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(54) Title: COMPOSITIONS FOR TREATING BREAST CANCER

231 VIFP cell survival

% survival

100

EC50

8.4 µM

licoha!cone (µ M)

FIG. 5

(57) Abstract: Disclosed herein are compositions useful for inhibiting prostaglandin reductase 1 (PTGR1) activity. Further provided is a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a PTGR1 inhibitor. In another aspect is provided a method of treating triple negative breast cancer, the method including administering to a subject in need thereof an effective amount of a PTGR1 inhibitor. In another aspect is provided a pharmaceutical composition including a PTGR1 inhibitor and a pharmaceutically acceptable excipient. In preferred embodiments, the PTGR1 inhibitor is a compound described herein.
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COMPOSITIONS FOR TREATING BREAST CANCER

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/457,709, filed February 10, 2017, which is incorporated herein by reference in its entirety and for all purposes.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII FILE

[0002] The Sequence Listing written in file 052103-501001WO Sequence Listing_ST25.txt, created January 22, 2018, 4,768 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0003] This invention was made with government support under CA1 72667 awarded by the National Institutes of Health and under W81XWH-15-1-0050 awarded by the ARMY/MRMC. The government has certain rights in the invention.

BACKGROUND

[0004] In the United States, it is estimated that over 200,000 women will be diagnosed with breast cancer and nearly 40,000 women will die of breast cancer in 2016. Studies over the past decade have uncovered certain breast cancer cell-types, such as estrogen/progesterone/HER2 receptor (ER/PR/HER2)-negative (triple-negative) breast cancers (TNBCs) that show poor prognosis and chemotherapy-resistance within breast tumors. Eliminating these breast cancer types are critical in reducing the mortality associated with breast cancer. Disclosed herein, inter alia, are solutions to these and other problems in the art.

BRIEF SUMMARY

[0005] In an aspect is provided a compound having the formula:

\[(R^1)_{z1} \equiv \equiv (R^2)_{z2}\]

(I).
R is independently halogen, -CXS, -CHX, -CH2X, -OCX, -OCH2X, -OCHX, -CN, -SO\textsubscript{NR\textsubscript{A}}, -SO\textsubscript{NR\textsubscript{B}}, ... In an aspect is provided a PTGR1 inhibitor. In embodiments, the PTGR1 inhibitor is a compound described herein.

heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R\textsubscript{1} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol z\textsubscript{1} is an integer from 0 to 5. R\textsubscript{2} is independently halogen, -CX, -CHX, -CH\textsubscript{2}X, -OCX, -CX, -CN, -SO\textsubscript{NR\textsubscript{A}}, -SO\textsubscript{NR\textsubscript{B}}, ... In two adjacent R\textsubscript{2} substituents may optionally be joined to form a substituted or unsubstituted heteroaryl; two adjacent R\textsubscript{1} substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heteroaryl. The symbol z\textsubscript{2} is an integer from 0 to 5. Each R\textsubscript{1}, R\textsubscript{1b}, R\textsubscript{1c}, R\textsubscript{1d} is independently hydrogen, -CX, -CN, -COOH, -CONH\textsubscript{2}, -CHX, -CH\textsubscript{2}X, substituted or unsubstituted alky, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl; R\textsubscript{1a} and R\textsubscript{1b} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\textsubscript{2a} and R\textsubscript{2b} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each X, X\textsubscript{1}, and X\textsubscript{2} is independently -F, -Cl, -Br, or -I. The symbols n1 and n2 are independently an integer from 0 to 4. The symbols m1, m2, vl, and v2 are independently an integer from 1 to 2.

In an aspect is provided a PTGR1 inhibitor. In embodiments, the PTGR1 inhibitor is a compound described herein.
[0008] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a PTGRI inhibitor. In embodiments, the PTGRI inhibitor is a compound described herein.

[0009] In an aspect is provided a method of treating triple negative breast cancer, the method including administering to a subject in need thereof an effective amount of a PTGRI inhibitor. In embodiments, the PTGRI inhibitor is a compound described herein.

[0010] In an aspect is provided a method of treating cancer including administering to a subject in need thereof an effective amount of a compound described herein.

[0011] In an aspect is provided a method of treating a disease associated with PTGRI activity including administering to a subject in need thereof an effective amount of a PTGRI inhibitor.

[0012] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a PTGRI inhibitor.

[0013] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a compound described herein.

[0014] In an aspect is provided a PTGRI protein covalently bonded to a PTGRI inhibitor (a PTGRI protein-PTGRI inhibitor complex).

[0015] In an aspect is provided a PTGRI protein covalently bonded to a compound described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIGS. 1A-1C. Screening a library of drugs and drug candidates in TNBC cells. (FIGS. 1A,1B) A library of drugs and drug candidates were screened in 231MFP and HCC38 TNBC cell lines for impairments in serum-free cell survival. (FIG. 1C) Cell survival of drugs and drug candidates that reproducibly and significantly impaired 231MFP, HCC38, and HCC70 viability by >50 %. Cells in (FIGS. 1A-1C) were treated with DMSO vehicle or compound (10 µM) in serum-free media and cell survival was assessed 48 h after treatment by Hoescht staining. Data in (A,B) are from an n=1 screen. Data in (FIG. 1C) are presented as mean ± sem, n=3/group and all data in (FIG. 1C) showed significant (p<0.05) cell survival impairments compared to DMSO-treated controls. FIG. 1A x-axis (left to right):

Mitoxantrone HCI, ES 1-09, TIC 10, Romidepsin (FK228, Depsipeptide), Crizotinib (PF-
02341066), Mitoxantrone, AT9283, MI-773 (SAR405838), SH -4-54, NU7441 (KU-57788), INH6, INH1, MLN2238, MLN9708, Daunorubicin HCl (Daunomycin HCl), YM155, WP1 130, TG101348 (SAR302503), Idarubicin HCl, JNK-IN-8, GW4064, Doxorubicin (Adriamycin), GSK461364, PTC-209 HBr, RG-71 12, SRT1720, Dacomitinib (PF299804,PF-00299804), Torin 2, Licochalcone A, Imatinib (Gleevec), BI6727 (Volasertib), PF-3758309, MLN8237 (Alisertib), Danusertib (PHA-739358), Bafetinib (INNO-406), ARQ 621, Ispinesib (SB-715992), Axitinib, SB939 (Pracinostat), TMP269, Quercetin (Sophoretin), PD173074, Dovitinib (TKI258) Lactate, HS-173, Triciribine (Triciribine phosphate), Fingolimod (FTY720), YM201636, Cabozantinib malate (XL184), AZD9291, CUDC-101, GSK2126458, PCI-24781, LY3009120, BI-847325, Refametinib (RDEA19, Bay 86-9766), Picropodophyllin (PPP), PD 0332991 (Palbociclib) HCl, SU1 1274, AZ 3146, HJC0350, LDC000067, B1 2536, BIBF1 120 (Vargatef), MK-2206 2HCI, Masitinib (ABIO10), Simvastatin (Zocor), SB590885, ABT-751, Vatalanib 2HCI (PTK787), G-749, Belinostat (PXD101), Tartrate, GS1904529A, GSK923295, HO-3867, GS K2334470, Motesanib Diphosphate (AMG-706), Tie2 kinase inhibitor, TNJ-26481585, Cyt387, Linsitinib (OSI-906), Nocodazole, BMS-536924, AZD7762, Tivozanib (AV-951), WZ4002, GS K2606414, CB-839, CDC-0879, AZD6244 (Selumetinib), AT7519, GSK1 120212 (Trametinib), Evista (Raloxifene HCl), Sorafenib (Nexavar), Ezetimibe (Zetia), 6H05, EW-7197, AEE788 (NVP-AEE788), Y-27632 2HCI, Estradiol, CW069, SB 216763, Pexmetinib (ARRY-614), Sotrastaurin (AEB071), BX-795, WAY-362450, PF-562271, LY294002, INJ-38877605, Dalcetrapib (JTT-705), Triptolide, PND-1 186 (VS-4718), XMD8-92, Cyclosporin A (Cyclosporine A), CH5132799, AZ5104, Brivanib (BMS-540215), SGI-1776 free base, Pilaralisib (XL147), ZSTK474, Fluvasatin sodium (Lewd), PF-06463922, MI-2 (MALT1 inhibitor), Topotecan HCl, Tofacitinib (CP-690550, Tasocitinib), TNJ-7706621, Temsirolimus (Torisel), Aminoglutethimide (Cytadren), CYC1 16, TPCA-1, YH239-EE, 4SC-202, Maraviroc, KU-55933, AG14361, CH5 138303, AZD1208, Lapatinib Ditosylate (Tykerb), BIRB 796 (Dorapamipod), E7080 (Lenvatinib), Tubacin, Phosphoramidon Disodium Salt, ABT-888 (Veliparib), Mycophenolate mofetil (CellCopt), RG108,
Pioglitazone (Actos), Lenalidomide (Revlimid), R04929097, Gossypol, VER-50589, AMG 900, PF 573228, Lonidamine, PF-04217903, Z-VAD-FMK, BMS-599626 (AC480),
Toremifene Citrate (Fareston, Acapodene), Mifepstone (Mifeprax), Gefitinib (Iressa),
Ponalidomide, Afuresertib (GSK21 10183), WIKI4, Tipifarnib (Zarnestra), SGX-523, TW-37, BV-6, CHIR-99021 (CT99021) HCl, SB 203580, CEP33779, Vismodegib (GDC-0449),
MK-0752, Oltipraz, 2-Methoxyestradiol, Ifosfamide, Bexarotene, Medroxyprogesterone acetate, Santacruzamate A (CAY10683), AUY922 (NVP-AUY922), Hydroxyurea (Cytodrox), BKM120 (NVP-BKM120), Imatinib Mesylate, Ku-60019, GDC-0623, Endoxifen HCl, ODM-201, CPI-203, LDE225 (NVP-LDE225. Erismodegib), Flavopindol (Alvocidib) HCl, Tasquinimod, Flavopiridol (Alvocidib), U25584702 Tosylate, IWP-2,
Afatinib (BIBW2992), Quizzartinib (AC220), Adrucil (Fluorouracil), Epithilone A, A-769662, PI-1840, Doxercalciferol (Hectorol), CI-1040 (PD 184352), BAY 73-17082, 73-17821), Mycophenolic (Mycophenolate), JNJ 26854165 (Serdemetan), Ro3280, K-

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Ras(G12C) inhibitor 9, 3-Methyladenine, INK 128 (MLN0128), Nutlin-3a, Dacarbazine (DTIC-Dome), Geldanamycin, P0173955, VS-5584 (SB2343), Decitabine, DCC-2036 (Rebastinib), SF1670, Vorinostat (SAHA), Busulfan (Myleran, Busulfex), TAME, Telatinib (BAY 57-9352), Olaparib (AZD2281), Teniposide (Vumon), ABT-737, Fludarabine (Fludara), OS 1-420, Irinotecan HCl Trihydrate (Campto), AT13148, Valproic acid sodium salt (Sodium valproate), Anagrelide HCl, CAL-101 (GS-1 101), 17-AAG (Tanespimycin), Xanthohumol, TAPI-1, P00325901, Triamcinolone Acetonide, S-Ruxolitinib, Voreloxin (SNS-595), VX-680 (MK-0457, Tozasertib), Hydrocortisone (Cortisol), Nutlin-3b, Bicalutamide (Casodex), Sirtinol, Zileuton, Capecitabine (Xeloda), 17-DMAGHZI (Alvespimycin), GSK650394, Megestrol Acetate, Everolimus (RAD001), PI-103, Allopurinol Sodium, Ruxolitinib (INCB018424), SB 525334, Floraflur, C.NX-2006, SNS-314 Mesylate, Bleomycin sulfate, Nelarabine (Arranon), Ostarine (MK-2866), Iniparib (BSI-201), Pelitinib (EKB-569), CX-6258 HCl, Dexamethasone acetate, Oxaliplatin (Eloxatin), Carmofur, Canagliflozin, Trichostatin A (TSA), Disulfiram (Antabuse), Aprepitant (MK-0869), PIK-75, Vandetanib (Zactima), Betapar (Meprednisone), IOX1, BTZ043 racemate, Isotretinoin, BIBR 1532, Elesclomol, Gemcitabine (Gemzar), PAC-1, PHA-793887, Mercaptopurine, Irinotecan, HSP990 (NVP-HSP990), Anastrozole, Raltitrexed (Tomudex), Deltarasin, PFK15, Temozolomide, Dexamethasone, Dimesna, Plinabulin (NPI-2358), and R05 126766 (CH5 126766). FIG. IB x-axis (left to right): AEE788 (NVP-AEE788), Vemurafenib (PLX4032), Gossypol, Mitoxantrone HCl, PHA-793887, SH-4-54, ESI-09, WP1 130, Doxorubicin (Adriamycin), PIK-93, G-749, B16727 (Volasfirtib), Pelitinib (EKB-569), Licochalcone A, Daunorubicin HCl (Daunomycin HCl), CX-6258 HCl, Mitoxantrone, Romidepsin (FK228, Depsipeptide), PF-3758209, RG-71 12, Torin 2, Xanthohumol, AZD9291, AZ5104, KX2-391, GSK650394, GW3965 HCl, BV-6, NIH6, Deltarasin, GS K2126458, Tretinoin (Aberela), Triptolide, BMS 794833, (-)-Epigallocatechin gallate, Lapatinib, PF-562271, BI-847325, TG101348 (SAR302503), Idarubicin HCl, YM201636, ABT-737, Plinabulin (NPI-2358), LY2874455, CUDC-101, Tubacin, DCC-2036 (Rebastinib), MLN9708, Tivozanib (AV-951), Crenolanib (CP-868596), Bexarotene, SNS-314 Mesylate, Vinorelbine Tartrate, AZD7762, NU7441 (KU-57788), MLN2238, Bortezomib (Velcade), Ponatinib (AP24534), Evista (Raloxisene HCl), Vincristine, G W4064, ABT-751, Ispinesib (SB-7 15992), ABT-263 (Navitoclax), Cyt387, Sorafenib (Nexavar), Tamoxifen Citrate (Nolvadex), Geldanamycin, GS K461364, HS-173, JNJ 26854165 (Seremetan), INK 128 (MLN0128), Flavopiridol (Alvocidib) HCl, PIK-75, BX-795, Cyclosporin A (Cyclosporine A), TW-37, BIBR 1532, Amuvatinib (MP-470),
Clofarabine, Cladribine, YM155, Teniposide (Vumon), Nmn.-9n7R, BKM120 (NVP-BKM120), Trichostatin A (TSA), Ganetespib (STA-9090), Belinostat (PXD101), JNJ-26481585, Voreloxin (SNS-595), CX-4945 (Silmitasertib), AT7519, BIIB021, Picropodophyllin (PPP), CYT997 (Lexibulin), Gemcitabine (Gemzar), PTC-209 HBr, Regorafenib (BAY 73-4506), SB939 (Pracinostat), Topotecan HCl, PD 173074, PCI-24781, XL765 (SAR245409), Tipifarnib (Zarnestra), AT7519 HCl, Cabozantinib (XL184), 4SC-202, INJ-7706621, PF 573228, FH535, CYC1 16, KU-60019, Azacitidine (Vidaza), Fludarabine (Fludara), Dovitinib (TKI258) Lactate, Obatoclax mesylate (GX15-070), AZD8055, Etoposide (VP-16), AT9283, Nocodazole, AZD1480, BMS-536924, Vorinostat (SAHA), Docetaxel (Taxotere), Ku-0063794, Mocetinostat (MGCD0103), Cediranib (AZD2171), 2-Methoxyestradiol, BI2536, Dacomitinib (PF299804,PF-00299804), WYE-354, HSP990 (NVP-HSP990), OS 1-930, SGI-1776 free base, PU-H71, Flouxuridine (Fludara), ARQ 621, INK Inhibitor IX, Toremifene Citrate (Fareston, Acatopene), VER-50589, Isotretinoin, Flavopiridol (Alvocidib), ARQ621, INK Inhibitor IX, Toremifene Citrate (Fareston, Acatopene), VER-50589, Isotretinoin, Flavopiridol (FTY720), Paclitaxel (Taxol), Nilotinib (AMN-107), Phloretin (Dihydronaringenin), Raltitrexed (Tomudex), GF109203X, CNX-2006, Rosiglitazone (Avandia), Epothilone B (EP0906), Quizartinib (AC220), Entinostat (MS-275, SNDX-275), HO-3867, LDC000067, Sunitinib Malate (Sutent), Rigosertib (ON-01910), SF-1670, Ro3280, Bafetinib (INNO-406), CH5138303, Fludarabine Phosphate (Fludara), SB52334, MI-773 (SAR405838), PAC-1, LY3009120, LY2603618 (IC-83), GSX2606414, AUY922 (NVP-AUY922), AZD6738, LY2228820, Simvastatin (Zocor), Adrucil (Flourouracil), SU1 1274, Bosutinib (SKI-606), Flavopiridol (Alvocidib), Dovitinib (TK1-258), 17-AAG (Tanespimycin), 17-DMAGHCI (Alvespimycin), TPCA-1, Quercetin (Sophoretin), SNS-032 (BMS-387032), Pilaralisib (XL147), K-Ras(G12C) inhibitor 9, Carmofur, BIRB 796 (Doramapimod), CI-1040 (PD184352), Abitrexate (Methotrexate), Vandetanib (Zactima), Afuresertib (GSK21 10183), Temozolomide, Mercaptopunne, Imatinib (Gleevec), VS-5584 (SB2343), Dasatinib (BMS-354825), CH5183284 (Debio-1347), PCI-32765 (lbrutinib), Aprepitant (MK-0869), Bleomycin sulfate, Endoxifen HCl, SB590885, TAK-733, ZSTK474, GSK1 120212 (Trametinib), PI-103, CH5132799, Irinotecan HCl Trihydrate (Campto), Refametinib (RDEA1 19, Bay 86-9766), PD173955, R406 (free base), CEP33779, PH A-665752, Pemaxetinib (ARRY-614), AXitinib, PD0325901, GDC-0623, Flutamide (Eulexin), CPI-203, NVP-BSK805 2HCl, XMD8-92, AZ628, Fluvasatin sodium (Lescol), Afatinib (BIBW2992), GDC-0941, Doxercalciferol (Hectorol), Danusertib (PHA-739358), VX-680 (MK-0457, Tozasertib), JNK-IN-8, Rucaparib (AG-014699, PF-
01367338), XL147, Irinotecan, MLN8237 (Alisertib), AMG 900, PF-3845, BIBF1 120
(Vargatef), Pazopanib, CHIR-00-21 (CT9021) HCl, Brivanib (BMS-540215), YH239-E E,
Azathioprine (Azasan, Imuran), Lapatinib Ditosylate (Tykerb), EW-7197, PND-1186 (VS-
4718), KU-55933, GSK922395, Crizotinib (PF-02341066), LY294002, Temsirolimus
(Torisel), AZD6244 (Selumetinib), GSK2334470, Rapamycin (Sirolimus), Barasertib
(AZD 1152-HQP A), SRT1720, PI-1840, Gefitinib (Iressa), MI-2 (MALT1 inhibitor),
Mifepristone (Mifeprax), Nutlin-3b, Nutiiin-3a, BMS-599626 (AC480), ML323, PD 0332991
(Palbociclib) HCl, AZD8186, WIK14, Sirtinol, PKF15, HJC0350, Lenalidomide (Revlimid),
INH1, Saracatinib (AZD0530), Dalcetrapib (JTT-705), AZ 3146, SB-3CT, 1NCB024360,
Olaparib (AZD2281), Everolimus (FiADO01), TAPI-1, Motesanib Diphasphate (AMG-706),
AZD 1208, RG108, Erlotinib HCl, GDC-0994, CW069, Canagliflozin, PF-06463922, S-
Ruxolitinib, AG14361, PH-797804, Tasquinimod, YO-01027, ABT-888 (Veliparib),
Lonidamine, Linifanib (ABT-869), ODM-201, MK-0752, Triciribine (Triciribine phosphate),
Oltipraz, Nutlin-3, Epothilone A, LY2584702 Tosylate, Santacruzamate A (CAY10683),
Linsitinib (OSI-906), SGX-523, Mycophenolate mofetil (CellCept), A-769662, Epacadostat
(INCB024360), 3-Methyladenine, PX-478 2HCl, SB 431542, Phosphoramidon Disodium
Salt, IWP-2, Imatin ih McmylAtA, GSK 1904529A, Anagrelide HCl, Ostarine (MK-2866),
CB-839, TIC10, Enzastaunn (LY3 17615), 'viatalanib nuns (PTK787), Flydroxyurea
(Cytodrox), PF-042 17903, BTZ043 racemate, InipArib (Fml-nl), Estradiol, Pioglitazone
(Actos), Z-VAD-F MK, Y-27632 2HCl, GS K690693, WAY-362450, Medroxyprogesterone
acetate, BAY 11-7082 (BAY 11-7821), WZ4002, Dexamethasone acetate, nhloroamb.ucil,
Masitinib (881010), AT13148, SB 216763, Sotastaurin (AEB071), Tofacitinib (C P-690550, 
Tasocitinib), Elasctmol, OSI-420, IOX1, Vismodegib (GDC-0449), ABC294640, MK -2208
2HC1, R05 126766 (CH5 126766), SR 203580, Dacarbazine (DTIC-Dome), Andarine (GTX-
007), XAV-939, BMS 777607, Oxiplatin (Eloxatin), GDC-0879, 6H05, Lumostine
(CeeNU), Decitabine, DMXAA (ASA404), LY2157299, PF-543, Letrozole, Ranolazine
(Ranexa), EX 527, Celecoxib, Megestrol Acetate, Febuxostat (Uloric), Mycophenolic
(Mycophenolate), Bendamustine, Thalidomide, Fulvestrant (Faslodex), Exemestane,
Nieralabine (Arranon), Caocitabine (Xeloda), Anastrozole, Dapagliflozin, Estrone,
Itraconazole (Sporanox), Bicalutamide (Casodex), Ezatimiba (Zeta), Valproic acid sodium
salt (Sodium valproate), Dimesna, Mesna (Uromitexan, Mesnex), Chrysophanic acid
(Chrysophanol), Betapar (Meprednise), Busulfan (Myleran, Busulfex), Prednisone
(Adasone), Allopurinol Sodium, Telatinib (BAY 57-9352), LDE225 (NVP-LDE225, 
Erismodegib), Hydrocortisone (Cortisol), Aminoglutethimide (Cytadren), Triamcinolone
Acetonide, Pomalidomide, Disulfiram (Antabuse), RO4929097, TMP269, MDV3100 (Enzalutamide), Cyclophosphamide monohydrate, Maraviroc, Zileuton, DAPT (GSI-IX), TAME, Dexamethasone, CAL-101 (GS-1 101), Zibotentan (ZD4054), Formestane, Ruxolitinib (INCBO 18424), Florafur, Altretamine (Hexalen), Streptozotocin (Zanosar), and Ifosfamide.

[0017] FIGS. 2A-2G. IsoTOP-ABPP analysis of Licochalcone A in TNBC cells. (FIG. 2A) Structure of Licochalcone A. (FIG. 2B) Competitive isoTOP-ABPP to map Licochalcone targets. Licochalcone A bears a Michael acceptor that is potentially cysteine-reactive. We mapped the cysteine-reactivity of Licochalcone A by pre-incubating Licochalcone A (10 μM) for 30 min in 231MFP breast cancer cell proteomes, prior to labeling with the cysteine-reactive iodoacetamide-alkyne (IAyne) probe (100 μM, 30 min). Probe labeled proteins were then tagged with an isotopically light (for control) or heavy (for Licochalcone A-treated) biotin-azide tag bearing a TEV protease recognition site by CuAAC. Control and treated proteomes were then mixed in a 1:1 ratio, probe labeled proteins were avidin-enriched and tryptically digested, probe-labeled tryptic peptides were avidin-enriched again, and released by TEV protease and analyzed by quantitative proteomic methods and light to heavy peptide ratios were quantified. (FIG. 2C) Competitive isoTOP-ABPP analysis of Licochalcone A cysteine-reactivity in 231MFP breast cancer cell proteomes. Light to heavy ratios of ~1 indicate peptides that were labeled by IAYne, but not bound by Licochalcone A. We designate light to heavy ratios of >10 as targets that were bound by Licochalcone A. The top target was C239 of PTGR1. Shown in this FIG. is also validation of PTGR1 as a target of Licochalcone A. Licochalcone A was pre-incubated with pure human PTGR1 protein followed by IAYne. Probe-labeled proteins conjugated to rhodamine-azide by CuAAC and analyzed by SDS/PAGE and in-gel fluorescence. (FIG. 2D) Crystal structure of PTGR1 showing C239 (shown in yellow) and NADP+ shown in ball and stick form. PDB structure used is 2Y05. (FIG. 2E) PTGR1 expression in shPTGR1 231MFP cells. PTGR1 was stably knocked down with three independent shRNA oligonucleotides and expression was determined by qPCR. (FIGS. 2F, 2G) Serum-free cell survival and proliferation in shPTGR1 231MFP cells. Cell survival and proliferation were assessed 48 h after seeding by Hoescht staining. Data in (FIGS. 2E-2G) are presented as mean ± sem, n=3-5/group. Significance is presented as *p<0.05 compared to shControl cells.

[0018] FIGS. 3A-3D. Metabolomic profiling of drug responses in TNBC cells. (FIG. 3A) Metabolomic profiling of 231MFP TNBC cells treated with the 20 compounds that impaired
TNBC cell survival. 231MFP cells were treated with DMSO vehicle or each compound (10 μM) for 6 h. Lipid levels were analyzed by single reaction monitoring (SRM)-based liquid chromatography-mass spectrometry (LC-MS/MS). Heatmap shows fold-changes in log (2) compared to vehicle-treated controls where red and blue designates increased and decreased levels, respectively. (FIG. 3B) C16:0 AC levels in 231MFP cells treated with each of the 20 compounds that impaired TNBC cell survival. Data is from experiment described in (FIG. 3A). (FIG. 3C) Cell survival in 231MFP cells. 231MFP cells were treated with DMSO control or deubiquitinase inhibitors PR619 and P5091 (10 μM) and serum-free cell survival was assessed 48 h after treatment by Hoescht staining. (FIG. 3D) AC levels in 231MFP cells treated with deubiquitinase inhibitors. Cells were treated with DMSO vehicle or inhibitors (10 μM) for 6 h and AC levels were determined by SRM-based LC-MS/MS. Data in (A) is from an n=5/group. Data in (FIGS. 3B-3D) are presented as mean ± sem, n=5/group. Significance is presented as *p<0.05 compared to vehicle-treated control cells. FIG. 3A y-axis (top to bottom): C16:0 FFA, C18:0 FFA, C18:1 FFA, C20:4 FFA, C16:0 MAG, C18:0 MAG, C16:0/C18:1 DAG, C1:6:0/C20:4 DAG, C18:0/C18:1 DAG, C1:8:0/C20:4 DAG,
C16:0/C16:0 TAG, C16:0/C18:1/C16:0 TAG, C16:0/C20:4/C16:0 TAG,
C18:0/C18:1/C18:0 TAG, C18:0/C20:4/C18:0 TAG, C16:0 AC, C18:0 AC, 06:0/08:1 PC, C16:0/C20:4 PC, 08:0/08:1 PC, C18:0/C20:4 PC, 06:0108:1 PE, C16:01C20:4 PE, 08:0/08:1 PE, C18:0/C20:4 PE, 06:0108:1 PS, C16:01C20:4 PS, 08:0/08:1 PS, C18:0/C20:4 PS, 06:0/08:1 PG, C1 6:0/C20:4 PG, 06:0/08:1 PA, 08:0/08:1 PA, 06:0/08:1 PI, C16:0/C20:4 PI, 08:0/08:1 PI, C18:0/C20:4 PI, 06:0 LPC, 08:0 LPC, C18:1 LPC, C20:4 LPC, 06:0 LPE, 08:0 LPE, C18:1 LPE, C20:4 LPE, 08:0 LPS, C18:1 LPS, C20:4 LPS, 08:0 LPI, C18:1 LPI, C20:4 LPI, 08:1/08:1/08:1/08:1 Cardiolipin, 06:0 NAE, 08:0 NAE, C18:1 NAE, C18:1

NAT, C18:0e MAGe, C18:0p MAGp, C16:0e/C2:0 MAGe, C18:0e/C2:0 MAGe, C16:0e/C18:1 PCe, C16:0e/C20:4 PCe, C16:0p/C20:4 PCp, C18:0e/C18:1 PCe, C18:0e/C20:4 PCe, C18:0p/C20:4 PCp, C16:0e/C18:1 PPe, C16:0e/C20:4 PPe, C16:0p/C20:4 PPe, C18:0e/C20:4 PPe, C18:0p/C20:4 PPe, C16:0e/C18:1 PSe, C18:0e/C18:1 PSe, C18:0e/C20:4 PSe, C16:0e/C20:4 PGe, C18:0e/C18:1 PGe, C18:0e/C20:4 PGe, C18:0e/C20:4 PGe, C18:0e/C20:4 PGe, C16:0e/C18:1 Pie, C18:0e/C20:4 Pie, C16:0e LPCe, C18:0e LPCe, C18:0p LPCp, C18:0e LPEe, C18:0p LPEp, Sphingosine, Sphinaganine, 06:0 Ceramide, 08:0 Ceramide, C20:4 Ceramide, 06:0 SM, 08:0 SM, C18:1 SM, C20:4 SM, 08:1/08:0
lactosylceramide, C18:1/C16:0 ceramide-1-P, 08:0106:0 ceramide-1-P, cholesteryl ester, and cholesterol.

[0019] FIGS. 4A-4D. The role of AC in deubiquitinase inhibitor-mediated cell survival impairments in TNBC cells. (FIG. 4A) 231MFP cell survival upon treatment of cells with AC. Cells were treated with AC and serum-free cell survival was assessed 48 h after treatment by Hoescht staining. (FIG. 4B) 231MFP cell survival upon treatment of cells with AC and deubiquitinase inhibitor WP1 130. Cells were co-treated with water or 06:0 AC (1 µM) at a concentration that does not impair viability when treated alone and DMSO or WP1 130 and cell survival was assessed 48 h treatment by Hoescht staining. (FIG. 4C and 4D) Oxygen consumption rates in cells treated with DMSO vehicle or AC or WP1 130. Compounds were treated at cycle 6 (injection from port B). Oxygen consumption was measured using a Seahorse XF24 Analyzer. Data in (FIGS. 4A-4C) are presented as mean ± sem, n=3-5/group. Significance is presented as *p<0.05 compared to vehicle-treated control cells.

[0020] FIG. 5. Licochalcone A dose-response in 231MFP cells. 231MFP cells were treated with DMSO vehicle or Licochalcone A and serum-free cell survival was assessed 48 h post-treatment by Hoescht staining. Survival values are expressed in relation to vehicle-treated controls. Data are presented as mean ± sem, n=3/group.

[0021] FIG. 6. Levels of representative lipids. Levels of representative lipids from 231MFP TNBC cells treated with the 20 compounds that impaired TNBC cell survival. These data are taken from FIG. 3A. 231MFP cells were treated with DMSO vehicle or each compound (10 µM) for 6 h. Lipid levels were analyzed by single reaction monitoring (SRM)-based liquid chromatography-mass spectrometry (LC-MS/MS). Data are presented as mean ± sem, n=5/group.

[0022] FIGS. 7A-7C. Characterizing the role of LPE in TNBC cell survival. (FIG. 7A) 231MFP cell survival upon treatment of cells with LPE. Cells were treated with LPE and serum-free cell survival was assessed 48 h after treatment by Hoescht staining. (FIG. 7B) 231MFP cell survival upon treatment of cells with LPE and proteosome inhibitor MLN9708. Cells were co-treated with 2:1 chloroform:methanol or 06:0 LPE (1 µM) at a concentration that does not impair viability when treated alone and DMSO or MLN9708 and cell survival was assessed 48 h treatment by Hoescht staining. (FIG. 7C) Oxygen consumption rates in cells treated with 2:1 chloroform:methanol vehicle or LPE or palmitate. Lipids were treated at
cycle 6. Oxygen consumption was measured using a Seahorse XF24 Analyzer. Data in (FIGS. 7A-7C) are presented as mean ± sem, n=3-5/group. Significance is presented as *p<0.05 compared to vehicle-treated control cells.

FIG. 8. Model of licochalcone A binding site on PTGR1.

DETAILED DESCRIPTION

I. Definitions

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH2O- is equivalent to -OCH2-.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C1-C10 means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated. An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds.

The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -
CH2CH2CH2CH2-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0028] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, or S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH2-CH2-O-CH3, -CH2-CH2-NH-CH3, -CH2-CH2-N(CH3)-CH3, -CH2-S-CH2-CH3, -CH2-CH2, -S(ο)-CH3, -CH2-CH2-S(ο)2-CH3, -CH=CH-ο-CH3, -Si(CH3)3, -CH2-CH=N-OCH3, -CH=CH-N(CH3)-CH3, -ο-CH3, -ο-CH2-CH3, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH2-NH-OCH3 and -CH2-ο-Si(CH3)3. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0029] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH2-CH2-S-CH2-CH2- and -CH2-CH2-CH2-NH-CH2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(ο)2R'- represents both -C(ο)2R' and -R'C(ο)2-. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(ο)R', -C(ο)NR', -NR'R", -OR, -SR, and/or -SO2R. Where
"heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0030] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0031] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(Ci-C4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0032] The term "acyl" means, unless otherwise stated, -C(0)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0033] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom
such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thieryl, pyridyl, pyrimidyl, benzothiazolyl, benzooxazolyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spiroyclic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0035] The symbol “~~~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0036] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0037] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:

\[
\begin{array}{c}
\text{6} \\
\text{2, 3, 4}
\end{array}
\]

[0038] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₂, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -N₂, -SH, -S₂CH₃, -S₂H₂, -OS₂H₂, -S₂NH₂, -ONH₂, -S₂H₃, substituted or unsubstituted C₁-C₅ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0039] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0040] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl,
heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of
groups selected from, but not limited to, -OR, =OR, =NR, =N-OR, -NR'R", -SR, -halogen, -
SiRR'R", -OC(0)R, -C(0)R, -C0₂R, -CONR'R", -OC(0)NR'R", -NR"C(0)R, -NR'-
C(0)NR'R", -NR'C(0)₂R, -NR-C(NR'R"R")=NR"", -NR-C(NR'R")=NR"", -S(0)R, -
S(0)₂R, -S(0)₂NR'R", -NR S0₂R, -NRRNR"R", -ONR"R", -NRC(0)NR"R", -NR'C(0)NR"R", -NOR", in a number ranging from zero to
(2m'+l), where m' is the total number of carbon atoms in such radical. R, R', R", and R'''
each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl,
substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups,
and arylalkyl groups. When a compound described herein includes more than one R group, for
example, each of the R groups is independently selected as are each R', R", R', and R''' group
when more than one of these groups is present. When R and R" are attached to the same
nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-
membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-
morpholinyl. From the above discussion of substituents, one of skill in the art will understand
that the term "alkyl" is meant to include groups including carbon atoms bound to groups
other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -
-\text{C(0)CH}_₃, -\text{C(0)CF}_₃, -\text{C(0)CH}_₂OCH}_₃, and the like).

[0041] Similar to the substituents described for the alkyl radical, substituents for the aryl
and heteroaryl groups are varied and are selected from, for example: -OR, -NR'R", -SR, -
halogen, -SiRR'R", -OC(0)R, -C(0)R, -C₀₂R, -CONR'R", -OC(0)NR'R", -NR"C(0)R, -
NR'-C(0)NR'R", -NR'C(0)₂R, -NR-C(NR'R"R")=NR"", -NR-C(NR'R")=NR"", -S(0)R, -
S(0)₂R, -S(0)₂NR'R", -NR S0₂R, -NRRNR"R", -ONR"R", -NRC(0)NR"R", -NR'C(0)NR"R", -NOR", in a number ranging from zero to the total number
of open valences on the aromatic ring system; and where R, R', R", and R''' are preferably
independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
heteroaryl. When a compound described herein includes more than one R group, for example,
each of the R groups is independently selected as are each R, R", R", and R"" groups when more than one of these groups is present.

[0042] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0043] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic
structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula \(-T-C(0)-(CRR')_q-U_1\), wherein T and U are independently \(-NR_1-\), \(-O-\), \(-S(O)-\), or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula \(-A-(CH_2)_r-B_1\), wherein A and B are independently \(-CRR'^s-X'^r\), \(-C(R'R'')_s-\), \(-NR'_1-\), \(-S(O)-\), \(-S(0)-\), \(-S(0)_2-\), or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula \(-C(R'R'')_s-X'^r\), \(-C(R'R'')_s-\), \(-NR'_1-\), \(-S(O)-\), \(-S(0)-\), \(-S(0)_2-\), or \(-S(0)_3-\). The substituents R, R', R", and R" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A "substituent group," as used herein, means a group selected from the following moieties: (A) oxo, halogen, \(-CCl_3\), \(-CBr_3\), \(-CF_3\), \(-Cl_3\), CN, \(-OH\), \(-NH_2\), \(-COOH\), \(-CONH_2\), \(-N0_2\), \(-SH\), \(-SO_2H\), \(-S\), \(-NH_2\), \(-NH\), \(-NO\), \(-NHHC\), \(-NHCC\), \(-OC\), or \(-OCC\).

unsubstituted alkyl (e.g., C1-C4 alkyl, C5-C6 alkyl, or C7-C10 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C3-C8 cycloalkyl, C6-C14 cycloalkyl, or C5-C6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C6-C10 aryl, C10 aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and
(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo,
halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃-CN, -OH, -NH₂, -COOH, -CONH₂, -N0₂, -SH, -S0₂H, -S
0₄H, -S0₂NH₂, -NHNH₂, -ONH₂, -NHC(0)NH₂, -NHC(0)NH₂, -NHS0₂H,
-NHC(0)H, -NHC(0)OH, -NH₂OH, -OCCb, -OCF₃, -OCBr₃, -OCI₃, -OCHCl₂, -OCHBr₂, -OC
HI₂, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl),
unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or
2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₅-C₆
cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered
heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl),
unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5
to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least
one substituent selected from:

(a) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃-CN, -OH, -NH₂, -COOH, -CONH₂, -N0₂, -SH,
-S0₂H, -SO₄H, -S0₂NH₂, -NH₂NH₂, -ONH₂, -NHC(0)NH₂, -NHC(0)NH₂, -NHS0₂H,
-NHSO₂H, -NHC(0)O, -NHOH, -OCCb, -OCF₃, -OCCBr₃, -OCI₃, -OCHCl₂, -O
CHBr₂, -OCH₂, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl),
unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or
2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₅-C₆
cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered
heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl),
unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5
to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least
one substituent selected from: oxo,
halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃-CN, -OH, -NH₂, -COOH, -CONH₂, -N0₂, -SH, -S0₂H,
-S0₄H, -S0₂NH₂, -NH₂NH₂, -ONH₂, -NHC(0)NH₂, -NHC(0)NH₂, -NHS0₂H,
-NHC(0)H, -NHC(0)O, -NHOH, -OCCb, -OCF₃, -OCCBr₃, -OCI₃, -OCHCl₂, -O
CHBr₂, -OCH₂, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl),
unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or
2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C3-C8 cycloalkyl, C3-C6 cycloalkyl, or C5-C6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C6-C10 aryl, C10 aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0047] A "size-limited substituent" or a "size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C1-C20 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0048] A "lower substituent" or a "lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C1-C6 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0049] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.
In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C1-C20 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkyylene is a substituted or unsubstituted C1-C20 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C3-C8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C6-C10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted Ci-Cs alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C3-C7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C6-C10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.
In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroarylene, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, wherein if the substituted moiety is substituted with a plurality of substituent groups, each substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of substituent groups, each substituent group is different.

In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroarylene, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one size-limited substituent group, wherein if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group is different.

In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroarylene, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one lower substituent group, wherein if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroarylene, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent
groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group is different.

[0056] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synths or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0057] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0058] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0059] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0060] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.
[0061] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{12}$C- or $^{14}$C-enriched carbon are within the scope of this invention.

[0062] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^3$H), iodine-125 ($^{125}$I), or carbon-14 ($^{14}$C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0063] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0064] "Analog," or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0065] The terms "a" or "an," as used herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C1-C20 alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C1-C20 alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0066] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with
at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple $R^{13}$ substituents are present, each $R^{13}$ substituent may be distinguished as $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc., wherein each of $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc. is defined within the scope of the definition of $R^{13}$ and optionally differently.

[0067] A "covalent cysteine modifier moiety" as used herein refers to a substituent that is capable of reacting with the sulfhydryl functional group of a cysteine amino acid (e.g. cysteine corresponding to C239 of the human prostaglandin reductase 1 (PTGR1)) to form a covalent bond. Thus, the covalent cysteine modifier moiety is typically electrophilic (e.g., an electrophilic group).

[0068] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0069] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic,
monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0070] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, propionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0071] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0072] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted in vivo after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0073] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain
compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

"Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

A "prostaglandin reductase 1 inhibitor" and "PTGRI inhibitor" is a substance (e.g., oligonucleotide, composition, protein, or compound) that negatively affects (e.g. decreases) the activity or function of PTGRI relative to the activity or function of PTGRI in the absence of the inhibitor (e.g., wherein the PTGRI inhibitor binds PTGRI). A "prostaglandin reductase 1 inhibitor compound" or "PTGRI inhibitor compound" refers to a compound (e.g. a compound described herein) that reduces the activity of PTGRI when compared to a control, such as absence of the compound or a compound with known inactivity.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in
which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0078] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (e.g. non-native or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, e.g., in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed in vitro or in vivo from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0079] An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. For example, a selected residue in a selected protein corresponds to C239 of the human prostaglandin reductase 1 (PTGR1) when the selected residue occupies the same essential spatial or other structural relationship as C239 in human prostaglandin reductase 1 (PTGR1), for example in SEQ ID NO:1. In some embodiments, where a selected protein is aligned for maximum homology with the human PTGR1 protein (e.g., SEQ ID NO: 1), the position in the aligned selected protein aligning with C239 is said to correspond to C239. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the human PTGR1 protein (e.g., SEQ ID NO: 1) and the overall structures compared. In this case, an amino acid that occupies the same essential position as C239 in the structural model is said to correspond to the C239 residue.

[0080] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.
The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

As defined herein, the term "activation", "activate", "activating", "activator" and the like in reference to a protein-inhibitor interaction means positively affecting (e.g. increasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the activator. In embodiments activation means positively affecting (e.g. increasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the activator. The terms may reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease. Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein associated with a disease (e.g., a protein which is decreased in a disease relative to a non-diseased control). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein.

As defined herein, the term "inhibition", "inhibitor", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction in activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction in activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).
The terms "prostaglandin reductase 1" and "PTGR1" and "LTB4DH" refer to a protein (including homologs, isoforms, and functional fragments thereof) with PTGR1 activity. The protein is involved in the inactivation of the chemotactic factor, leukotriene B4. The protein specifically catalyzes the NADP+ dependent conversion of leukotriene B4 to 12-oxo-leukotriene B4. The term includes any recombinant or naturally-occurring form of PTGR1 or variants thereof that maintain PTGR1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype PTGR1). In embodiments, the PTGR1 protein encoded by the PTGR1 gene has the amino acid sequence set forth in or corresponding to Entrez 22949, UniProt Q14914 or RefSeq (protein)

NP_001139580. In embodiments, the PTGR1 gene has the nucleic acid sequence set forth in RefSeq (mRNA) NM_001146108. In embodiments, the amino acid sequence or nucleic acid sequence is the sequence known at the time of filing of the present application. In embodiments, the sequence corresponds to NP_001139580.1. In embodiments, the sequence corresponds to NM_001146108.1. In embodiments, the PTGR1 is a human PTGR1, such as a human cancer causing PTGR1. In embodiments, the PTGR1 protein encoded by the PTGR1 gene has the amino acid sequence:

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MVRTKTWTLKKHFGYPTNSDFELKTAELPPKLNGEVLLHEALFLTVDPYMRVAAKRLKEG
DTMGQQVAKWESKVALPKGTIVLASPGWTTHSISDGKDLLEKLEWPDTEPLDSLALG
TVGMGMLTAYFGLLEEICVGKGETVMANAAAGAVSWSQAIKLKGCWGVAGVSDEKVA
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(SEQ ID NO:1)

The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. The disease may be stroke. The disease may be an inflammatory disease. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including
hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma.

[0087] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0088] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocyticem leukemia, basophilic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia,

[0089] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leulosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocyte sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0090] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0091] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar

[0092] The term "triple negative breast cancer" and "TNBC" is used in accordance with their plain ordinary meaning in oncology and refers to a breast cancer which does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu. In embodiments, TNBC cells overexpress epidermal growth factor receptor (EGFR) or transmembrane glycoprotein NMB (GPNMB). TNBC may be correlated with germline mutations within the BRCA1 and BRCA2 genes.
The terms "treating", or "treatment" refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing. In embodiments, the treating or treatment is no prophylactic treatment.

"Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

A "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme.
relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0096] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0097] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0098] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0099] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional,
intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal) compatible with the preparation. Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

[0100] "Co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0101] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0102] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the
activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0103] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a PTGRI associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with PTGRI (e.g. cancer). A PTGRI modulator is a compound that increases or decreases the activity or function or level of activity or level of function of PTGRI.

[0104] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule.

[0105] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, a cancer associated with PTGRI activity, PTGRI associated cancer, PTGRI associated disease) means that the disease (e.g. cancer) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a cancer associated with PTGRI activity or function may be a cancer that results (entirely or partially) from aberrant PTGRI function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or a cancer wherein a particular symptom of the disease is caused (entirely or partially) by aberrant PTGRI activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a cancer associated with PTGRI activity or function or a PTGRI associated cancer, may be treated with a PTGRI modulator or PTGRI inhibitor, in the instance where PTGRI activity or function (e.g. signaling pathway activity) causes the cancer.

[0106] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-disease-associated samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by
administering a compound or using a method as described herein), results in reduction of the
disease or one or more disease symptoms.

[0107] The term "signaling pathway" as used herein refers to a series of interactions
between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small
molecules, ions, lipids) that conveys a change in one component to one or more other
components, which in turn may convey a change to additional components, which is
optionally propagated to other signaling pathway components. For example, binding of a
PTGRI protein with a compound as described herein may reduce the interactions between the
PTGRI protein and downstream effectors or signaling pathway components, resulting in
changes in cell growth, proliferation, or survival.

[0108] The term "electrophilic group" is used in accordance with its plain ordinary
meaning and refers to a chemical group that is electrophilic. In embodiments, the
electrophilic group is an "electrophilic chemical moiety", which is used in accordance with
its plain ordinary chemical meaning and refers to a monovalent chemical group that is
electrophilic. In embodiments, the electrophilic group is a covalent cysteine modifier moiety.
In embodiments, the electrophilic group is divalent. In embodiments, the electrophilic group
is . In embodiments, the reacted electrophilic group is .

[0109] The term "nucleophilic chemical group" is used in accordance with its plain
ordinary chemical meaning and refers to a chemical group (e.g., monovalent chemical group)
that is nucleophilic.

[0110] "Nucleic acid" refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides)
and polymers thereof in either single-, double- or multiple-stranded form, or complements
thereof. The terms "polynucleotide," "oligonucleotide," "oligo" or the like refer, in the usual
and customary sense, to a linear sequence of nucleotides. The term "nucleotide" refers, in the
usual and customary sense, to a single unit of a polynucleotide, i.e., a monomer. Nucleotides
can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of
polynucleotides contemplated herein include single and double stranded DNA, single and
double stranded RNA, and hybrid molecules having mixtures of single and double stranded
DNA and RNA. Examples of nucleic acid, e.g. polynucleotides contemplated herein include
any types of RNA, e.g. mRNA, siRNA, miRNA, and guide RNA and any types of DNA,
genomic DNA, plasmid DNA, and minicircle DNA, and any fragments thereof. The term
"duplex" in the context of polynucleotides refers, in the usual and customary sense, to double strandedness. Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, e.g., such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0111] Nucleic acids, including e.g., nucleic acids with a phosphothioate backbone, can include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, e.g., a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an amino acid reactive moiety that reacts with an amino acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

[0112] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphodiester derivatives including, e.g., phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate having double bonded sulfur replacing oxygen in the phosphate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see Eckstein, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, Oxford University Press) as well as modifications to the nucleotide bases such as in 5-methyl cytidine or pseudouridine; and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (e.g. phosphorodiimidate morpholino oligos or locked nucleic acids (LNA) as known in the art), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, CARBOHYDRATE MODIFICATIONS IN ANTISENSE RESEARCH, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made;
alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0113] Nucleic acids can include nonspecific sequences. As used herein, the term "nonspecific sequence" refers to a nucleic acid sequence that contains a series of residues that are not designed to be complementary to or are only partially complementary to any other nucleic acid sequence. By way of example, a nonspecific nucleic acid sequence is a sequence of nucleic acid residues that does not function as an inhibitory nucleic acid when contacted with a cell or organism.

[0114] An "antisense nucleic acid" as referred to herein is a nucleic acid (e.g., DNA or RNA molecule) that is complementary to at least a portion of a specific target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1) and is capable of reducing transcription of the target nucleic acid (e.g. mRNA from DNA), reducing the translation of the target nucleic acid (e.g. mRNA), altering transcript splicing (e.g. single stranded morpholino oligo), or interfering with the endogenous activity of the target nucleic acid. See, e.g., Weintraub, Scientific American, 262:40 (1990). Typically, synthetic antisense nucleic acids (e.g. oligonucleotides) are generally between 15 and 25 bases in length. Thus, antisense nucleic acids are capable of hybridizing to (e.g. selectively hybridizing to) a target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1). In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g. a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1) in vitro. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g. a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1) in a cell. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g. a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1) in an organism. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g. a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1)
under physiological conditions. Antisense nucleic acids may comprise naturally occurring nucleotides or modified nucleotides such as, e.g., phosphorothioate, methylphosphonate, and -anomeric sugar-phosphate, backbonemodified nucleotides.

[0046] In the cell, the antisense nucleic acids hybridize to the corresponding RNA (e.g., a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO:1) forming a double-stranded molecule. The antisense nucleic acids interfere with the endogenous behavior of the RNA (e.g., a nucleic acid coding for one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO:1) and inhibit its function relative to the absence of the antisense nucleic acid. Furthermore, the double-stranded molecule may be degraded via the RNAi pathway. The use of antisense methods to inhibit the in vitro translation of genes is well known in the art (Marcus-Sakura, Anal. Biochem., 172:289, (1988)). Further, antisense molecules which bind directly to the DNA may be used. Antisense nucleic acids may be single or double stranded nucleic acids. Non-limiting examples of antisense nucleic acids include siRNAs (including their derivatives or pre-cursors, such as nucleotide analogs), short hairpin RNAs (shRNA), micro RNAs (miRNA), saRNAs (small activating RNAs) and small nucleolar RNAs (snoRNA) or certain of their derivatives or pre-cursors.

[0092] The term "complement," as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanidine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement
of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[01 15] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[01 16] The term "antibody" refers to a polypeptide encoded by an immunoglobulin gene or functional fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

[01 17] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms "variable heavy chain," "VH" or "VH" refer to the variable region of an immunoglobulin heavy chain, including an Fv, scFv, dsFv or Fab; while the terms "variable light chain," "VL" or "VL" refer to the variable region of an immunoglobulin light chain, including of an Fv, scFv, dsFv or Fab.

[01 18] Examples of antibody functional fragments include, but are not limited to, complete antibody molecules, antibody fragments, such as Fv, single chain Fv (scFv), complementarity determining regions (CDRs), VL (light chain variable region), VH (heavy chain variable region), Fab, F(ab)2' and any combination of those or any other functional portion of an immunoglobulin peptide capable of binding to target antigen (see, e.g., FUNDAMENTAL IMMUNOLOGY (Paul ed., 4th ed. 2001). As appreciated by one of skill in the art, various antibody fragments can be obtained by a variety of methods, for example, digestion of an intact antibody with an enzyme, such as pepsin; or de novo synthesis. Antibody fragments

[0119] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue 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.

[0120] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (see, e.g., NCBI web site http://www.ncbi.nlm.nih.gov/BLAST/ or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is
at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0121] The term "irreversible covalent bond" is used in accordance with its plain ordinary meaning in the art and refers to the resulting association between atoms or molecules of (e.g., electrophilic chemical moiety (an electrophilic group such as a covalent cysteine modifier moiety) and nucleophilic moiety) wherein the probability of dissociation is low. In embodiments, the irreversible covalent bond does not easily dissociate under normal biological conditions. In embodiments, the irreversible covalent bond is formed through a chemical reaction between two species (e.g., electrophilic chemical moiety and nucleophilic moiety).

[0122] "Anti-cancer agent" and "anticancer agent" are used in accordance with their plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEKI, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD3 18088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, meclorothamine, uramustine, thiopeta, nitrosoureas, nitrogen mustards (e.g., meclorothamine, cyclophosphamide, chlorambucil, mephalan), ethylenimine and methylmelamines (e.g., hexamethylemelamine, thiopeta), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitine, semustine, streptozocin), triazenes (decarbazine), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, Adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based
compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracyclines (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all-trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminoolevulinic acid; amrubin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropririmine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambeisidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ofosfate; cytoytic factor; cytostatin; dacliximab; decitabine; dehydrodideemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl
spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; efornithine; elemene; emitefur; 
epirubicin; epiristeride; estramustine analogue; estrogen agonists; estrogen antagonists; 
etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; 
finasteride; flavopiridol; flezelaistine; fluasterone; fludarabine; fluorodaunorunicin 
hydrochloride; forfenimex; forustane; fostriecin; fotemustine; gadolinium texaphyrin; 
gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione 
inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; 
idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; 
imunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon 
agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; 
isogladine; isobenzazole; isohomohalicondrin B; itaseteron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide;leinamycin;lenograstim; lentinan sulfate; leptolstatin; letrozole; 
leukemia inhibiting factor; leukocyte alpha interferon; 
leuprolide+estrogen+progesterone; leuprolelin; levamisole; liarozole; linear polyamine 
analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lobramicine; lometrexol; lonidamine; losoxantrone; lovastatin;loxoridine; 
lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; 
menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; 
mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; 
mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; 
mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic 
gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple 
drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer 
agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-
substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterin; 
nartogрастim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; 
nisamycin; nitric oxide modulators; nitrooxide antioxidant; nitrullyn; 06-benzylguanine; 
octreotide; okicenone; oligonucleotides; onapristone; ondasetron; ondansetron; oracin; oral 
cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; 
palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; 
pegasparagase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; 
perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors;
picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B 1; ruboxy; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifien methodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfir; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoeitin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetylsiamine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vaperotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoteron; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclorubicin; acodazole hydrochloride; acronine; adozeleisin; aldesleukin; altretamine; ambomycin; amantanone acetate; aminogluthethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin
hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexoraplatin; dezaquamine; dezaquamine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflorenithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL-sub.2); interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-lb; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; pelymycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; roglitimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vaperotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980),
Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-3 10705), 21-hydroxyepothilone D (i.e. Desoxypeothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-1 12378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DFME), DDE-3 13 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemisterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetone, T-138026 (Tularik), Monsatrol, Inancine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-1 15781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaesotide, Caribaesol, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-1 10, trifluoroacetate salt) (Wyeth),
D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, iraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-onyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY3334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, petitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0123] The term "prostaglandin reductase 1 (PTGR1) activity" as used herein refers to the biological activity of the protein. Prostaglandin reductase 1 (PTGR1) activity may be quantified by measuring the rate of cell division, cell survival, or cell migration, measuring mitochondrial respiration, measuring the levels or activity of 15-keto-prostaglandin relative to a control (e.g., the absence of the inhibitor), measuring the levels or activity of leukotriene B4 relative to a control (e.g., the absence of the inhibitor), measuring the level of activity of carnitine palmitoyltransferase 1 (CPT1) (e.g. compared to a control such as absence of the composition), or quantifying the binding of NADP+ to PTGR1. In embodiments, the PTGR1 activity is reducing the level of 15-keto-prostaglandin or leukotriene B4. In embodiments, the PTGR1 activity is reducing the level of 15-keto-prostaglandin. In embodiments, the
PTGRl activity is reducing the level of leukotriene B4. In embodiments, the PTGRl activity is reducing the activity of 15-keto-prostaglandin. In embodiments, the PTGRl activity is reducing the activity of leukotriene B4. In embodiments, the PTGRl activity is binding NADP+. In embodiments, the PTGRl activity is converting leukotriene B4 to 12-oxo-leukotriene B4. In embodiments, a reduction in PTGRl activity results in a reduction in the levels of 12-oxo-leukotriene B4.

[0124] The term "prostaglandin reductase 1 (PTGRl) protein- prostaglandin reductase 1 (PTGRl) inhibitor complex" as used herein refers to a prostaglandin reductase 1 (PTGRl) protein bonded (e.g., covalently bonded) to a prostaglandin reductase 1 (PTGRl) inhibitor (e.g., a compound described herein).

II. Compounds

[0125] In an aspect is provided a compound having the formula:

![Chemical formula](image)

(R1)21
(R2)22

[0126] R1 is independently halogen, -CXS, -CHX^, -CH2X^, -OCX^, -

OCH2X^, -OCHX^, -CN, -SOxR^ idi, -SOxNR^ idi, NR^ idi, NH C(0)NR^ idi, -N(0) m, -NR^ idi, -C(0)R^ idc, -C(0)OR^ idc, -C(0)NR^ idi, -OR^ idd, -NR^ idA OR^ idB, -NR^ idA C(0)R^ ide, -NR^ idA C(0)R^ ide, R^ idc, -NR^ idA OR^ idC, -N^ id3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted ary1, or substituted or unsubstituted heteroaryl; two adjacent R1 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol z1 is an integer from 0 to 5.

[0127] R2 is independently halogen, -C^2, -CHX^, -CH2X^, -OCX^, -

OCH2X^, -OCHX^, -CN, -SOx2R^ 2id, -SOx2NR^ 2id, -NHC(0)NR^ 2id, -N(0) m2, -NR^ 2idA R^ 2idB, -C(0)R^ 2idc, -C(0)OR^ 2idc, -C(0)NR^ 2idB, -OR^ 2id, -NR^ 2idA S0^ 2idR^ 2idD, -NR^ 2idA C(0)R^ 2idC, -NR^ 2idA C(0)R^ 2idC, R^ 2idC, -NR^ 2idA OR^ 2idC, -N^ id3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R2 substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol z2 is an integer from 0 to 5.

[0128] Each \( R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C} \), and \( R^{2D} \) is independently hydrogen, -\( CX_3 \), -\( CN \), -\( COOH \), -\( CONH_2 \), -\( CHX_2 \), -\( CH_2X \), substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{2A} \) and \( R^{2B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each \( X, X^1 \), and \( X^2 \) is independently -F, -Cl, -Br, or -I. The symbols \( n1 \) and \( n2 \) are independently an integer from 0 to 4. The symbols \( m1, m2, v1, \) and \( v2 \) are independently an integer from 1 to 2.

[0129] In embodiments, the compound is not licochalcone A.

[0130] In embodiments, the compound has the formula:

![Diagram](image)

\[ (Ia). \]

[0131] \( R^{1A}, R^{1B}, R^{1C}, R^{1D}, \) and \( R^{1E} \) are independently hydrogen, halogen, -\( CX^\alpha \), -\( CHX^\alpha \), -\( CH_2X^\alpha \), -\( OCX^\alpha \), -\( OCHX^\alpha \), -\( CN \), -\( SO_2R^\beta \), -\( SO_2NR^\gamma R^\delta \), -\( NR^\gamma NR^\delta \), -\( NR^\gamma R^\delta \), -\( NH(CO)NR^\gamma R^\delta \), -\( N(0)_m \), -\( NR^\gamma R^\delta \), -\( C(0)R^\gamma \), -\( C(0)OR^\gamma \), -\( C(0)NR^\gamma R^\delta \), -\( OR^\gamma \), -\( NR^\gamma S_2R^\delta \), -\( NR^\gamma C(0)R^\gamma \), -\( NR^\gamma C(0)OR^\gamma \), -\( NR^\gamma A(0)OR^\gamma \), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0132] \( R^{2A}, R^{2B}, R^{2C}, R^{2D}, \) and \( R^{2E} \) are independently hydrogen, halogen, -\( CX^\gamma \), -\( CHX^\gamma \), -\( CH_2X^\gamma \), -\( OCHX^\gamma \), -\( OCH_2X^\gamma \), -\( CN \), -\( SO_2R^\delta \), -\( SO_2NR^\theta R^\nu \), -\( NH(CO)NR^\theta R^\nu \), -\( N(0)_m \), -\( NR^\theta R^\nu \), -\( C(0)R^\theta \), -\( C(0)OR^\theta \), -\( C(0)NR^\theta R^\nu \), -\( OR^\theta \), -\( NR^\theta S_2R^\nu \), -\( NR^\theta C(0)R^\theta \), -\( NR^\theta C(0)OR^\theta \), -\( NR^\theta A(0)OR^\theta \), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0133] In embodiments, the compound has the formula:

![Chemical structure](image)

(lb). $R_{1.2}^1$, $R_{1.3}^1$, $R_{1.5}^1$, and $R_{2.3}^2$ are as described herein.

[0134] In embodiments, $R_{1.2}^1$ is independently substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl. In embodiments, $R_{1.2}^1$ is independently unsubstituted alkyl. In embodiments, $R_{1.2}^1$ is independently unsubstituted Ci-Cs alkyl. In embodiments, $R_{1.2}^1$ is independently unsubstituted C1-C5 alkyl. In embodiments, $R_{1.2}^1$ is independently unsubstituted C1-C5 alkenyl. In embodiments, $R_{1.2}^1$ has the formula

\[
\text{[Chemical structure](image)}
\]

[0135] In embodiments, $R_{1.3}^1$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In embodiments, $R_{1.3}^1$ is independently -OR. In embodiments, $R_{1.3}^1$ is independently -OR. In embodiments, $R_{1.3}^1$ is independently not -OH. In embodiments, $R_{1.3}^1$ is independently not hydrogen.

[0136] In embodiments, $R_{1.5}^1$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In embodiments, $R_{1.5}^1$ is independently -OR. In embodiments, $R_{1.5}^1$ is independently -OCH3. In embodiments, $R_{1.5}^1$ is independently not -OH. In embodiments, $R_{1.5}^1$ is independently not hydrogen.

[0137] In embodiments, $R_{1.5}^2$ is independently hydrogen, -CX, -CHX, -CH2X, substituted or unsubstituted alkyl. In embodiments, $R_{1.5}^2$ is independently hydrogen or substituted or unsubstituted Ci-Cs alkyl. In embodiments, $R_{1.5}^2$ is independently hydrogen or unsubstituted C1-C4 alkyl. In embodiments, $R_{1.5}^2$ is independently unsubstituted C1-C2 alkyl.

[0138] In embodiments, $R_{2.3}^2$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In embodiments, $R_{2.3}^2$ is independently -OR. In embodiments, $R_{2.3}^2$ is independently -OR. In embodiments, $R_{2.3}^2$ is independently not -OH. In embodiments, $R_{2.3}^2$ is independently not -OH.
In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not -OH. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not -OH. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen.

In embodiments, $R^2$ is independently not -OH. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen. In embodiments, $R^2$ is independently not hydrogen.

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[0139] In embodiments, $R^{2D}$ is independently hydrogen, -CX3, -CHX2, -CH2X, substituted or unsubstituted alkyl. In embodiments, $R^{2D}$ is independently hydrogen or substituted or unsubstituted Ci-Cs alkyl.

[0140] In embodiments, $R^{12}$ is independently substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl; $R^{13}$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; $R^{15}$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and $R^{23}$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and $R^{23}$ is independently -OCX, -OCH2X, -OCHX, -OR, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In embodiments, $R^{12}$ is independently unsubstituted alkyl; $R^{13}$ is independently -OR; $R^{15}$ is independently -OR; $R^{23}$ is independently -OR; and each $R^{13}$ and $R^{2D}$ is independently unsubstituted alkyl. In embodiments, $R^{12}$ is independently unsubstituted Ci-Cs alkyl; $R^{13}$ is independently -OR; $R^{15}$ is independently -OR; $R^{23}$ is independently -OR; and each $R^{13}$ and $R^{2D}$ is independently unsubstituted Ci-Cs alkyl. In embodiments, $R^{12}$ is independently unsubstituted C1-C5 alkyl; $R^{13}$ is independently -OH; $R^{15}$ is independently -OH; $R^{23}$ is independently -OH; and $R^{13}$ and $R^{2D}$ is independently unsubstituted C1-C5 alkyl. In embodiments, $R^{12}$ is independently unsubstituted C1-C5 alkyl; $R^{13}$ is independently -OH; $R^{15}$ is independently -OH; $R^{23}$ is independently -OH; and $R^{13}$ and $R^{2D}$ is independently unsubstituted C1-C5 alkyl. In embodiments, $R^{12}$ has the formula.
: \( R^{13} \) is independently -OH; \( R^{15} \) is independently -OR\(^b\); \( R^{23} \) is independently -OH; and \( R^{1d} \) is independently unsubstituted C1-C2 alkyl.

[0141] In embodiments, \( R^1 \) is independently halogen, -CX\(^a\), -CHX\(^a\), -CH2X\(^1\), -OCSX, -OCH2X\(^1\), -OCHX\(^1\), -CN, -SR\(^{1b}\), -NR\(^1\)R\(^2\), -C(0)R\(^{1c}\), -C(0)OR\(^1\)R\(^2\), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0142] In embodiments, \( R^1 \) is independently halogen, -CX\(^a\), -CHX\(^a\), -CH2X\(^1\), -OCSX, -OCH2X\(^1\), -OCHX\(^a\), -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, unsubstituted or substituted Ci-C\(_8\) alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\(_3\)-C\(_8\) cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\(_6\)-Ci2 aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0143] In embodiments, \( R^1 \) is independently halogen, -CX\(^a\), -CHX\(^a\), -CH2X\(^1\), -OCSX, -OCH2X\(^1\), -OCHX\(^a\), -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, substituted or unsubstituted Ci-C\(_8\) alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\(_3\)-C\(_8\) cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0144] In embodiments, two adjacent \( R^1 \) substituents are joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, two adjacent \( R^1 \) substituents are joined to form an unsubstituted cycloalkyl. In embodiments, two adjacent \( R^1 \) substituents are joined to form an unsubstituted C\(_3\)-C\(_6\) cycloalkyl.

[0145] In embodiments, \( R^1 \) is independently -CI. In embodiments, \( R^1 \) is independently halogen. In embodiments, \( R^1 \) is independently unsubstituted methyl. In embodiments, \( R^1 \) is independently unsubstituted ethyl. In embodiments, \( R^1 \) is independently unsubstituted propyl. In embodiments, \( R^1 \) is independently unsubstituted isopropyl. In embodiments, \( R^1 \) is independently unsubstituted n-propyl. In embodiments, \( R^1 \) is independently unsubstituted n-butyl. In embodiments, \( R^1 \) is independently unsubstituted t-butyl. In embodiments, \( R^1 \) is independently unsubstituted...
pentyl. In embodiments, R¹ is independently unsubstituted n-pentyl. In embodiments, R¹ is independently unsubstituted hexyl. In embodiments, R¹ is independently unsubstituted n-hexyl. In embodiments, R¹ is independently unsubstituted n-heptyl. In embodiments, R¹ is independently unsubstituted n-heptyl. In embodiments, R¹ is independently unsubstituted octyl. In embodiments, R¹ is independently unsubstituted n-octyl. In embodiments, R¹ is independently unsubstituted C₈ alkyl. In embodiments, R¹ is independently halo-substituted methyl. In embodiments, R¹ is independently halo-substituted ethyl. In embodiments, R¹ is independently halo-substituted isopropyl. In embodiments, R¹ is independently halo-substituted n-propyl. In embodiments, R¹ is independently halo-substituted n-butyl. In embodiments, R¹ is independently halo-substituted t-butyl. In embodiments, R¹ is independently halo-substituted n-pentyl. In embodiments, R¹ is independently halo-substituted benzyl. In embodiments, R¹ is independently halo-substituted C₁-C₈ alkyl. In embodiments, R¹ is independently unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 2 to 7 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 2 to 9 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 2 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 3 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 4 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 5 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 6 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 7 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 8 to 10 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted 9 to 10 membered heteroalkyl.

[0146] In embodiments, R¹ is independently -CXV. In embodiments, R¹ is independently -CHX₁₂. In embodiments, R¹ is independently -CH₂X¹. In embodiments, R¹ is independently -OCXS. In embodiments, R¹ is independently -OCH₂X¹. In embodiments, R¹ is independently -OCHX₁₂. In embodiments, R¹ is independently -CN. In embodiments, R¹ is independently -SOₙᵢR¹D. In embodiments, R¹ is independently -SOₜᵢNR¹A¹R¹B. In embodiments, R¹ is independently -NHC{(0)NR¹}A¹R¹B. In embodiments, R¹ is independently -NR¹A¹R¹B. In embodiments,
R is independently -C(0)R. In embodiments, R is independently -C(0)-OR. In embodiments, R is independently -OR. In embodiments, R is independently -NR\(^{1}\)R\(^{2}\). In embodiments, R is independently -NR\(^{1}\)SO\(_{2}\)R\(^{3}\). In embodiments, R is independently -NR\(^{1}\)C(0)R. In embodiments, R is independently -NR\(^{1}\)C(0)OR. In embodiments, R is independently -NH\(_{2}\). In embodiments, R is independently -COOH. In embodiments, R is independently -CONHR. In embodiments, R is independently -NOR. In embodiments, R is independently -SH. In embodiments, R is independently halogen. In embodiments, R is independently -F. In embodiments, R is independently -Cl. In embodiments, R is independently -Br. In embodiments, R is independently -I. In embodiments, R is independently -CF\(_{3}\). In embodiments, R is independently -CHF\(_{2}\). In embodiments, R is independently -CH\(_{2}\)F. In embodiments, R is independently -OCF\(_{3}\). In embodiments, R is independently -OCH\(_{2}\)F. In embodiments, R is independently -OCH\(_{3}\). In embodiments, R is independently -OCH\(_{2}\)CH\(_{3}\). In embodiments, R is independently -OCH(CH\(_{3}\))\(_{2}\). In embodiments, R is independently -OC(CH\(_{3}\))\(_{3}\). In embodiments, R is independently -SCH\(_{3}\). In embodiments, R is independently -SCH\(_{2}\)CH\(_{3}\). In embodiments, R is independently -SCH\(_{2}\)CH\(_{2}\)CH\(_{3}\). In embodiments, R is independently -SCH(CH\(_{3}\))\(_{2}\). In embodiments, R is independently -SC(CH\(_{3}\))\(_{3}\). In embodiments, R is independently -CH\(_{3}\). In embodiments, R is independently -CH\(_{2}\)CH\(_{3}\). In embodiments, R is independently -CH\(_{2}\)CH\(_{2}\)CH\(_{3}\). In embodiments, R is independently -CH(CH\(_{3}\))\(_{2}\). In embodiments, R is independently -CH\(_{2}\)X. In embodiments, R is independently hydrogen, halogen, -CX\(_{3}\), -CHX\(_{2}\), -CH\(_{2}\)X, -OCX\(_{3}\). Submitted or unsubstituted alkyl (e.g., C\(_{1}-C_{8}\), C\(_{1}-C_{6}\), C\(_{1}-C_{4}\), or C\(_{1}-C_{2}\)), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C\(_{3}-C_{6}\), C\(_{3}-C_{6}\), C\(_{4}-C_{5}\), or C\(_{5}-C_{6}\)), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, 5 to 6 membered), substituted or unsubstituted aryl (e.g., C\(_{6}-C_{12}\), G\(_{5}-C_{10}\), or phenyl), or substituted or...
unsubstituted heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0148] In embodiments, \(R^1\) is independently substituted or unsubstituted alkyl (e.g., \(C_1-C_8\), \(C_1-C_6\), \(C_1-C_4\), or \(C_1-C_2\)). In embodiments, \(R^1\) is independently substituted alkyl (e.g., \(C_1-C_8\), \(C_1-C_6\), \(C_1-C_4\), or \(C_1-C_2\)). In embodiments, \(R^1\) is independently unsubstituted alkyl (e.g., \(C_1-C_8\), \(C_1-C_6\), \(C_1-C_4\), or \(C_1-C_2\)). In embodiments, \(R^1\) is independently unsubstituted methyl. In embodiments, \(R^1\) is independently unsubstituted ethyl. In embodiments, \(R^1\) is independently unsubstituted propyl. In embodiments, \(R^1\) is independently unsubstituted isopropyl. In embodiments, \(R^1\) is independently unsubstituted tert-butyl. In embodiments, \(R^1\) is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \(R^1\) is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \(R^1\) is independently substituted or unsubstituted cycloalkyl (e.g., \(C_3-C_8\), \(C_3-C_6\), \(C_4-C_6\), or \(C_5-C_6\)). In embodiments, \(R^1\) is independently substituted cycloalkyl (e.g., \(C_3-C_8\), \(C_3-C_6\), \(C_4-C_6\), or \(C_5-C_6\)). In embodiments, \(R^1\) is independently unsubstituted cycloalkyl (e.g., \(C_3-C_8\), \(C_3-C_6\), \(C_4-C_6\), or \(C_5-C_6\)). In embodiments, \(R^1\) is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \(R^1\) is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \(R^1\) is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \(R^1\) is independently substituted or unsubstituted aryl (e.g., \(C_6-C_{12}\), \(C_6-C_{10}\), or phenyl). In embodiments, \(R^1\) is independently substituted aryl (e.g., \(C_6-C_{12}\), \(C_6-C_{10}\), or phenyl). In embodiments, \(R^1\) is independently unsubstituted aryl (e.g., \(C_6-C_{12}\), \(C_6-C_{10}\), or phenyl). In embodiments, \(R^1\) is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \(R^1\) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
[0149] In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form an unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form an unsubstituted or unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form an unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent $R^1$ substituents may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0150] In embodiments, $R^{1A}$ is independently hydrogen. In embodiments, $R^{1A}$ is independently -CX$^{1A}$. In embodiments, $R^{1A}$ is independently -CHX$^{1A}$. In embodiments, $R^{1A}$ is independently -CH$_2$X$^{1A}$. In embodiments, $R^{1A}$ is independently -CN. In embodiments, $R^{1A}$ is independently -COOH. In embodiments, $R^{1A}$ is independently -CONH$_2$. In embodiments, $X^{1A}$ is independently -F, -Cl, -Br, or -I.

[0151] In embodiments, $R^{1A}$ is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C3). In embodiments, $R^{1A}$ is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C3). In embodiments, $R^{1A}$ is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C3). In embodiments, $R^{1A}$ is independently unsubstituted.
methyl. In embodiments, $R^{1A}$ is independently unsubstituted ethyl. In embodiments, $R^{1A}$ is independently unsubstituted propyl. In embodiments, $R^{1A}$ is independently unsubstituted isopropyl. In embodiments, $R^{1A}$ is independently unsubstituted tert-butyl. In embodiments, $R^{1A}$ is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, $R^{1A}$ is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, $R^{1A}$ is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, $R^{1A}$ is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^{1A}$ is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^{1A}$ is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^{1A}$ is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, $R^{1A}$ is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, $R^{1A}$ is independently substituted or unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, $R^{1A}$ is independently substituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, $R^{1A}$ is independently unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, $R^{1A}$ is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{1A}$ is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{1A}$ is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0152] In embodiments, $R^{1b}$ is independently hydrogen. In embodiments, $R^{1b}$ is independently -CX1a. In embodiments, $R^{1b}$ is independently -CHX1a. In embodiments, $R^{1b}$ is independently -CH2X1b. In embodiments, $R^{1b}$ is independently -CN. In embodiments, $R^{1b}$ is independently -COOH. In embodiments, $R^{1b}$ is independently -CONH2. In embodiments, $X^{1b}$ is independently -F, -Cl, -Br, or -I.
In embodiments, R\textsuperscript{1B} is independently substituted or unsubstituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{i}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1A} is independently substituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{i}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1n} is independently unsubstituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{i}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1B} is independently unsubstituted methyl. In embodiments, R\textsuperscript{1n} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{1B} is independently unsubstituted propyl. In embodiments, R\textsuperscript{1n} is independently unsubstituted isopropyl. In embodiments, R\textsuperscript{1B} is independently unsubstituted tert-butyl. In embodiments, R\textsuperscript{1n} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1n} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1B} is independently substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1n} is independently substituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1n} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1n} is independently substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1B} is independently substituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1n} is independently substituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1n} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1B} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1B} is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered).
membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

[0155] In embodiments, \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0156] In embodiments, \( R^{1C} \) is independently hydrogen. In embodiments, \( R^{1C} \) is independently substituted or unsubstituted alkyl (e.g., \( \text{C}_1 \text{-C}_8 \), \( \text{C}_8 \text{-C}_6 \), \( \text{C}_1 \text{-C}_4 \), or \( \text{C}_1 \text{-C}_2 \)). In embodiments, \( R^{1C} \) is independently substituted alkyl (e.g., \( \text{C}_1 \text{-C}_8 \), \( \text{C}_8 \text{-C}_6 \), \( \text{C}_1 \text{-C}_4 \), or \( \text{C}_1 \text{-C}_2 \)). In embodiments, \( R^{1C} \) is independently unsubstituted alkyl (e.g., \( \text{C}_1 \text{-C}_8 \), \( \text{C}_8 \text{-C}_6 \), \( \text{C}_1 \text{-C}_4 \), or \( \text{C}_1 \text{-C}_2 \)). In embodiments, \( R^{1C} \) is independently unsubstituted methyl. In embodiments, \( R^{1C} \) is independently unsubstituted ethyl. In embodiments, \( R^{1C} \) is independently unsubstituted propyl. In embodiments, \( R^{1C} \) is independently unsubstituted isopropyl. In embodiments, \( R^{1C} \) is independently unsubstituted tert-butyl. In embodiments, \( R^{1C} \) is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^{1C} \) is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^{1C} \) is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^{1C} \) is independently substituted or
unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R\textsuperscript{1C} is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R\textsuperscript{1C} is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R\textsuperscript{1C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1C} is independently substituted or unsubstituted aryl (e.g., C\textsubscript{6}t-C\textsubscript{12}, C\textsubscript{6}-Cio, or phenyl). In embodiments, R\textsuperscript{1C} is independently substituted aryl (e.g., C\textsubscript{6}t-C\textsubscript{12}, C\textsubscript{6}-Cio, or phenyl). In embodiments, R\textsuperscript{1C} is independently unsubstituted aryl (e.g., C\textsubscript{6}t-C\textsubscript{12}, C\textsubscript{6}-Cio, or phenyl). In embodiments, R\textsuperscript{1C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1C} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0158] In embodiments, R\textsuperscript{1b} is independently hydrogen. In embodiments, R\textsuperscript{1b} is independently -CX \textsubscript{1b}3. In embodiments, R\textsuperscript{1b} is independently -CHX \textsubscript{1b}2. In embodiments, R\textsuperscript{1b} is independently -CH \textsubscript{1b}X. In embodiments, R\textsuperscript{1b} is independently -CN. In embodiments, R\textsuperscript{1b} is independently -COOH. In embodiments, R\textsuperscript{1b} is independently -CONH2. In embodiments, X \textsuperscript{1b} is independently -F, -Cl, -Br, or -I.

[0159] In embodiments, R\textsuperscript{1b} is independently substituted or unsubstituted alkyl (e.g., C1-C\textsubscript{8}, C1-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{1b} is independently substituted alkyl (e.g., C1-C\textsubscript{8}, C1-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{1b} is independently unsubstituted alkyl (e.g., C1-C\textsubscript{8}, C1-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{1b} is independently unsubstituted methyl. In embodiments, R\textsuperscript{1b} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{1b} is independently unsubstituted isopropyl. In embodiments, R\textsuperscript{1b} is independently unsubstituted tert-butyl. In embodiments, R\textsuperscript{1b} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1b} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6
membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R¹ is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R¹ is independently unsubstituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R¹ is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R¹ is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R¹ is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R¹ is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R¹ is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R¹ is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-Cio, or phenyl). In embodiments, R¹ is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-Cio, or phenyl). In embodiments, R¹ is independently substituted aryl (e.g., C₆-C₁₂, C₆-Cio, or phenyl). In embodiments, R¹ is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹ is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0160] In embodiments, R¹ is independently hydrogen, halogen, -CXⁿ, -CHXⁿ, -CH₂Xⁿ, -OCXⁿ, -OCH₂Xⁿ, -OCHXⁿ, -CN, -OH, -NH₂, COOH, -CONH₂, NO₂, -SH, SO₃H, -SO₄H, -SO₂NH₂, -NO₂H, -NH₂, -NH=C(0)NH₁NH₂, NH₂, -NHSO₂H, -NHC(0)H, -NHC(0)-OH, -NO₂H, R²₀-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R²₀-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R²₀-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R²₀-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²₀-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-Cio, or phenyl), or R²₀-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹ is independently
halogen, -CX^, -CHX^, -CH2X^, -OCX^, -OCH2X^, -OCHX^, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2, -NOH2, -OHNH2, -NHC=(0)NH, -NHC=(0)H, -NHC=0H, -NH2, R^20-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, Ci-C4, or Ci-C2), R^20-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^20-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6), R^20-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^20-substituted or unsubstituted aryl (e.g., (e.g., C6-Ci2, C6-Cio, or phenyl), or R^20-substituted or unsubstituted heteroary (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0161] In embodiments, R^1 is independently hydrogen, halogen, -CX^, -CHX^, -CH2X^, -OCX^, -OCH2X^, -OCHX^, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2, -NOH2, -NHC=(0)NH, -NHC=(0)H, -NHC=(0)H, -NH=0H, unsubstituted alkyl (e.g., Ci-C8, Ci-C6, Ci-C4, or Ci-C2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C6-Ci2, C6-Cio, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^1 is independently -F, -Cl, -Br, or -I. In embodiments, R^1 is independently hydrogen. In embodiments, R^1 is independently unsubstituted methyl. In embodiments, R^1 is independently unsubstituted ethyl.

[0162] In embodiments, two adjacent R^1 substituents may optionally be joined to form a R^20-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-C6). In embodiments, two adjacent R^1 substituents may optionally be joined to form a R^20-substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent R^1 substituents may optionally be joined to form an unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent R^1 substituents may optionally be joined to form a R^20-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R^1 substituents may optionally be joined to form a R^20-substituted heterocycloalkyl
(e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R¹ substituents may optionally be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R¹ substituents may optionally be joined to form a R²⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, two adjacent R¹ substituents may optionally be joined to form a R²⁰-substituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, two adjacent R¹ substituents may optionally be joined to form an unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, two adjacent R¹ substituents may optionally be joined to form a R²⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R¹ substituents may optionally be joined to form a R²⁰-substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R¹ substituents may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0163] R²⁰ is independently oxo, halogen, -CX²⁰, -CHX²⁰, -CH₂X²⁰, -OCX²⁰, -OCH₂X²⁰, -OCHX²⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂H, -SO₂NH₂, -NH₂, -NH-NH₂, -NHC≡(0)NHNH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHC(O)-OH, -NHOH, R²¹-substituted or unsubstituted alkyl (e.g., C₁-C₆, C₁-C₄, or C₁-C₇), R²¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R²¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R²¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²¹-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl), or R²¹-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁰ is independently oxo, halogen, -CX²⁰, -CHX²⁰, -CH₂X²⁰, -OCX²⁰, -OCH₂X²⁰, -OCHX²⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂H, -SO₂NH₂, -NH₂, -NH-NH₂, -NHC≡(0)NHNH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₆, C₁-C₄, or C₁-C₇), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁰ is independently -F, -Cl, -Br, or -I. In embodiments, R²⁰ is independently unsubstituted methyl. In

[0164] R²¹ is independently oxo,
halogen, -CX²¹, -CHX²¹, -CH₂X²¹, -OCX²¹, -OCH₂X²¹, -OCHX²¹, -CN, -OH, -NH₂, -COOH,
-H₂CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC(O)H₄, -NHC(0)NH₂,
-NHC(0)NH₂, -NH₂SO₂H, -NHC(0)H, -NHC(0)-OH, -NHOH, R²²-substituted or
unsubstituted alkyl (e.g., Cᵢ-C₈, Cᵢ-C₆, C₈-C₄, or C₄-C₂), R²²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R²²-substituted or unsubstituted cycloalkyl (e.g., C₃₈-C₈, C₅₆-C₄, C₄-C₆, or C₅-C₆), R²²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R³²-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²¹ is independently oxo,
halogen, -CX²¹, -CHX²¹, -CH₂X²¹, -OCX²¹, -OCH₂X²¹, -OCHX²¹, -CN, -OH, -NH₂, -COOH,
-H₂CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC(O)H₄, -NHC(0)NH₂,
-NHC(0)NH₂, -NH₂SO₂H, -NHC(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., Cᵢ-C₈, Cᵢ-C₆, C₈-C₄, or C₄-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃₈-C₈, C₅₆-C₄, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²¹ is independently -F, -Cl, -Br, or -I. In embodiments, R²¹ is independently unsubstituted methyl. In
embodiments, R²¹ is independently unsubstituted ethyl.

[0165] R²² is independently oxo,
halogen, -CX²², -CHX₂², -CH₂X₂², -OCX₂², -OCH₂X₂², -OCHX₂², -CN, -OH, -NH₂, -COOH,
-H₂CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC(O)H₂, -NHC(O)NH₂,
-NHC(0)NH₂, -NH₂SO₂H, -NHC(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C₈, Ci-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6
membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
unsubstituted aryl (e.g., C₆-C₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12
membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X₂² is independently -
F, -Cl, -Br, or -I. In embodiments, R² is independently unsubstituted methyl. In
embodiments, R² is independently unsubstituted ethyl.

[0166] In embodiments, R₁ is 0. In embodiments, R₁ is 1. In embodiments, R₁ is 2. In
embodiments, R₁ is 3. In embodiments, R₁ is 4. In embodiments, R₁ is 5.

[0167] In embodiments, R² is independently halogen, -CX₂₃, -CHX₂₂, -CH₂X₂, -OCX₂₃, -
OCH₂X₂, -OCHX₂, -CN, -SR₂D, -NR₂AR₂B, -C(=O)R²C, -C(=O)OR²C, -C(=O)NR₂AR₂B, -OR₂D,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0168] In embodiments, R² is independently halogen, -CX₂₃, -CHX₂₂, -CH₂X₂, -OCX₂₃, -
OCH₂X₂, -OCHX₂, -CN, -SH, -NH₂, -C(=O)OH, -C(=O)NH₂, -OH, substituted or unsubstituted
Ci-C₈ alky, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or
unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered
heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ aryl, or substituted or unsubstituted 5 to
12 membered heteroaryl.

[0169] In embodiments, R² is independently halogen, -CX₂₃, -CHX₂₂, -CH₂X₂, -OCX₂₃, -
OCH₂X₂, -OCHX₂, -CN, -SH, -NH₂, -C(=O)OH, -C(=O)NH₂, -OH, substituted or unsubstituted
Ci-C₈ alky, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or
unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered
heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6
membered heteroaryl.

[0170] In embodiments, two adjacent R² substituents are joined to form a substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, two adjacent
R² substituents are joined to form an unsubstituted cycloalkyl. In embodiments, two adjacent
R² substituents are joined to form an unsubstituted C₃-C₈ cycloalkyl.
In embodiments, R² is independently -CX₂³. In embodiments, R² is independently -CHX₂². In embodiments, R² is independently -OCX₂³. In embodiments, R² is independently -OCH₂X. In embodiments, R² is independently -OCHX₂³. In embodiments, R² is independently -OCHX₂. In embodiments, R² is independently -CN. In embodiments, R² is independently -SO₃R². In embodiments, R² is independently -SO₄R². In embodiments, R² is independently -NH(C₅H₄)NR²ₐR²ᵇ. In embodiments, R² is independently -N(OH)₂. In embodiments, R² is independently -C(O)R₂. In embodiments, R² is independently -C(O)OR₂. In embodiments, R² is independently -C(O)NR₂ₐR₂ᵇ. In embodiments, R² is independently -NRC(O)R₂. In embodiments, R² is independently -OR₂. In embodiments, R² is independently -NR₂ₐR₂ᵇ. In embodiments, R² is independently -C(0)R₂. In embodiments, R² is independently -C(0)OR₂. In embodiments, R² is independently -CONH₂. In embodiments, R² is independently -COOH. In embodiments, R² is independently -SH. In embodiments, R² is independently halogen. In embodiments, R² is independently -F. In embodiments, R² is independently -Cl. In embodiments, R² is independently -Br. In embodiments, R² is independently -I. In embodiments, R² is independently -CF₃. In embodiments, R² is independently -CHF₂. In embodiments, R² is independently -OCF₃. In embodiments, R² is independently -OCH₂F. In embodiments, R² is independently -OCHF₂. In embodiments, R² is independently -OCH₃. In embodiments, R² is independently -OCH₂CH₃. In embodiments, R² is independently -OCH₂CH₂CH₃. In embodiments, R² is independently -OCH(CH₃)₂. In embodiments, R² is independently -OC(CH₃)₃. In embodiments, R² is independently -SCH₃. In embodiments, R² is independently -SCH₂CH₃. In embodiments, R² is independently -SCH(CH₃)₂. In embodiments, R² is independently -SC(CH₃)₃. In embodiments, R² is independently -CH₃. In embodiments, R² is independently -CH₂CH₃. In embodiments, R² is independently -CH₂CH₂CH₃. In embodiments, R² is independently -CH(CH₃)₂. In embodiments, R² is independently -C(CH₃)₃.
R²C, -NR²AOR²C, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0173] In embodiments, R² is independently substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₄, or C₁-C₂). In embodiments, R² is independently substituted alkyl (e.g., C₁-C₈, C₁-C₄, or C₁-C₂). In embodiments, R² is independently unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R² is independently unsubstituted methyl. In embodiments, R² is independently unsubstituted ethyl. In embodiments, R² is independently unsubstituted propyl. In embodiments, R² is independently unsubstituted isopropyl. In embodiments, R² is independently unsubstituted tert-butyl. In embodiments, R² is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R² is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R² is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R² is independently substituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R² is independently unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R² is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, R² is independently substituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, R² is independently unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, R² is
independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R² is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R² is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, two adjacent R² substituents may optionally be joined to form an unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl).

In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R² substituents may optionally be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R² substituents may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R²A is independently hydrogen. In embodiments, R²A is independently -CX²A. In embodiments, R²A is independently -CHX²A. In embodiments, R²A is independently -CH₂X²A. In embodiments, R²A is independently -CN. In
embodiments, R^2A is independently -COOH. In embodiments, R^2A is independently -CONH2. In embodiments, X^2A is independently -F, -Cl, -Br, or -I.

[0176] In embodiments, R^2A is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^2A is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^2A is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^2A is independently unsubstituted ethyl. In embodiments, R^2A is independently unsubstituted isopropyl. In embodiments, R^2A is independently unsubstituted tert-butyl. In embodiments, R^2A is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R^2A is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R^2A is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R^2A is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C5-C6, C4-G5, or C5-C6). In embodiments, R^2A is independently substituted cycloalkyl (e.g., C3-C8, C5-C6, C4-C6, or C5-C6). In embodiments, R^2A is independently unsubstituted cycloalkyl (e.g., C3-C8, C5-C6, C4-C6, or C5-C6). In embodiments, R^2A is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^2A is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^2A is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^2A is independently substituted or unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, R^2A is independently substituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, R^2A is independently unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, R^2A is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^2A is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
In embodiments, R² is independently hydrogen. In embodiments, R² is independently -CX². In embodiments, R² is independently -CHX². In embodiments, R² is independently -CH₂X². In embodiments, R² is independently -CN. In embodiments, R² is independently -COOH. In embodiments, R² is independently -CONH₂.

In embodiments, X² is independently -F, -Cl, -Br, or -I.

In embodiments, R² is independently substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C1-C₂). In embodiments, R² is independently substituted or unsubstituted heteroalkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C1-C₂). In embodiments, R² is independently unsubstituted methyl. In embodiments, R² is independently unsubstituted ethyl. In embodiments, R² is independently unsubstituted propyl. In embodiments, R² is independently unsubstituted isopropyl. In embodiments, R² is independently unsubstituted tert-butyl. In embodiments, R² is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R² is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R² is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R² is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-G₅, or C₅-C₆). In embodiments, R² is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-G₅). In embodiments, R² is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R² is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, R² is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, R² is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R² is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered).
membered, or 5 to 6 membered). In embodiments, R^{2B} is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0179] In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

[0180] In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0181] In embodiments, R^{2C} is independently hydrogen. In embodiments, R^{2C} is independently -CX^{2C}_3. In embodiments, R^{2C} is independently -CHX^{2C}_2. In embodiments, R^{2C} is independently -CHX^{2C}. In embodiments, R^{2C} is independently -CN. In embodiments, R^{2C} is independently -COOH. In embodiments, R^{2C} is independently -CONH2. In embodiments, X^{2C} is independently -F, -Cl, -Br, or I.

[0182] In embodiments, R^{2C} is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^{2C} is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^{2C} is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R^{2C} is independently unsubstituted methyl. In embodiments, R^{2C} is independently unsubstituted ethyl. In embodiments, R^{2C} is independently unsubstituted propyl. In embodiments, R^{2C} is independently unsubstituted tert-butyl. In embodiments, R^{2C} is independently substituted or unsubstituted heteroaryl (e.g., 2 to 8 membered, 2 to 6
membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^2C \) is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^2C \) is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, \( R^2C \) is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^2C \) is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^2C \) is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^2C \) is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^2C \) is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^2C \) is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^2C \) is independently substituted or unsubstituted aryl (e.g., \( C_6^1-C_{12}^1 \), \( C_6^1-Cio \), or phenyl). In embodiments, \( R^2C \) is independently substituted aryl (e.g., \( C_6^1-C_{12}^1 \), \( C_6^1-Cio \), or phenyl). In embodiments, \( R^2C \) is independently unsubstituted aryl (e.g., \( C_6^1-C_{12}^1 \), \( C_6^1-Cio \), or phenyl). In embodiments, \( R^2C \) is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^2C \) is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^2C \) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0183] In embodiments, \( R^{2D} \) is independently hydrogen. In embodiments, \( R^{2D} \) is independently -\( CX^{2D} \). In embodiments, \( R^{2D} \) is independently -\( CHX^{2D} \). In embodiments, \( R^{2D} \) is independently -\( CH_2X^{2D} \). In embodiments, \( R^{2D} \) is independently -\( CN \). In embodiments, \( R^{2D} \) is independently -\( COOH \). In embodiments, \( R^{2D} \) is independently -\( CONH2 \). In embodiments, \( X^{2D} \) is independently -\( F \), -\( CI \), -\( Br \), or -\( I \).

[0184] In embodiments, \( R^{2D} \) is independently substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). In embodiments, \( R^{2D} \) is independently substituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). In embodiments, \( R^{2D} \) is independently unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). In embodiments, \( R^{2D} \) is independently unsubstituted methyl. In embodiments, \( R^{2D} \) is independently unsubstituted ethyl. In embodiments, \( R^{2D} \) is
independently unsubstituted propyl. In embodiments, R²D is independently unsubstituted isopropyl. In embodiments, R²D is independently unsubstituted tert-butyl. In embodiments, R²D is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R²D is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R²D is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R²D is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R²D is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R²D is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R²D is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R²D is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R²D is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R²D is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R²D is independently substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, R²D is independently substituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, R²D is independently unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₅, or phenyl). In embodiments, R²D is independently substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²D is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²D is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0185] In embodiments, R² is independently hydrogen, halogen, -CX₂, -CHX₂, -CH₂X₂, -OCX₂, -OCH₂X₂, -OCHX₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NH₂NH₂, -ONH₂, -NH_C=(0)NHNH₂, -NH_C=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NH₂OH, R₂³-substituted or unsubstituted alkyl (e.g., C₁-C₅, C₁-C₆, C₁-C₅, or C₁-C₆), R₂³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R₂³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆).
C₆), R²⁺-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²⁻ substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R²⁻ substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R² is independently halogen, -CX₂₃, -CHX₂₄, -CH₂X₂₁, -OCX₂₃, -OCH₂X₂₁, -OCHX₂₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂H₂, -SO₂NH₂, -NHSO₂H₂, -NHC=(0)NH, -NHC(0)-OH, -NHOH, R²⁻ substituted or unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, C₁⁻C₄, or C₁⁻C₂), R²⁻ substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R²⁻ substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R²⁻ substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²⁻ substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R²⁻ substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0186] In embodiments, R² is independently hydrogen, halogen, -CX₂₃, -CHX₂₄, -CH₂X₂₁, -OCX₂₃, -OCH₂X₂₁, -OCHX₂₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂H₂, -SO₂NH₂, -NHSO₂H₂, -NHC=(0)NH, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, C₁⁻C₄, or C₁⁻C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X² is independently -F, -Cl, -Br, or -I. In embodiments, R² is independently hydrogen. In embodiments, R² is independently unsubstituted methyl. In embodiments, R² is independently unsubstituted ethyl.

[0187] In embodiments, two adjacent R² substituents may optionally be joined to form a R²⁻ substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-G₅, or C₅-C₆). In embodiments, two adjacent R² substituents may optionally be joined to form a R²⁻ substituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, two adjacent R²
substituents may optionally be joined to form an unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent R2 substituents may optionally be joined to form a R23-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R2 substituents may optionally be joined to form a R23-substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R2 substituents may optionally be joined to form a unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, two adjacent R2 substituents may optionally be joined to form a R23-substituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, two adjacent R2 substituents may optionally be joined to form an unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, two adjacent R2 substituents may optionally be joined to form a unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R2 substituents may optionally be joined to form a R23-substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R2 substituents may optionally be joined to form a unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0188] R23 is independently oxo, halogen, -CX23, -CHX23, -CH2X23, -OCX23, -OCH2X23, -OCHX23, -CN, -OH, -NH2, -COOH, -CONH2, -N02, -SH, -S02H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC=(0)NHNM, -NHC=(0)NHNM2, -NH2, -NH2SO2H, -NHC=(0)H, -NHC(0)-OH, -NH2OH, R24-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or Ci-C3g), R24-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R24-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6g), R24-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R24-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R23 is independently oxo, halogen, -CX23, -CHX23, -CH2X23, -OCX23, -OCH2X23, -OCHX23, -CN, -OH, -NH2, -COO
H, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH2,
-NHC=(0) NH2, -NHSO2H, -NHC=(O)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C8, Ci-C6, C1-C4, or C1-C2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6
membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
cycloalkyl (e.g., C3-C8, C5-C6, C4-C6, or C5-C6), unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl), or unsubstituted heteroaryl (e.g.,
5 to 12 membered, 5 to 9 membered, or 5 to 6 membered).  X23 is independently -
F, -Cl, -Br, or -I.  In embodiments, R23 is independently unsubstituted methyl.  In
embodiments, R23 is independently unsubstituted ethyl.

[0189] R24 is independently oxo,
halogen, -CX24, -CHX24, -CH2X24, -OCX24, -OCH2X24, -OCHX24, -CN, -OH, -NH2, -COO
H, -CONH2, -NO2, -SH, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH2,
-NHC=(0) NH2, -NHSO2H, -NHC=(O)H, -NHC(0)-OH, -NHOH, R25-substituted or
unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2), R25-substituted or unsubstituted
heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4
to 5 membered), R25-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-
C6), R25-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6
membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R25-substituted or
unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl), or R25-substituted or unsubstituted
heteroaryl (e.g., 5 to 12 membered, 5 to 9 membered, or 5 to 6 membered).  In embodiments, R24 is independently oxo,
halogen, -CX24, -CHX24, -CH2X24, -OCX24, -OCH2X24, -OCHX24, -CN, -OH, -NH2, -COO
H, -CONH2, -NO2, -SH, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH2,
-NHC=(0) NH2, -NHSO2H, -NHC=(O)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C8, Ci-C6, C1-C4, or C1-C2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6
membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
cycloalkyl (e.g., C3-C8, C5-C6, C4-C6, or C5-C6), unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl), or unsubstituted heteroaryl (e.g.,
5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).  X24 is independently -
F, -Cl, -Br, or -I.  In embodiments, R24 is independently unsubstituted methyl.  In
embodiments, R24 is independently unsubstituted ethyl.
[0190] R_{25} is independently oxo, halogen, -CX_{3}, -CH_{2}X_{2}, -OCX_{2}, -OCH_{2}X_{2}, -OCX_{2}, -OCH_{2}X_{2}, -CN, -OH, -NH_{2}, -COO H, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NH_{2}H_{2}, -ON_{2}H_{2}, -NH_{2}C=(0)NH_{2}, -NH_{2}C=(0)H, -NH_{2}C(0)-OH, -NH_{2}OH, unsubstituted alkyl (e.g., Ci-C_{8}, Ci-C_{6}, C1-C4, or C1-C2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C4-C6, or C_{5}-C_{6}), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_{6}-Ci_{2}, C_{6}-Cio, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X_{25} is independently -F, -Cl, -Br, or -I. In embodiments, R_{25} is independently unsubstituted methyl. In embodiments, R_{25} is independently unsubstituted ethyl.

[0191] In embodiments, z2 is 0. In embodiments, z2 is 1. In embodiments, z2 is 2. In embodiments, z2 is 3. In embodiments, z2 is 4.

[0192] In embodiments, X is -F. In embodiments, X is -Cl. In embodiments, X is -Br. In embodiments, X is -I. In embodiments, X is -F. In embodiments, X is -Cl. In embodiments, X is -Br. In embodiments, X is -I. In embodiments, X is -F. In embodiments, X is -Cl. In embodiments, X is -Br. In embodiments, X is -I.

[0193] In embodiments, n1 is 0. In embodiments, n1 is 1. In embodiments, n1 is 2. In embodiments, n1 is 3. In embodiments, n1 is 4. In embodiments, n2 is 0. In embodiments, n2 is 1. In embodiments, n2 is 2. In embodiments, n2 is 3. In embodiments, n2 is 4.

[0194] In embodiments, m1 is 1. In embodiments, m1 is 2. In embodiments, m2 is 1. In embodiments, m2 is 2.

[0195] In embodiments, v1 is 1. In embodiments, v1 is 2. In embodiments, v2 is 1. In embodiments, v2 is 2.

[0196] In some embodiments, a compound as described herein may include multiple instances of R_{1} or R_{2}, and/or other variables. In such embodiments, each variable may optional be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each R_{1} and/or R_{2}, is different, they may be referred to, for example, as R_{1,1}, R_{1,2}, R_{1,3}, R_{1,4}, R_{1,5}, R_{2,1}, R_{2,2}, R_{2,3}, or R_{2,4}, respectively, wherein the definition of R_{1} is assumed by R_{1,1}, R_{1,2}, R_{1,3}, R_{1,4}, R_{1,5}; and/or R_{2} is assumed by R_{2,1}, R_{2,2}, R_{2,3}, R_{2,4}. The
variables used within a definition of $R^1$ and/or $R^2$, and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity. In some embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, claim, table, scheme, drawing, or figure).

5 [0197] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer. In embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, figure, table, scheme, or claim).

15 [0198] In an aspect is provided a PTGR1 inhibitor. In embodiments, the PTGR1 inhibitor is a compound described herein. In embodiments, the PTGR1 inhibitor is an oligonucleotide (e.g., DNA, RNA, shRNA, or siRNA), protein (e.g., antibody, anti-PTGR1 antibody, anti-PTGR1 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGR1 inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGR1. In embodiments, the PTGR1 inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of human PTGR1. In embodiments, the PTGR1 inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of human PTGR1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to C239 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to P48 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to M124 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to T128 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to A149 in human PTGR1.
embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A153 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V154 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to N217 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to Y245 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V271 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V271 in human PTGRI. In embodiments, the PTGRI inhibitor includes an electrophilic group (e.g., electrophilic chemical group, electrophilic moiety, divalent electrophilic group, covalent cysteine modifier).

[0199] In an aspect is provided a PTGRI inhibitor. In embodiments, the PTGRI inhibitor is a compound described herein. In embodiments, the PTGRI inhibitor is an oligonucleotide (e.g., DNA, RNA, shRNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGRI antibody, anti-PTGRI binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGRI inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to M124 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to T128 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A153 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V154 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to N217 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to Y245 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V271 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V272 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor includes an electrophilic group (e.g., electrophilic chemical group, electrophilic moiety, divalent electrophilic group, covalent cysteine modifier).
In embodiments, the compound is a compound described herein, including in an aspect, embodiment, claim, figure, table, example, or scheme.

In embodiments, the compound has the formula:
In embodiments, the compound has the formula:

[0202]  

[0203]  

[0204]  

[0205]  

[0206]
In embodiments, the compound has the formula:

![Chemical Structure](image1)

In embodiments, the compound has the formula:

![Chemical Structure](image2)

In embodiments, the compound has the formula:

![Chemical Structure](image3)

In embodiments, the compound has the formula:

![Chemical Structure](image4)
In embodiments, the compound has the formula:

\[
\text{HO} - \text{O} - \text{C} = \text{C} - \text{HO} - \text{OH} \\
\text{HO} - \text{OH}
\]

In embodiments, the compound has the formula:

\[
\text{OH} - \text{O} - \text{C} = \text{C} - \text{OH} \\
\text{HO} - \text{OH}
\]

In embodiments, the compound has the formula:

\[
\text{HO} - \text{O} - \text{C} = \text{C} - \text{OH} \\
\text{HO} - \text{OH}
\]

In embodiments, the compound is licochalcone A, having the formula:

\[
\text{O} - \text{C} = \text{C} - \text{O} - \text{OH} \\
\text{HO} - \text{O} - \text{O} - \text{OH}
\]

In embodiments, the compound is not licochalcone A. In embodiments, the compound is a derivative of licochalcone A. In embodiments, the compound is an analog of licochalcone A. In embodiments, the compound is a prodrug (e.g., physiologically hydrolyzable ester thereof) of licochalcone A. In embodiments, the compound is not 2-hydroxychalcone. In embodiments, the compound is not xanthohumol. In embodiments, the compound is not an analog, derivative, or prodrug of 2-hydroxychalcone. In embodiments, the compound is not an analog, derivative, or prodrug of xanthohumol.
III. Pharmaceutical compositions

[0217] In an aspect is provided a pharmaceutical composition including a PTGR1 inhibitor and a pharmaceutically acceptable excipient. In embodiments, the PTGR1 inhibitor is a compound described herein. In embodiments, the PTGR1 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-PTGR1 antibody, anti-PTGR1 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGR1 inhibitor is included in a therapeutically effective amount. In embodiments, the pharmaceutical composition does not include licochalcone A.

[0218] In an aspect is provided a pharmaceutical composition including a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0219] In embodiments of the pharmaceutical compositions, the compound, or pharmaceutically acceptable salt thereof, is included in a therapeutically effective amount.

[0220] In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g. therapeutic agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g. therapeutic agent) in a therapeutically effective amount. In embodiments of the pharmaceutical compositions, the second agent is an agent for treating cancer. In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic.

IV. Methods of Treatment

[0221] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a PTGR1 inhibitor. In embodiments, the PTGR1 inhibitor is a compound described herein. In embodiments, the PTGR1 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGR1 antibody, anti-PTGR1 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGR1 inhibitor is included in a therapeutically effective amount.

[0222] In an aspect is provided a method of treating triple negative breast cancer, the method including administering to a subject in need thereof an effective amount of a PTGR1 inhibitor. In embodiments, the PTGR1 inhibitor is a compound described herein. In
In embodiments, the PTGR1 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGR1 antibody, anti-PTGR1 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGR1 inhibitor is included in a therapeutically effective amount.

In embodiments, the PTGR1 inhibitor is a chalcone or chalconoid (e.g., 1,3-diphenyl-2-propenone, butein, isoliquiritigenin, methyl hydroxychalcone, okanin, licochalcone a, sophoradin, tephrospinosin (3',5'-diisopentenyl-2',4'-dihydroxychalcone), xanthohumol, cardamomin, flavokawin b, okanin ((E)-3-(3,4-dihydroxyphenyl)-1-(2,3,4-trihydroxyphenyl)prop-2-en-1-one), methylated okanin derivatives (e.g., okanin 3,4,3',4'-tetramethyl ether, okanin 3,4,3'-trimethyl ether 4'-glucoside, okanin 4-methyl ether 4'-glucoside and okanin 4-methyl ether 4'-glucoside monoacetate), pashanone (2',6'-dihydroxy-3',4'-dimethoxychalcone), flavokavain b, flavokavain c, or (E)-1-[2,4-Dihydroxy-3-(3-methylbut-2-enyl)phenyl]-3-[4-hydroxy-3,5-bis(3-methylbut-2-enyl)phenyl]prop-2-en-1-one. In embodiments, the PTGR1 inhibitor is a chalcone having the formula:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
(R^2)_2 & \quad (R^1)_2 \quad (R^2)_2 \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

wherein \(R^1, R^2, z_1, \text{and} z_2\) are as described herein.

In embodiments, the PTGR1 inhibitor has the following formula:
In an aspect is provided a method of treating cancer including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the cancer is lung cancer. In embodiments, the cancer is prostate cancer. In embodiments, the cancer is breast cancer. In embodiments, the cancer is estrogen receptor positive breast cancer. In embodiments, the cancer is estrogen receptor (ER) negative breast cancer. In embodiments, the cancer is tamoxifen resistant breast cancer. In embodiments, the cancer is HER2 negative breast cancer. In embodiments, the cancer is HER2 positive breast cancer. In embodiments, the cancer is low grade (well differentiated) breast cancer. In embodiments, the cancer is intermediate grade (moderately differentiated) breast cancer. In embodiments, the cancer is high grade (poorly differentiated) breast cancer. In embodiments, the cancer is stage 0 breast cancer. In embodiments, the cancer is stage I breast cancer. In embodiments, the cancer is stage II breast cancer. In embodiments, the cancer is stage III breast cancer. In
embodiments, the cancer is stage IV breast cancer. In embodiments, the cancer is triple negative breast cancer.

[0226] In an aspect is provided a method of treating a disease associated with PTGRI activity including administering to a subject in need thereof an effective amount of a PTGRI inhibitor. In embodiments, the PTGRI inhibitor is a compound described herein. In embodiments, the PTGRI inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGRI antibody, anti-PTGRI binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the disease is associated with aberrant PTGRI activity.

[0227] In embodiments, the method includes administering a second agent (e.g. therapeutic agent). In embodiments, the method includes administering a second agent (e.g. therapeutic agent) in a therapeutically effective amount. In embodiments, the second agent is an agent for treating cancer. In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic.

[0228] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a substance (e.g., composition) capable of increasing the level of an acyl carnitine (AC) (e.g., compared to a control such as absence of the composition). In embodiments, the composition capable of increasing the level of an acyl carnitine is a compound described herein. In embodiments, the composition capable of increasing the level of an acyl carnitine is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody), or compound (e.g., compound described herein). In embodiments, the composition capable of increasing the level of an acyl carnitine is included in a therapeutically effective amount. In embodiments, the composition capable of increasing the level of an acyl carnitine is a deubiquitinase inhibitor (e.g., deubiquitinase inhibitor described herein, WP1 130, ESI09, GW4604). In embodiments, the acyl carnitine is described herein, for example in FIGS. 3A-3D. In embodiments, the acyl carnitine is C16:0 AC. In embodiments, the method includes reducing mitochondrial respiration. In embodiments, the cancer is breast cancer (e.g., triple negative breast cancer). In embodiments, the method increases the level of activity of carnitine palmitoyltransferase 1 (CPT1) (e.g, compared to a control such as absence of the inhibitor).
V. Methods of Inhibition

[0229] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a PTGRI inhibitor. In embodiments, the PTGRI is a human PTGRI. In embodiments, the PTGRI inhibitor is a compound described herein. In embodiments, the PTGRI inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-PTGRI antibody, anti-PTGRI binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGRI inhibitor is provided in an therapeutically effective amount. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGRI. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of human PTGRI. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of human PTGRI. In embodiments, the PTGRI inhibitor covalently binds an amino acid corresponding to C239 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to C239 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to P48 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to M124 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to T128 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A149 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A153 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V154 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to N217 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to Y245 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V271 in human PTGRI. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V272 in human PTGRI.

[0230] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a compound described herein. In embodiments, the PTGRI is a human PTGRI. In embodiments, the compound is provided in an effective amount. In
embodiments, the compound is provided in a therapeutically effective amount. In embodiments, the method includes contacting the PTGRI protein with an effective amount of a compound described herein. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGRI. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of human PTGRI. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of human PTGRI. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, C239, V271, or V272 of human PTGRI. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, V271, or V272 of human PTGRI. In embodiments, the compound contacts an amino acid corresponding to C239 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to C239 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to P48 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to M124 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to T128 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to A149 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to A153 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to V154 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to N217 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to Y245 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to V271 in human PTGRI. In embodiments, the compound contacts an amino acid corresponding to V272 in human PTGRI.

[0231] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a PTGRI inhibitor. In embodiments, the PTGRI is a SEQ ID NO: 1. In embodiments, the PTGRI inhibitor is a compound described herein. In embodiments, the PTGRI inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGRI antibody, anti-PTGRI binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGRI inhibitor is provided in a therapeutically effective amount. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGRI inhibitor
contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGRI inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to M124 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to T128 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to A153 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V154 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to N217 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to Y245 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V271 in SEQ ID NO: 1. In embodiments, the PTGRI inhibitor contacts an amino acid corresponding to V272 in SEQ ID NO: 1.

[0232] In an aspect is provided a method of inhibiting PTGRI activity including contacting the PTGRI with a compound described herein. In embodiments, the PTGRI is a SEQ ID NO: 1. In embodiments, the compound is provided in an effective amount. In embodiments, the compound is provided in a therapeutically effective amount. In embodiments, the method includes contacting the PTGRI protein with an effective amount of a compound described herein. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound
covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to M124 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to T128 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to A153 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V154 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to N217 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to Y245 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V271 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V272 in SEQ ID NO: 1.

[0233] In embodiments, the inhibition is competitive inhibition. In embodiments, the inhibition is irreversible. In embodiments, the inhibition is reversible. In embodiments, the compound covalently binds to the PTGRI protein (e.g., the covalent bond forming via a reaction involving the electrophilic group and a cysteine (e.g., C239 of SEQ ID NO: 1).

[0234] Where the compound covalently binds to the PTGRI a PTGRI protein (e.g., human PTGRI) covalently bonded to a PTGRI inhibitor is formed (also referred to herein as a "PTGRI-compound adduct"), as described below. In embodiments, the resulting covalent bond is reversible. Where the resulting covalent bond is reversible, the bonding reverses upon denaturation of the protein. Thus, in embodiments, the reversibility of a covalent bond between the compound and the PTGRI upon denaturation of the PTGRI avoids or decreases autoimmune response in a subject subsequent to administration of the compound (relative to irreversibility). Moreover, in embodiments, the reversibility of a covalent bond between the compound and the PTGRI upon denaturation of the PTGRI avoids or decreases the toxicity (e.g. liver toxicity) of the compound in a subject (relative to irreversibility).

[0235] In embodiments, the PTGRI activity is reducing (e.g., reducing the levels of or reducing the activity of) 15-keto-prostaglandin or leukotriene B4 relative to a control. In embodiments, the PTGRI activity is reducing the level of 15-keto-prostaglandin. In embodiments, the PTGRI activity is reducing the level of leukotriene B4. In embodiments, the PTGRI activity is reducing the activity of 15-keto-prostaglandin. In embodiments, the
PTGR1 activity is reducing the activity of leukotriene B4. In embodiments, the PTGR1 activity is binding NADP+.

[0236] In an aspect is provided a method of increasing the level of an acyl carnitine (AC) (e.g., compared to a control such as absence of the substance) including contacting a cell with a substance (e.g., composition) capable of increasing the level of an acyl carnitine. In embodiments, the substance (e.g., composition) capable of increasing the level of an acyl carnitine is a compound described herein. In embodiments, the substance (e.g., composition) capable of increasing the level of an acyl carnitine is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody), or compound (e.g., compound described herein). In embodiments, the substance (e.g., composition) capable of increasing the level of an acyl carnitine is included in an effective amount. In embodiments, the substance (e.g., composition) capable of increasing the level of an acyl carnitine is a deubiquitinase inhibitor (e.g., deubiquitinase inhibitor described herein, WP1 130, ESI09, GW4604). In embodiments, the acyl carnitine is C16:0 AC. In embodiments, the method includes reducing mitochondrial respiration. In embodiments, the method increases the level of activity of carnitine palmitoyltransferase 1 (CPT1) (e.g., compared to a control such as absence of the composition).

VI. PTGR1 protein

[0237] In an aspect is provided a PTGR1 protein covalently bonded to a PTGR1 inhibitor (a PTGR1 protein-PTGR1 inhibitor complex). In embodiments, the PTGR1 is a human PTGR1 (e.g., SEQ ID NO:1). In embodiments, the PTGR1 inhibitor is a compound described herein. In embodiments, the PTGR1 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g., antibody, anti-PTGR1 antibody, anti-PTGR1 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the PTGR1 inhibitor is provided in a therapeutically effective amount.

[0238] In embodiments, the PTGR1 inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGR1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272of human PTGR1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in human PTGR1. In embodiments, the PTGR1 inhibitor
contacts an amino acid corresponding to C239 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to P48 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to M124 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to T128 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to A149 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to A153 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V154 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to N217 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to Y245 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V271 in human PTGR1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V272 in human PTGR1.

[0239] In an aspect is provided a PTGR1 protein covalently bonded to a compound described herein. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGR1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of human PTGR1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of human PTGR1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of human PTGR1. In embodiments, the compound covalently binds an amino acid corresponding to C239 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to C239 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to P48 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to M124 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to T128 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to A149 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to A153 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to V154 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to V154 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to V154 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to N217 in human PTGR1. In embodiments, the compound contacts an amino acid preceeding the
corresponding to Y245 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to V271 in human PTGR1. In embodiments, the compound contacts an amino acid corresponding to V272 in human PTGR1.

[0240] In embodiments, the compound is bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is reversibly covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is irreversibly covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the cysteine residue corresponds to C239 of human PTGR1.

[0241] In an embodiment, the PTGR1 protein is covalently bonded (e.g., reversibly or irreversibly) to a portion (e.g., the product of an electrophilic reaction with C239 of human PTGR1 or cysteine corresponding to C239 of human PTGR1) of a compound described herein (e.g., portion of a PTGR1 inhibitor or portion (e.g., through reacted electrophilic moiety) of a compound described herein).

[0242] In embodiments, the PTGR1 inhibitor is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of SEQ ID NO:1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to M124 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to T128 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to A153 in SEQ ID NO:1.
embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to V154 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to N217 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to Y245 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to V271 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor is capable of contacting an amino acid corresponding to V272 in SEQ ID NO:1.

[0243] In embodiments, the PTGR1 inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO:1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of SEQ ID NO:1. In embodiments, the PTGR1 inhibitor covalently binds an amino acid corresponding to C239 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to C239 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to P48 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to M124 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to T128 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to A149 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to A153 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V154 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to N217 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to Y245 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V271 in SEQ ID NO:1. In embodiments, the PTGR1 inhibitor contacts an amino acid corresponding to V272 in SEQ ID NO:1.

[0244] In an aspect is provided a PTGR1 protein covalently bonded to a compound described herein. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO:1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of SEQ ID NO:1. In embodiments, the compound contacts one or more amino acids corresponding to
P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound covalently binds an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to T128 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to A153 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V154 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to N217 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to Y245 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V271 in SEQ ID NO: 1. In embodiments, the compound contacts an amino acid corresponding to V272 in SEQ ID NO: 1.

[0245] In an aspect is provided a PTGR1 protein covalently bonded to a compound described herein. In embodiments, the compound is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of SEQ ID NO: 1. In embodiments, the compound is capable of covalently binding an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to C239 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to P48 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to M124 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to T128 in SEQ ID NO: 1. In embodiments, the compound is capable of
contacting an amino acid corresponding to A149 in SEQ ID NO: 1. In embodiments, the
compound is capable of contacting an amino acid corresponding to A153 in SEQ ID NO: 1.
In embodiments, the compound is capable of contacting an amino acid corresponding to
V154 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to N217 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to Y245 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to V271 in SEQ ID NO: 1. In embodiments, the compound is capable of contacting an amino acid corresponding to V272 in SEQ ID NO: 1.

[0246] In embodiments, the compound is bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is reversibly covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the compound is irreversibly covalently bonded to a cysteine residue of the PTGR1 protein. In embodiments, the cysteine residue corresponds to C239 of SEQ ID NO: 1.

[0247] In an embodiment, the PTGR1 protein is covalently bonded (e.g., reversibly or irreversibly) to a portion (e.g., the product of an electrophilic reaction with C239 of SEQ ID NO: 1 or cysteine corresponding to C239 of SEQ ID NO: 1) of a compound described herein (e.g., portion of a PTGR1 inhibitor or portion of a compound described herein).

[0248] In an aspect is provided a PTGR1 protein (e.g., human PTGR1) covalently bonded to a PTGR1 inhibitor (e.g., PTGR1 inhibitor, compound described herein, or a portion of a compound described herein).

[0249] In embodiments, the PTGR1 protein (e.g., human PTGR1) is covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., human PTGR1) is irreversibly covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., human PTGR1) is reversibly covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., human PTGR1) is covalently bonded to a portion of a PTGR1 inhibitor (e.g., compound described herein). In embodiments, the PTGR1 protein (e.g., human PTGR1) is irreversibly covalently bonded to a portion of a PTGR1 inhibitor (e.g., compound described herein). In embodiments, the
PTGR1 protein (e.g., human PTGR1) is reversibly covalently bonded to a portion of a PTGR1 inhibitor (e.g., compound described herein). In embodiments, the PTGR1 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., C239 of human PTGR1) or cysteine corresponding to C239 of human PTGR1 of the PTGR1 protein (e.g., human PTGR1). In embodiments, the portion (e.g., the product of an electrophilic reaction with C239 of human PTGR1 or cysteine corresponding to C239 of human PTGR1) of a PTGR1 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., C239 of human PTGR1 or cysteine corresponding to C239 of human PTGR1) of the PTGR1 protein (e.g., human PTGR1).

[0250] In embodiments, the PTGR1 protein (e.g., SEQ ID NO: 1) is covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., SEQ ID NO:1) is irreversibly covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., SEQ ID NO:1) is reversibly covalently bonded to a PTGR1 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the PTGR1 protein (e.g., SEQ ID NO:1) is covalently bonded to a portion of a PTGR1 inhibitor (e.g., compound described herein). In embodiments, the PTGR1 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., C239 of SEQ ID NO: 1 or cysteine corresponding to C239 of SEQ ID NO: 1) of the PTGR1 protein (e.g., SEQ ID NO: 1). In embodiments, the portion (e.g., the product of an electrophilic reaction with C239 of SEQ ID NO: 1 or cysteine corresponding to C239 of SEQ ID NO: 1) of a PTGR1 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., C239 of SEQ ID NO: 1 or cysteine corresponding to C239 of SEQ ID NO: 1) of the PTGR1 protein (e.g., SEQ ID NO:1).

[0251] In embodiments, the PTGR1 protein covalently bonded to a PTGR1 inhibitor or compound described herein is the product of a reaction between the PTGR1 protein and a PTGR1 inhibitor or compound described herein (e.g., a reaction between the electrophilic group and a cysteine of the PTGR1 protein). It will be understood that the covalently bonded PTGR1 protein and PTGR1 inhibitor (e.g., compound described herein) are the remnants of
the reactant PTGR₁ protein and PTGR₁ inhibitor or compound, wherein each reactant now participates in the covalent bond between the PTGR₁ protein and PTGR₁ inhibitor or compound. In embodiments of the covalently bonded PTGR₁ protein and compound described herein, the remnant of the covalently bonded PTGR₁ protein and compound herein, the remnant of the alkenyl containing substituent is a linker including a covalent bond between the PTGR₁ protein and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when a PTGR₁ protein is covalently bonded to a PTGR₁ inhibitor (e.g., compound described herein), the PTGR₁ inhibitor (e.g., compound described herein) forms a remnant of the pre-reacted PTGR₁ inhibitor (e.g., compound described herein) wherein a bond connects the remnant of the PTGR₁ inhibitor (e.g., compound described herein) to the remnant of the PTGR₁ protein (e.g., cysteine sulfur, sulfur of amino acid corresponding to C239 of human PTGR₁, sulfur of C239 of human PTGR₁ (e.g., SEQ ID NO:1)). The remnant of the PTGR₁ inhibitor (e.g., a compound described herein) may also be called a portion of the PTGR₁ inhibitor. In embodiments, the remnant of the alkenyl containing moiety is a linker selected from a bond, -S(0)₂-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -NHC(O)NH-, -C(0)O-, -OC(O)-, -CH₂NH-, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkenylene (e.g., C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocy cloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

As a non-limiting example, the PTGR₁ protein covalently bonded to a PTGR₁ inhibitor may have the formula:
wherein \( S \) is the sulfur of a PTGRI protein cysteine (e.g., corresponding to C239 of human PTGRI, SEQ ID NO: 1), which is bonded to the remainder of the PTGRI protein and wherein \( R^1, R^2, z_1 \), and \( z_2 \) are as described herein. As a non-limiting example, the PTGRI protein covalently bonded to a PTGRI inhibitor may have the formula:

wherein \( S \) is the sulfur of a PTGRI protein cysteine (e.g., corresponding to C239 of human PTGRI), which is bonded to the remainder of the PTGRI protein and wherein \( R^{1.1}, R^{1.2}, R^{1.3}, R^{1.4}, R^{1.5}, R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, \) and \( R^{2.5} \) are as described herein. As a non-limiting example, the PTGRI protein covalently bonded to a PTGRI inhibitor may have the formula:

wherein \( S \) is the sulfur of a PTGRI protein cysteine (e.g., corresponding to C239 of human PTGRI, SEQ ID NO: 1), which is bonded to the remainder of the PTGRI protein and wherein \( R^{1.2}, R^{1.3}, R^{1.5}, \) and \( R^{2.3} \) are as described herein. As a non-limiting example, the PTGRI protein covalently bonded to a PTGRI inhibitor may have the formula:

wherein \( S \) is the sulfur of a PTGRI protein cysteine (e.g., corresponding to C239 of human PTGRI, SEQ ID NO: 1), which is bonded to the remainder of the PTGRI protein.
VII. Embodiments

[0252] Embodiment P1. A compound having the formula:

![Chemical Structure](I)

wherein,

- $R^1$ is independently halogen, -CX$^2$, -CHX$^2$, -CH$^2$X, -OCX$^2$, -OCH$^2$X, -OCHX$^2$, -CN, -SO$_n$R$^{1b}$, -SO$_m$NR$_{B}$R$_{B}$, -NHC(0)NR$_{A}$R$_{A}$, -N(0)$_{m}$, -NR$_{A}$R$_{B}$, -C(0)R$^{1c}$, -C(0)-OR$^{1c}$, -C(0)NR$_{A}$R$_{B}$, -OR$_{B}$, -NR$_{A}$SO$_2$R$_{B}$, -NR$_{A}$C(0)R$^{1c}$, -NR$_{A}$C(0)R$_{B}$, -NR$_{A}$O R$^{1c}$, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

- $R^2$ is independently halogen, -CX$^2$, -CHX$^2$, -CH$^2$X, -OCX$^2$, -OCH$^2$X, -OCHX$^2$, -CN, -SO$_n$R$^{2D}$, -SO$_m$NR$_{2A}$R$^{2B}$, -NHC(0)NR$_{2A}$R$_{2B}$, -N(0)$_{m}$, -NR$_{2A}$R$_{2B}$, -C(0)R$^{2C}$, -C(0)-OR$^{2C}$, -C(0)NR$_{2A}$R$_{2B}$, -OR$^{2D}$, -NR$_{2A}$SO$_2$R$_{2D}$, -NR$_{2A}$C(0)R$^{2C}$, -NR$_{2A}$C(0)R$_{2D}$, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

- $z_1$ is an integer from 0 to 5;

- $z_2$ is an integer from 0 to 5;

- Each $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{2A}$, $R^{2B}$, $R^{2C}$, and $R^{2D}$ is independently hydrogen, -CX$^2$, -CN, -COOH, -CONH$_2$, -CHX$^2$, -CH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroaryl; $R^{1A}$ and $R^{1B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl; R$^{2A}$ and R$^{2B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or 
unsubstituted heteroaryl:

each X, X$^1$, and X$^2$ is independently -F, -Cl, -Br, or -I;

n1 and n2 are independently an integer from 0 to 4; and

m1, m2, v1, and v2 are independently an integer from 1 to 2.

[0253] Embodiment P2. The compound of embodiment P1 having the formula:

![Diagram](image)

wherein,

R$^{1A}$, R$^{1B}$, R$^{1C}$, and R$^{1D}$ are independently hydrogen, halogen, -CX$^1$-$\alpha$,$\beta$,
-CHX$^2$-$\alpha$,$\beta$, -OCX$^3$-$\alpha$,$\beta$,

OCH$^1$-$\alpha$,$\beta$, -OCH$^2$-$\alpha$,$\beta$, -CN, -SO$^1$-$\alpha$,$\beta$,$\gamma$,$\delta$,-SO$^1$-$\alpha$,$\beta$,$\gamma$,$\delta$,
-NHC(0)$\alpha$,$\beta$-$\alpha$,$\beta$,-NR$^1$-$\alpha$,$\beta$,$\gamma$,$\delta$,-NR$^1$-$\alpha$,$\beta$,$\gamma$,$\delta$,
-C(0)$\alpha$,$\beta$,-C(0)$\alpha$,$\beta$-OR$^1$-$\alpha$,$\beta$,-C(0)$\alpha$,$\beta$-NHR$^1$-$\alpha$,$\beta$,-N(0)$\alpha$,$\beta$,$\gamma$,$\delta$,-NR$^1$-$\alpha$,$\beta$,$\gamma$,$\delta$,

R$^{1C}$,-NR$^1$-$\alpha$,$\beta$R$^{1C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R$^{2A}$, R$^{2B}$, R$^{2C}$, and R$^{2D}$ are independently hydrogen, halogen, -CX$^2$-$\alpha$,$\beta$,
-CHX$^2$-$\alpha$,$\beta$, -OCX$^3$-$\alpha$,$\beta$,

OCH$^2$-$\alpha$,$\beta$, -OCH$^2$-$\alpha$,$\beta$, -CN, -SO$^1$-$\alpha$,$\beta$,$\gamma$,-SO$^1$-$\alpha$,$\beta$,$\gamma$,-NHC(0)$\alpha$,$\beta$-$\alpha$,$\beta$,-NR$^1$-$\alpha$,$\beta$,$\gamma$,-NR$^1$-$\alpha$,$\beta$,$\gamma$,
-C(0)$\alpha$,$\beta$,-C(0)$\alpha$,$\beta$-OR$^1$,-C(0)$\alpha$,-NR$^2$-$\alpha$,$\beta$,$\gamma$,-NR$^2$-$\alpha$,$\beta$,$\gamma$,$\delta$,

R$^{2C}$,-NR$^2$-$\alpha$,$\delta$R$^{2C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0254] Embodiment P3. The compound of embodiment P2 having the formula:

![Diagram](image)

[0255] Embodiment P4. The compound of one of embodiments P2 to P3, wherein R$^{1A}$ is
substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl; R$^{1C}$ is -OCX$^1$-$\alpha$,$\beta$,
OCH2X¹, -OCHX², -OR¹, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R¹ is -OCX², -OCH2X¹, -OCHX², -OR¹, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and R² is -OCX³, -OCH2X², -OCHX², -OR², substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

[0256] Embodiment P5. The compound of embodiment P4, wherein R¹ is unsubstituted alkyl; R¹ is -OR¹; R¹ is -OR¹; R² is -OR²; and each R¹ and R² is independently hydrogen, -CX³, -CHX₂, -CH₂X, substituted or unsubstituted alkyl.

[0257] Embodiment P6. The compound of embodiment P4, wherein R¹ is unsubstituted Ci-C₈ alkyl; R¹ is -OR¹; R¹ is -OR¹; R² is -OR²; and each R¹ and R² is independently hydrogen or substituted or unsubstituted Ci-Cs alkyl.

[0258] Embodiment P7. The compound of embodiment P4, wherein R¹ is unsubstituted C₁-C₅ alkyl; R¹ is -OH; R¹ is -OR¹; R² is -OH; and R¹ is independently hydrogen or unsubstituted C₁-C₄ alkyl.

[0259] Embodiment P8. The compound of embodiment P4, wherein R¹ is unsubstituted C₁-C₅ alkyl; R¹ is -OH; R¹ is -OR¹; R² is -OH; and R¹ is independently unsubstituted C₁-C₂ alkyl.

[0260] Embodiment P9. The compound of embodiment P4, wherein R¹ has the formula

\[
\begin{align*}
\text{R}^1 & \text{ is } -\text{OH}; \text{R}^1 & \text{ is } -\text{OR}^1; \text{R}^2 & \text{ is } -\text{OH}; \text{and } \text{R}^1 & \text{ is independently unsubstituted C1-C2 alkyl.}
\end{align*}
\]

[0261] Embodiment P10. The compound of one of embodiments P1 to P9, wherein the compound is not licochalcone A.


[0264] Embodiment P13. A method of inhibiting prostaglandin reductase 1 (PTGR1) activity, said method comprising contacting the PTGR1 protein with an effective amount of a prostaglandin reductase 1 (PTGR1) inhibitor.
[0265] Embodiment P14. The method of embodiment P13, wherein the prostaglandin reductase 1 (PTGR1) inhibitor is an oligonucleotide (e.g., siRNA or shRNA), protein (e.g., antibody), or compound.

[0266] Embodiment P15. The method of embodiment P14, wherein the prostaglandin reductase 1 (PTGR1) inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGR1.

[0267] Embodiment P16. The method of embodiment P14, wherein the prostaglandin reductase 1 (PTGR1) inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, N217, Y245, V271, or V272 of human PTGR1.

[0268] Embodiment P17. A method of inhibiting prostaglandin reductase 1 (PTGR1) activity, said method comprising contacting the PTGR1 protein with an effective amount of a compound of one of embodiments P1 to P10.

[0269] Embodiment P18. The method of embodiment P17, wherein the compound is covalently bonded to the amino acid corresponding to C239 of human PTGR1.

[0270] Embodiment P19. The method of embodiment P17, wherein the compound contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of human PTGR1.

[0271] Embodiment P20. The method of one of embodiments P13 to P19, wherein the PTGR1 activity is reducing a 15-keto-prostaglandin or leukotriene B4.

[0272] Embodiment P21. The method of one of embodiments P13 to P19, wherein the PTGR1 activity is binding NADP+.

[0273] Embodiment P22. A method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a prostaglandin reductase 1 (PTGR1) inhibitor.


[0275] Embodiment P24. The method of one of embodiments P22 to P23, wherein the cancer is lung cancer, prostate cancer, or breast cancer.
Embodiment P25. The method of one of embodiments P22 to P23, wherein the cancer is triple negative breast cancer.

Embodiment P26. A PTGRI protein covalently bonded to a prostaglandin reductase 1 (PTGRI) inhibitor.

Embodiment P27. A PTGRI protein covalently bonded to a compound of one of embodiments P1 to P10 through the reacted residue of an electrophilic group.

Embodiment P28. The PTGRI protein of embodiment P27, wherein the compound is bonded to a cysteine residue of the protein.

Embodiment P29. The PTGRI protein of embodiment P27, covalently bonded to a portion of a compound of one of embodiments P1 to P10.

Embodiment P30. The PTGRI protein of embodiment P27, irreversibly covalently bonded to a portion of a compound of one of embodiments P1 to P10.

Embodiment P31. The PTGRI protein of one of embodiments P27 to P30, wherein the compound or portion of the compound is covalently bonded to an amino acid corresponding to C239 of human PTGRI.

VIII. Additional Embodiments

Embodiment 1. A method of inhibiting prostaglandin reductase 1 (PTGRI) activity, said method comprising contacting a PTGRI protein with an effective amount of a prostaglandin reductase 1 (PTGRI) inhibitor, wherein said PTGRI inhibitor contacts one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1; and said PTGRI inhibitor is covalently bonded to the amino acid corresponding to C239 of SEQ ID NO: 1, thereby forming a PTGRI protein covalently bonded to said PTGRI inhibitor.

Embodiment 2. The method of embodiment 1, wherein the prostaglandin reductase 1 (PTGRI) inhibitor has the formula: (I),

\[
\text{(I)} \\
\text{wherein,}
\]

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R\(^1\) is independently halogen, -CX\(^{1}\), -CHX\(^{1}\), -CH2X \(^{1}\), -OCX\(^{1}\), -OCH2X \(^{1}\), -OCHX\(^{1}\), -CN, -SO\(_{2}\)R \(^{1}\), -SO\(_{2}\)NR \(^{1}\), -NH\(_{C}(0)\)NR \(^{1}\), -N(0) \(^{1}\), -NR \(^{1}\), -NR \(^{1}\), -C(O)R \(^{1}\), -C(0)-OR \(^{1}\), -C(0)NR \(^{1}\), -OR \(^{1}\), -NR \(^{1}\)SO \(_{2}\)R \(^{1}\), -NR \(^{1}\)C(0)R \(^{1}\), -NR \(^{1}\)C(0)R \(^{1}\), -NR \(^{1}\)A0R \(^{1}\), -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R\(^1\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; 

z1 is an integer from 0 to 5; 

R\(^2\) is independently halogen, -CX \(^{2}\), -CHX \(^{2}\), -CH2X \(^{2}\), -OCX \(^{2}\), -OCH2X \(^{2}\), -OCHX \(^{2}\), -CN, -SO\(_{2}\)R \(^{2}\), -SO \(_{2}\)NR \(^{2}\), -NH\(_{C}(0)\)NR \(^{2}\), -N(0) \(^{2}\), -NR \(^{2}\), -NR \(^{2}\), -C(O)R \(^{2}\), -C(0)-OR \(^{2}\), -C(0)NR \(^{2}\), -OR \(^{2}\), -NR \(^{2}\)SO \(_{2}\)R \(^{2}\), -NR \(^{2}\)C(0)R \(^{2}\), -NR \(^{2}\)C(0)R \(^{2}\), -NR \(^{2}\)A0R \(^{2}\), -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; 

z2 is an integer from 0 to 5; 

Each R \(^{1A}\), R \(^{1B}\), R \(^{1C}\), R \(^{1D}\), R \(^{2A}\), R \(^{2B}\), R \(^{2C}\), and R \(^{2D}\) is independently hydrogen, -CX \(^{3}\), -CN, -COOH, -CONH2, -CHX \(^{2}\), -CH2X \(^{2}\), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; 

unsubstituted heteroaryl; R \(^{1A}\) and R \(^{1B}\) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R \(^{2A}\) and R \(^{2B}\) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; 

each X, X \(^1\), and X \(^2\) is independently -F, -Cl, -Br, or -I;  
n1 and n2 are independently an integer from 0 to 4; and  
ml, m2, vl, and v2 are independently an integer from 1 to 2.
Embodiment 3. A method of inhibiting prostaglandin reductase 1 (PTGR1) activity, said method comprising contacting a PTGR1 protein with an effective amount of a compound having the formula: (R^1)_{z1} (I), wherein,

R^1 is independently halogen, -CX^-, -CHX^-, -CH2X^-, -OCX^-, -

OCH2X^1, -OCHX^2, -CN, -SO_{nR}^{1D}, -SO_{iNR}^{1A,R^{1B}, -NH}C(0)NR^{1A,R^{1B}, -N(0)_{m}i}, -NR^{1A,R^{1B}, -C(O)R^{1C}, -C(O)-OR^{1C}, -C(0)NR^{1A,R^{1B}, -OR^{1D}, -NR^{1A}SO^{2}R^{1D}, -NR^{1A}C(0)R^{1C}, -NR^{1A}C(0)O R^{1C}, -NR^{1A}OR^{1C}, -N_{3}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

two adjacent R^1 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z1 is an integer from 0 to 5;

R^2 is independently halogen, -CX^3, -CHX^2, -CH_{2}X^2, -OCX^2, -

OCH2X^2, -OCHX^3, -CN, -SO_{2R}^{2D}, -SO_{2iNR}^{2A,R^{2B}, -NH}C(0)NR^{2A,R^{2B}, -N(0)_{m}2}, -NR^{2A,R^{2B}, -C(O)R^{2C}, -C(O)-OR^{2C}, -C(0)NR^{2A,R^{2B}, -OR^{2D}, -NR^{2A}SO^{2}R^{2D}, -NR^{2A}C(0)R^{2C}, -NR^{2A}C(0)O R^{2C}, -NR^{2A}OR^{2C}, -N_{3}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

two adjacent R^2 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z2 is an integer from 0 to 5;

Each R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, and R^{2D} is independently hydrogen, -CX, -CN, -COOH, -CONH2, -CHX^2, -CH_{2}X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X', and X'' is independently -F, -Cl, -Br, or -I;

n1 and n2 are independently an integer from 0 to 4; and

ml, m2, vl, and v2 are independently an integer from 1 to 2.

[0286] Embodiment 4. The method of embodiment 3, wherein the compound is capable of covalently bonding to the amino acid corresponding to C239 of SEQ ID NO: 1.

[0287] Embodiment 5. The method of embodiments 3 or 4, wherein the compound is capable of contacting one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NCvl.

[0288] Embodiment 6. The method of one of embodiments 1 to 5, wherein the PTGR1 activity is reducing the activity of 15-keto-prostaglandin or leukotriene B4.

[0289] Embodiment 7. The method of one of embodiments 1 to 5, wherein the PTGR1 activity is binding NADP+.

[0290] Embodiment 8. The method of any one of embodiments 3 to 7, wherein the compound has the formula:

![Chemical Structure](image)

(1a), wherein,

R^1, R^2, R^3, R^4, and R^5 are independently hydrogen, halogen, -CX^3, -CHX^2, -CH2X^1, -OCX^1, -OCH2X^1, -OCHX^A, -CN, -SO^2NR^1, -SO^2iNR^1R^2, -NHC(0)NR^1R^2, -N(N(0)mi), -NR^1R^2, -C(0)OR^1C, -C(0)-OR^1C, -C(0)NR^1R^2, -OR^1C, -NR^1SO_2R^1D, -NR^1A(C(0))OR^1C, -NR^1AOR^1C, -N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^2, R^2, R^3, R^4, and R^5 are independently hydrogen, halogen, -CX^2, -CHX^2, -CH2X^2, -OCX^2, -OCH2X^2, -OCHX^2, -CN, -SO^2AR^2D, -SO^2NR^2AR^2B, -NHC(0)NR^2AAR^2B, -N(0)m2, -NR^2AAR^2B, -C(0)R^2C, -C(0)-OR^2C, -C(0)NR^2AAR^2B, -OR^2D, -NR^2AOR^2C, -N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0291] Embodiment 9.  The method of embodiment 8, wherein the compound has the

\[
\text{formula: } \text{(Ib)}
\]

[0292] Embodiment 10.  The method of embodiments 8 or 9, wherein: \(R^{1,2}\) is independently substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl; \(R^{1,3}\) is independently \(-\text{OCX}_1\), \(-\text{OCH}_2\), \(-\text{OCHX}\), \(-\text{OR}^\circ\), substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; \(R^{1,5}\) is independently \(-\text{OCX}\), \(-\text{OCH}_2\), \(-\text{OCHX}\), \(-\text{OR}^\circ\), substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and \(R^{2,3}\) is independently \(-\text{OCX}^\circ\), \(-\text{OCH}_2\), \(-\text{OCHX}\), \(-\text{OR}^\circ\), substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

[0293] Embodiment 11.  The method of embodiments 8 or 9, wherein \(R^{1,2}\) is independently unsubstituted alkyl; \(R^{1,3}\) is independently \(-\text{OR}^\circ\); \(R^{1,5}\) is independently \(-\text{OR}^\circ\); \(R^{2,3}\) is independently \(-\text{OR}^\circ\); and each \(R^\circ\) and \(R^{2,3}\) is independently hydrogen, \(-\text{CX}_3\), \(-\text{CHX}_2\), \(-\text{CH}_2\), substituted or unsubstituted alkyl.

[0294] Embodiment 12.  The method of embodiments 8 or 9, wherein \(R^{1,2}\) is independently unsubstituted \(C_1-C_5\) alkyl; \(R^{1,3}\) is independently \(-\text{OR}^\circ\); \(R^{1,5}\) is independently \(-\text{OR}^\circ\); \(R^{2,3}\) is independently \(-\text{OR}^\circ\); and each \(R^\circ\) and \(R^{2,3}\) is independently hydrogen or substituted or unsubstituted \(C_1-C_5\) alkyl.

[0295] Embodiment 13.  The method of embodiments 8 or 9, wherein \(R^{1,2}\) is independently unsubstituted \(C_1-C_5\) alkyl; \(R^{1,3}\) is independently \(-\text{OH}\); \(R^{1,5}\) is independently \(-\text{OR}^\circ\); \(R^{2,3}\) is independently \(-\text{OH}\); and \(R^\circ\) is independently hydrogen or unsubstituted \(C_1-C_4\) alkyl.

[0296] Embodiment 14.  The method of embodiments 8 or 9, wherein \(R^{1,2}\) is independently unsubstituted \(C_1-C_5\) alkenyl; \(R^{1,3}\) is independently \(-\text{OH}\); \(R^{1,5}\) is independently \(-\text{OR}^\circ\); \(R^{2,3}\) is independently \(-\text{OH}\); and \(R^\circ\) is independently unsubstituted \(C_1-C_2\) alkyl.
[0297] Embodiment 15. The method of embodiments 8 or 9, wherein R₁ is independently 
has the formula \( R^{1,3} \) is independently -OH; \( R^{1,5} \) is independently -OR \( ^{1,0} \); \( R^{2,3} \) is independently -OH; and \( R^{1,0} \) is independently unsubstituted C₁-C₂ alkyl.

[0298] Embodiment 16. The method of any one of embodiments 3 to 15, wherein the 
compound is not licochalcone A.

administering to a subject in need thereof an effective amount of a prostaglandin reductase 1 
(PTGR1) inhibitor.

[0300] Embodiment 18. The method of embodiment 17, wherein the cancer is lung 
cancer, prostate cancer, or breast cancer.

[0301] Embodiment 19. The method of embodiment 17, wherein the cancer is triple 
negative breast cancer.

[0302] Embodiment 20. The method of any one of embodiments 17 to 19, said method 
comprising administering to a subject in need thereof an effective amount of a compound 

having the formula: \((R^{1})_{z1}\) (I), wherein,

\( R^{1} \) is independently halogen, -CXⁿ, -CHXⁿ, -CHX², -OCXⁿ, - 
OCH₂X, -OCHXⁿ, -CN, -SOₙR, -SOₙNR, -NR C(0)NR, -NR C(0)ₙi, -NR C(0)R \( ^{1,0} \), 
-OR \( ^{1,0} \), -NR C(0)SOₙR, -NR C(0)R \( ^{1,0} \), -NR C(0)C(0)R \( ^{1,0} \) 
R \( ^{1,0} \) C, -NR CₙOR \( ^{1,0} \), -Nₙ, substituted or unsubstituted alkyl, substituted or unsubstituted 
heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted 
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; 
two adjacent \( R^{1} \) substituents may optionally be joined to form a substituted or unsubstituted 
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or 
substituted or unsubstituted heteroaryl;

\( z₁ \) is an integer from 0 to 5;

\( R^{2} \) is independently halogen, -CX ², -CHX ², -CH₂X ², -OCX ², - 
OCH₂X ², -OCHX ², -CN, -SO₂R ²D, -SO₂R ²B, -SO₂NR ²D, -NH C(0)NR ²D, 
-NR ²D, -NR ²D, -NR ²D, -NR ²D, -NR ²C(0)R ²C, -NR ²C(0)R ²C, 
-NR ²C(0)R ²C, -NR ²C(0)R ²C,
R\textsuperscript{2C}, -NR\textsuperscript{2A}OR\textsuperscript{2C}, -N\textsubscript{3}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R\textsuperscript{2} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

\(z_2\) is an integer from 0 to 5;

Each R\textsuperscript{1A}, R\textsuperscript{1B}, R\textsuperscript{1C}, R\textsuperscript{1d}, R\textsuperscript{2A}, R\textsuperscript{2B}, R\textsuperscript{2C}, and R\textsuperscript{2D} is independently hydrogen, -CX\textsubscript{3}, -CN, -COOH, -CONH\textsubscript{2}, -CHX\textsubscript{2}, -CH\textsubscript{2}X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\textsuperscript{2A} and R\textsuperscript{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X\textsuperscript{1}, and X\textsuperscript{2} is independently -F, -Cl, -Br, or -I;

n\textsubscript{1} and n\textsubscript{2} are independently an integer from 0 to 4; and

m\textsubscript{1}, m\textsubscript{2}, v\textsubscript{1}, and v\textsubscript{2} are independently an integer from 1 to 2; wherein the compound does not have the formula:

\[\text{[0303] Embodiment 21. The use of a compound for the preparation of a medicament for the treatment of cancer, wherein the compound has the formula:}\]

\[\text{(I), wherein,}\]

R\textsuperscript{1} is independently halogen, -CX\textsubscript{3}, -CHX\textsubscript{3}, -CH\textsubscript{2}X\textsubscript{1}, -OCX\textsubscript{3}, -OCH\textsubscript{X}, -OC\textsubscript{X}\textsubscript{3}, -CN, -SO\textsubscript{N}R\textsuperscript{1d}, -SO\textsubscript{vi}NR\textsuperscript{1A}R\textsuperscript{1b}, -NH\textsubscript{C}(0)NR\textsuperscript{1A}R\textsuperscript{1B}, -N(0)\textsubscript{m}i, -NR\textsuperscript{1A}R\textsuperscript{1B}, -C(0)R\textsuperscript{1C}, -C(0)-OR\textsuperscript{1C}, -C(0)NR\textsuperscript{1A}R\textsuperscript{1B}, -OR\textsuperscript{1d}, -NR\textsuperscript{1A}SO\textsubscript{2}R\textsuperscript{1d}, -NR\textsuperscript{1A}C(0)R\textsuperscript{1C}, -NR\textsuperscript{1A}C(0)R\textsuperscript{1C}, -NR\textsuperscript{1A}R\textsuperscript{1C}, -NR\textsuperscript{1A}R\textsuperscript{1C}, -N\textsubscript{3}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
two adjacent $R^1$ substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

$$z_1 \text{ is an integer from 0 to 5;}$$

$R^2$ is independently halogen, -CX$_2$, -CHX$_2$, -CH$_2$X, -OCX$_2$, -OCH$_2$X, -OCHX$_2$, -CN, -SO$_2$R, -SO$_2$NR$_2$, -NHC(0)NR$_2$, -N(0)$_m$, -NR$_2$, -C(0)R, -C(0)OR, -C(0)NR$_2$, -C(0)NR$_2$OR, -C(0)NR$_2$SO$_2$, -C(0)NR$_2$C(O)R, -NR$_2$C(O)R, -NR$_2$OR, -N$_3$. substituted or unsubstituted alkyl, substituted or unsubstituted

two adjacent $R^2$ substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

$$z_2 \text{ is an integer from 0 to 5;}$$

Each $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{2A}$, $R^{2B}$, $R^{2C}$, and $R^{2D}$ is independently hydrogen, -CX$_3$, -CN, -COOH, -CONH$_2$, -CHX$_2$, -CH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
unsubstituted heteroaryl; $R^{1A}$ and $R^{1B}$ substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl; $R^{2A}$ and $R^{2B}$ substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl;

$$\text{each } X, X^1, \text{ and } X^2 \text{ is independently } -F, -Cl, -Br, \text{ or } I;$$

$n_1$ and $n_2$ are independently an integer from 0 to 4; and

$m_1$, $m_2$, $v_1$, and $v_2$ are independently an integer from 1 to 2, wherein the

$$\text{compound is not}$$

![Chemical structure](image)
Embodiment 22. A PTGR1 protein covalently bonded to a compound through the reacted residue of an electrophilic group, wherein the compound has the formula:

![Chemical structure](image)

(1), wherein,

- \( R^1 \) is independently halogen, -CX^3, -CHX^5, -CH2X \(^1\), -OCX \(^1\), -OCH2X \(^1\), -OCHX \(^1\), -CN, -SO\(_2\)NR \(^1\)A, -SO\(_3\)_iNR \(^1\)A, -NHC(0)NR \(^1\)A, -N(0) \(_m_2\), -NR \(^1\)A, -C(0)R \(^1\)C, -C(0)-OR \(^1\)C, -C(0)NR \(^1\)A, -OR \(^1\)B, -NR \(^1\)A\(_2\)SO \(_2\)R \(^1\)B, -NR \(^1\)A\(_2\)C(0)R \(^1\)C, -NR \(^1\)A(0)C(0)R \(^1\)C, -NR \(^1\)A\(_1\)O R \(^1\)C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- \( z_1 \) is an integer from 0 to 5;

- \( R^2 \) is independently halogen, -CX\(^2\), -CHX\(^2\), -CH\(_2\)X\(^2\), -OCX\(^2\), -OCH\(_2\)X\(^2\), -CN, -SO\(_2\)NR \(^3\)A, -SO\(_3\)_iNR \(^3\)A, -NHC(0)NR \(^3\)A, -N(0) \(_m_2\), -NR \(^3\)A, -C(0)R \(^3\)C, -C(0)-OR \(^3\)C, -C(0)NR \(^3\)A, -OR \(^3\)B, -NR \(^3\)A\(_2\)SO \(_2\)R \(^3\)B, -NR \(^3\)A\(_2\)C(0)R \(^3\)C, -NR \(^3\)A(0)C(0)R \(^3\)C, -NR \(^3\)A\(_1\)O R \(^3\)C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- two adjacent \( R^2 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- \( z_2 \) is an integer from 0 to 5;

- Each \( R^1A, R^1B, R^1C, R^1D, R^2A, R^2B, R^2C, \) and \( R^2D \) is independently

- hydrogen, -CX\(_3\), -CN, -COOH, -CONH\(_2\), -CHX\(_2\), -CH\(_2\)X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^1A \) and \( R^1B \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^2A \) and \( R^2B \) substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X', and X'' is independently -F, -Cl, -Br, or -I;
n1 and n2 are independently an integer from 0 to 4; and
ml, ml', vl, and v2 are independently an integer from 1 to 2.

[0305] Embodiment 23. The PTGR1 protein of embodiment 22, wherein the compound is bonded to a cysteine residue of the protein.


[0307] Embodiment 25. The PTGR1 protein of embodiment 22, wherein the compound or portion of the compound is covalently bonded to an amino acid corresponding to C239 of SEQ ID NO:1.


[0309] Embodiment 27. The pharmaceutical composition of embodiment 26, wherein

the PTGR1 inhibitor has the formula: \((\text{R}^1)_{\text{z}1}\) (I), wherein,

\(\text{R}^1\) is independently halogen, -CX^, -CHX^, -CH2X^, -OCX^, -
OCH2X^, -OCHX^, -CN, -SO2NR^1b, -SO2NR, 1^A R^1b, -NH (0)NR^1A R^1b, -N (0)m^i, -NR^1A R^1b, -
-C (0)R^1C, -C (0)-OR^1c, -C (0)NR^1A R^1b, -NR^1A SO2^2R^1b, -NR^1A C (0)R^1C, -NR^1A C (0)0

20 R^1C, -NR^1A OR^1C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
two adjacent \(\text{R}^1\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
25 substituted or unsubstituted heteroaryl;

z1 is an integer from 0 to 5;

\(\text{R}^2\) is independently halogen, -CX^, -CHX^, -CH2X^, -OCX^, -
OCH2X^, -OCHX^, -CN, -SO2NR^1d, -SO2NR, 2^A R^2b, -NH (0)NR^2A R^2b, -N (0)m^22, -NR^2A R^2b, -
-C (0)R^2C, -C (0)-OR^2c, -C (0)NR^2A R^2b, -OR^2d, -NR^2A SO2^2R^2b, -NR^2A C (0)R^2C, -NR^2A C (0)0
\[ R^2C, -NR^2AOR^2C, -N_3, \text{substituted or unsubstituted alkyl}, \text{substituted or unsubstituted heteroalkyl}, \text{substituted or unsubstituted cycloalkyl}, \text{substituted or unsubstituted heterocycloalkyl}, \text{substituted or unsubstituted aryl}, \text{or} \text{substituted or unsubstituted heteroaryl}; \]

\text{two adjacent} \ R^2 \text{substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;}

\( z2 \) \ is \ an \ integer \ from \ 0 \ to \ 5;

Each \ R^{1b}, R^{1c}, R^{1d}, R^{2a}, R^{2b}, R^{2c}, \text{and} \ R^{2d} \ is \ independently \ hydrogen, \ -\text{CX}_3, -\text{CN}, -\text{COOH}, -\text{CONH}_2, -\text{CHX}_2, -\text{CH}_2X, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;} \ R^{1a} \text{and} \ R^{1b} \text{substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;} \ R^{2a} \text{and} \ R^{2b} \text{substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;}

\text{each} \ X, X^l, \text{and} \ X^2 \ is \ independently \ -\text{F}, -\text{Cl}, -\text{Br}, \text{or} -\text{I};

n1 \text{and} \ n2 \text{are independently an integer from} \ 0 \text{to} \ 4; \text{and}

m1, m2, v1, \text{and} \ v2 \text{are independently an integer from} \ 1 \text{to} \ 2.

[0310] Embodiment 28. \ A \ method \ of \ treating \ triple \ negative \ breast \ cancer, \ said \ method \ comprising \ administering \ to \ a \ subject \ in \ need \ thereof \ an \ effective \ amount \ of \ a \ compound

\text{having the formula:} \ (R^1)^{z_1} \ (R^2)^{z_2} \quad \text{(I), wherein,}

\text{R}^1 \text{is independently halogen,} \ -\text{CX}^\wedge, -\text{CHX}^\wedge, -\text{CH}_2X^\wedge, -\text{OCX}^\wedge, -\text{OCH}_2X^\wedge, -\text{OCHX}^\wedge, -\text{CN, -SONiR}^{1d}, -\text{SOvNR}^{1a}R^{1b}, -\text{NHC}(0)NR^{1a}R^{1b}, -\text{N}(0)_m^i, -\text{NR}^{1a}R^{1b}, -\text{C}(0)R^{1c}, -\text{C}(0)-OR^{1c}, -\text{C}(0)NR^{1a}R^{1b}, -\text{OR}^{1d}, -\text{NR}^{1a}S_2R^{1d}, -\text{NR}^{1a}C(0)R^{1c}, -\text{NR}^{1a}C(0)0R^{1c}, -\text{NR}^{1a}0R^{1c}, -\text{N}_3, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent} \ R^1 \text{substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;}
z1 is an integer from 0 to 5;
R2 is independently halogen, -CX2, -CHX2, -CH2X2, -OCX2, -OCH2X2, -OCHX2, -CN, -SO2R2, -SO2NR2R2B, -NH2C(0)NR2A2R2B, -NR2A2R2B, -C(0)R 2C, -C(0)-OR 2C, -C(0)NR 2A2R2B, -OR 2D, -NR2ASOR2D, -NR2A(C(0)R 2C, -NR2A(C(0)R 0
5 R2C, -NR2AOR2C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R2 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
z2 is an integer from 0 to 5;
Each R1A, R1B, R1C, R1D, R2A, R2B, R2C, and R2D is independently hydrogen, -CX2, -CN, -COOH, -CONH2, -CHX2, -CH2X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R1A and R1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R2A and R2B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;
each X, X1, and X2 is independently -F, -Cl, -Br, or -I;
n1 and n2 are independently an integer from 0 to 4; and
ml, m2, ml, and m2 are independently an integer from 1 to 2.

[0311] Embodiment 29. The method of embodiment 28, wherein the compound has the

![Diagram](image)

formula: (la), wherein,

R11, R12, R13, R14, and R15 are independently hydrogen, halogen, -CX1, -CHX, -CH2X, -OCX1, -OCH2X, -OCX, -CN, -SO2R1D, -SO2NR1A2R1B, -NH2C(0)NR1A2R1B, -NR1A2R1B, -N(0)mi, -NR1A2R1B, -C(0)R 1C, -C(0)-OR 1C, -C(0)NR1A2R1B, -OR 1D, -NR 1A2SO 2R1D, -NR1A2C(0)R 1C, -NR1A2C(0)OR 1C, -NR1A20 R 1C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

\[ R^{2,1}, R^{2,2}, R^{2,3}, R^{2,4}, \text{ and } R^{2,5} \text{ are independently hydrogen, halogen, } -\text{CX}_2^3, -\text{CHX}_2^2, -\text{CH}_2\text{X}_2^2, -\text{OCH}_2\text{X}_2^2, -\text{OCHX}_2^2, -\text{CN}, -\text{SO}_3^2\text{R}^{2D}, -\text{SO}_2\text{NR}^{2A}\text{R}^{2B}, \]

\[ -\text{NH}_2(\text{NR})^2\text{R}^{2B}, -\text{N}(\text{NR})^2\text{R}^{2B}, -\text{C}(\text{NR})^2\text{R}^{2C}, -\text{C}(\text{N})^2\text{R}^{2A}\text{R}^{2B}, -\text{OR}^{2D}, -\text{NR}^{2A}\text{SO}_2^2\text{R}^{2D}, -\text{NR}^{2A}\text{C}(\text{NR})^2\text{R}^{2C}, -\text{NR}^{2A}\text{C}(\text{N})^2\text{R}^{2C}, -\text{NR}^{2A}\text{OR}^{2C}, -\text{N}_3, \]

substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

10 **[0312]** Embodiment 30. The method of embodiment 28, wherein the compound has the formula:

![Chemical Structure](attachment:image.png)

(1b).

15 **[0313]** Embodiment 31. The method of embodiments 28 or 29, wherein: \( R^{1,2} \) is independently substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl; \( R^{1,3} \) is independently -\text{OXS}, -\text{OCH}_2\text{X}^1, -\text{OCHX}^\wedge, -\text{OR}^{1D}, \) substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; \( R^{1,5} \) is independently -\text{OCH}_2\text{X}^1, -\text{OCHX}^\wedge, -\text{OR}^{1D}, \) substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and \( R^{2,3} \) is independently -\text{OCH}_2^2, -\text{OCH}_2\text{X}^2, -\text{OCHX}_2^2, -\text{OR}^{2D}, \) substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

**[0314]** Embodiment 32. The method of embodiments 28 or 29, wherein \( R^{1,2} \) is independently unsubstituted alkyl; \( R^{1,3} \) is independently -\text{OR}^{1D}; \( R^{1,5} \) is independently -\text{OR}^{1D}; \( R^{2,3} \) is independently -\text{OR}^{2D}; and each \( R^{1D} \) and \( R^{2D} \) is independently hydrogen, -\text{CX}_3, -\text{CHX}_2, -\text{CH}_2\text{X}, substituted or unsubstituted alkyl.

**[0315]** Embodiment 33. The method of embodiments 28 or 29, wherein \( R^{1,2} \) is independently unsubstituted \text{Ci-Cs} alkyl; \( R^{1,3} \) is independently -\text{OR}^{1D}; \( R^{1,5} \) is independently -\text{OR}^{1D}; \( R^{2,3} \) is independently -\text{OR}^{2D}; and each \( R^{1D} \) and \( R^{2D} \) is independently hydrogen or substituted or unsubstituted \text{Ci-Cs} alkyl.

**[0316]** Embodiment 34. The method of embodiments 28 or 29, wherein \( R^{1,2} \) is independently unsubstituted \text{C1-C5} alkyl; \( R^{1,3} \) is independently -\text{OH}; \( R^{1,5} \) is independently
independently -OR\textsuperscript{10}; \( R^{2,3} \) is independently -OH; and \( R^{19} \) is independently hydrogen or unsubstituted C1-C4 alkyl.

[0317] Embodiment 35. The method of embodiments 28 or 29, wherein \( R^{1,2} \) is independently unsubstituted C1-C5 alkenyl; \( R^{1,3} \) is independently -OH; \( R^{1,5} \) is independently -OR\textsuperscript{10}; \( R^{2,3} \) is independently -OH; and \( R^{19} \) is independently unsubstituted Ci-C\(_2\) alkyl.

[0318] Embodiment 36. The method of embodiments 28 or 29, wherein \( R^{1,2} \) independently has the formula \(  \text{\textbullet} \text{\textbullet} \text{\textbullet} \ ); \( R^{1,3} \) is independently -OH; \( R^{1,5} \) is independently -OR\textsuperscript{10}; \( R^{2,3} \) is independently -OH; and \( R^{19} \) is independently unsubstituted Ci-C\(_2\) alkyl.

[0319] Embodiment 37. The method of any one of embodiments 2, 3, 22, 27, or 28, wherein the compound has the the formula:

\[
\begin{align*}
\text{\textbullet} & \text{\textbullet} \text{\textbullet} \\
\text{\textbullet} & \text{\textbullet} \text{\textbullet} \\
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\end{align*}
\]
Embodiment 38. The method of any one of embodiments 2, 3, 22, 27, or 28, wherein the compound has the formula:

Embodiment 39. The method of any one of embodiments 2, 3, 20, 21, 22, 27, or 28, wherein the compound has the formula:
[0322] Embodiment 40. A compound covalently bonded to a sulfur atom of a cysteine residue of a PTGR1 protein of the formula:

\[
P-S- \\
\]

wherein,

\[
P-S- \text{ is said PTGR1 protein and said sulfur atom;} \\
\]

10
R\(^1\) is independently halogen, -CX, -CHX, -CH\(_2\)X, -OCX, -OCH\(_2\)X, -CN, -SO\(_\text{NiR}^1\), -SO\(_\text{VIR}^1\), -CN, -SOniR, -NH\(_C\left(0\right)NR\), -NR\(_A^1\), -N\(_S\), -NR\(_B^1\), -CH\(_2\)X, -OCH\(_2\)X, -C\(_X\), -C\(_X\)-OR\(_1\), -C\(_X\)-NR\(_2\), -C\(_X\)-SO\(_2\), -C\(_X\)-NR\(_2\), -N\(_R\), -N\(_S\), -NR\(_B\), -CR\(_X\), -CR\(_X\)-OR\(_1\), -CR\(_X\)-NR\(_2\), -CR\(_X\)-SO\(_2\), -CR\(_X\)-NR\(_2\) are independently an integer from 0 to 4; and m, m\(_2\), v, and v\(_2\) are independently an integer from 1 to 2.

R\(^2\) is independently halogen, -CX, -CHX, -CH\(_2\)X, -OCX, -OCH\(_2\)X, -CN, -SO\(_2\)R, -SO\(_\text{vNR}^2\), -NH\(_C\left(0\right)NR\), -NR\(_A^2\), -N\(_S\), -NR\(_B^2\), -C\(_X\)-OR\(_1\), -C\(_X\)-NR\(_2\), -C\(_X\)-SO\(_2\), -C\(_X\)-NR\(_2\), -N\(_R\), -N\(_S\), -NR\(_B\), -CR\(_X\), -CR\(_X\)-OR\(_1\), -CR\(_X\)-NR\(_2\), -CR\(_X\)-SO\(_2\), -CR\(_X\)-NR\(_2\) are independently an integer from 0 to 5.

Each R\(_A^1\), R\(_B^1\), R\(_C^1\), R\(_D\), R\(_E\), R\(_F\), and R\(_G\) is independently hydrogen, -CX, -CN, -COOH, -CONH\(_2\), -CHX, -CH\(_2\)X, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted heteroaryl; two adjacent R\(_1\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted heteroaryl; two adjacent R\(_2\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted heteroaryl; R\(_1\) and R\(_2\) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\(_A\) and R\(_B\) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each x, x\(_1\), and x\(_2\) is independently -F, -Cl, -Br, or -I; n\(_1\) and n\(_2\) are independently an integer from 0 to 4; and m, m\(_2\), v, and v\(_2\) are independently an integer from 1 to 2.
Embodiment 41. The PTGR1 protein of embodiment 40, irreversibly covalently bonded to the compound.

Embodiment 42. The PTGR1 protein of embodiments 40 or 41, wherein the compound or portion of the compound is covalently bonded to an amino acid corresponding to C239 of SEQ ID NCvl.

Embodiment 43. The PTGR1 protein of embodiment 40, wherein the PTGR1 protein is covalently bonded to a PTGR1 inhibitor having the formula:

![Chemical structure]

EXAMPLES

Example 1 - Mapping Novel Metabolic Nodes Targeted by Drugs that Impair Triple-Negative Breast Cancer Pathogenicity

Triple-negative breast cancers (TNBCs) are estrogen receptor, progesterone receptor, and HER2 receptor-negative subtypes of breast cancers that show the worst prognoses and lack targeted therapies. Here, we have coupled the screening of approximately 400 compounds that are under development or in the clinic with chemoproteomic and metabolomic profiling to identify novel metabolic mechanisms for agents that impair TNBC pathogenicity. We identify 20 compounds that significantly impaired cell survival across multiple types of TNBC cells. Among these 20 leads, the phytoestrogenic natural product licochalcone A was of interest, since TNBCs are unresponsive to estrogenic therapies, indicating that licochalcone A was likely acting through another target. Using chemoproteomic profiling approaches, we reveal that licochalcone A impairs TNBC pathogenicity, not through modulating estrogen receptor activity, but rather through inhibiting prostaglandin reductase 1, a metabolic enzyme involved in leukotriene B4 inactivation. We also more broadly performed metabolomic profiling to map additional metabolic mechanisms of compounds that impair TNBC pathogenicity. Overlaying lipidomic profiling with drug responses, we find that deubiquitinase inhibitors cause dramatic elevations in acyl carnitine levels, which impair mitochondrial respiration and contribute to TNBC pathogenic impairments. We thus put forth two unique metabolic nodes that are
targeted by drugs or drug candidates that impair TNBC pathogenicity. Our results also showcase the utility of coupling drug screens with chemoproteomic and metabolomic profiling to uncover unique metabolic drivers of TNBC pathogenicity.

In the United States, it is estimated that over 200,000 women will be diagnosed with breast cancer and nearly 40,000 women will die of breast cancer in 2016 (1). Mortality from breast cancer is almost always attributed to metastatic spread of the disease to other organs, thus precluding resection as a treatment method (2). Unfortunately, conventional chemotherapy fails to eradicate many aggressive breast cancers (3). Studies over the past decade have uncovered certain breast cancer cell-types, such as estrogen/progesterone/HER2 receptor (ER/PR/HER2)-negative (triple-negative) breast cancers (TNBCs) that show poor prognosis and chemotherapy-resistance within breast tumors (3-5). Eliminating these breast cancer types are critical in reducing the mortality associated with breast cancer.

Current therapeutic strategies for breast cancer include resection, non-specific therapies such as radiation or chemotherapy, and targeted strategies for combating certain types of breast cancers (6). However, there are no targeted strategies for combating the most aggressive types of breast cancers, including TNBCs. Since the discoveries of Otto Warburg in the 1920's showing that cancer cells are addicted to glucose metabolism, we have known that cancer cells possess fundamentally altered metabolism that drives nearly every aspect of their pathogenicity (7). The past decade has seen a resurgence of interest in targeting metabolic drivers of cancer for therapy. As such, many metabolic pathways, targets, and inhibitors have been discovered for potential cancer therapy, including pyruvate kinase activators that target glycolytic metabolism, isocitrate dehydrogenase mutant-specific inhibitors that impair oncometabolite synthesis, fatty acid synthase inhibitors that impair lipogenesis, and phosphoglycerate dehydrogenase inhibitors that target serine metabolism. These targets and pathways are likely just the tip of the iceberg in terms of potential metabolic targets and pathways that may be exploited for cancer therapy.

In this study, we sought to identify unique and novel metabolites and metabolic targets that may be targeted to impair TNBC pathogenicity by coupling the screening of existing drugs or clinical candidates with metabolomic and chemoproteomic profiling. Our hope was to discover compounds that could impair TNBC pathogenicity and determine metabolic mechanisms through which these compounds may operate. Here, we have identified several drugs and drug candidates that impair TNBC pathogenicity and reveal a
metabolic signature for each drug’s response in TNBC cells as well as distinct and novel metabolic mechanisms underlying a phytoestrogenic natural product licochalcone A and deubiquitinase inhibitors.

[0330] To discover drugs and drug candidates that impair TNBC pathogenicity, we screened an library consisting of 424 compounds spanning a diverse range of molecular targets to identify small-molecules that impaired serum-free cell survival in 231MFP and HCC38 TNBC cells (FIGS. 1A, 1B). We then filtered this list for those compounds that showed >75% survival impairments in both 231MFP and HCC38 cells. We subsequently retested the filtered list of compounds to identify agents that significantly (p<0.05) impaired cell survival across 231MFP, HCC38, and HCC70 TNBC cells by over 50%. This resulted in a list of 20 compounds spanning 15 different molecular targets that reproducibly and significantly impaired cell survival by >50% across three TNBC lines (FIG. 1C).

[0331] Several of these 20 compounds inhibit proteins that are currently being targeted in TNBC patients or are in clinical development including proteasome inhibitors MLN2238 and MLN9708, topoisomerase inhibitors Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone, JAK2 inhibitor TGI01348, mTOR inhibitor Torin 2, EGFR inhibitor Dacomitinib, polo-like kinase 1 (PLK) inhibitor BI6727, kinesin spindle protein (KSP) inhibitor Ispenisib, and Aurora kinase (AURK) inhibitor AT9283 (4,8-13). Other compounds modulate protein targets that have been previously shown to be important in TNBCs including HDAC inhibitors SB939 and Romidepsin (14). The remaining compounds and their targets, while previously shown to be important in cancer, are less understood in regards to their efficacy or roles in advanced-stage breast cancers or TNBCs. These include deubiquitinase inhibitor WP1130, exchange proteins directly activated by cAMP isoform 1 (EPAC) inhibitor ESI-09, kinesin inhibitor ARQ 621, FXR activator GW4064, and the phytoestrogenic natural product licochalcone A (15-19), and may represent promising therapeutic strategies for combating TNBCs. Among these compounds with poorly understood roles in TNBCs, licochalcone A showed the greatest impairment (>95%) in cell survival across the three TNBC cells tested here with a 50% effective concentration (EC50) of 8.4 μM (FIG. 5).

[0332] The target of licochalcone A is classified as estrogen or progesterone receptors due to its previous characterization as an estrogenic flavonoid (17). Licochalcone A is a flavonoid extracted from licorice root that has been shown to possess anti-inflammatory and anti-
parasitic activity and has been tested on humans as an anti-inflammatory moisturizer (17,20-
25). However, the cell survival impairments of licochalcone A in TNBC cells resistant to ER
and PR signaling indicated that this compound may be acting through alternate targets.

[0333] Licochalcone A belongs to a larger group of natural products known as chalcones
characterized by their aromatic enone structures (FIG. 2A). These enones can potentially
undergo Michael addition to cysteine thiols on proteins to modulate protein function. To
identify the potential anti-cancer targets of licochalcone A, we mapped the cysteine-reactivity
of this compound in TNBC cells using a chemoproteomic platform termed isotopic tandem
orthogonal proteolysis-enabled activity-based protein profiling (isoTOP-ABPP). IsoTOP-
ABPP uses reactivity-based probes to map proteome-wide reactive, functional, and
ligandable hotspots directly in complex proteomes. When used in a competitive manner,
small-molecules like licochalcone A can be competed against reactivity-based probes to map
the proteome-wide reactivity and targets of covalently-acting compounds (FIG. 2B) (26-28).
We profiled the proteome-wide cysteine-reactivity of licochalcone A through competition of
this agent against the broad cysteine-reactive iodoacetamide-alkyne probe using the isoTOP-
ABPP platforms directly in 231MFP proteomes. We subsequently tagged probe-labeled
proteins with isotopically light (for control) or heavy (for licochalcone-treated) handles
bearing a biotin for avidin-enrichment and a TEV protease recognition sequence by copper-
catalyzed azide-alkyne cycloaddition (CuAAC) for subsequent TEV protease release of
probe-modified peptides for quantitative proteomic analysis of light to heavy peptide ratios
(FIG. 2B).

[0334] We identified the primary target of this agent as cysteine 239 of the metabolic
enzyme target prostaglandin reductase 1 (PTGR1) (FIG. 2C). We validated this target using
gel-based ABPP methods where we observed competition of licochalcone A against
iodoacetamide-alkyne labeling of pure human PTGR1 protein (FIG. 2C). PTGR1 is involved
in inactivating prostaglandins, including 15-keto-prostaglandins and leukotriene B4 (29).
While recently shown to be important in lung and prostate cancers, PTGR1 represents a novel
target for breast cancer (30,31). Leukotriene B4, through stimulating leukotriene B4 receptor
BLT1, has also been shown to fuel TGF-P-mediated proliferation in breast cancer cells (32).
Interestingly, C239 of PTGR1 represents the binding region for NADP+, required for the
reductase catalytic activity of this enzyme (33) (FIG. 2D), suggesting that licochalcone A
binding to this site would displace NADP+ binding and inhibit PTGR1 activity. To further
confirm the importance of PTGR1 in TNBC pathogenicity, we knocked down the expression
of PTGR1 in 231MFP TNBC cells using three independent short-hairpin RNA oligonucleotides and show that PTGR1 knockdown dramatically impairs 231MFP cell survival and proliferation, thus recapitulating the effects observed with licochalcone A (FIGS. 2E-2G). Thus, we put forth a novel metabolic mechanism of licochalcone A, in which it inhibits PTGR1 to impair TNBC pathogenicity.

[0335] We next sought to take a broader approach towards identifying unique metabolic mechanisms underlying agents that impair TNBC pathogenicity. We performed lipidomic profiling to map metabolic changes conferred by treatment of 231MFP TNBC cells with the 20 lead compounds that impaired TNBC cell survival (FIG. 3A). We focused this study on measuring -100 lipid metabolites spanning phospholipids, fatty acids, neutral lipids, sphingolipids, sterols, and fatty acid derivatives such as acyl carnitines, N-acyl ethanolamines (NAEs) and N-acyl taurines (NATs). We performed lipidomic profiling on cells that were treated for 6 h before any cell death to avoid confounding effects that may arise from differing cell numbers. Interestingly, we find that each compound gives a unique lipidomic signature, suggesting that metabolomic profiling may be used as a potential biomarker of drug response (FIG. 3A, FIG. 6). We also see common changes in specific metabolites that correlate with certain mechanisms of action. For example, we observe that topoisomerase inhibitor-treated cells show reduced levels of 08:0/08:1 diacylglycerol (DAG) and 08:0 ceramide, not seen with most of the other drug treatments, potentially indicating that these lipid species may be more specifically controlled by topoisomerase-mediated pathways (FIG. 6). We also see certain lipid classes that are similarly regulated by multiple drugs that do not necessarily share a common mechanism of action. For example, 06:0 and 08:0 lysophosphatidylethanolamines (LPE), 06:0 lysophosphatidyl choline (LPC), and C18:0e lysophosphatidylcholine-ether (LPce) levels are significantly elevated upon treatment of 231MFP cells with proteasome inhibitors MLN2238 and MLN9708, HDAC inhibitor Romidepsin, JAK2 inhibitor TGI 01348, KSP inhibitor Ispinenib, PLK inhibitor BI6727, EGFR inhibitor Dacomitinib, and Licochalcone A (FIG. 6). Perhaps this common regulation of different types of lysophospholipids by compounds that act through different targets may suggest a common downstream pathway targeted across all of these mechanisms—potentially through an activation of phospholipase enzymes that would generate lysophospholipids. We do not believe these lipidomic signatures to be a general signature of cell death, as all 20 of these drugs impair TNBC cell survival. Rather, we believe that these lipidomic signatures likely represent unique metabolic mechanisms underlying the action of each drug.
Among the lipidomic profiles, the most significant changes were in acyl carnitine (AC) levels with a >60-fold elevation in C16:0 AC with the deubiquitinase inhibitor WPI 130 and >10-fold elevation with EPAC inhibitor ESI09 and FXR activator GW4604 (FIG. 3B). ACs are metabolites generated by carnitine palmitoyltransferase 1 (CPT1) at the mitochondrial membrane to import fatty acids into the mitochondria for fatty acid oxidation (34). We show that other deubiquitinase inhibitors PR619 and P5091 also impair 231MFP cell survival and elevate AC levels, FIGS. 3C-3D. While PR619 and WPI 130 inhibit several deubiquitinases, P5091 selectively inhibits USP7 and USP47, which may explain the less dramatic AC elevations with P5091. We show that AC treatment impairs cell survival (FIG. 4A). We also find that treatment of 231MFP cells with a concentration of AC that does not impair cell survival dramatically sensitizes cells to WPI 130, likely because AC treatment synergizes with WPI 130-mediated elevations in AC to impair 231MFP viability (FIG. 4B). Previous studies have shown that ischemic injury elevates the levels of AC and that AC uncouples the mitochondria and impairs cellular respiration (35-37). We show that treatment of 231MFP cells with both AC and WPI 130 impairs maximal cellular respiration to a comparable degree (FIG. 4C). Our data thus suggest that inhibition of deubiquitinase enzymes lead to elevation in AC levels which, in turn, impair cellular respiration and may contribute to the cell survival impairments.

We also tested the role of LPE, since lysophospholipid species were among the lipid species dramatically changed with several drugs. We show that LPE treatment also impairs 231MFP cell survival and potentiates the cell survival impairments conferred by the proteasome inhibitor MLN9708 that elevates LPE levels (FIG.6, FIGS. 7A-7C). We further demonstrate that, unlike AC treatment, LPE or palmitate treatment in 231MFP cells does not affect cellular respiration, indicating that the lysophospholipid effects are driven through an alternate mechanism (FIGS. 7A-7C).

In summary, we reveal several unique and novel metabolic mechanisms underlying small-molecule drugs and drug candidates that impair TNBC pathogenicity by coupling drug screening with chemoproteomic and metabolomic profiling. In our first example, using isoTOP-ABPP platforms, we show here that licorhcalcone A dramatically and effectively impairs TNBC cell survival through inhibiting PTGR1. In our second example, using metabolomic platforms, we identify that deubiquitinase inhibitors also impair TNBC cell survival and that inhibiting these enzymes massively elevate AC levels to potentially impair cellular respiration and contribute to the viability impairments. Both PTGR1 inhibition and
acyl carnitine-mediated respiratory impairments in TNBC cells represent novel metabolic
modalities that affect TNBC pathogenicity. It will be of future interest to better understand
the inhibitory mechanisms of licochalcone A on PTGRI, develop more potent and selective
PTGRI inhibitors, and to ascertain the role of PTGRI, leukotriene B4, and BLT1 signaling
pathways on TNBC pathogenicity. It would also be of interest to better understand the
mechanisms and molecular targets through which AC impairs mitochondrial respiration,
since targeting this mechanism may prove to be a unique therapeutic strategy for TNBCs.
Collectively, our data point to the utility of using chemoproteomic and metabolomic
platforms to uncover novel metabolic drivers of cancer, towards developing novel cancer
therapies.

[0339] Materials. The compound library consisting of 424 compounds at 10 mM in DMSO
was purchased from Selleck Chemicals. IAyne was obtained from CHESS Gmbh. Heavy and
light TEV-biotin tags were synthesized per previously described methods (28,38). Palmitoyl
carnitine was obtained from Sigma-Aldrich and resuspended in deionized water to 100 mM
stock. Lysophosphatidyl ethanolamine was obtained from Avanti Polar Lipids and
resuspended in 2:1 chloroform:methanol to a 10 mM stock.

[0340] Cell Culture. The 231MFP cells were obtained from Professor Benjamin Cravatt
and were generated from explanted tumor xenografts of MDA-MB-231 cells. HCC38,
HCC70, and HEK293T cells were obtained from the American Type Culture Collection
(ATCC). 231MFP cells were cultured in L15 (HyClone) medium containing 10% FBS,
supplemented with 2% glutamine (200 mM stock), and maintained at 37°C with 0% CO2.
HCC38 and HCC70 cells were cultured in RPMI (Gibco) medium containing 10% FBS,
supplemented with 2% glutamine (200 mM stock), and maintained at 37°C with 5% CO2.
HEK293T cells were cultured in DMEM (Corning) containing 10% FBS, supplemented with
2% glutamine (200 mM stock) and maintained at 37°C with 5% CO2.

[0341] Cellular Survival and Proliferation Studies. Cell survival assays were performed as
previously described using Hoechst 33342 dye (Invitrogen) according to manufacturer's
protocol (39). Cells were seeded into 96-well plates (40,000 cells) in a volume of 150 µL
serum-free media and allowed to adhere overnight. Once adhered, an additional 50 µL of
serum-free media containing 1:250 dilution of 1000x compound stock in DMSO was added
to each well and allowed to incubate for 48 hours before fixation. Medium was removed from
each well and 100 µL of staining solution containing 10% formalin and Hoechst 33342 dye
was added to each well and incubated for 15 min in the dark at room temperature. Staining solution was then removed and 100 µl of PBS was added for imaging on a SpectraMax i3 fluorescent plate reader. Studies with HCC38 cells and HCC70 were also performed as above but were seeded with 20,000 and 30,000 cells, respectively. Cell proliferation assays were performed as above but cells were seeded (20,000 for 23 IMFP cells) and treated in medium containing FBS.

[0342] IsoTOP-ABPP. IsoTOP-ABPP studies were done as previously reported (26,28). Proteome samples diluted in PBS were treated with Withaferin A or vehicle for 30 min at 37°C. Then, IAyne labeling was performed for 1 h at room temperature. CuAAC was used by sequential addition of tris(2-carboxyethyl)phosphine (1 mM, Sigma), tris[(1-benzyl-lH-1,2,3-triazol-4-yl)methyl]amine (34 µM, Sigma), copper (II) sulfate (1 mM, Sigma), and biotin-linker-azide, the linker functionalized with a TEV protease recognition sequence along with an isotopically light or heavy valine for treatment of control or treated proteome, respectively. After click reactions, proteomes were precipitated by centrifugation at 6500 xg, washed in ice-cold methanol, combined in a 1:1 control/treated ratio, washed again, then denatured and resolubilized by heating in 1.2% SDS/PBS to 80°C for 5 minutes. Insoluble components were precipitated by centrifugation at 6500 xg and soluble proteome was diluted in 5 ml 0.2% SDS/PBS. Labeled proteins were bound to avidin-agarose beads (170 µl resuspended beads/sample, Thermo Pierce) while rotating overnight at 4°C. Bead-linked proteins were enriched by washing three times each in PBS and water, then resuspended in 6 M urea/PBS (Sigma) and reduced in TCEP (1 mM, Sigma), alkylated with iodoacetamide (18 mM, Sigma), then washed and resuspended in 2 M urea and trypsinized overnight with 0.5 mg/ml sequencing grade trypsin (Promega). Tryptic peptides were eluted off. Beads were washed three times each in PBS and water, washed in TEV buffer solution (water, TEV buffer, 100 mM dithiothreitol) and resuspended in buffer with Ac-TEV protease and incubated overnight. Peptides were diluted in water and acidified with formic acid (1.2 M, Spectrum) and prepared for analysis.

[0343] MS Analysis. Peptides from all proteomic experiments were pressure-loaded onto a 250 mm inner diameter fused silica capillary tubing packed with 4 cm of Aqua C18 reverse-phase resin (Phenomenex # 04A-4299) which was previously equilibrated on an Agilent 600 series HPLC using gradient from 100% buffer A to 100% buffer B over 10 min, followed by a 5 min wash with 100% buffer B and a 5 min wash with 100% buffer A. The samples were then attached using a MicroTee PEEK 360 mm fitting (Thermo Fisher Scientific #p-888) to a
13 cm laser pulled column packed with 10 cm Aqua C18 reverse-phase resin and 3 cm of strong-cation exchange resin for isoTOP-ABPP studies. Samples were analyzed using an Q Exactive Plus mass spectrometer (Thermo Fisher Scientific) using a 5-step Multidimensional Protein Identification Technology (MudPIT) program, using 0%, 25%, 50%, 80%, and 100% salt bumps of 500 mM aqueous ammonium acetate and using a gradient of 5-55% buffer B in buffer A (buffer A: 95:5 water:acetonitrile, 0.1% formic acid; buffer B: 80:20 acetonitrile:water, 0.1% formic acid). Data was collected in data-dependent acquisition mode with dynamic exclusion enabled (60 s). One full MS (MS1) scan (400-1800 m/z) was followed by 15 MS2 scans (ITMS) of the nth most abundant ions. Heated capillary temperature was set to 200°C and the nanospray voltage was set to 2.75 kV.

[0344] Data were extracted in the form of MSI and MS2 files using Raw Extractor 1.9.9.2 (Scripps Research Institute) and searched against the Uniprot mouse database using ProLuCID search methodology in IP2 v.3 (Integrated Proteomics Applications, Inc) (40). Cysteine residues were searched with a static modification for carboxyaminomethylation (+57.02146) and up to two differential modifications for methionine oxidation and either the light or heavy TEV tags (+464.28596 or +470.29977, respectively). Peptides were required to have at least one tryptic end and to contain the TEV modification. ProLUCID data was filtered through DTASelect to achieve a peptide false-positive rate below 1%.

[0345] Gel-Based ABPP. Gel-based ABPP methods were performed as previously described (41). Recombinant PTGR1 (0.1 μg) protein (Origene) was pre-treated with DMSO or Licochalcone A, respectively, for 1 h at 37°C in an incubation volume of 50 mL PBS, and were subsequently treated with IAyne (1 mM final concentration) for 30 min at 37°C. CuAAC was performed to append rhodamine-azide onto IAyne probe-labeled proteins. The samples were separated by SDS/PAGE and scanned using a ChemiDoc MP (Bio-Rad Laboratories, Inc). Inhibition of target labeling was assessed by densitometry using ImageStudio Light software.

[0346] Metabolomic Profiling. Metabolomic profiling was performed as previously reported (39, 42). For metabolomic profiling, 2 million cells were seeded in complete media and allowed to adhere overnight. They were then washed with PBS and refed with serum-free media containing 10 μM of compound in DMSO or DMSO vehicle control at 0.1% DMSO final concentration for 6 hours. The cells were harvested, flash-frozen, and metabolomes were extracted in 3 mL of 2:1 chloroform:methanol and 1 mL of PBS with inclusion of
internal standards dodecyl glycerol (10 nmol, Santa Cruz Biotechnology) and pentadecanoic acid (10 nmol, Sigma-Aldrich). Organic and aqueous layers were separated by centrifugation at 1000 x g for 5 min and the organic layer was collected, dried under a stream of nitrogen and dissolved in 120 μL chloroform. An aliquot of the extracts was then injected into an Agilent 6430 QQQ-LC/MS/MS. Metabolomes were separated using reverse-phase chromatography with a Luna C5 column (50 mm x 4.6 mm with 5 mm diameter particles, Phenomenex). Mobile phase A consisted of 95:5 ratio of water/methanol and mobile phase B consisted of 2-propanol, methanol, and water in a 60:35:5 ratio. Solvent modifiers 0.1 % formic acid with 5 mM ammonium formate and 0.1 % ammonium hydroxide were used to assist ion formation as well as to improve the LC resolution in both positive and negative ionization modes, respectively. The flow rate for each run started at 0.1 ml/min for 5 min to alleviate backpressure associated with injecting chloroform. The gradient started at 0 % B and increased linearly to 100 % B over the course of 45 min with a flow rate of 0.4 ml/min, followed by an isocratic gradient of 100 % B for 17 min at 0.5 ml/min before equilibrating for 8 min at 0 % B with a flow rate of 0.5 ml/min.

[0347] MS analysis was performed with an electrospray ionization (ESI) source on an Agilent 6430 QQQ LC-MS/MS (Agilent Technologies). The capillary voltage was set to 3.0 kV, and the fragmentor voltage was set to 100 V. The drying gas temperature was 350°C, the drying gas flow rate was 10 l/min, and the nebulizer pressure was 35 psi. Metabolites were identified by SRM of the transition from precursor to product ions at associated optimized collision energies and retention times as previously described (39,42). Metabolites were quantified by integrating the area under the curve, and then normalized to internal standard values. Metabolite levels are expressed as relative abundances as compared to controls.

[0348] PTGR1 Knockdown. Targets were knocked down stably with shRNA as previously described (39,42). shControl (targeting GFP) or shPTGR1 constructs (Sigma) were transfected into HEK293T (ATCC) cells alongside lentiviral vectors using lipofectamine 2000 (Thermo Fisher Scientific). Lentivirus was collected from filtered cultured medium 48 h post-transfection and used to infect the target cancer cell line with Polybrene (0.01 mg/ml). Target cells were selected over 3 days with 1 mg/mL puromycin. The short hairpin sequences for the generation of PTGR1 knockdown lines were:

shPTGR1-1:
CCGGCTTTGGATTTGATGTCGTTTTCTCGAGAAAGACGACATCAAATCCAAAGTTT
TT (SEQ ID NO:2);
shPTGR1-2:
CCGGCTATCCTACTAATAGTGACTTCTCGAGAAGTCACTATTAGTAGGATAGTTTT
TT (SEQ ID NO:3);

shPTGR1-3:
CCGGGCCTACTTTGGCCTACTTGAACTCGAGTTCAAGTAGGCCAAAGTAGGCTTT
TT (SEQ ID NO:4);

control shRNA against GFP:
GCAAGCTGACCCTGAAGTTCAT (SEQ ID NO:5).

Knockdown was confirmed by qPCR.

[0349] qPCR. qPCR was performed using the manufacturer’s protocol for Fisher Maxima SYBR Green with 10 µM primer concentrations. Primer sequences for Fisher Maxima SYBR Green were derived from Harvard Primer Bank. Primer sequences are as follows:

PTGR1 forward: AGCACTTTGTTGGCTATCCTAC (SEQ ID NO:6)
PTGR1 reverse: CCCCATCATTGTATCACCTTCC (SEQ ID NO:7)

Cyclophilin forward: CCCACCGTGTTCTTCGACATT (SEQ ID NO:8)
Cyclophilin reverse: GGACCCGTATGCTTTAGGATGA (SEQ ID NO:9).

[0350] Cellular respiration measurements. 231MFP cells were seeded at 50,000 cells/well in an XF24 cell culture microplate (Seahorse Bioscience) and analyzed the following day. On the day of analysis cells were washed once with Seahorse respiration buffer made up of XF base medium minimal DMEM containing 25 mM glucose and 5 mM sodium pyruvate pH adjusted to 7.4. The cells were then placed in 0.5 mL Seahorse respiration buffer and incubated in a CCh-free incubator for 1 h. 10x port injection solutions, in Seahorse respiration buffer all pH adjusted to 7.4, were prepared as follows (final concentrations in parentheses):

port A - 10 µM oligomycin (1 µM final); port B - 1 mM palmitoyl carnitine (100 µM final)
or 100 µM WP130 (10 µM final); port C - 3 µM FCCP (0.3 µM final); port D - 5 µM rotenone and 5 µM antimycin A (0.5 µM final). The Seahorse program ran as follows: basal measurement, 3 cycles; inject port A (oligomycin), 3 cycles; inject port B (compounds), 3 cycles; inject port C (FCCP), 3 cycles; inject port D (rotenone and antimycin A), 3 cycles.

Each cycles consisted of mix for 3 min, wait for 2 min, measure for 3 min.

REFERENCES

WHAT IS CLAIMED IS:

1. A method of inhibiting prostaglandin reductase 1 (PTGR1) activity,
said method comprising contacting a PTGR1 protein with an effective amount of a
prostaglandin reductase 1 (PTGR1) inhibitor, wherein
   said PTGR1 inhibitor contacts one or more amino acids corresponding to P48,
   M124, T128, A149, A153, V154, N217, C239, Y245, V271, or V272 of SEQ ID NO: 1; and
   said PTGR1 inhibitor is covalently bonded to the amino acid corresponding to
   C239 of SEQ ID NO: 1, thereby forming a PTGR1 protein covalently bonded to said PTGR1
   inhibitor.

2. A method of inhibiting prostaglandin reductase 1 (PTGR1) activity,
said method comprising contacting a PTGR1 protein with an effective amount of a compound
having the formula:

   \[
   \begin{align*}
   &\text{(I),} \\
   &\text{R}^1 \text{ is independently halogen, -CX}^\text{a}, \text{-CHX}^\text{a}, \text{-CH2X}^\text{1}, \text{-OCX}^\text{a}, \text{-} \\
   &\text{OCH2X}^1, \text{-OCHX}^\text{a}, \text{-CN, -SOiNR}^\text{1b}, \text{-SOi}^\text{2iNR}^\text{1A} \text{R}^\text{1b}, \text{-NHC(0)NR}^\text{1A} \text{R}^\text{1b}, \text{-N(0)}^\text{m} \text{i}, \text{-NR}^\text{1A} \text{R}^\text{1b}, \\
   &\text{-C(0)R}^\text{1C}, \text{-C(0)-OR}^\text{1C}, \text{-C(0)NR}^\text{1A} \text{R}^\text{1b}, \text{-OR}^\text{1D}, \text{-NR}^\text{1A} \text{SO}^\text{2i} \text{R}^\text{1D}, \text{-NR}^\text{1A} \text{C(0)} \text{R}^\text{1C}, \text{-NR}^\text{1A} \text{C(0)0} \\
   &\text{R}^\text{1C}, \text{-NR}^\text{1A} \text{OR}^\text{1C}, \text{-N}_3, \text{substituted or unsubstituted alkyl, substituted or unsubstituted} \\
   &\text{heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted} \\
   &\text{heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;} \\
   &\text{two adjacent R}^\text{1} \text{ substituents may optionally be joined to form a substituted or unsubstituted} \\
   &\text{cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or} \\
   &\text{substituted or unsubstituted heteroaryl; } \\
   &\text{z1 is an integer from 0 to 5; } \\
   &\text{R}^\text{2} \text{ is independently halogen, -CX}^\text{21}, \text{-CHX}^\text{22}, \text{-CH}^\text{2} \text{X}^\text{2}, \text{-OCX}^\text{21}, \text{-} \\
   &\text{OCH2X}^2, \text{-OCHX}^\text{22}, \text{-CN, -SOi}^\text{22NR}^\text{2A} \text{R}^\text{2B}, \text{-NHC(0)NR}^\text{2A} \text{R}^\text{2B}, \text{-N(0)}^\text{m2}, \text{-NR}^\text{2A} \text{R}^\text{2B}, \\
   &\text{-C(0)R}^\text{2C}, \text{-C(0)-OR}^\text{2C}, \text{-C(0)NR}^\text{2A} \text{R}^\text{2B}, \text{-OR}^\text{2D}, \text{-NR}^\text{2A} \text{SO}^\text{2i} \text{R}^\text{2D}, \text{-NR}^\text{2A} \text{C(0)} \text{R}^\text{2C}, \text{-NR}^\text{2A} \text{C(0)0} \\
   &\text{R}^\text{2C}, \text{-NR}^\text{2A} \text{OR}^\text{2C}, \text{-N}_3, \text{substituted or unsubstituted alkyl, substituted or unsubstituted} \\
   &\text{heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted} \\
   &\text{heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;}
   \end{align*}
\]
two adjacent $R^2$ substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

$z_2$ is an integer from 0 to 5:

Each $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{2A}$, $R^{2B}$, $R^{2C}$, and $R^{2D}$ is independently
hydrogen, -$\text{CX}_3$, -$\text{CN}$, -$\text{COOH}$, -$\text{CONH}_2$, -$\text{CHX}_2$, -$\text{CH}_2\text{X}$, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
unsubstituted heteroaryl; $R^{1A}$ and $R^{1B}$ substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl; $R^{2A}$ and $R^{2B}$ substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl;

each $X$, $X^1$, and $X^2$ is independently -$\text{F}$, -$\text{Cl}$, -$\text{Br}$, or -$\text{I}$;

$n_1$ and $n_2$ are independently an integer from 0 to 4; and

$m_1$, $m_2$, $v_1$, and $v_2$ are independently an integer from 1 to 2.

3. The method of claim 2, wherein the compound is capable of covalently
bonding to the amino acid corresponding to C239 of SEQ ID NO: 1.

4. The method of claim 2, wherein the compound is capable of contacting
one or more amino acids corresponding to P48, M124, T128, A149, A153, V154, N217,
C239, Y245, V271, or V272 of SEQ ID NO: 1.

5. The method of claim 2, wherein the compound has the formula:

$$\begin{align*}
\text{(Ia)}, \\
\text{wherein,}
\end{align*}$$

$R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, and $R^{15}$ are independently hydrogen, halogen, -$\text{CX}^1_3$,-
$\text{CHX}^A$, -$\text{CH}_2\text{X}^1$, -$\text{OCX}^1_3$, -$\text{OCH}_2\text{X}^1$, -$\text{OCHX}^A$, -$\text{CN}$, -$\text{SO}_2\text{NR}^{1A}\text{R}^{1B}$,
$\text{NR}^{1A}\text{R}^{1B}$, -$\text{N}(0)_i\text{NR}^{1A}\text{R}^{1B}$, -$\text{C}(0)\text{R}^{1C}$, -$\text{C}(0)\text{OR}^{1C}$, -$\text{C}(0)\text{NR}^{1A}\text{R}^{1B}$, -$\text{OR}^{1D}$, -$\text{NR}^{1A}\text{SO}_2\text{R}^{1D}$,
$\text{NR}^{1A}\text{C}(0)\text{R}^{1C}$, -$\text{NR}^{1A}\text{C}(0)\text{OR}^{1C}$, -$\text{NR}^{1A}\text{O}^{1C}$, -$\text{N}_3$, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl; and

R_{2,1}, R_{2,2}, R_{2,3}, R_{2,4}, and R_{2,5} are independently hydrogen, halogen, -CX^2, -
CHX^2, -CH_2X^2, -OCX^2, -OCHX^2, -CN, -SO_{2}NR^2A, -SO_{2}NR^2B,
-NHC(0)NR^2A, -N(0)_{m}, -NR^2A, -C(0)R^2C, -C(0)OR^2C, -C(0)NR^2A, -OR^2D, -NR
2ASO_2R^2D, -NR^2AOC(0)R^2C, -NR^2AOOR^2C, -N_3, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl.

6. The method of claim 5, wherein the compound has the formula:

7. The method of claim 6, wherein:
R^{1,2} is independently substituted or unsubstituted alkyl or substituted or
unsubstituted heteroalkyl;

R^{1,3} is independently -OCX, -OCH2X, -OCHX, -OR, substituted or
unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;
R^{1,5} is independently -OCX, -OCH2X, -OCHX, -OR, substituted or
unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and
R^{2,3} is independently -OCX_2, -OCH2X_2, -OCHX_2, -OR_2D, substituted or
unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

8. The method of claim 8, wherein
R^{1,2} is independently unsubstituted alkyl;
R^{1,3} is independently -OR;
R^{1,5} is independently -OR;
R^{2,3} is independently -OR_2D; and
each R^{1D} and R^{2D} is independently hydrogen, -CX_3, -CHX_2, -CH_2X,
substituted or unsubstituted alkyl.

9. The method of claim 8, wherein
R^{1,2} is independently unsubstituted Ci-Cs alkyl;
10. The method of claim 8, wherein
R₁^2 is independently unsubstituted C₁-C₅ alkyl;
R₁^3 is independently -OH;
R₁^5 is independently -OR₁ᵇ;
R₂^3 is independently -OH; and
R₁ᵇ is independently hydrogen or unsubstituted C₁-C₄ alkyl.

11. The method of claim 8, wherein
R₁^2 is independently unsubstituted C₁-C₅ alkenyl;
R₁^3 is independently -OH;
R₁^5 is independently -OR₁ᵇ;
R₂^3 is independently -OH; and
R₁ᵇ is independently unsubstituted C₁-C₂ alkyl.

12. The method of claim 8, wherein
R₁^₂ independently has the formula
R₁^3 is independently -OH;
R₁^5 is independently -OR₁ᵇ;
R₂^3 is independently -OH; and
R₁ᵇ is independently unsubstituted C₁-C₂ alkyl.

13. The method of claim 2, wherein the compound is not licochalcone A.

14. A method of treating cancer, said method comprising administering to
a subject in need thereof an effective amount of a prostaglandin reductase 1 (PTGRI)
inhibitor.

15. The method of claim 14, wherein the cancer is lung cancer, prostate
cancer, or breast cancer.
16. The method of claim 14, wherein the cancer is triple negative breast cancer.

17. The method of claim 14, wherein said PTGR1 inhibitor is of the formula:

![Chemical Structure](image)

wherein,

- $R^1$ is independently halogen, -CX^\$\text{X}$^, -CHX^\$\text{X}$^, -CH2X, -OCX^\$\text{X}$^, -
- OCH2X, -OCHX, -CN, -SO\text{$_{\text{t=1}}$}NR\text{$_{\text{t=1}}$}, -SO\text{$_{\text{t=1}}$}iNR\text{$_{\text{t=1}}$}, -NH\text{$_{\text{t=1}}$}C(0)NR\text{$_{\text{t=1}}$}, -N(0)\text{$_{\text{t=1}}$}, -NR\text{$_{\text{t=1}}$}1AR\text{$_{\text{t=1}}$}, -C(0)\text{$_{\text{t=1}}$}, -C(0)-OR\text{$_{\text{t=1}}$}, -C(0)NR\text{$_{\text{t=1}}$}, -OR\text{$_{\text{t=1}}$}, -NR\text{$_{\text{t=1}}$}1AR\text{$_{\text{t=1}}$}, -NR\text{$_{\text{t=1}}$}1A\text{$_{\text{t=1}}$}S0\text{$_{\text{t=1}}$}2R\text{$_{\text{t=1}}$}, -NR\text{$_{\text{t=1}}$}1A\text{$_{\text{t=1}}$}C(0)R\text{$_{\text{t=1}}$}, -NR\text{$_{\text{t=1}}$}1AC(0)0

- R\text{$_{t=1}$}C, -NR\text{$_{t=1}$}1AR\text{$_{t=1}$}C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R\text{$_{t=1}$} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; z1 is an integer from 0 to 5;

- R\text{$_{t=2}$} is independently halogen, -CX\text{$_{2}$}3, -CHX\text{$_{2}$}2, -CH2X2, -OCX\text{$_{2}$}3, -
- OCH2X, -OCHX, -CN, -SO\text{$_{2}$}2R\text{$_{2}$}D, -SO\text{$_{2}$}2NR\text{$_{2}$}2AR\text{$_{2}$}B, -NH\text{$_{2}$}C(0)NR\text{$_{2}$}2AR\text{$_{2}$}B, -N(0)\text{$_{2}$}m2, -NR\text{$_{2}$}2AR\text{$_{2}$}B,

- C(0)\text{$_{2}$}R\text{$_{2}$}2C, -C(0)-OR\text{$_{2}$}2C, -C(0)NR\text{$_{2}$}2AR\text{$_{2}$}B, -OR\text{$_{2}$}2D, -NR\text{$_{2}$}2AR\text{$_{2}$}2S0\text{$_{2}$}2R\text{$_{2}$}2D, -NR\text{$_{2}$}2AC(0)R\text{$_{2}$}2C, -NR\text{$_{2}$}2AC(0)0

- R\text{$_{2}$}C, -NR\text{$_{2}$}2AR\text{$_{2}$}2C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; z2 is an integer from 0 to 5;

- Each $R^{1\text{t=1}}$, $R^{1\text{t=2}}$, $R^{1\text{C}}$, $R^{1\text{D}}$, $R^{2\text{t=1}}$, $R^{2\text{t=2}}$, $R^{2\text{C}}$, and $R^{2\text{D}}$ is independently hydroge, -CX\text{$_{3}$}, -CN, -COOH, -CONH2, -CHX2, -CH2X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
unsubstituted heteroaryl; \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{2A} \) and \( R^{2B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each \( X, X^1, \) and \( X^2 \) is independently -F, -Cl, -Br, or -I;

\( n1 \) and \( n2 \) are independently an integer from 0 to 4; and

\( ml, ml, vl, \) and \( v2 \) are independently an integer from 1 to 2; wherein the compound does not have the formula:

\[
\text{HO} \quad \text{HO}
\]

18. The use of a compound for the preparation of a medicament for the treatment of cancer, wherein the compound has the formula:

![Chemical Structure](image)

wherein,

- \( R^1 \) is independently halogen, -CX^\^, -CHX^\^, -CH2X^\^, -OCX^\^, -
- OCH2X^\^, -OCHX^\^, -CN, -SOniR^\^, -SO_3NR^\^A^\^R^\^B^\^, -NHC(0)NR^\^A^\^R^\^B^\^, -N(0)_m^\^i, -NR^\^A^\^R^\^B^\^,
- -C(0)R^\^C^\^, -C(0)-OR^\^C^\^, -C(0)NR^\^A^\^R^\^B^\^, -OR^\^C^\^, -NR^\^A^\^S_0^\^2^\^R^\^D^\^, -NR^\^A^\^C(0)R^\^C^\^, -NR^\^A^\^C(0)0
- R^\^C^\^, -NR^\^A^\^0 R^\^C^\^, -N^\^3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( z1 \) is an integer from 0 to 5;

- \( R^2 \) is independently halogen, -CX^\^2^\^3, -CHX^\^2^\^2, -CH_2X^\^2, -OCX^\^2^\^2, -
- OCH2X^\^2, -OCHX^\^2, -CN, -SO_2R^\^2D, -SO_3NR^\^2A^\^R^\^2B, -NHC(0)NR^\^2A^\^R^\^2B, -N(0)_m^\^2, -NR^\^2A^\^R^\^2B,
- -C(0)R^\^2C, -C(0)-OR^\^2C, -C(0)NR^\^2A^\^R^\^2B, -OR^\^2D, -NR^\^2A^\^S_0^\^2^\^R^\^2D, -NR^\^2A^\^C(0)R^\^2C, -NR^\^2A^\^C(0)0
- R^\^2C, -NR^\^2AOR^\^2C, -N^\^3, substituted or unsubstituted alkyl, substituted or unsubstituted
heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R\(^2\) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; 

\(z_2\) is an integer from 0 to 5;

Each R\(^1\)A, R\(^1\)B, R\(^1\)C, R\(^1\)D, R\(^2\)A, R\(^2\)B, and R\(^2\)D is independently hydrogen, -CX\(_3\), -CN, -COOH, -CONH\(_2\), -CHX\(_2\), -CH\(_2\)X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R\(^1\)A and R\(^1\)B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\(^2\)A and R\(^2\)B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X\(^1\), and X\(^2\) is independently -F, -Cl, -Br, or -I;

n\(^1\) and n\(^2\) are independently an integer from 0 to 4; and

ml, m\(^2\), vl, and v\(^2\) are independently an integer from 1 to 2, wherein the compound is not

\[ \text{P-S-i} \]

19. A compound covalently bonded to a sulfur atom of a cysteine residue of a PTGR1 protein of the formula:

\[ \text{P-S-i} \]

wherein,

P-S- is said PTGR1 protein and said sulfur atom;

R\(^1\) is independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH\(_2\)X\(^1\), -OCX\(^\wedge\), -

OCH\(_2\)X\(^1\), -OCHX\(^\wedge\), -CN, -SO\(_n\)R\(^{1d}\), -SCviNR\(^{1a}\)R\(^{1b}\), -NHC(0)NR\(^{1a}\)R\(^{1b}\), -N(0)\(^m\)R\(^{1a}\), -NR\(^{1a}\)R\(^{1b}\),

OCH\(_2\)X\(^1\), -OCHX\(^\wedge\), -CN, -SO\(_n\)R\(^{1d}\), -SCviNR\(^{1a}\)R\(^{1b}\), -NHC(0)NR\(^{1a}\)R\(^{1b}\), -N(0)\(^m\)R\(^{1a}\), -NR\(^{1a}\)R\(^{1b}\),
19. The PTGR1 protein of claim 19, irreversibly covalently bonded to the
unsubstituted

heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
two adjacent R1 substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

\[ z1 \] is an integer from 0 to 5;

R2 is independently halogen, -CX2, -CHX2, -CH2X, -OCX2, -

OCH2X2, -OCHX2, -CN, -SO2R2D, -SOy2NR2AR2B, -NHC(0)NR2AR2B, -N(0)m2, -NR2AR2B,

-C(0)R2C, -C(0)-OR2C, -C(0)NR2AR2B, -OR2D, -NR2ASO2R2D, -NR2AC(0)R2C, -NR2AC(0)0

R2C, -NR2AOR2C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
two adjacent R2 substituents may optionally be joined to form a substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

\[ z2 \] is an integer from 0 to 5;

Each R1A, R1B, R1C, R1D, R2A, R2B, R2C, and R2D is independently
hydrogen, -CX3, -CN, -COOH, -CONH2, -CHX2, -CH2X, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
unsubstituted heteroaryl; R1A and R1B substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl; R2A and R2B substituents bonded to the same nitrogen atom may
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl;

each X, X1, and X2 is independently -F, -Cl, -Br, or -I;
n1 and n2 are independently an integer from 0 to 4; and
m1, m2, nl, and v2 are independently an integer from 1 to 2.

20. The PTGR1 protein of claim 19, irreversibly covalently bonded to the
compound.
21. The PTGR1 protein of claim 19, wherein the compound is covalently bonded to an amino acid corresponding to C239 of SEQ ID NO: 1.

22. A pharmaceutical composition comprising a prostaglandin reductase 1 (PTGR1) inhibitor and a pharmaceutically acceptable excipient.

23. The pharmaceutical composition of claim 22, wherein the PTGR1 inhibitor has the formula:

![Chemical Structure](image)

wherein,

- $R^1$ is independently halogen, -CX^+, -CHX^+, -CH2X^, -OCX^, -
- OCH2X^, -OCHX^, -CN, -SO\text{ii}R^1D, -SO\text{ii}NR^1A\text{R}^1B, -NH\text{C}(0)NR, -NR^1A\text{R}^1B, -N(0) m^i, -NR^1A\text{R}^1B, -C(0)R^1C, -C(0)NR^1A\text{R}^1B, -OR^1D, -NR^1A\text{SO}_2R^1D, -NR^1A\text{C}(0)R^1C, -NR^1A\text{C}(0)0
- R^1C, -NR^1A\text{O} R^1C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted ary1, or substituted or unsubstituted heteroaryl; two adjacent $R^1$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted ary1, or substituted or unsubstituted heteroaryl;
- $z1$ is an integer from 0 to 5;
- $R^2$ is independently halogen, -CX^2, -CHX^2, -CH2X^2, -OCX^2, -
- OCH2X^2, -OCHX^2, -CN, -SO,2R\text{2D}, -SO\text{vii}NR\text{2A}R\text{2B}, -NH\text{C}(0)NR\text{2A}R\text{2B}, -N(0) m^2, -NR\text{2A}R\text{2B}, -C(0)R^2C, -C(0)NR\text{2A}R\text{2B}, -OR\text{2D}, -NR\text{2A}SO_2R\text{2D}, -NR\text{2A}C(0)R^2C, -NR\text{2A}C(0)0
- R^2C, -NR\text{2A}OR^2C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted ary1, or substituted or unsubstituted heteroaryl; two adjacent $R^2$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted ary1, or substituted or unsubstituted heteroaryl;
- $z2$ is an integer from 0 to 5;
Each \( R^{1A} \), \( R^{1B} \), \( R^{1C} \), \( R^{1D} \), \( R^{2A} \), \( R^{2B} \), \( R^{2C} \), and \( R^{2D} \) is independently hydrogen, -CX\(^3\), -CN, -COOH, -CONH\(_2\), -CH\(_X\)_2, -CH\(_2\)_X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{2A} \) and \( R^{2B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each \( X \), \( X^1 \), and \( X^2 \) is independently -F, -Cl, -Br, or -I;

\( m_1 \) and \( m_2 \) are independently an integer from 0 to 4; and

\( m_1 \), \( m_1 \), \( v_1 \), and \( v_2 \) are independently an integer from 1 to 2.

24. A method of treating triple negative breast cancer, said method comprising administering to a subject in need thereof an effective amount of a compound having the formula:

\[
\text{(I),}
\]

wherein,

\( R^1 \) is independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH\(_2\)_X\(^1\), -OCX\(^\wedge\), -

- \( OCH2 \)_X\(^1\), -OCHX\(^\wedge\), -CN, -SO\(_n\)R\(^{1b}\), -SC\(_ni\)NR\(^{1A}\)R\(^{1b}\), -NHC(\(0\))NR\(^1\)A\(^{1B}\), -N(\(0\))\(_m\), -NR\(^1\)A\(^{1B}\),

- \( C(0)R \)_\(^{1C}\), -C(\(0\))OR\(^{1C}\) -C(\(0\))NR\(^1\)AR\(^{1B}\), -OR\(^{1D}\), -NR\(^1\)A\(^{1B}\)SO\(_2\)R\(^{1D}\), -NR\(^1\)A\(^{1C}\)C(\(0\))R\(^{1C}\), -NR\(^1\)A\(^{1C}\)(\(0\))R\(^{1C}\),

\( R^{1C} \), -NR\(^1\)A\(^{1D}\)R\(^{1C}\), -N\(_3\), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

\( z_1 \) is an integer from 0 to 5;

\( R^2 \) is independently halogen, -CX\(^3\), -CHX\(^2\), -CH\(_2\)_X\(^2\), -OCX\(^2\), -

- \( OCH2 \)_X\(^2\), -OCHX\(^2\), -CN, -SO\(_2\)R\(^{2D}\), -SO\(_{ni}\)NR\(^2\)A\(^{2B}\), -NHC(\(0\))NR\(^2\)A\(^{2B}\), -N(\(0\))\(_m\), -NR\(^2\)A\(^{2B}\),

- \( C(0)R \)_\(^2\), -C(\(0\))OR\(^2\), -C(\(0\))NR\(^2\)A\(^{2B}\), -OR\(^2\), -NR\(^2\)A\(^{2B}\)SO\(_2\)R\(^2D\), -NR\(^2\)A\(^{2C}\)C(\(0\))R\(^2\), -NR\(^2\)A\(^{2C}\)(\(0\))R\(^2\),
R, -NR OR, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;  

z₂ is an integer from 0 to 5;  

Each R¹, R¹', R¹C, R¹D, R²A, R²B, R²C, and R²D is independently hydrogen, -CX₃, -CN, -COOH, -CONH₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹A and R¹B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R²A and R²B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;  

each X, X¹, and X² is independently -F, -Cl, -Br, or -I;  
n₁ and n₂ are independently an integer from 0 to 4; and  
ml, m₂, vl, and v₂ are independently an integer from 1 to 2. 

The method of claim 24, wherein the compound has the formula:
**FIG. 1A**

Cell survival screen in 231MFP breast cancer cells

**FIG. 1B**

Cell survival screen in HCC38 breast cancer cells
FIG. 1C

anti-cancer agents that impair triple-negative breast cancer cell survival

cell survival (% of control)

anti-cancer compounds

MLN2238  MLN9708  WP1130  SB938  Romidepsin  TG101348  Doxorubicin  Idoxuridine  Mitoxantrone HCl

targets

proteosome  deubiquitrase  HDAC  JAK2  topoisomerase

kinesin  EPAC1  KSP  mTORI  PLK1  EGFR  FXR1  AURK1  ER/PR  DNA-PK/Ck

FIG. 2A

licochalcone A

\[ \text{Chemical structure of licochalcone A} \]
FIG. 2B

1. mix
2. avidin enrichment
3. tryptic digestion
4. TEV digestion

protein 1
YWKDAC*SHR

protein 2
SYC*WHIL

LC-MS/MS

light/heavy: 1
not inhibited

light/heavy: 5
inhibited

target identification of Licochalcone A
FIG. 2C

isoTOP-ABPP analysis of Licochalcone A in 231MFP cells

FIG. 2D

PTGR1 structure
FIG. 2E

PTGR1 expression

FIG. 2F

231MFP cell survival

FIG. 2G

231MFP cell proliferation
FIG. 3A

Lipidomic profiling of compounds that impair TNBC pathogenicity

targets
- panobinostat
-SAuy001
- HDAC
- JAK2
- hypoxia-inducible factor
- Kras
- EPAC
- HSP
- MYC
- PI3K
- ERK
- PR
- FGFR
- NR1
- MYCN
- DNA-PKc

anti-cancer compounds
- fatty acids
- neutral lipids
- acyl carnitines
- phospholipids
- NAEs
- NAT
- ether lipids
- sphingolipids
- sterols

fold-changes compared to control (log(2))
FIG. 3B

levels of representative lipid metabolites

C16:0 AC

fold over control

FIG. 3C

deubiquitinase inhibitor survival

% survival

Control  PR619  P5091
**FIG. 3D**

Deubiquitinase inhibitor
acyl carnitine levels

**FIG. 4A**

Cell survival
C16:0 AC

**FIG. 4B**

Cell survival
AC + WP1130
FIG. 4C

![Graph showing OCR (pmoles/min) measurements with control and C16:0 AC conditions.]

FIG. 4D

![Graph showing OCR (pmoles/min) measurements with control and WP1130 conditions.]

FIG. 5

231MFP cell survival

EC50
8.4 μM

% survival
0 100
0 0.01 0.1 1 10 100
licochalcone (μM)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - 9/02; A61 K 36/48; A61 K 36/484; A61P 35/00; C07C 45/00; C07C 45/41; C07C 45/45 (2018.01)
CPC - A61 K 36/48; A61 K 36/484; A61P 35/00; C07C 45/00; C07C 45/41; C07C 45/45; C07C 45/62; C07C 49/21.5; C07C 49/813; C07C 49/835; C12N 9/001; C12Q 1/26; C12Q 1/6886; C12Y 103/01; C12Y 103/01 048; C12Y 103/01 074 (2018.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/757; 424/94.4; 435/23; 435/7.23 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CN 103768042 A (SHANGHAI TRADITIONAL CHINESE MEDICINE UNIVERSITY) 07 May 2014 (07.05.2014) entire document; see machine translation</td>
<td>14-16, 22-25</td>
</tr>
<tr>
<td>P, X</td>
<td>ROBERTS et al. &quot;Mapping Novel Metabolic Nodes Targeted by Anti-Cancer Drugs that Impair Triple-Negative Breast Cancer Pathogenicity,&quot; ACS Chemical Biology, 01 March 2017 (01.03.2017), Vol. 12, Iss. 4, Pgs. 1133-1140. entire document</td>
<td>1-12, 14-16, 22-25</td>
</tr>
<tr>
<td>A</td>
<td>US 8,889,674 B2 (AHMED et al) 18 November 2014 (18.11.2014) entire document</td>
<td>1-12, 14-16, 22-25</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "A" document member of the same patent family

Date of the actual completion of the international search 14 June 2018
Date of mailing of the international search report 17 JUL 2018

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-273-6300

Authorized officer Blaine R. Copenheaver
PCT Helpdesk: 571-272-4300
PCT GSP: 571-272-7774
<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2009/0275608 A 1 (OSSOVSKAYA et al) 05 November 2009 (05.11.2009) entire document</td>
<td>1-12, 14-16, 22-25</td>
</tr>
</tbody>
</table>
1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. [x] forming part of the international application as filed:
      - in the form of an Annex C/ST.25 text file.
      - on paper or in the form of an image file.
   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:
      - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
      - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
   SEQ ID NO:1 was searched.
<table>
<thead>
<tr>
<th>Box No. II</th>
<th>Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</td>
<td></td>
</tr>
<tr>
<td>1.☐</td>
<td>Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:</td>
</tr>
<tr>
<td>2.☐</td>
<td>Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:</td>
</tr>
<tr>
<td>3.☐</td>
<td>Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box No. III</th>
<th>Observations where unity of invention is lacking (Continuation of item 3 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This International Searching Authority found multiple inventions in this international application, as follows:</td>
<td></td>
</tr>
<tr>
<td>See extra sheet(s).</td>
<td></td>
</tr>
<tr>
<td>1.☐</td>
<td>As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.</td>
</tr>
<tr>
<td>2.☐</td>
<td>As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</td>
</tr>
<tr>
<td>3.☐</td>
<td>As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</td>
</tr>
<tr>
<td>4.☒</td>
<td>No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-12, 14-16, and 22-25 to the extent that they read on a compound of Formula 1, wherein the compound is licochalcone A.</td>
</tr>
</tbody>
</table>

**Remark on Protest**

☐ | The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee. |
☐ | The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation. |
☐ | No protest accompanied the payment of additional search fees. |
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-25 are drawn to compounds of Formula I, methods and compositions comprising the same.

The first invention of Group I is restricted to a compound of Formula I, methods and compositions comprising the same, wherein the compound of Formula I is selected to be:

\[
\text{HO-}<\text{Q}\text{-CH-}<\text{R1-CH2-CH2-CH2-CH2-CH2-OH}
\]

It is believed that claims 1-12, 14-16, and 22-25 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above chemical structure.

Applicant is invited to elect additional compounds of Formula I, each with specified chemical structure, to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of Formula I, methods and compositions comprising the same, wherein the compound of Formula I is selected to be:

\[
\text{HO-}<\text{Q}\text{-CH-}<\text{R1-CH2-CH2-CH2-CH2-CH2-OH}
\]

Additional compounds of Formula I will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "I" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I formulas do not share a significant structural element responsible for inhibiting prostaglandin reductase 1 and/or treating cancer, requiring the selection of alternatives for the structure of the PTGR1 inhibitor, where "[the] compound having the formula (I), wherein R1 is independently halogen, -CX(1)3, -CH(X1)2, -OC(X1)1, -OCH(X1)2, -OH, and/or -SO2R1B; -SO2R1A OR1C, -NR1AOR1C, -N3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; x is an integer from 0 to 5; R2 is independently halogen, -CX(X2)3, -CH(X2)2, -OC(X2)1, -OCH(X2)2, -OH, -CN, -SO2R1D, -SO2R1B, -SO2R1A OR2B, -NR2A OR2C, -NR2A OR2C, -N3; substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; y is an integer from 0 to 5; each R1A, R1B, R1C, R1D, R2A, R2B, R2C, and R2D is independently hydrogen, -CX(X3)1, -CN, -COOH, -CONT-12, -CHX2, -CHX2, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; x and y are independently an integer from 0 to 2; and m, n, m', n2, v1, and v2 are independently an integer from 1 to 2."

Additionally, even if Groups I were to be considered to share the technical features of a method of inhibiting prostaglandin reductase 1 (PTGR1) activity, said method comprising contacting a PTGR1 protein with an effective amount of a compound of formula (I) (see structure, instant claim 2); A method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a prostaglandin reductase 1 (PTGR1) inhibitor; the use of a compound for the preparation of a medicament for the treatment of cancer, wherein the compound has the formula (I) (see structure, instant claim 18), wherein the compound is not (see compound, instant claim 18); A compound covalently bonded to a sulfur atom of a cysteine residue of a PTGR1 protein of the formula (see structure, instant claim 19); A pharmaceutical composition comprising a prostaglandin reductase 1 (PTGR1) inhibitor and a pharmaceutically acceptable excipient; A method of treating triple negative breast cancer, said method comprising administering to a subject in need thereof an effective amount of a compound; these shared technical features do not represent a contribution over the prior art.
Specifically, “Knockdown of prostaglandin reductase 1 (PTGR1) suppresses prostate cancer cell proliferation by inducing cell cycle arrest and apoptosis” to Xue et al. discloses a method of inhibiting prostaglandin reductase 1 (PTGR1) activity (Two PTGR1 short hairpin RNAs (shRNAs) were designed and cloned in plV-GV1 15-entiviral vectors, Pg. 134, left-hand column, third full paragraph; flow cytometry was used to study the effects of shPTGR1#1-mediated downregulation of PTGR1 on cell cycle progression., Pg. 137, left-hand column, second paragraph).

US 2009/0124688 A1 to Lin et al. discloses a method of inhibiting a prostaglandin reductase (PTGR1) activity (A method of inhibiting 15-keto prostaglandin-delta 13-reductase 2 by contacting 15-keto prostaglandin-A’-reductase 2 with an aryl compound of Formula 11, Abstract), said method comprising contacting with an effective amount of a compound of formula (I), wherein z1 is 1; R1 is -OR1 D; R1D is H; z2 is 1; -OR2D; and R2D is H, wherein the compound is not licochalcone A (Shown below are exemplary compounds, Para. [0014]; see compound 50, Pg. 6, right-hand column, middle of page); a method of treating cancer (this invention also features a method of treating a PPARs related disease such as...cancer, Para. [0022]), said method comprising administering to a subject in need thereof an effective amount of a prostaglandin reductase inhibitor (Shown below are exemplary compounds that can be used as 15-keto PGR-2 inhibitors, Para. [0014]; The method includes administering to a subject an effective amount of a 15-keto PGR-2 modulator, Para. [0022]); the use of a compound for the preparation of a medicament for the treatment of cancer (this invention also features a method of treating a PPARs related disease such as...cancer, Para. [0022]); as well as the use of such a composition for the manufacture of a medicament for treating PPAR related diseases, Para. [0024]); wherein the compound is a compound of formula (I), wherein z1 is 1; R1 is -OR1 D; R1D is H; z2 is 1; -OR2D; and R2D is H, wherein the compound is not licochalcone A (Shown below are exemplary compounds, Para. [0014]; see compound 50, Pg. 6, right-hand column, middle of page); a pharmaceutical composition comprising a prostaglandin reductase 1 (PTGR1) inhibitor and a pharmaceutically acceptable excipient (Also within the scope of this invention is a composition containing a 15-keto PGR-2 modulator (e.g., a compound of any of formulas (I), (II), (III), and (IV) and a pharmaceutically acceptable carrier for use in treating PPAR related diseases, Para. [0024]; pharmaceutically acceptable excipient, Para. [0038]).

Further, US 2009/0275608 A1 to Ososkovskaia et al. discloses a method of treating triple negative breast cancer (and treating a patient with said breast cancer with inhibitors to PARP and the co-regulated gene. One embodiment is the treatment of triple negative breast cancer, Para. [0026]; Other co-differentially expressed genes may also include without limitation ...LTB4DH, Para. [0088]), said method comprising administering to a subject in need thereof an effective amount of a compound (PARP1 inhibitors and inhibitors of co-regulated genes may be administered to the patient as in Example 11, Para. [0475]).

Further, "PPARs and lipid ligands in inflammation and metabolism," to Harmon et al. discloses a compound covalently bonded to a sulfur atom of a cysteine residue of a PTGR1 protein (It was subsequently demonstrated to covalently bind to the sulfhydryl group of cysteine 285 in the PPAR-γ ligand binding pocket through a Michael addition reaction by the α,β-unsaturated carbonyl168 that readily reacts with substances containing nucleophilic groups such as cysteinyli thiols, Pg. 11, bottom of page; This later enzyme also exhibits NADP+ dependent leukotriene B4 12-hydroxydehydrogenase (12-LTB4DH) activity, Pg. 17, second paragraph).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.