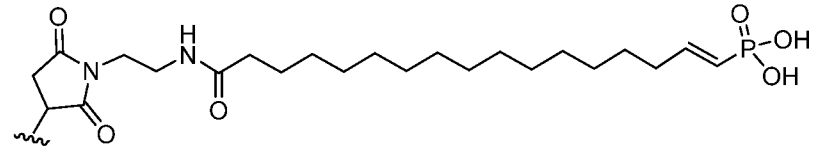
Mal-C6-C12-C12-PEG2-C18 Diacid



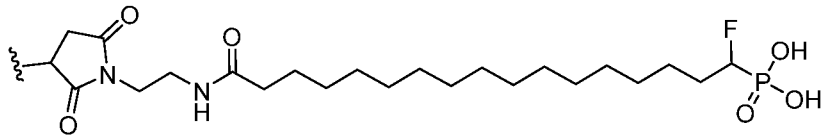
Mal-C6-C12-C12-C12-PEG2-C18-Diacid



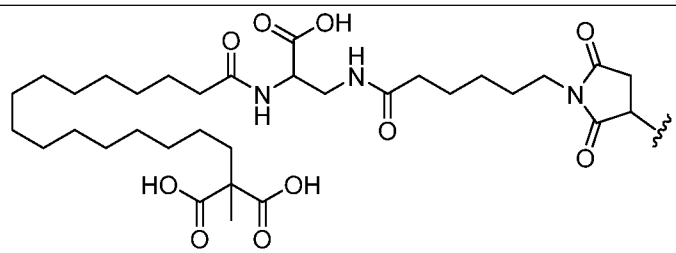
Mal-C6-C12-C12-C12-PEG2-C12 Diacid



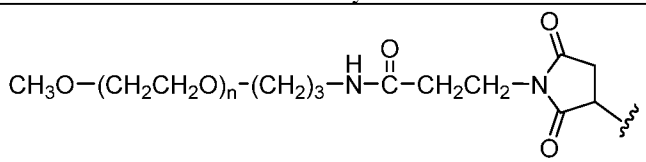
Mal-C_{17}-vinyl-PO_3



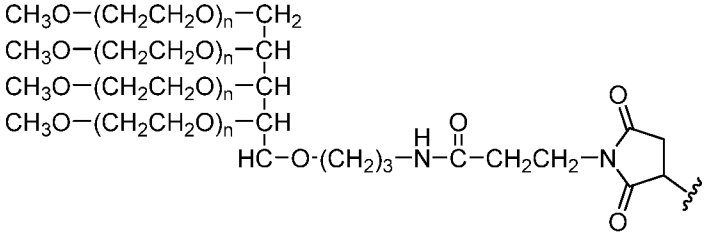
Mal-C_{17}-Fluoro-PO_3



Mal-C_{18}-methyl-triacid



PEG40K,
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



PEG40K (4-arm),
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons

wherein ≀ indicates the point of attachment to the RNAi agent.

27. The RNAi agent of any one of claims 1-26, wherein the targeting ligand is linked to the sense strand.

28. The RNAi agent of any one of claims 23-27, wherein the PK enhancer is linked to the sense strand.

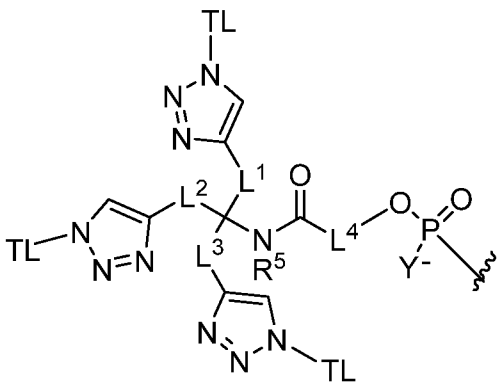
29. The RNAi agent of any one of claims 1-28, wherein the RNAi agent is linked to 2 to 10 targeting ligands.

30. The RNAi agent of any one of claims 1-29, wherein the RNAi agent is linked to a targeting group comprising two or more targeting ligands at the 5' terminal end of the sense strand.

31. The RNAi agent of any one of claims 1-30, wherein at least one targeting ligand is linked to the 5' terminal end of the sense strand, and at least one targeting ligand is linked to a non-terminal nucleotide of the sense strand.

32. The RNAi agent of any one of claims 1-31, linked to two or more targeting ligands, wherein the two or more targeting ligands are linked at a branch point to form a targeting group.

33. The RNAi agent of claim 32, wherein the targeting group comprises three targeting ligands and the targeting group is of the formula:



wherein,

L^1, L^2 and L^3 are each independently linkers comprising an optionally substituted alkylene;

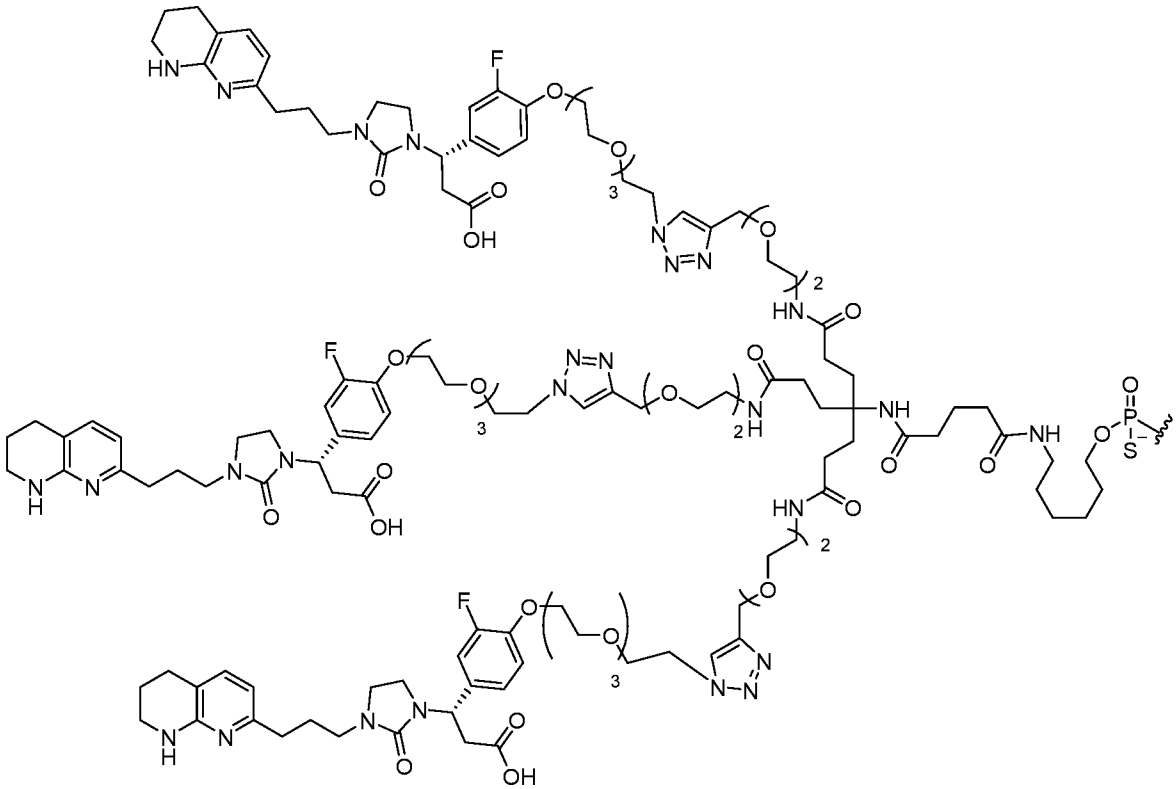
L^4 is a linker comprising an optionally substituted alkylene, optionally substituted aryl, or optionally substituted cycloalkyl;

R^5 is H or optionally substituted alkyl;

TL is a targeting ligand; and

Y is O or S.

34. The RNAi agent of claim 33, wherein the targeting group is of the formula:



.

35. The RNAi agent of any one of claims 1-34, wherein a tridentate targeting group is linked to the 5' terminal end of the sense strand, and wherein at least two additional targeting ligands are linked to one or more nucleotides of the sense strand.

36. The RNAi agent of claim 31 or 35, wherein at least 10 nucleotides are positioned between the targeting group located on the 5' end of the sense strand and the targeting ligand located on the sense strand.

37. The RNAi agent of any one of claims 1-36, wherein at least one targeting ligand is linked to the 2' position of a nucleotide of the sense strand of the RNAi agent.

38. The RNAi agent of any one of claims 23-37, wherein the PK enhancer is linked to the 3' terminal end of the sense strand.

39. The RNAi agent of any one of claims 1-38, wherein 5 to 8 targeting ligands are linked to the sense strand.

40. The RNAi agent of claim 39, wherein the sense strand of the RNAi agent is linked to at least one tridentate targeting group and at least two targeting ligands linked to one or more nucleotides of the sense strand.

41. The RNAi agent of claim 40, wherein the sense strand of the RNAi agent is linked to (i) a tridentate targeting group at the 5' terminal end of the sense strand, and (ii) 2 to 4 targeting ligands linked to nucleotides other than the 5' terminal nucleotide of the sense strand.

42. The RNAi agent of any one of claims 29-41, wherein the targeting ligands are linked to the sense strand as follows: (i) a tridentate targeting group comprising 3 individual targeting ligands is located at the 5' terminal end of the sense strand; and (ii) the additional targeting ligands are individual targeting ligands linked to individual nucleotides of the sense strand that are at least 10 nucleotides away from the 5' terminal end of the sense strand.

43. The RNAi agent of claim 42, wherein the targeting ligands are linked to the sense strand nucleotides located at positions 2, 4, 6, and 8 (3' → 5') from the 3' nucleotide of the sense strand that forms a base pair with the 5' terminal nucleotide of the antisense strand.

44. The RNAi agent of claim 43, wherein at least one targeting ligand is linked to an individual nucleotide at the 2' position of the ribose ring, the 3' position of the ribose ring,

the 1' position of the ribose ring or to the nucleobase of the nucleotide, the 4' position of the ribose ring, or the 5' position of the nucleotide.

45. The RNAi agent of claim 44, wherein at least one targeting ligand is linked to the 2' position of the ribose ring of an individual nucleotide.

46. The RNAi agent of any one of claims 1-45, wherein the sense strand is between 18 and 49 nucleotides in length, and the antisense strand is between 18 and 49 nucleotides in length.

47. The RNAi agent of claim 46, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.

48. The RNAi agent of claim 47, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.

49. The RNAi agent of claim 48, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

50. The RNAi agent of any one of claims 46-49, wherein the RNAi agent has two blunt ends.

51. The RNAi agent of any one of claims 1-50, wherein the sense strand comprises one or two terminal caps.

52. The RNAi agent of any one of claims 1-51, wherein the sense strand comprises one or two inverted abasic residues.

53. The RNAi agent of any one of claims 1-52, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 5.

54. The RNAi agent of any one of claims 51-53, wherein the sense strand further includes inverted abasic residues at the 3' end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both the 3' end and the 5' end of the nucleotide sequence.

55. A HIF-2 alpha RNAi agent comprising:

(i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3; and

(ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

56. An RNAi agent capable of inhibiting expression of a HIF-2 alpha (*EPAS1*) gene comprising:

(i) an antisense strand that is between 18 and 49 nucleotides in length that is at least partially complementary to a HIF-2 alpha (*EPAS1*) gene (SEQ ID NO:1);

(ii) a sense strand that is at least partially complementary to the antisense strand;

(iii) a targeting ligand linked to the sense strand; and

(iv) a PK enhancer linked to the sense strand.

57. The RNAi agent of claim 56, wherein the targeting ligand is linked to the 5' terminal end of the sense strand.

58. The RNAi agent of claim 56 or 57, wherein the PK enhancer is linked to the 3' terminal end of the sense strand.

59. The RNAi agent of any one of claims 56-58, wherein one or more targeting ligands are linked to one or more nucleotides of the sense strand.

60. The RNAi agent of claim 59, wherein 2 to 12 targeting ligands are linked to nucleotides of the sense strand.

61. The RNAi agent of any one of claims 56-60, wherein a tridentate targeting group comprised of three targeting ligands is linked to the 5' terminal end of the sense strand; a PK

enhancer is linked to the 3' terminal end of the sense strand; and between 2 to 12 targeting ligands are linked to individual nucleotides of the sense strand.

62. The RNAi agent of claim 61, wherein the targeting ligands that are linked to individual nucleotides of the sense strand are linked at the 2' position of each respective nucleotide.

63. The RNAi agent of any one of claims 56-62, wherein targeting ligands are linked to nucleotides of the sense strand located at positions 2, 6, 15, and 19 (3' → 5') from the first nucleotide that forms a base pair with the antisense strand.

64. The RNAi agent of any one of claims 56-62, wherein targeting ligands are linked to nucleotides of the sense strand located at positions 2, 4, 6, and 8 (3' → 5') from the first nucleotide that forms a base pair with the antisense strand.

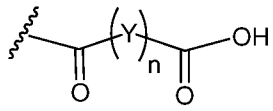
65. The RNAi agent of any one of claims 56-62, wherein targeting ligands are linked to nucleotides of the sense strand that are across from nucleotides 2, 4, 6, and 8 (5' → 3') of the antisense strand.

66. The RNAi agent of any one of claims 56-65, wherein a tridentate targeting group comprising three targeting ligands is located at the 5' terminal end of the sense strand, the sense strand further includes two to four targeting ligands that are linked to nucleotides of the sense strand, and there are at least 10 nucleotides separating the tridentate targeting group at the 5' terminal end of the sense strand and the next closest targeting ligand that is attached to a nucleotide.

67. The RNAi agent of claim 66, wherein four targeting ligands are linked to individual nucleotides of the sense strand.

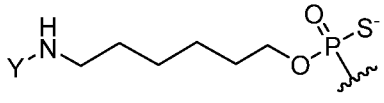
68. The RNAi agent of any one of claims 56-67, wherein the targeting ligand is an integrin targeting ligand that includes a compound that has affinity for integrin alpha-v-beta-3.

69. The RNAi agent of any one of claims 56-68, wherein the PK enhancer is of the formula:



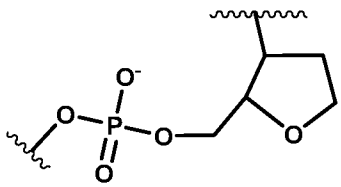
, wherein Y is an optionally substituted saturated or unsaturated aliphatic chain and n is an integer from 5-25.

70. An RNAi agent comprising an antisense strand comprising the sequence usUfsusCfaUfgAfaAfuCfgUfuAfcGfuUfsg (SEQ ID NO: 30), and a sense strand comprising the sequence Y-(NH-C6)scsaacguaaCfGfAfuuu^{Z}ca^{Z}ug^{Z}aa^{Z}sa(invAb)(6-S)-X (SEQ ID NO: 761), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage; u^{Z}, a^{Z}, g^{Z}, and c^{Z} represent uridine, adenosine, guanosine and cytidine, respectively, with a pharmacological moiety comprising *Z* linked at the 2′ position of the nucleotide; Y-(NH-C6)s represents:



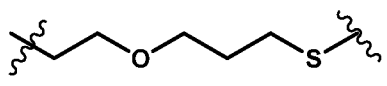
; (invAb) represents:

linkage towards 5' end



linkage towards 3' end

; (6-S) represents:



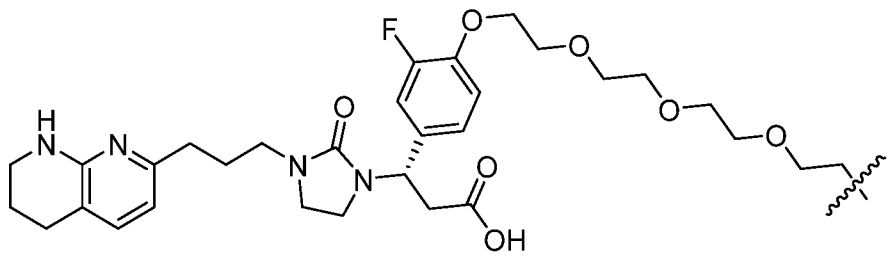
, and each X, Y and Z independently represents:

(iv) a targeting group comprising one or more targeting ligands, wherein the targeting ligand is selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a;

(v) a targeting ligand having a structure selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a; or

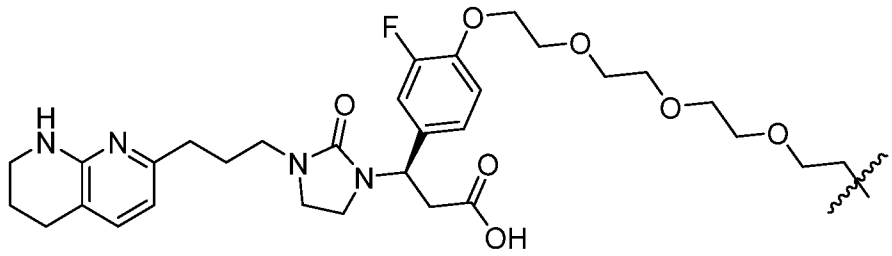
(vi) a PK enhancer having a structure selected from the group consisting of C-18 diacid, C-18 triacid, Mal-C_{17}-vinyl-PO_3, and C20 acid.

71. The RNAi agent of claim 70, wherein each Z is a targeting ligand having a structure of Structure 2a:



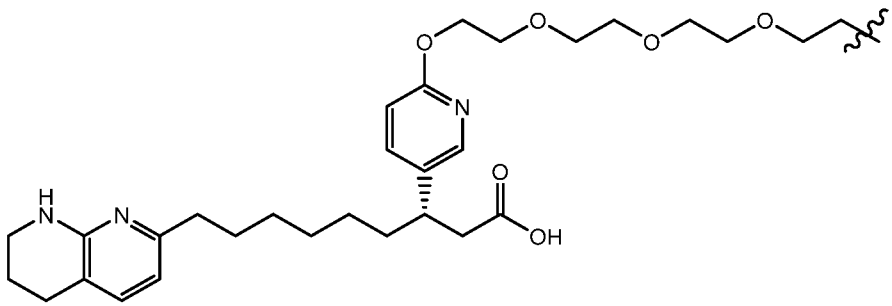
wherein ≈ indicates the point of attachment.

72. The RNAi agent of claim 70, wherein each Z is a targeting ligand having a structure of Structure 2.11a:



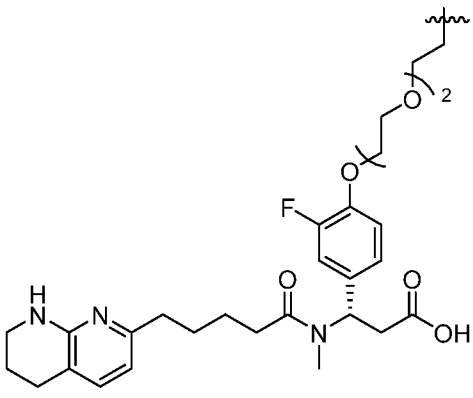
wherein ≈ indicates the point of attachment.

73. The RNAi agent of claim 70, wherein each Z is a targeting ligand having a structure of Structure 29a:

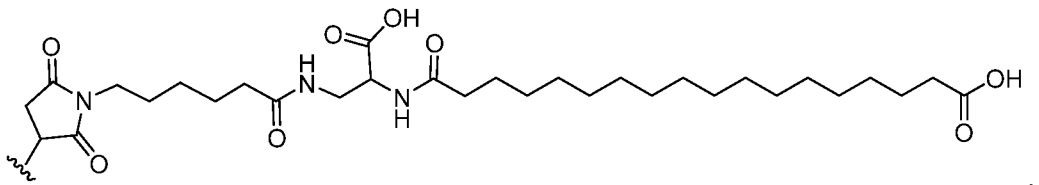


,

wherein ≈ indicates the point of attachment.

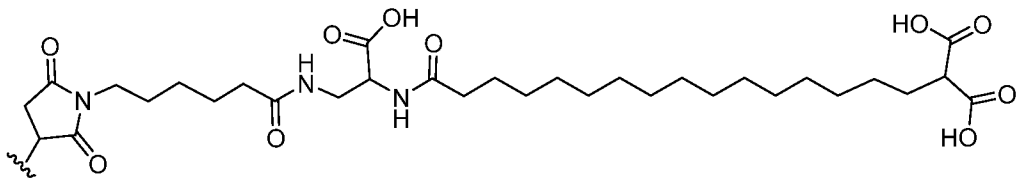
74. The RNAi agent of claim 70, wherein each Z is a targeting ligand having a structure of Structure 32a: , wherein ≈ indicates the point of attachment.

75. The RNAi agent of any one of claims 70-74, wherein X is a PK enhancer having a structure of C-18 diacid:

,

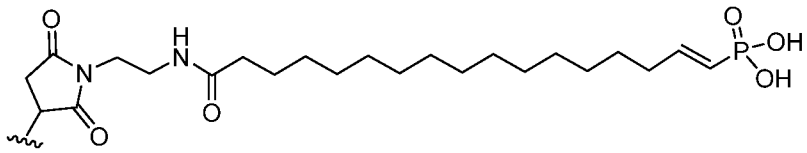
wherein ≈ indicates the point of attachment.

76. The RNAi agent of any one of claims 70-74, wherein X is a PK enhancer having a structure of Mal-C-18 triacid:



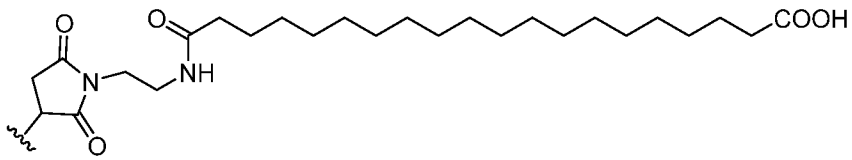
wherein ≈ indicates the point of attachment.

77. The RNAi agent of any one of claims 70-74, wherein X is a PK enhancer having a structure of Mal-C17-vinyl PO3:



, wherein ≈ indicates the point of attachment.

78. The RNAi agent of any one of claims 70-74, wherein X is a PK enhancer having a structure of Mal-C_{20} acid:

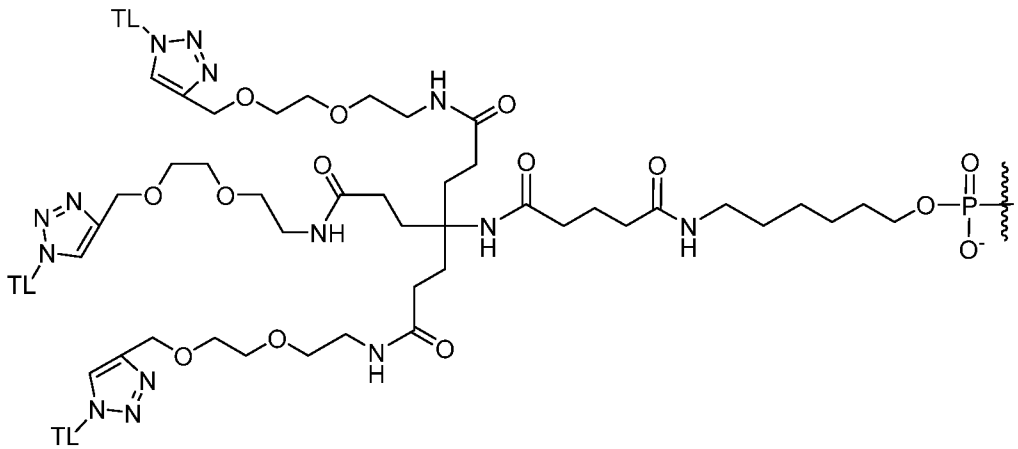


, wherein ≈ indicates the point of attachment.

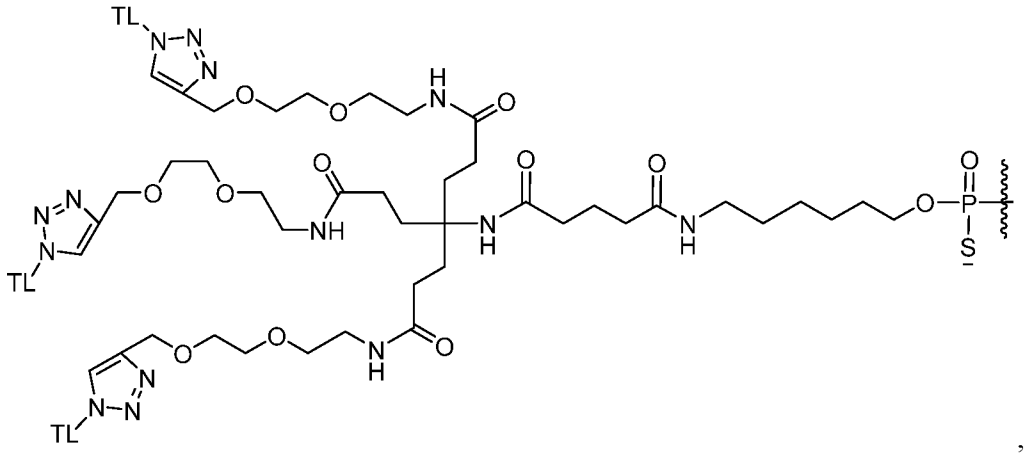
79. The RNAi agent of any one of claims 70-78, wherein the RNAi agent includes 2, 3, 4, 5, 6, 7, 8, 9, or 10 targeting ligands.

80. The RNAi agent of claim 79, wherein the RNAi agent includes 7 targeting ligands.

81. The RNAi agent of claim 80, wherein Y is a targeting group having the structure of TriAlk 14:

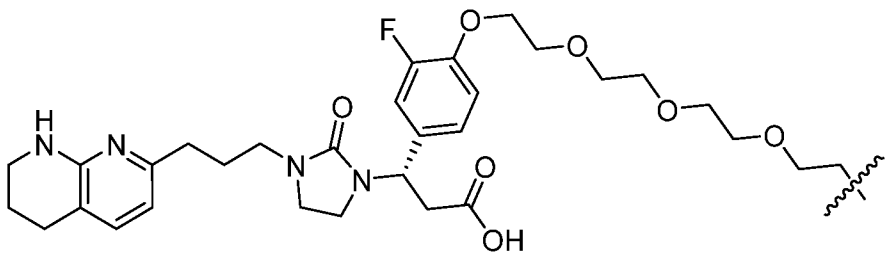


or TriAlk

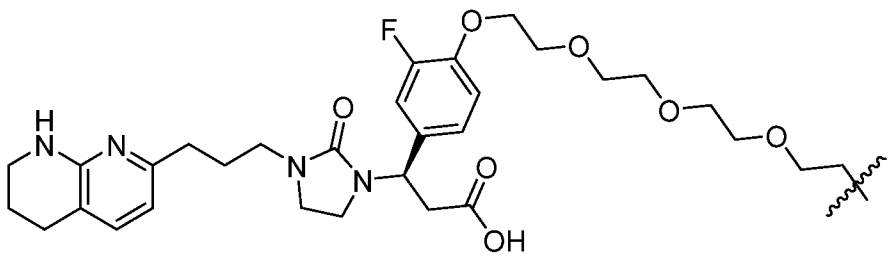
14s: ,

wherein TL comprises a targeting ligand selected from the group consisting of: Structure 2a, Structure 2.11a, Structure 29a, and Structure 32a.

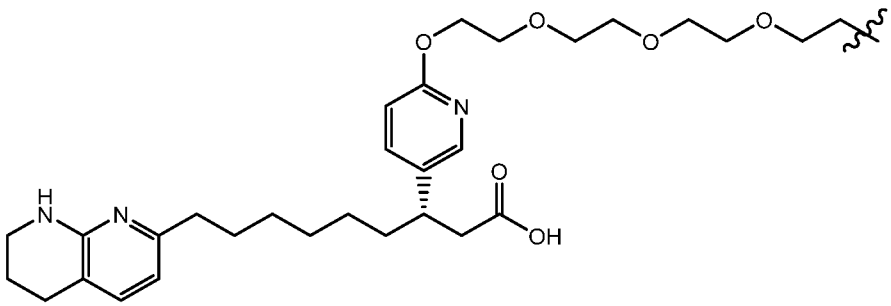
82. The RNAi agent of claim 81, wherein each TL comprises Structure 2a:

 wherein ≈ indicates the point of attachment.

83. The RNAi agent of claim 81, wherein each TL comprises Structure 2.11a:

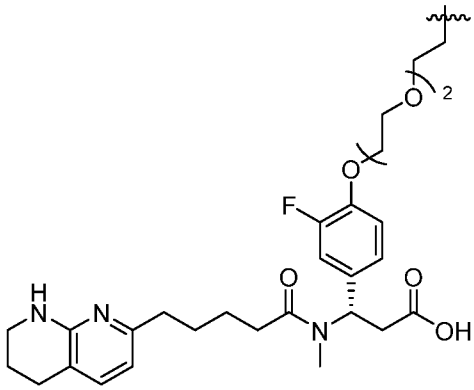
 wherein ≈ indicates the point of attachment.

84. The RNAi agent of claim 81, wherein each TL comprises Structure 29a:



, wherein ≈ indicates the point of attachment.

85. The RNAi agent of claim 81, wherein each TL comprises Structure 32a:



, wherein ≈ indicates the point of attachment.

86. The RNAi agent of any one of claims 70-85, wherein the nucleotides of the antisense strand consist of the nucleotides of SEQ ID NO: 30.

87. The RNAi agent of any one of claims 70-86, wherein the nucleotides of the sense strand consist of the nucleotides of SEQ ID NO: 761.

88. A composition comprising the RNAi agent of any one of claims 1-87, wherein the composition comprises a pharmaceutically acceptable excipient.

89. The composition of claim 88, further comprising a second RNAi agent for inhibiting the expression of HIF-2 alpha.

90. The composition of claim 88 or 89, further comprising one or more additional therapeutics.

91. A method for inhibiting expression of a HIF-2 alpha (*EPAS1*) gene in a cell, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of claims 1-88 or the composition of any one of claims 88-90.

92. The method of claim 91, wherein the cell is within a subject.

93. The method of claim 92, wherein the subject is a human subject.

94. The method of any one of claims 91-93, wherein the HIF2-alpha gene expression is inhibited by at least about 30% *in vivo*.

95. A method of treating a HIF2-alpha-related disease or disorder, the method comprising administering to a human subject in need thereof a therapeutically effective amount of the composition of any one of claims 88-90.

96. The method of claim 95, wherein the disease or disorder is cancer, renal cancer, clear cell renal cell carcinoma, non-small cell lung cancer, astrocytoma (brain cancer), bladder cancer, breast cancer, chondrosarcoma, colorectal carcinoma, gastric carcinoma, glioblastoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, neuroblastoma, melanoma, multiple myeloma, ovarian cancer, rectal cancer, metastases, gingivitis, psoriasis, Kaposi's sarcoma-associated herpesvirus, preeclampsia, inflammation, chronic inflammation, neovascular diseases, or rheumatoid arthritis

97. The method of claim 95 or 96, wherein the disease is clear cell renal cell carcinoma (ccRCC).

98. The method of any one of claims 91-97, wherein the RNAi agent is administered at a dose of about 3 mg/kg to about 80 mg/kg of body weight of the human subject.

99. The method of claim 98, wherein the RNAi agent is administered at a dose of about 5 mg/kg to about 20 mg/kg of body weight of the human subject.

100. The method of claim 98 or 99, wherein the RNAi agent is administered in a split dose, wherein about half of the desired daily amount is administered in an initial administration, and the remaining about half of the desired daily amount is administered approximately four hours after the initial administration.

101. The method of any one of claims 98-100, wherein the dose or doses of the RNAi agent is administered once a week.

102. The method of any one of claims 99-101, wherein the dose or split doses of the RNAi agent is administered biweekly (once every other week).

103. Use of the RNAi agent of any one of claims 1-88 or the composition according to any one of claims 88-90, for the treatment of a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression.

104. Use according to claim 103, wherein the disease is ccRCC.

105. Use of the RNAi agent of any one of claims 1-88 or the composition according to any one of claims 88-90, for the preparation of a pharmaceutical composition for treating a disease, disorder, or symptom that is mediated at least in part by HIF-2 alpha (*EPAS1*) gene expression.

106. Use of claim 105, wherein the disease is ccRCC.

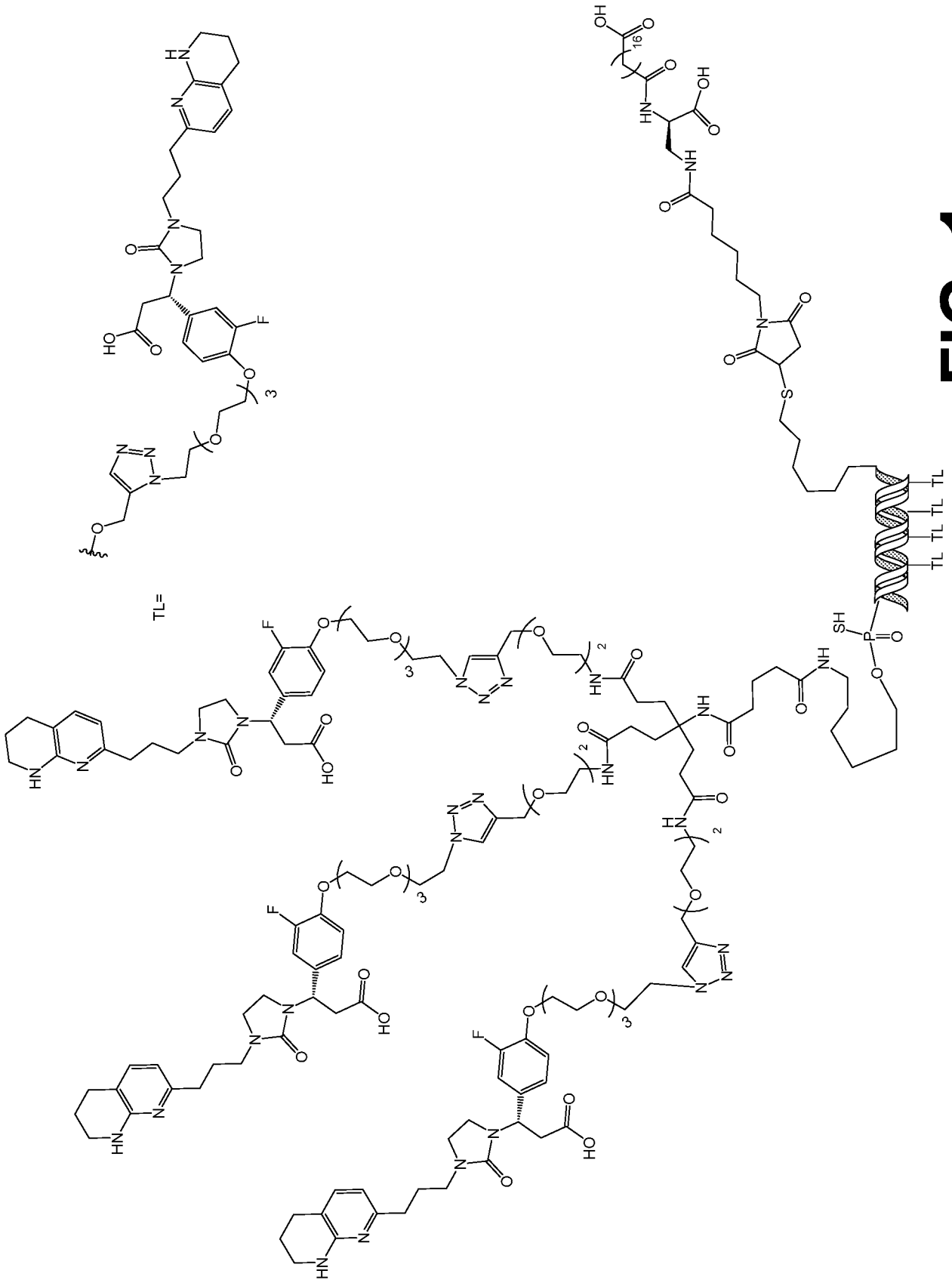


FIG. 1

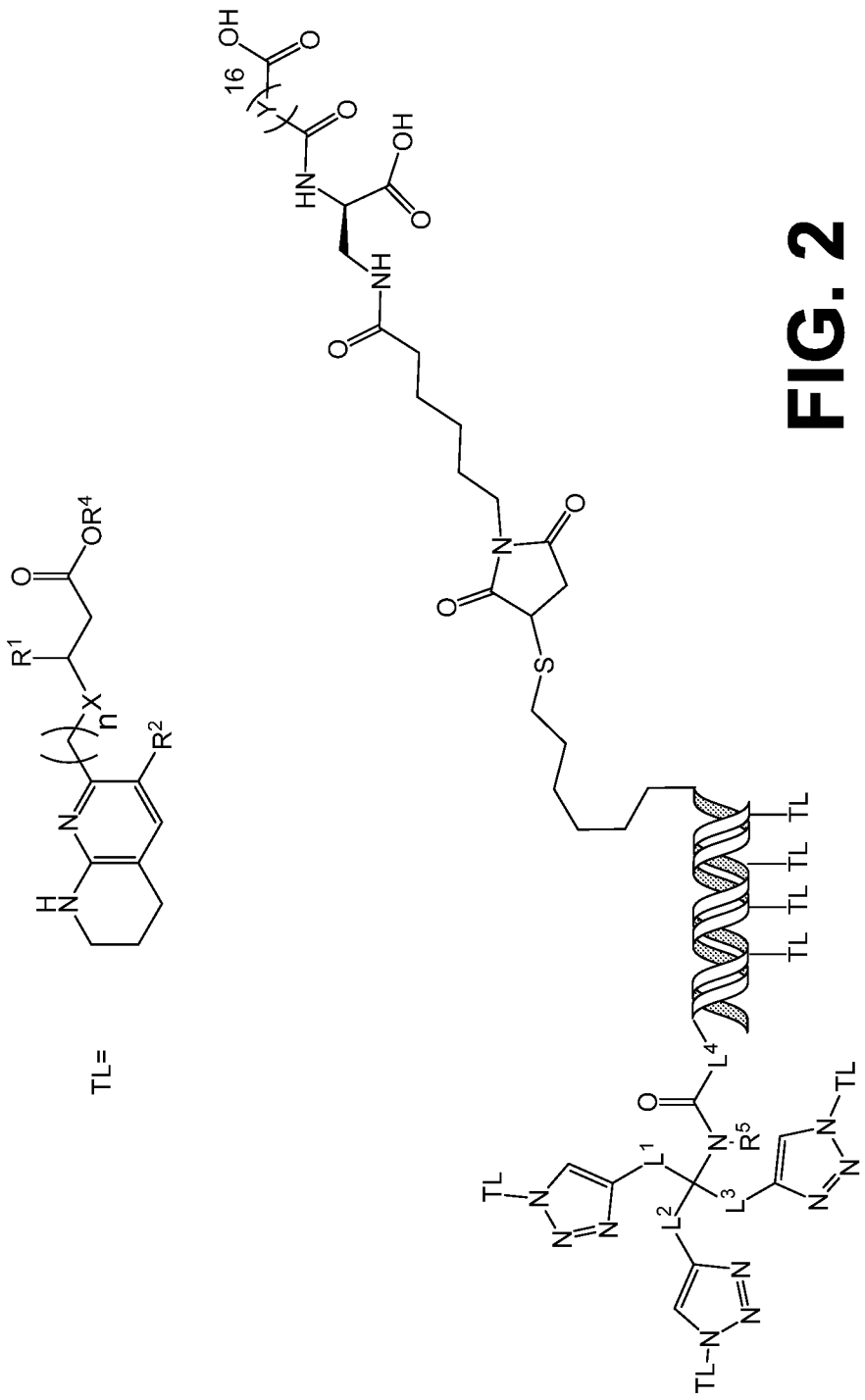


FIG. 2

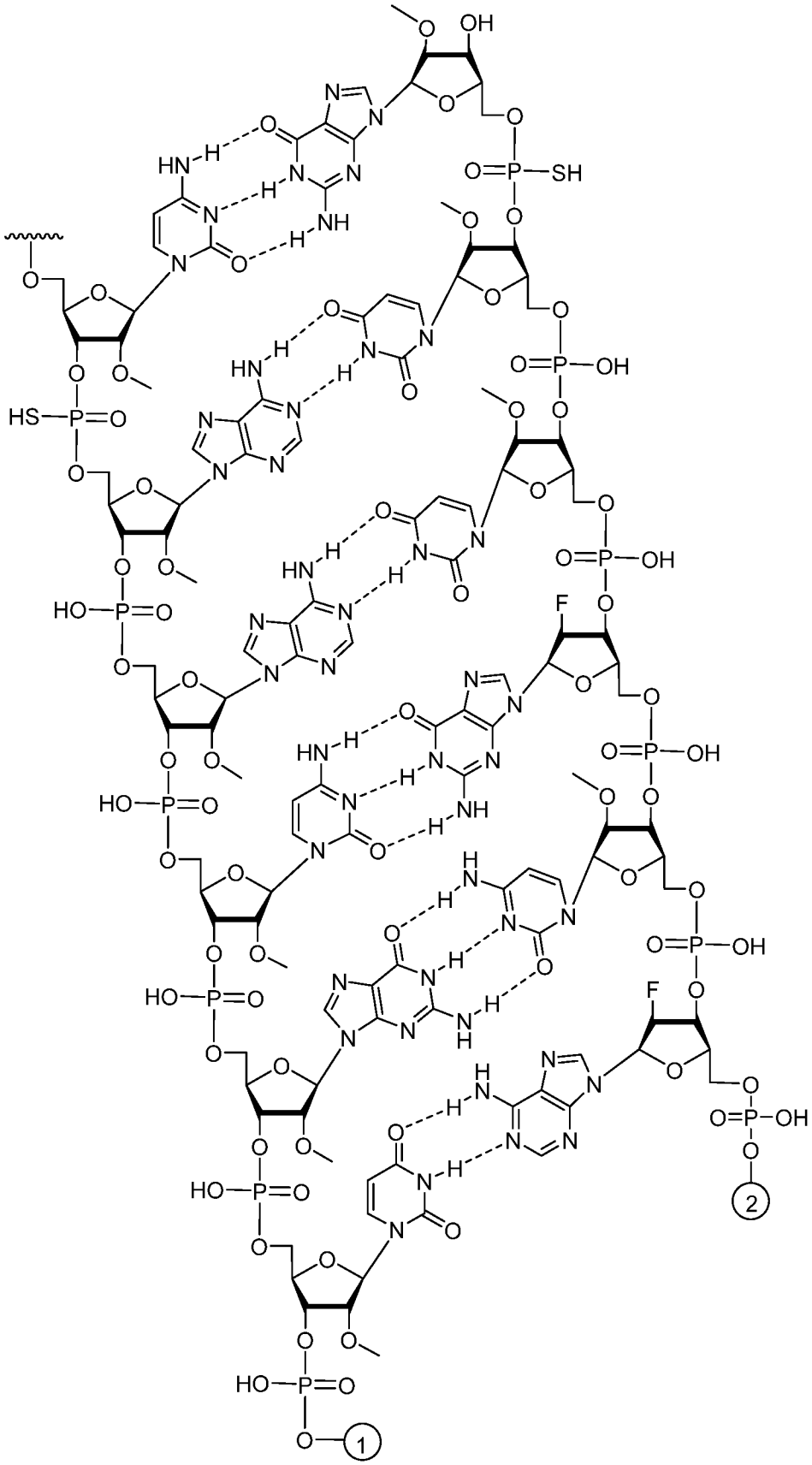


FIG. 3A

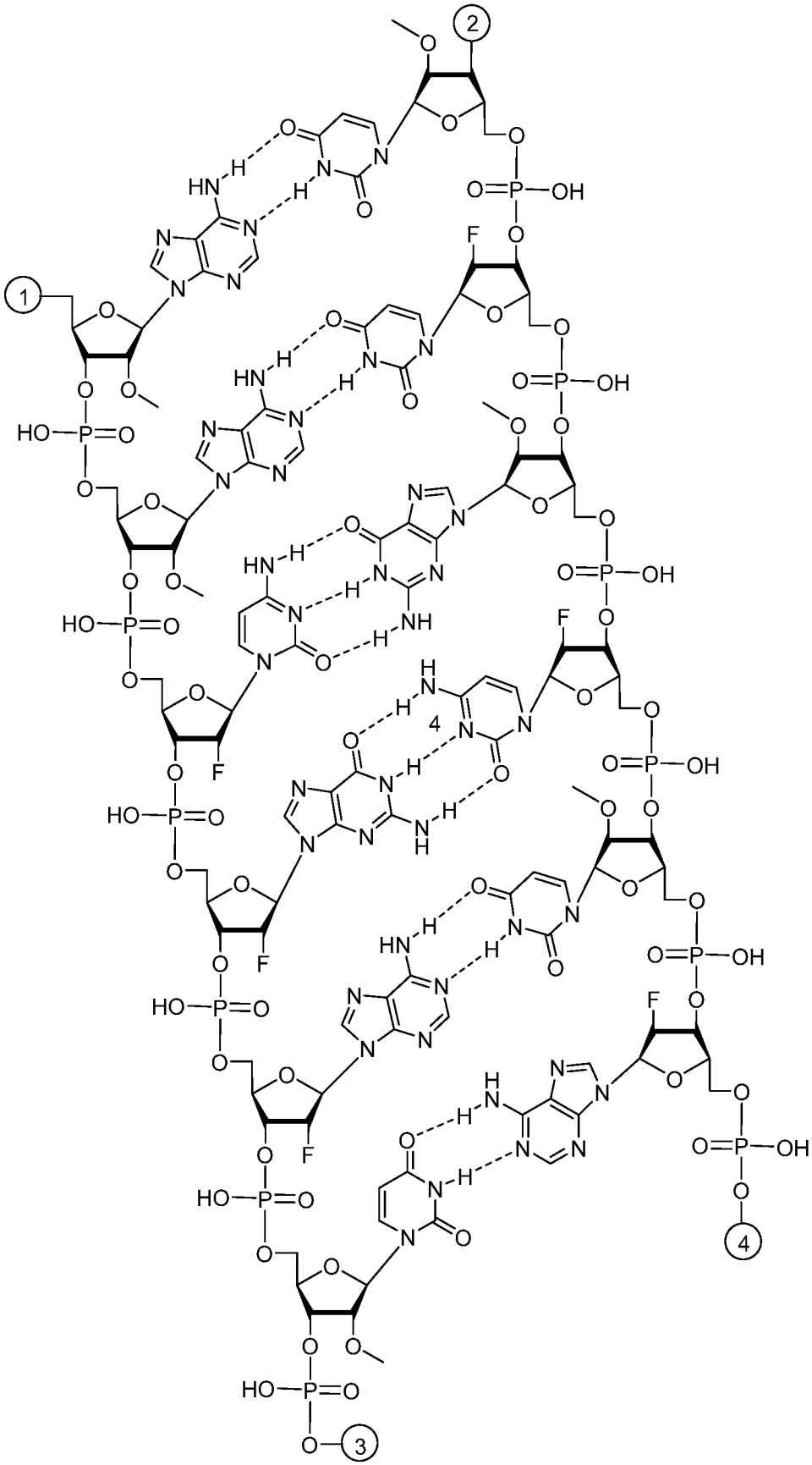


FIG. 3B

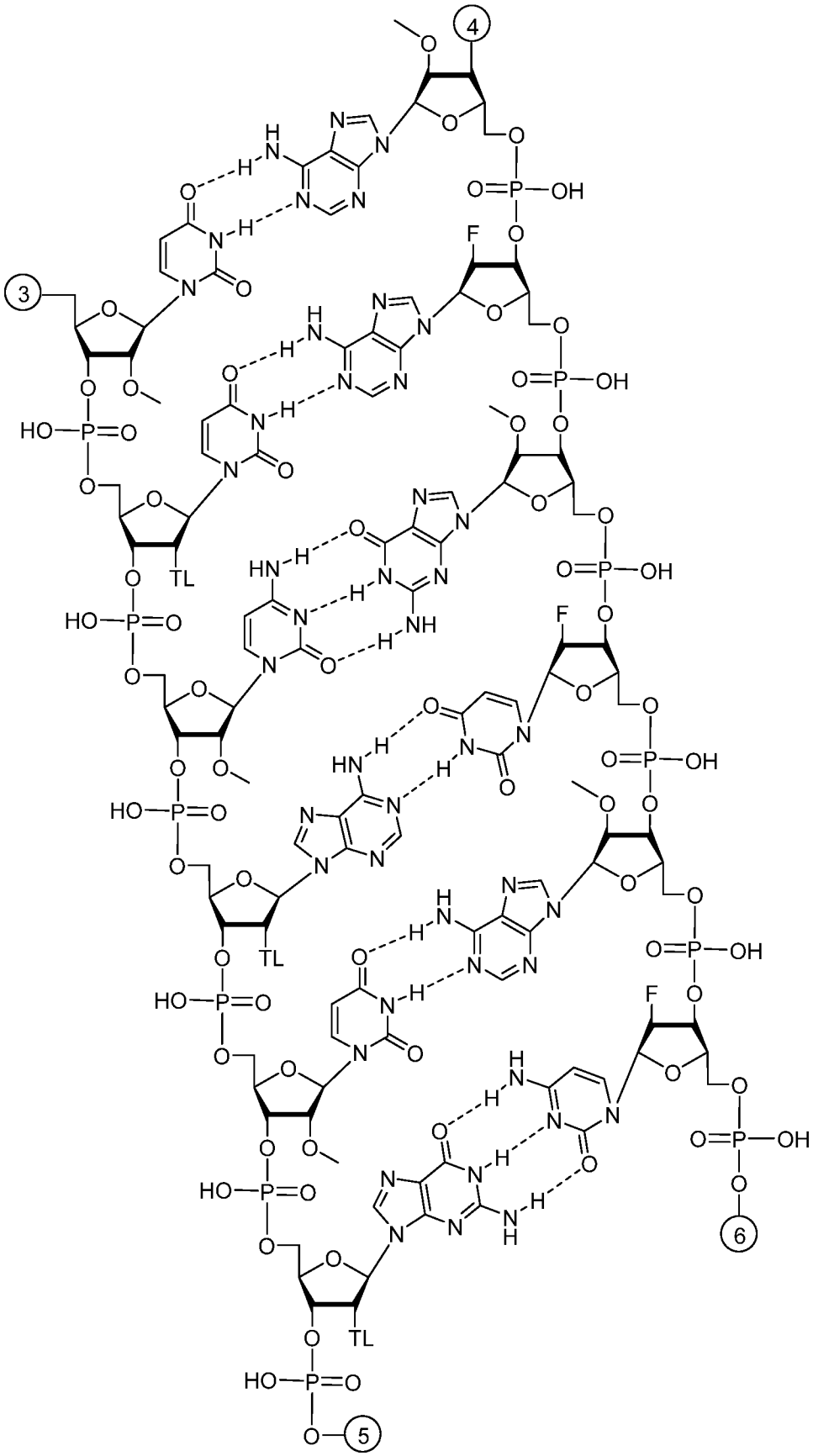


FIG. 3C

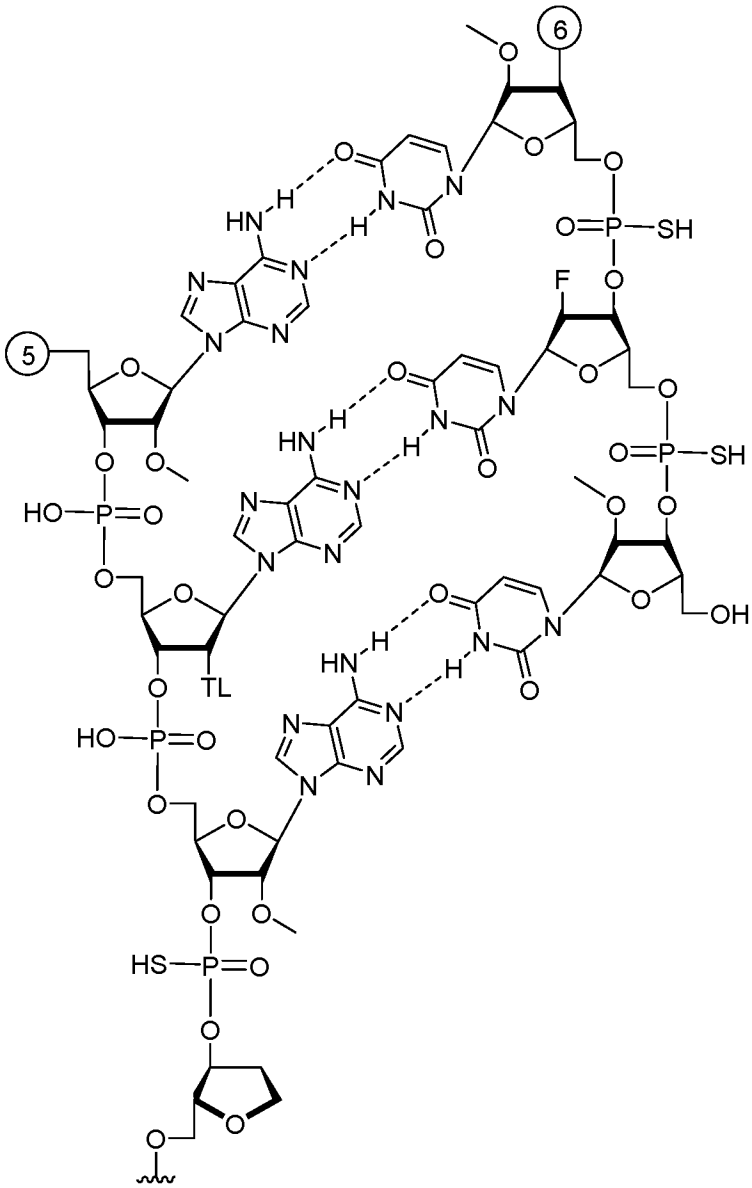


FIG. 3D

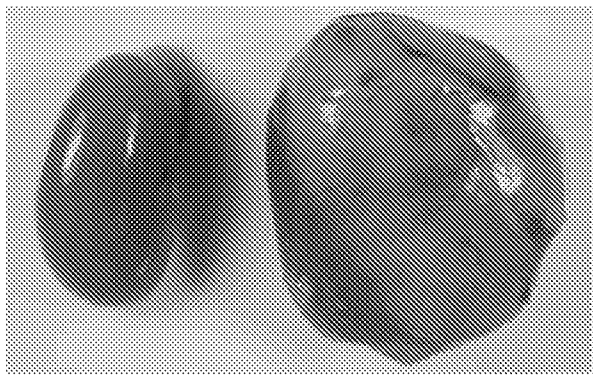


FIG. 4A

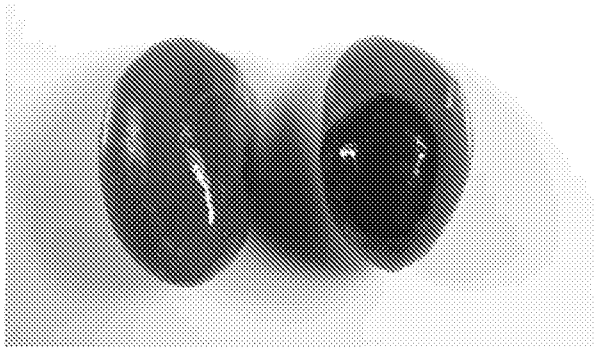


FIG. 4B

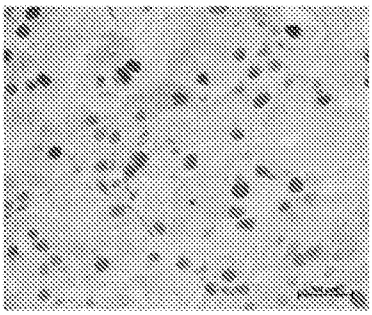


FIG. 5A

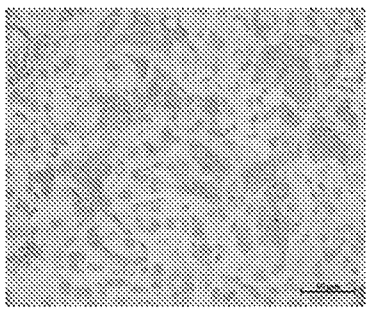


FIG. 5B

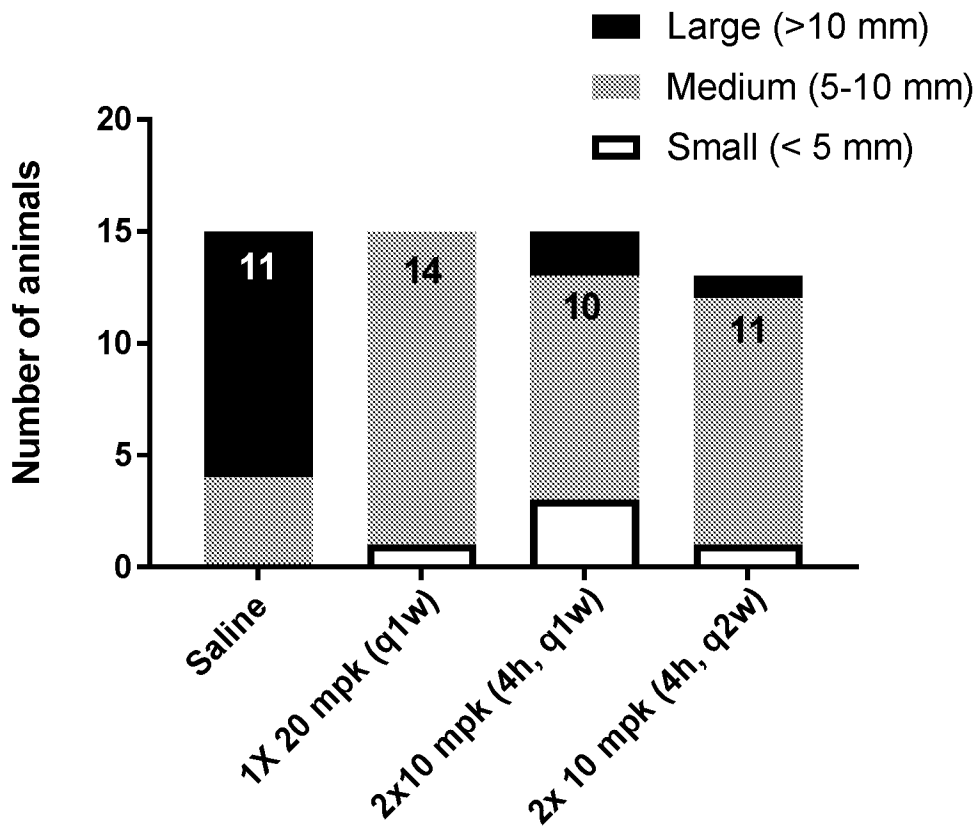

Large (>10 mm)
Medium (5-10 mm)
Small (< 5 mm)
Number of animals
20
15
10
5
0
11
14
10
11
Saline
1X 20 mpk (q1w)
2x10 mpk (4h, q1w)
2x 10 mpk (4h, q2w)

FIG. 6

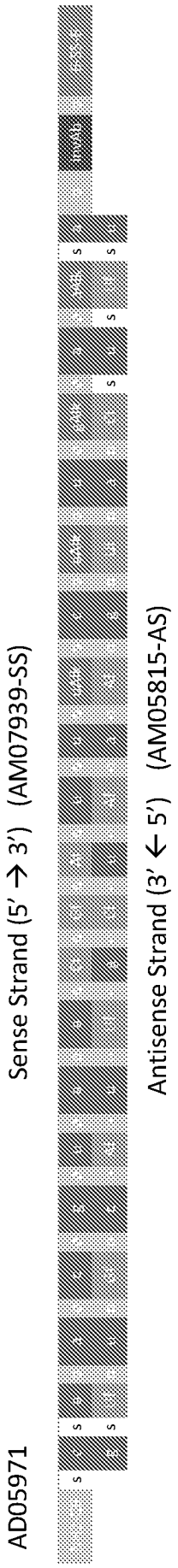


FIG. 7A

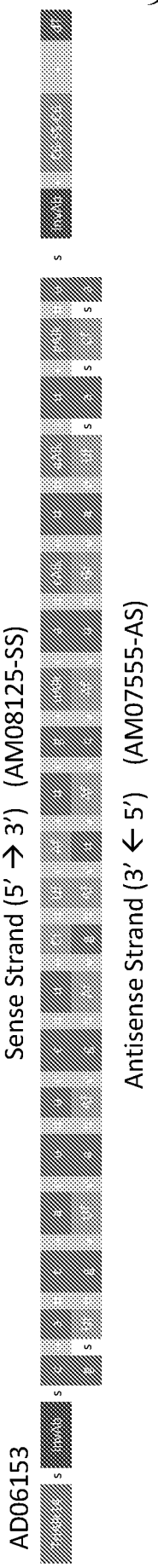


FIG. 7B

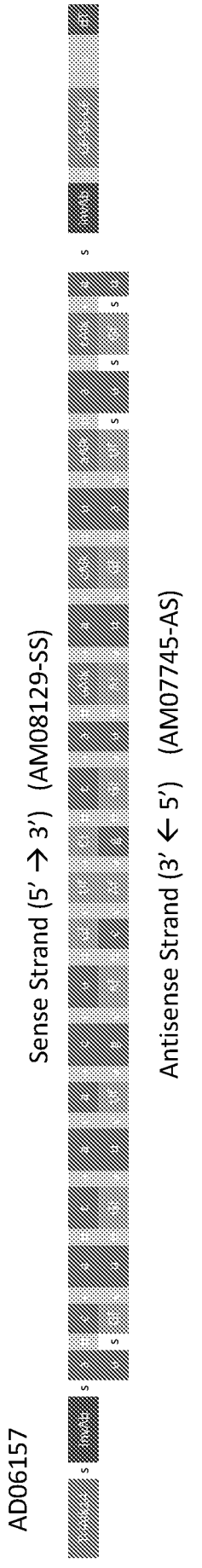


FIG. 7C

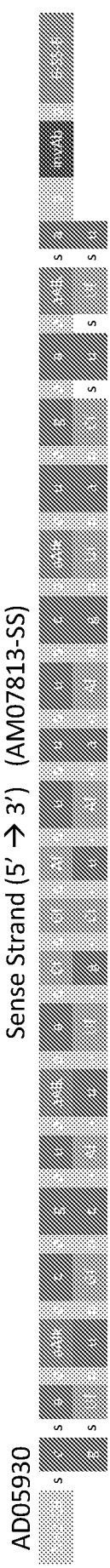


FIG. 7D

FIG. 7E



FIG. 7F

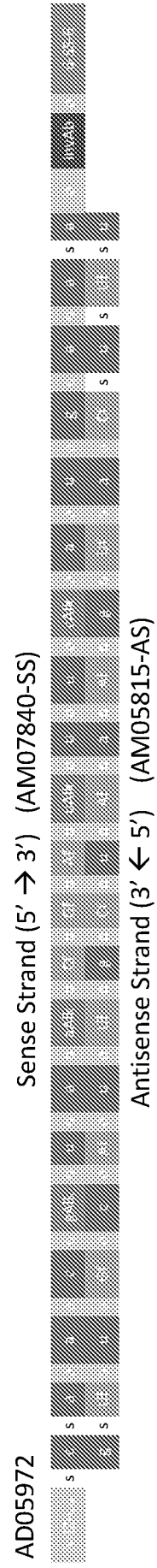


FIG. 7G

SEQUENCE LISTING

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