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(71) **Applicant**: **EXELIXIS, INC.** [US/US]; 210 East Grand Ave., South San Francisco, CA 94080 (US).

(72) **Inventors**: **AFTAB, Dana, T**; 736 Tamarack Drive, San Rafael, CA 94903 (US). **SCHIMMOLLER, Frauke**; 666 Fourteenth Avenue, Menlo Park, CA 94025 (US).

(74) **Agents**: **BERVEN, Heidi, M.** et al.; Honigman Miller Schwartz And Cohn LLP, 350 East Michigan Ave., Suite 300, Kalamazoo, MI 49007-3800 (US).

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(54) **Title**: DUAL INHIBITOR OF MET AND VEGF FOR TREATING CANCER

(57) **Abstract**: This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

DUAL INHIBITOR OF MET AND VEGF FOR TREATING CANCER

Cross-Reference to Related Applications

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 61/557,358, filed, November 8, 2011, the entire contents of which is incorporated herein by reference.

Field of the Invention

[0002] This invention is directed to the treatment of cancer, particularly castration-resistant prostate cancer and bone metastases, with a dual inhibitor of MET and VEGF.

Background of the Invention

[0003] Castration-Resistant Prostate Cancer (CRPC) is a leading cause of cancer-related death in men. Despite progress in systemic therapy for CRPC, improvements in survival are modest, and virtually all patients succumb to this disease within about 2 years. The primary cause of morbidity and mortality in CRPC is metastasis to the bone, which occurs in about 90% of cases.

[0004] Metastasis to the bone is a complex process that involves interactions between cancer cells and components of the bone microenvironment including osteoblasts, osteoclasts, and endothelial cells. Bone metastases cause local disruption of normal bone remodeling, and lesions generally show a propensity for either osteoblastic (bone-forming) or osteolytic (bone-resorbing) activity. Although most CRPC patients with bone metastases display features of both types of lesions, prostate cancer bone metastases are often osteoblastic, with abnormal deposition of unstructured bone accompanied by increased skeletal fractures, spinal cord compression, and severe bone pain.

[0005] The receptor tyrosine kinase MET plays important roles in cell motility, proliferation, and survival, and it has been shown to be a key factor in tumor angiogenesis, invasiveness, and metastasis. Prominent expression of MET has been observed in primary and metastatic prostate carcinomas, with evidence for higher levels of expression in bone metastases compared to lymph node metastases or primary tumors.

[0006] Vascular endothelial growth factor (VEGF) and its receptors on endothelial cells are widely accepted as key mediators in the process of tumor angiogenesis. In prostate cancer, elevated VEGF in either plasma or urine is associated with shorter overall survival. VEGF may also play a role in activating the MET pathway in tumor cells by binding to neuropilin-1, which is frequently unregulated in prostate cancer and appears to activate MET

in a co-receptor complex. Agents targeting the VEGF signaling pathway have demonstrated some activity in patients with CRPC.

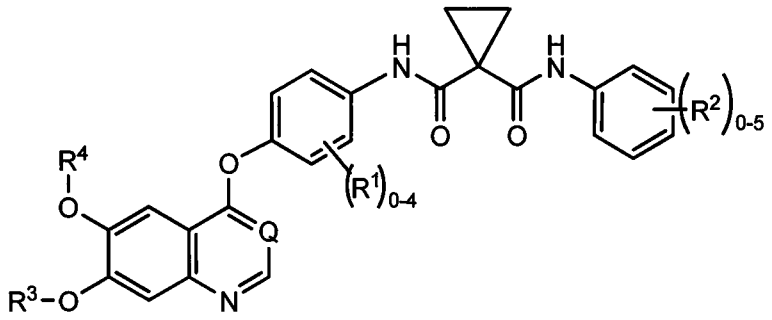
[0007] Thus, a need remains for methods of treating prostate cancer, including CRPC and the associated bone metastases.

Summary of the Invention

[0008] These and other needs are met by the present invention which is directed to a method for treating bone cancer, prostate cancer, or bone cancer associated with prostate cancer. The method comprises administering a therapeutically effective amount of a compound that modulates both MET and VEGF to a patient in need of such treatment. In one embodiment, the bone cancer is osteoblastic bone metastases. In a further embodiment, the prostate cancer is CRPC. In a further embodiment, the bone cancer is bone metastases associated with CRPC.

[0009] In one aspect, the present invention is directed to a method for treating bone metastases, CRPC, or osteoblastic bone metastases associated with CRPC, comprising administering a therapeutically effective amount of a compound that dually modulates MET and VEGF to a patient in need of such treatment.

[0010] In one embodiment of this and other aspects, the dual acting MET/VEGF inhibitor is a compound of formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo;

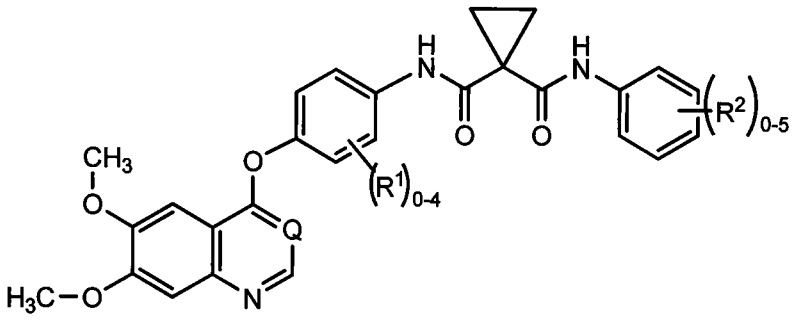
R^2 is halo;

R^3 is $(C_1\text{-}C_6)$alkyl;

R^4 is $(C_1\text{-}C_6)$alkyl; and

Q is CH or N.

[0011] In another embodiment, the compound of formula I is a compound of formula Ia:



Formula Ia

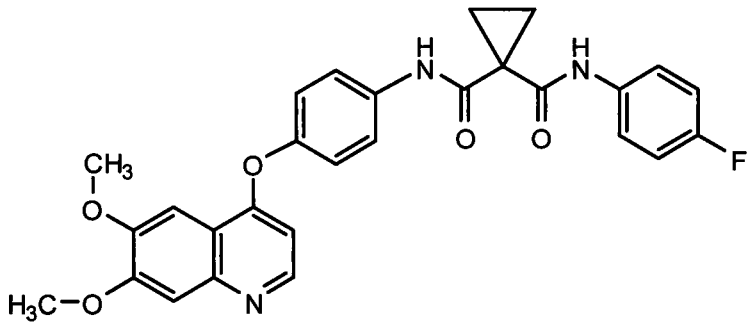
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo;

R^2 is halo; and

Q is CH or N.

[0012] In another embodiment, the compound of formula I is compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof. Compound 1 is known as N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and by the name Cabozantinib (cabo).

[0013] In another embodiment, the compound of formula I, formula Ia, or compound 1 is administered as a pharmaceutical composition comprising a pharmaceutically acceptable additive, diluent, or excipient.

[0014] In another aspect, the invention provides a method for treating osteoblastic bone metastases associated with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1.

[0015] In another aspect, the invention provides a method for reducing or stabilizing metastatic bone lesions associated with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I, formula Ia or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1.

[0016] In another aspect, the invention provides a method for reducing bone pain due to metastatic bone lesions associated with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1.

[0017] In another aspect, the invention provides a method for treating or minimizing bone pain due to metastatic bone lesions associated with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1.

[0018] In another aspect, the invention provides a method for strengthening bones in patients with metastatic bone lesions associated with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1. Bone strengthening can occur when the disruption in normal bone remodeling due to bone metastases is minimized, for instance by administering a compound of formula I as provided herein.

[0019] In another aspect, the invention provides a method for preventing bone metastases associated with CRPC, comprising administering a therapeutically effective amount of a compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In one embodiment, the compound of formula I is administered as a pharmaceutical composition. In a specific embodiment, the compound of formula I is compound 1.

[0020] In another aspect, the invention provides a method for preventing bone metastases in patients with prostate cancer who are castration resistant but have not yet advanced to metastatic disease, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In a specific embodiment, the compound of formula I is compound 1.

[0021] In another aspect, the invention provides a method for extending the overall survival in patients with CRPC, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment.

[0022] In another aspect, the invention provides a method for inhibiting osteoblastic and osteolytic progression in bone cancer associated with prostate cancer, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In one embodiment, the compound of formula I is administered as a pharmaceutical composition. In a specific embodiment, the compound of formula I is compound 1.

[0023] In another aspect, the invention provides a method for inhibiting osteoblastic progression in bone cancer associated with prostate cancer, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I or the malate salt of compound of formula I or another pharmaceutically acceptable salt of compound of formula I, to a patient in need of such treatment. In one embodiment, the compound of formula I is administered as a pharmaceutical composition. In a specific embodiment, the compound of formula I is compound 1.

[0024] In these and other aspects, the ability of the compound of formula I to treat, ameliorate, or reduce the severity of bone metastases can be determined both qualitatively and quantitatively using various physiological markers, such as circulating tumor cell (CTC) counts and imaging technologies. The imaging technologies include positron emission tomography (PET) or computerized tomography (CT) and magnetic resonance imaging. By using these imaging techniques, it is possible to monitor and quantify the reduction in tumor

size and the reduction in the number and size of bone lesions in response to treatment with the compound of formula I.

[0025] In these and other aspects, shrinkage of soft tissue and visceral lesions has been observed to result when the compound of formula I is administered to patients with CRPC. Moreover, administration of the compound of formula I leads to increases in hemoglobin concentration in patients CRPC patients with anemia.

Brief Description of the Figures

[0026] Figure 1 depicts the role for MET and VEGFR in tumor-bone interactions in CRPC.

[0027] Figure 2 shows the $ARCaP_M$ in vivo efficacy study overview.

[0028] Figure 3 depicts the in vitro osteoclast (OC) differentiation and activity assays.

[0029] Figure 4 depicts the in vitro osteoblast (OB) differentiation and activity assays.

[0030] Figure 5 shows that compound 1 blocks progression of CRPC $ARCaP_M$ tumor xenografts in bone.

[0031] Figure 6 shows that compound 1 blocks progression of CRPC $ARCaP_M$ tumor xenografts in bone.

[0032] Figure 7 shows that compound 1 treatment preserves volume and mineral density relative to vehicle.

[0033] Figure 8 shows that compound 1 treatment compared to vehicle results in decreased tumor area and increased bone area in the analyzed tibia sections.

[0034] Figure 9 shows that compound 1 treatment compared to vehicle results in increased OBs and no change in OCs along the trabecular bone in the analyzed tibia sections.

[0035] Figure 10 depicts that compound 1 treatment is associated with decreased IHC staining of p-MET and proteins related to the VEGF pathway in $ARCaP_M$ tumors.

[0036] Figure 11 shows that compound 1 inhibits in vitro osteoclast (OC) differentiation in a dose-dependent manner, but does not affect the ability of mature OCs to resorb bone.

[0037] Figure 12 depicts that compound 1 shows biphasic effects on osteoblast (OB) differentiation and bone forming activity in vitro.

[0038] Figures 13A-C show the bone scan (Figure 13A), bone scan response (Figure 13B), and CT scan data (Figure 13C) for Patient 1.

[0039] Figures 14A-C show the bone scan (Figure 14A), bone scan response (Figure 14B), and CT scan data (Figure 14C) for Patient 2.

[0040] Figures 15A-B show the bone scan (Figure 15A), bone scan response (Figure 15B) for Patient 3.

Detailed Description of the Invention

Abbreviations and Definitions

[0041] The following abbreviations and terms have the indicated meanings throughout:

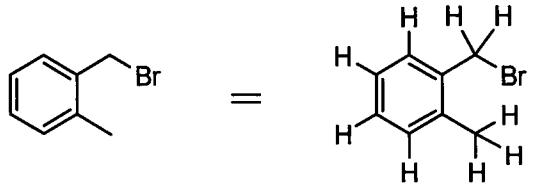
Abbreviation	Meaning
Ac	Acetyl
br	Broad
°C	Degrees Celsius
c-	Cyclo
CAB	Combined androgen blockade
CT	Computed tomography
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
DCM	Dichloromethane
DES	Diethylstillbestrol
DMA	N,N-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-bis(diphenylphosphano)ferrocene
Et	Ethyl
g	Gram(s)
Gy	Gray
h or hr	Hour(s)

Abbreviation	Meaning
HPLC	High pressure liquid chromatography
KF	Karl Fisher water content determination
kg	Kilogram
L	Liter(s)
LOD	Loss on drying
Me	Methyl
M	Molar or molarity
m	Multiplet
mm	Millimeter
MEK	Methyl ethyl ketone
mg	Milligram(s)
Min	Minute(s)
mL	Milliliter(s)
µL	Microliter(s)
µm	Micrometer
µM	Micromole(s) or micromolar
mM	Millimolar
mmol	Millimole(s)
Mol	Mole(s)
MS	Mass spectral analysis
MTBE	Methyl t-butyl ether
N	Normal or normality
nM	Nanomolar
ng	Nanogram
NMR	Nuclear magnetic resonance spectroscopy

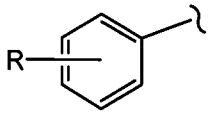
Abbreviation	Meaning
q	Quartet
PSA	Prostate Specific Antigen
rpm	Revolutions per minute
RH	Relative humidity
RT	Room temperature
s	Singlet
t or tr	Triplet
TFA	Trifluoroacetic acid
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
w/w	Weight to weight

[0042] The symbol "-" means a single bond, "=" means a double bond.

[0043] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

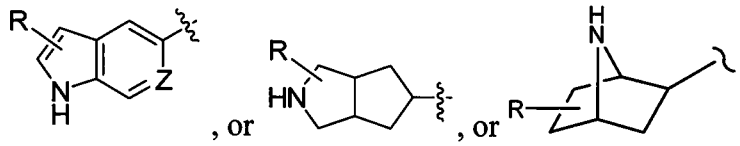


[0044] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:

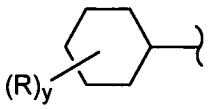


then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

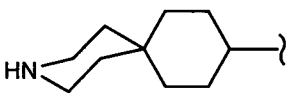
[0045] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "Z" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0046] "(C_1-C_6)Alkyl" or "alkyl" means a linear or branched hydrocarbon group having one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl,

isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl, and the like. "C_6 alkyl" refers to, for example, *n*-hexyl, *iso*-hexyl, and the like.

[0047] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine.

[0048] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0049] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In another embodiment the patient is a mammal, and in another embodiment the patient is human.

[0050] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[0051] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, malic acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[0052] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl

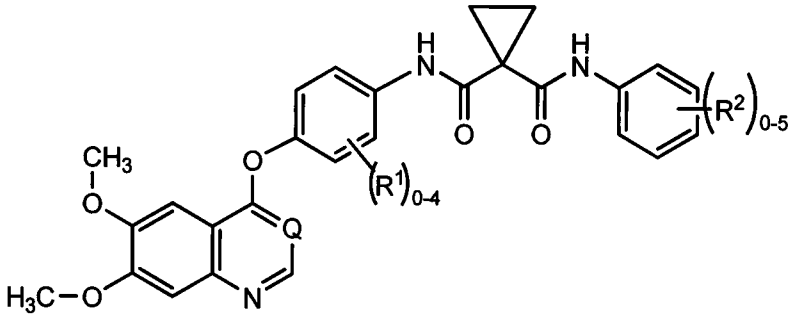
esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0053] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. A therapeutically effective amount is intended to include an amount of a compound alone or in combination with other active ingredients effective to modulate c-Met, and/or VEGFR2, or effective to treat or prevent cancer. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[0054] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, i.e., arresting its development; and (iii) relieving the disease, disorder, or syndrome, i.e., causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experience.

Embodiments

[0055] In one embodiment, the compound of formula I is the compound of formula Ia:



Formula Ia

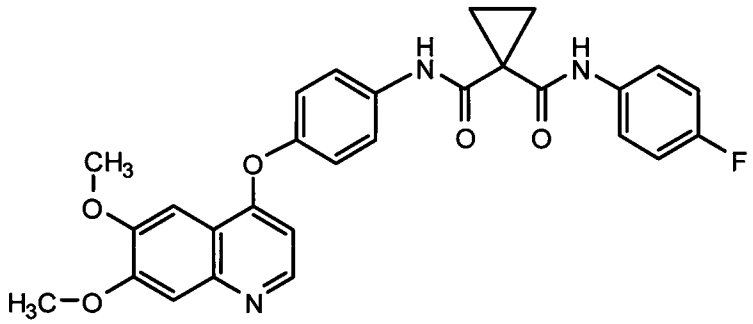
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo;

R^2 is halo; and

Q is CH or N.

[0056] In another embodiment, the compound of formula I is compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof. As indicated previously, compound 1 is referred to herein as N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. WO 2005/030140 discloses compound 1 and describes how it is made (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this compound to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

[0057] In other embodiments, the compound of formula I, formula Ia, or compound 1, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition, wherein the pharmaceutical composition additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent. In a specific embodiment, the compound of formula I is compound 1.

[0058] The compound of formula I, formula Ia, and compound 1, as described herein, includes both the recited compounds as well as individual isomers and mixtures of isomers. In each instance, the compound of formula I includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

[0059] In other embodiments, the compound of formula I, formula Ia, or compound 1 can be the (L)-malate salt. The malate salt of the compound of formula I and of compound 1 is disclosed in PCT/US2010/021194 and U.S. Patent Application Serial No. 61/325095.

[0060] In other embodiments, the compound of formula Ia can be malate salt.

[0061] In other embodiments, the compound of formula I can be the (D)-malate salt.

[0062] In other embodiments, the compound of formula Ia can be the (L)-malate salt.

[0063] In other embodiments, compound 1 can be the malate salt.

[0064] In other embodiments, compound 1 can be (D)-malate salt.

[0065] In other embodiments, compound 1 can be the (L)-malate salt.

[0066] In another embodiment, the malate salt is in the crystalline N-1 form of the (L) malate salt and/or the (D) malate salt of the compound 1 as disclosed in U.S. Patent Application Serial No. 61/325095. *Also see* WO 2008/083319 for the properties of crystalline enantiomers, including the N-1 and/or the N-2 crystalline forms of the malate salt of compound 1. Methods of making and characterizing such forms are fully described in PCT/US10/21194, which is incorporated herein by reference in its entirety.

[0067] In another embodiment, the invention is directed to a method for ameliorating the symptoms of osteoblastic bone metastases, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I in any of the embodiments disclosed herein. In a specific embodiment, the compound of formula I is compound 1.

[0068] In another embodiment, the compound of formula I is administered post-taxotere treatment. In a specific embodiment, the compound of formula I is compound 1.

[0069] In another embodiment, the compound of formula I is as effective or more effective than mitoxantrone plus prednisone. In a specific embodiment, the compound of formula I is compound 1.

[0070] In another embodiment, the compound of formula I, formula Ia, or compound 1 or a pharmaceutically acceptable salt thereof is administered orally once daily as a tablet or capsule.

[0071] In another embodiment, compound 1 is administered orally as its free base or malate salt as a capsule or tablet.

[0072] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing up to 100 mg of compound 1.

[0073] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 100 mg of compound 1.

[0074] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 95 mg of compound 1.

[0075] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 90 mg of compound 1.

[0076] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 85 mg of compound 1.

[0077] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 80 mg of compound 1.

[0078] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 75 mg of compound 1.

[0079] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 70 mg of compound 1.

[0080] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 65 mg of compound 1.

[0081] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 60 mg of compound 1.

[0082] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 55 mg of compound 1.

[0083] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 50 mg of compound 1.

[0084] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 45 mg of compound 1.

[0085] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 40 mg of compound 1.

[0086] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 35 mg of compound 1.

[0087] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 30 mg of compound 1.

[0088] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 25 mg of compound 1.

[0089] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 20 mg of compound 1.

[0090] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 15 mg of compound 1.

[0091] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 10 mg of compound 1.

[0092] In another embodiment, compound 1 is administered orally once daily as its free base or as the malate salt as a capsule or tablet containing 5 mg of compound 1.

[0093] In another embodiment, compound 1 is administered as its free base or malate salt orally once daily as a tablet as provided in the following table.

Ingredient	**(% w/w)**
Compound 1	31.68
Microcrystalline Cellulose	38.85
Lactose anhydrous	19.42
Hydroxypropyl Cellulose	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

[0094] In another embodiment, compound 1 is administered orally as its free base or malate salt once daily as a tablet as provided in the following table.

Ingredient	**(% w/w)**
Compound 1	25.0-33.3
Microcrystalline Cellulose	q.s
Hydroxypropyl Cellulose	3
Poloxamer	0-3
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.5
Magnesium Stearate	0.5-1.0
Total	100

[0095] In another embodiment, compound 1 is administered orally as its free base or malate salt once daily as a tablet as provided in the following table.

Ingredient	Theoretical Quantity (mg/unit dose)
Compound 1	100.0
Microcrystalline Cellulose PH-102	155.4
Lactose Anhydrous 60M	77.7
Hydroxypropyl Cellulose, EXF	12.0
Croscarmellose Sodium	24
Colloidal Silicon Dioxide	1.2
Magnesium Stearate (Non-Bovine)	3.0
Opadry Yellow	16.0
Total	**416**

[0096] Any of the tablet formulations provided above can be adjusted according to the dose of compound 1 desired. Thus, the amount of each of the formulation ingredients can be proportionally adjusted to provide a table formulation containing various amounts of compound 1 as provided in the previous paragraphs. In another embodiment, the formulations can contain 20, 40, 60, or 80 mg of compound 1.

Administration

[0097] Administration of the compound of formula I, formula Ia, or compound 1, or a pharmaceutically acceptable salt thereof, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin dosages (which can be in capsules or tablets), powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

[0098] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of formula I as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

[0099] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens,

chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00100] If desired, a pharmaceutical composition of the compound of formula I may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[00101] The choice of composition depends on various factors such as the mode of drug administration (e.g., for oral administration, compositions in the form of tablets, pills or capsules) and the bioavailability of the drug substance. Recently, pharmaceutical compositions have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical composition having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical composition in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical composition that exhibits remarkably high bioavailability.

[00102] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[00103] One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[00104] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at

least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[00105] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00106] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., the compound of formula I, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00107] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[00108] Compositions for rectal administration are, for example, suppositories that can be prepared by mixing the compound of formula I with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[00109] Dosage forms for topical administration of the compound of formula I include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic compositions, eye ointments, powders, and solutions are also contemplated as being within the scope of this disclosure.

[00110] Compressed gases may be used to disperse the compound of formula I in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[00111] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of formula I, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of formula I, formula Ia, or compound 1, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[00112] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this disclosure.

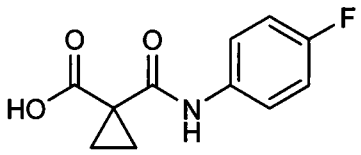
[00113] The compounds of this disclosure, or their pharmaceutically acceptable salts or solvates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compound of formula I, formula Ia, or compound 1, can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per

kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[00114] In other embodiments, the compound of formula I, formula Ia, or compound 1, can be administered to the patient concurrently with other cancer treatments. Such treatments include other cancer chemotherapeutics, hormone replacement therapy, radiation therapy, or immunotherapy, among others. The choice of other therapy will depend on a number of factors including the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy.

Preparation of Compound 1

Preparation of 1-(4-Fluorophenylcarbamoyl)cyclopropanecarboxylic acid (Compound A-1)



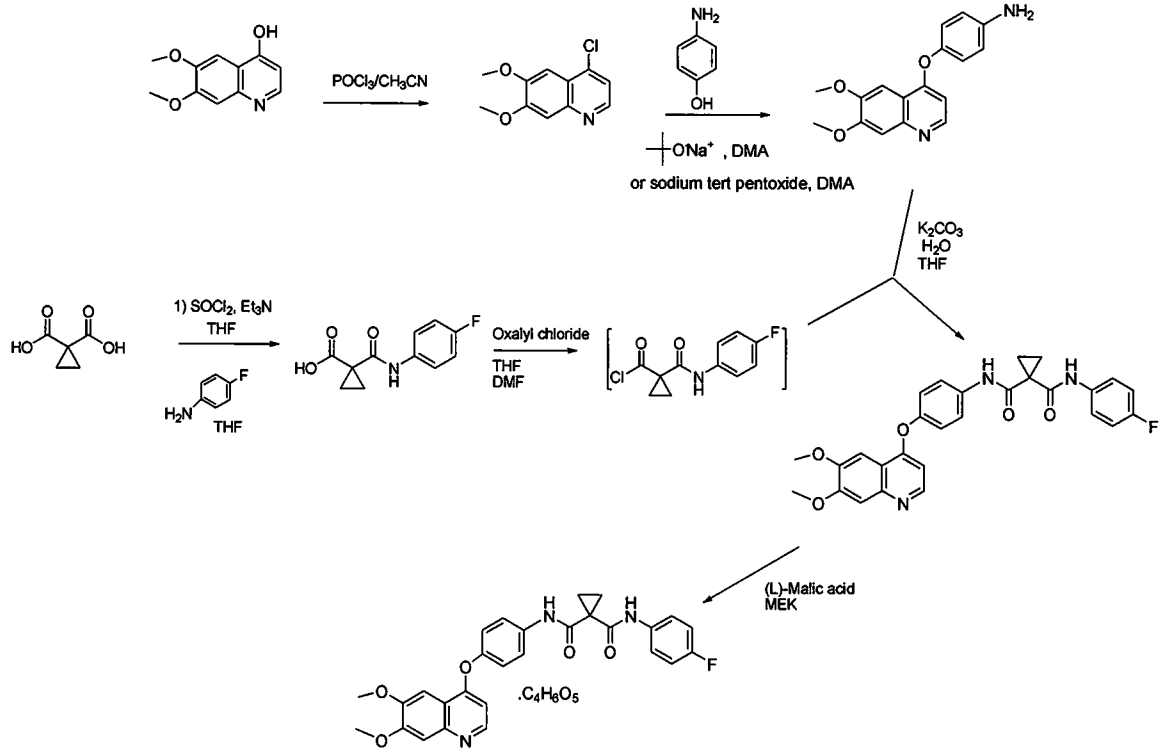
[00115] The starting 1,1-cyclopropanedicarboxylic acid was treated with thionyl chloride (1.05 equivalents) in approximately 8 volumes of isopropyl acetate at 25 °C for 5 hours. The resulting mixture was then treated with a solution of 4-fluoroaniline (1.1 equivalents) and triethylamine (1.1 equivalents) in isopropyl acetate (2 volumes) over 1 hour. The product slurry was quenched with 5N NaOH solution (5 volumes) and the aqueous phase is discarded. The organic phase was extracted with 0.5N NaOH solution (10 volumes) and the basic extract was washed with heptane (5 volumes) and subsequently acidified with 30% HCl solution to give a slurry. Compound A-1 was isolated by filtration.

[00116] Compound A-1 was prepared on a 1.00 kg scale using 1,1-cyclopropanedicarboxylic acid as the limiting reagent to furnish 1.32 kg of Compound A-1 (77% isolated yield; 84% mass balance) with 99.92% purity (HPLC) and 100.3% assay.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound 1) and the (L)-malate salt thereof.

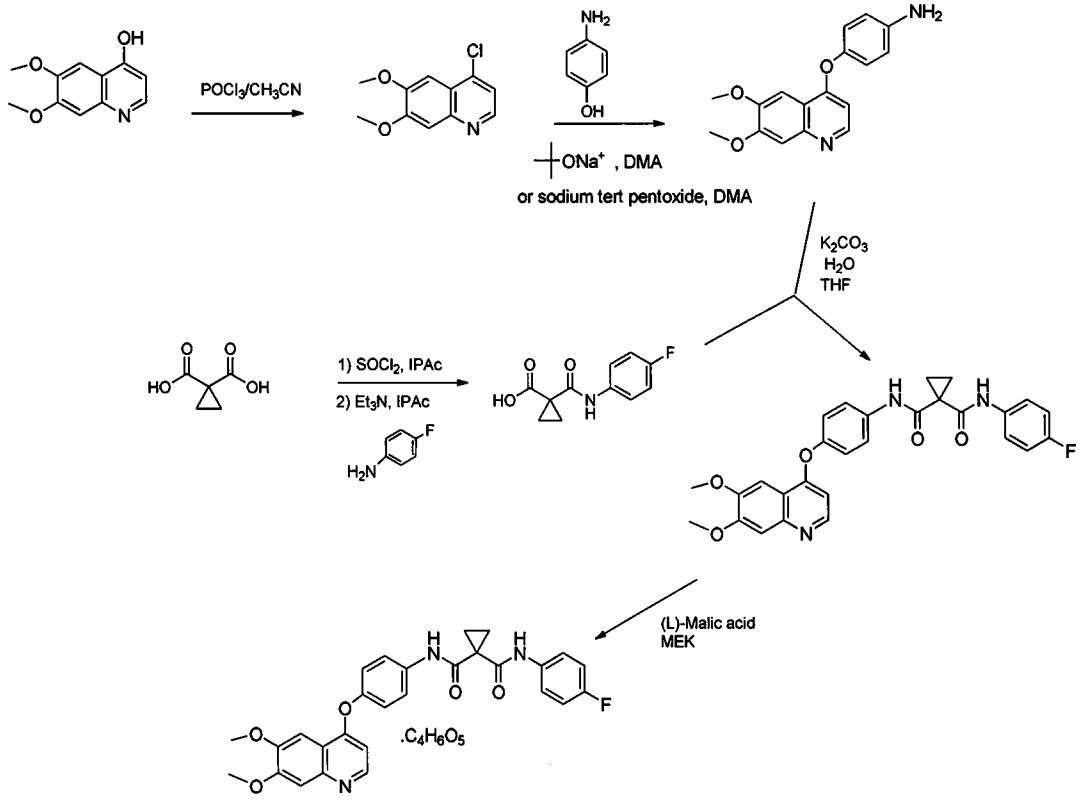
[00117] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1.

Scheme 1



[00118] Another synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 2.

Scheme 2



Preparation of 4–Chloro–6,7–dimethoxy–quinoline

[00119] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77°C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 to 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 to 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg), and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then

charged and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate, which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound (35.6 kg).

Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[00120] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg), and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour and then cooled to 0 to 5 °C and aged for approximately 1 hour after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 °C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[00121] 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-Aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 weight percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 to 115 °C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 25 °C. The crude product was collected by filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

[00122] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110 to 120 °C. In addition, the cool down temperature was increased to 35 to 40 °C and the starting temperature of the water addition was adjusted to 35 to 40 °C, with an allowed exotherm to 45 °C.

Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[00123] Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[00124] A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12 to 17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12 to 17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[00125] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20 to 25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[00126] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 kg K_2CO_3 in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20 to 30 °C over a minimum of two hours. The reaction mixture was stirred at 20 to 25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30 to 25 °C, and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15 to 25 °C for a minimum of 16 hours.

[00127] The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 kg THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30 to 35 °C for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours). The mixture was agitated at 15 to 25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 kg THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

[00128] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10 to 15 °C. The recrystallization temperature was changed from 15 to 25 °C to 45 to 50 °C for 1 hour and then cooled to 15 to 25 °C over 2 hours.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, XL184 (L) malate salt

[00129] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C, and the reactor contents were filtered. These sequential steps

described above were repeated two more times starting with similar amounts of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg), and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF < 0.5 % w/w) at approximately 74°C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours, resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50 °C to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt

[00130] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2 kg), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50 to 55 °C for approximately 1 to 3 hours, and then at 55 to 60 °C for an additional 4 to 5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20 to 25 °C and vacuum distilled with a vacuum at 150 to 200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558 to 731 L.

[00131] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An additional vacuum distillation was carried out by adjusting 245.7 kg methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20 to 25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

[00132] In an alternative procedure, the order of addition was changes so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

Case Studies

[00133] The MET and VEGF signaling pathways appear to play important roles in osteoblast and osteoclast function. Strong immunohistochemical staining of MET has been observed in both cell types in developing bone. HGF and MET are expressed by osteoblasts and osteoclasts *in vitro* and mediate cellular responses such as proliferation, migration, and expression of ALP. Secretion of HGF by osteoblasts has been proposed as a key factor in osteoblast/osteoclast coupling, and in the development of bone metastases by tumor cells that express MET. Osteoblasts and osteoclasts also express VEGF and its receptors, and VEGF signaling in these cells is involved in potential autocrine and/or paracrine feedback mechanisms regulating cell migration, differentiation, and survival.

[00134] Bone metastases are present in 90 percent of patients with castration-resistant prostate cancer (CRPC), causing significant morbidity and mortality. Activation of the MET and VEGFR signaling pathways is implicated in the development of bone metastases in CRPC. Three metastatic CRPC patients treated with compound 1, an inhibitor of MET and VEGFR, had dramatic responses with near complete resolution of bone lesions, marked reduction in bone pain and total serum alkaline phosphatase (tALP) levels, and reduction in measurable disease. These results indicate that dual modulation of the MET and VEGFR signaling pathways is a useful therapeutic approach for treating CRPC.

[00135] Compound 1 is an orally bioavailable multitargeted tyrosine kinase inhibitor with potent activity against MET and VEGFR2. Compound 1 suppresses MET and VEGFR2 signaling, rapidly induces apoptosis of endothelial cells and tumor cells, and causes tumor regression in xenograft tumor models. Compound 1 also significantly reduces tumor invasiveness and metastasis and substantially improves overall survival in a murine pancreatic neuroendocrine tumor model. In a phase 1 clinical study, compound 1 was generally well-tolerated, with fatigue, diarrhea, anorexia, rash, and palmar-plantar erythrodysesthesia being the most commonly observed adverse events.

[00136] Based on target rationale and observed antitumor activity in clinical studies, an adaptive phase 2 trial was undertaken in multiple indications including CRPC (http://clinicaltrials.gov/ct2/results?term=NCT00940225 for Study NCT00940225 *last visited September 20, 2011*)), in which compound 1 was administered as a 100 mg dose to patients. The findings in the first three CRPC patients with evidence of bone metastases on bone scan enrolled to this study are described in the following Case Studies. All patients provided informed consent before study screening.

[00137] Baseline characteristics for patients 1-3 are summarized in Table 1. The results for patients 1-3 are also depicted in Figures 13-15.

Table 1.
Summary of Baseline Characteristics and Preliminary Best Responses for CRPC Patients Treated with Compound 1.

Baseline Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	77	73	66
Diagnosis	1993	2009	2009
ECOG performance status	1	0	1
Disease location(s)	Lung, LN, bone	Liver, LN, bone	LN, bone
Prior cancer therapies	Radical prostatectomy, radiation to prostate bed, CAB, DES, docetaxel	Radiation to pubic ramus and acetabulum, CAB	CAB, docetaxel
Bisphophonates	No	No	Yes
Narcotics	Yes	No	No
Pain	Yes	Yes	Yes
PSA (ng/mL)	430.4	14.7	2.8
tALP (U/L)	689	108	869
Hemoglobin (g/dL)	13.5	13.3	10.2
Summary of Best Responses			
Tumor response	– 41%	– 20%	– 51%
Bone scan	Complete resolution	Improvement	Near resolution
Pain	Improvement	Pain-free	Pain-free
PSA	– 78%	+ 61%	– 57%
tALP	– 77%	– 6%	– 77%
Hemoglobin (g/dL)	+ 1.4	+ 1.8	+ 2.2

ADT, androgen-deprivation therapy; CAB, combined androgen blockade (leuprolide + bicalutamide); DES, diethylstilbestrol; LN, lymph node; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

[00138] Patient 1 was diagnosed with localized prostate cancer in 1993 and treated with radical prostatectomy (Gleason score unavailable; PSA, 0.99 ng/mL). In 2000, local disease recurrence was treated with radiation therapy. In 2001, combined androgen blockade (CAB) with leuprolide and bicalutamide was initiated for rising PSA (3.5 ng/mL). In 2006, diethystillbestrol (DES) was administered briefly. In 2007, 6 cycles of docetaxel were given for new lung metastases. Rising PSA was unresponsive to antiandrogen withdrawal. Androgen ablation therapy was continued until clinical progression. In October 2009, bone metastasis to the spine associated with impingement on the spinal cord and back pain, was treated with radiation therapy (37.5 Gy). In February 2010, a bone scan was performed due to

increasing bone pain and showed diffuse uptake of radiotracer in the axial and appendicular skeleton. A CT scan revealed new pulmonary and mediastinal lymph node metastases. PSA was 430.4 ng/mL.

[00139] Patient 2 was diagnosed in April of 2009 after presenting with a pathologic fracture (Gleason score, 4+5=9; PSA, 45.34 ng/mL). Bone scan showed uptake of radiotracer in the left iliac wing, left sacroiliac joint, femoral head, and the pubic symphysis. Biopsy of the left pubic ramus confirmed metastatic adenocarcinoma with mixed lytic and blastic lesions. CAB with leuprolide and bicalutamide and radiation therapy (8 Gy) to the left pubic ramus and acetabulum resulted in bone pain relief and PSA normalization. Rising PSA in November 2009 (16 ng/mL) was unresponsive to antiandrogen withdrawal. In February 2010, bone scan showed multiple foci throughout the axial and appendicular skeleton. A CT scan revealed retroperitoneal lymph node enlargement and liver metastases (PSA, 28.1 ng/mL). Further progression of disease was marked by recurrent bone pain, new lung and hepatic metastases.

[00140] Patient 3 was diagnosed in April 2009 after presenting with right hip pain (Gleason score, 4+5=9; PSA, 2.6 ng/mL). Bone scan showed uptake of radiotracer at multiple sites throughout the axial and appendicular skeleton. A CT scan revealed retroperitoneal, common iliac, and supraclavicular adenopathy. CAB with leuprolide and bicalutamide was initiated. The patient received 6 cycles of docetaxel through December 2009. Following treatment, a bone scan showed no changes. A CT scan revealed near resolution of the retroperitoneal and common iliac adenopathy. In March 2010, PSA began to rise, and bone pain worsened. A repeat bone scan showed new foci, and a CT scan showed an increase in the retroperitoneal, para-aortic, and bilateral common iliac adenopathy. Rising PSA in April 2010 (2.8 ng/mL) and increasing bone pain were unresponsive to antiandrogen withdrawal.

Results

[00141] Figure 1 depicts the role for MET and VEGFR in tumor-bone interactions in CRPC.

[00142] Figure 2 shows the $ARCaP_M$ in vivo efficacy study overview. Human CRPC $ARCaP_M$ cells express high levels of MET and VEGF co-receptor neuropilin-1 (MRP-1), and VEGF actives MET via NRP-1. Cells were injected into both tibiae of nude mice on day 1 (D1), and treatment started on day 31 (D31). Mice were sacrificed at the end of the 7 week treatment period and X-ray images of all tibiae taken. Five representative tibiae per group

were analyzed by micro-CT. One tibia from each mouse was fixed, decalcified, embedded and sectioned at the 50% bone level for histology and histomorphometry analyses.

[00143] Figure 3 depicts the in vitro osteoclast (OC) differentiation and activity assays. CD34+ cells derived from human bone marrow were cultured on bovine bone slices in the presence of growth factors including M-CSF and RANK-L.

[00144] Figure 4 depicts the in vitro osteoblast (OB) differentiation and activity assays. Mouse KS482 cells were utilized, which differentiate into OBs capable of forming mineralized bone nodules.

[00145] Figure 5 shows that compound 1 blocks progression of CRPC $ARCaP_M$ tumor xenografts in bone. It shows representative images from (5A) X-ray, (5B) whole bone (cortical) micro-CT, and (5C) sagittal section (trabecular bone) micro-CT analyses of tibiae after 7 weeks of treatment with vehicle or 30 mg/kg of compound 1.

[00146] Figure 6 shows that compound 1 blocks progression of CRPC $ARCaP_M$ tumor xenografts in bone. It shows the hematoxylin and Eosin (H&E) stain on sections taken from vehicle 1 and compound 1 tibiae.

[00147] Figure 7 shows that compound 1 treatment preserves volume and mineral density relative to vehicle. (7A) shows bone volume/tissue volume (BV/TV) and (7B) shows bone mineral density after 7 weeks of treatment with vehicle, or with 10 mg/kg or 30 mg/kg of compound 1. Micro-CT-based quantification (Scanco 40 instrument) of 5 tibiae per group with 2 measurements each were used. (•) indicates vehicle tibia lacking detectable tumor in the section evaluated by histology.

[00148] Figure 8 shows that compound 1 treatment compared to vehicle results in decreased tumor area and increased bone area in the analyzed tibia sections. (8A) shows the tumor area, and (8B) shows the bone area relative to total tissue area after 7 weeks of treatment with vehicle, or with 10 mg/kg or 30 mg/kg of compound 1. Bioquant® Image Analysis software was used for the histomorphometry of H&E-stained sections. Tumor (8A) and bone area (8B) were measured in the evaluated sections by tracing their outline within an area of $1x1mm^2$ (total tissue area) near the center of the growth plate. Percentages relative to the total tissue area were calculated.

[00149] Figure 9 shows that compound 1 treatment compared to vehicle results in increased OBs and no change in OCs along the trabecular bone in the analyzed tibia sections. It shows the (9A) osteoclast (OC) and (9B) osteoblast (OB) quantification after 7 weeks of treatment with vehicle, or with 10 mg/kg or 30 mg/kg of compound 1. Bioquant® Image Analysis software was used for the histomorphometry of consecutive H&E- and TRAP-

stained sections. (9A) Based on TRAP stain, OC numbers were counted along the border of the trabecular bone within the same tissue area used to assess tumor and bone area (Fig. 8). The ratio of OCs per bone perimeter (OC/mm) was calculated. (9B) OBs were counted along the trabecular bone surface in the same area on the H&E-stained sections and the number of OBs per bone perimeter (0B/mm) was calculated. (●) indicates vehicle-treated mice without detectable tumor in the corresponding tumor area analysis (Fig. 8A). (A) indicates compound 1-treated mice with detectable tumor in the corresponding tumor area analysis (Fig. 8A).

[00150] Figure 10 depicts that compound 1 treatment is associated with decreased IHC staining of p-MET and proteins related to the VEGF pathway in $ARCaP_M$ tumors. Analysis of (10A) shows activated MET (p-MET), (10B) VEGF, (10C) NRP-1, and (10D) HIF1α by IHC and single quantum-dot labeling (5013L) in sections from tibiae of three mice treated for 7 weeks with vehicle or with 10 mg/kg or 30 mg/kg of compound 1. The three sections were chosen based on relatively similar tumor/bone ratios. The IHC data was evaluated by three individuals and a representative picture taken from the stained tumor area. The SQDL quantification (fluorescence intensity per cell) was assessed by a Vectra multispectral imaging system. VEGF was previously shown to activate MET via NRP-1 in $ARCaP_M$ cells. Total MET was not analyzed.

[00151] Figure 11 shows that compound 1 inhibits in vitro osteoclast (OC) differentiation in a dose-dependent manner, but does not affect the ability of mature OCs to resorb bone. (11A) shows OC differentiation at day 7 based on secreted TRACP 5b levels. C, control, osteoprotegerin (5 nM). (11B) shows the activity of mature OCs at day 10, based on secreted CTX normalized to the number of differentiated OCs (TRACP 5b levels at day 7). C, control, cysteine protease inhibitor E64 (1 μM); BL, baseline (no added compound). ***P<0.0001

[00152] Figure 12 depicts that compound 1 shows biphasic effects on osteoblast (OB) differentiation and bone forming activity in vitro. (12A) shows OB differentiation (cellular ALP activity at day 8). (12B) shows OB bone-forming activity of organic (left panel) and inorganic bone matrix (right panel). C, control, 17-β-estradiol (10 nM); BL, baseline (no added compound). The OB activity assay determines net effects of differentiation and activity. *$P.< 0.05$; **$P< 0111$; ***$P <0.001$; asterisks in parentheses indicate significant effects in the opposite direction.

[00153] Patient 1 started compound 1 on February 12, 2010. Four weeks later, significant reduction in bone pain was reported. At Week 6, bone scan showed a dramatic decrease in radiotracer uptake by bone metastases (Figure 13A). A CT scan showed a partial response (PR) with a 33% decrease in measurable target lesions (Figure 13C). At Week 12, near

complete resolution of bone lesions and a 44% decrease in target lesions was observed and was stable through Week 18. Corresponding with the bone scan response, after an initial rise, serum tALP levels decreased from 689 U/L at baseline to 159 U/L at Week 18 (Figure 13B and Table 1). In addition, there was an increase in hemoglobin of 1.4 g/dL at Week 2 compared with baseline (Table 1). PSA decreased from 430 ng/mL at baseline to 93.5 ng/mL at Week 18 (Figure 13B and Table 1). The patient was on open-label treatment through Week 18 when he withdrew after developing Grade 3 diarrhea.

[00154] Patient 2 started compound 1 on March 31, 2010. At Week 4, reduction in bone pain was reported. At Week 6, bone scan showed a slight flair in radiotracer uptake by bone lesions (Figure 14A), and a CT scan showed a 13% decrease in target lesions (Figure 14C). At Week 12, a substantial reduction of radiotracer uptake (Figure 14A) and a 20% decrease in measurable disease were observed (Table 1). After randomization to placebo at Week 12 the patient developed severe bone pain and sacral nerve root impingement. Radiation to the spine was administered, and the patient crossed over to open-label compound 1 treatment at Week 15. Serum tALP levels were within the normal range (101-144 U/L) (Figure 14B). Hemoglobin increased by 1.8 g/dL at Week 12 compared with baseline (Table 1). PSA peaked at close to 6-fold of baseline by Week 16, but then decreased to 2-fold of baseline by Week 18 subsequent to crossing over to compound 1 from placebo (Figure 14B and Table 1). The patient continues on compound 1 treatment as of September 2010.

[00155] Patient 3 started compound 1 on April 26, 2010. After three weeks a complete resolution of pain was reported. At Week 6, bone scan showed a dramatic reduction in radiotracer uptake (Figure 15A), and a CT scan showed a PR with a 43% decrease in measurable target lesions. At Week 12 a complete resolution of bone lesions on bone scan (Figure 15A) and a 51% decrease in measurable disease were observed (Table 1 and Figure 3B)). After an initial rise, serum tALP levels steadily decreased, with tALP at 869 U/L at baseline and 197 U/L at Week 18 (Figure 15B and Table 1). Hemoglobin increased 2.2 g/dL at Week 2 compared with baseline (Table 1). PSA decreased from 2.4 ng/mL at screening to 1.2 ng/mL at Week 18 (Figure 15B and Table 1). The patient continues on compound 1 treatment as of September 2010.

Discussion

[00156] All three patients experienced a striking decrease in uptake of radiotracer on bone scan upon treatment with compound 1. These findings were accompanied by substantial reductions in bone pain and evidence of response or stabilization in soft tissue lesions during

therapy with compound 1. The onset of the effect was very rapid in two of the patients, with substantial improvement or near resolution of bone scan and improvement in pain occurring in the first 6 weeks. In the third patient, an apparent flare in the bone scan was observed at 6 weeks, followed by improvement by 12 weeks. To our knowledge, such a comprehensive and rapid impact on both osseous and soft tissue disease has not been observed in this patient population.

[00157] Uptake of radiotracer in bone depends on both local blood flow and osteoblastic activity, both of which may be pathologically modulated by the tumor cells associated with the bone lesion. Resolving uptake may therefore be attributable to either interruption of local blood flow, direct modulation of osteoblastic activity, a direct effect on the tumor cells in bone, or a combination of these processes. However, decreased uptake on bone scan in men with CRPC has only been rarely noted with VEGF/VEGFR targeted therapy, despite numerous trials with such agents. Similarly, observations of decreased uptake on bone scan in CRPC patients have only been reported rarely for abiraterone, which targets the cancer cells directly, and for dasatinib, which targets both cancer cells and osteoclasts. Thus, targeting angiogenesis alone, or selectively targeting the tumor cells and/or osteoclasts, has not resulted in effects similar to those observed in the patients treated with compound 1.

[00158] These results indicate a potential critical role for the MET and VEGF signaling pathways in the progression of CRPC and point to the promise that simultaneously targeting these pathways may hold in reducing morbidity and mortality in this patient population.

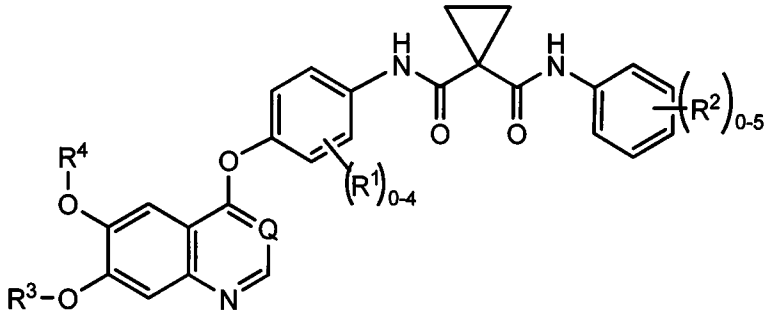
Other Embodiments

[00159] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive.

[00160] The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

1. A method for inhibiting osteoblastic and osteolytic progression in bone cancer associated with prostate cancer, comprising administering a therapeutically effective amount of a compound of formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is halo;

R^2 is halo;

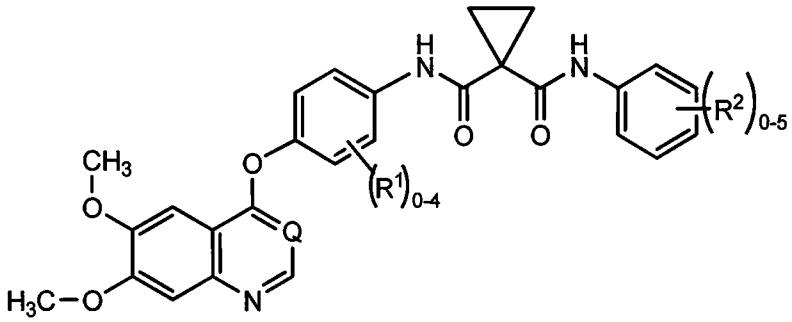
R^3 is $(C_1\text{-}C_6)$alkyl;

R^4 is $(C_1\text{-}C_6)$alkyl; and

Q is CH or N

to a patient in need of such treatment.

2. The method of claim 1, wherein the compound of formula I is a compound of formula Ia:



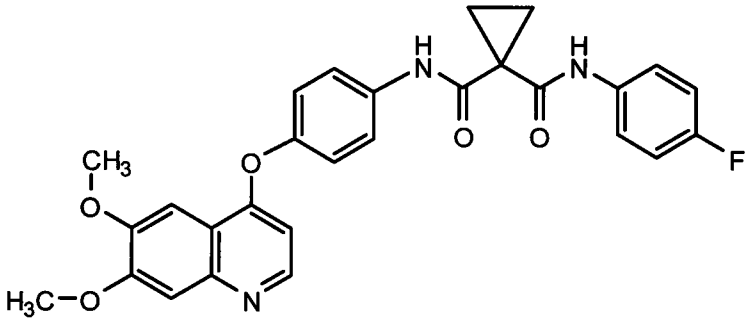
Formula I(a),

R^1 is halo;

R^2 is halo; and

Q is CH or N.

3. The method of claims 1-2, wherein the compound of formula I is compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, which is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

5. The method of claims 1-4, wherein the compound of formula (I), formula I(a) and compound I is the (L)- or (D)-malate salt.

6. The method of claims 1-5, wherein the compound of formula (I) is in the crystalline N-1 form of the (L) malate salt and/or the (D) malate salt.

7. A method for inhibiting osteoblastic progression in bone cancer associated with prostate cancer, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I, formula Ia, or compound 1 or the malate salt of compound of formula I, formula Ia, or compound 1 or another pharmaceutically acceptable salt of compound of formula I, formula Ia, or compound 1 to a patient in need of such treatment.

8. A method for inhibiting osteolytic progression in bone cancer associated with prostate cancer, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising compound of formula I, formula Ia, or compound 1 or the malate salt of compound of formula I, formula Ia, or compound 1 or another pharmaceutically acceptable salt of compound of formula I, formula Ia, or compound 1 to a patient in need of such treatment.

9. The method of claims 1-8, wherein the compound of formula I, formula Ia, or compound 1 is administered as a pharmaceutical composition.

10. The method of claims 1-3, wherein the prostate cancer is CRPC.

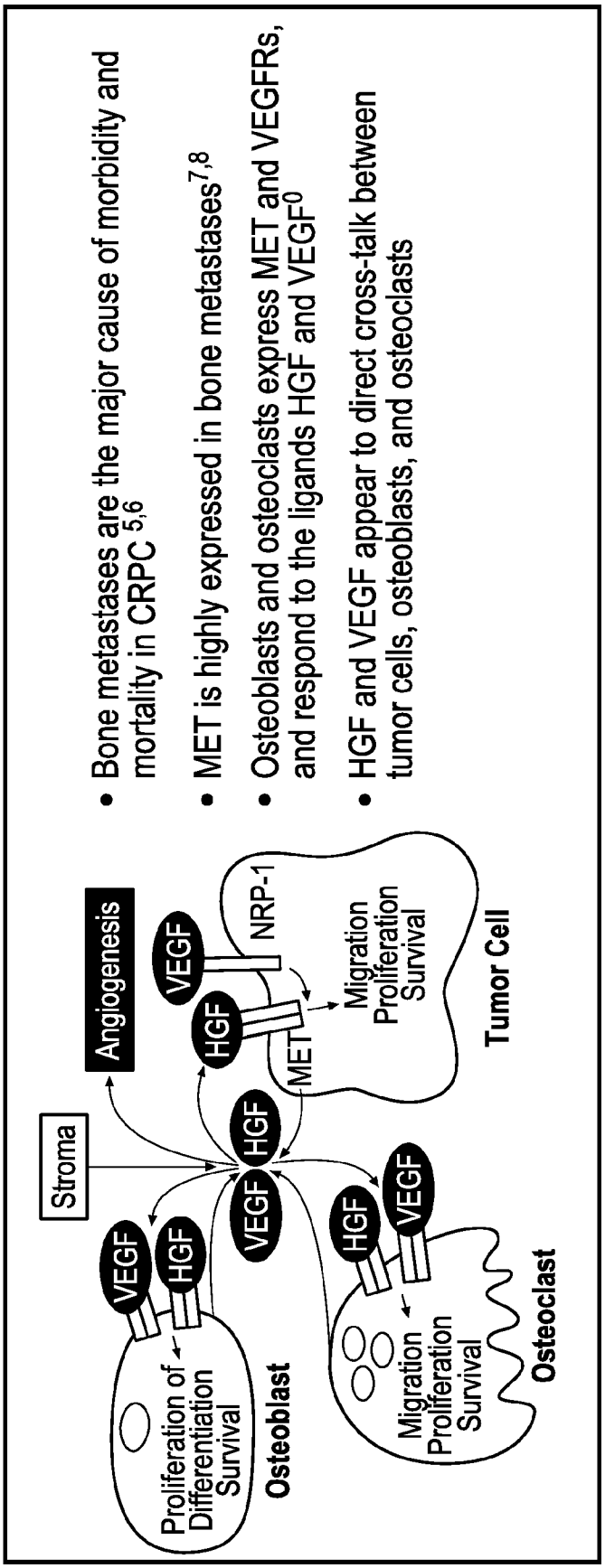

• Bone metastases are the major cause of morbidity and mortality in CRPC [5,6]
• MET is highly expressed in bone metastases [7,8]
• Osteoblasts and osteoclasts express MET and VEGFRs, and respond to the ligands HGF and VEGF[0]
• HGF and VEGF appear to direct cross-talk between tumor cells, osteoblasts, and osteoclasts
Stroma
Angiogenesis
VEGF
HGF
NRP-1
MET
Migration
Proliferation
Survival
Tumor Cell
Proliferation of
Differentiation
Survival
Osteoblast
Migration
Proliferation
Survival
Osteoclast

FIG. 1

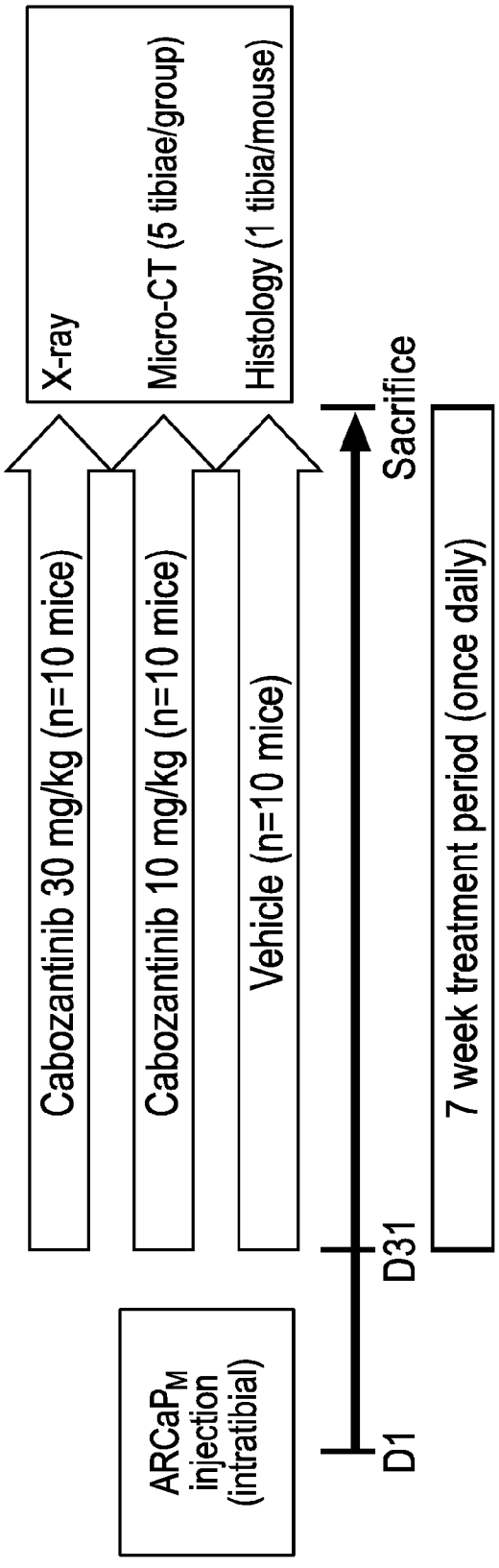

ARCaP$_M$ injection (intratibial)
D1
D31
Sacrifice
7 week treatment period (once daily)
Vehicle (n=10 mice)
Cabozantinib 10 mg/kg (n=10 mice)
Cabozantinib 30 mg/kg (n=10 mice)
Histology (1 tibia/mouse)
Micro-CT (5 tibiae/group)
X-ray

FIG. 2

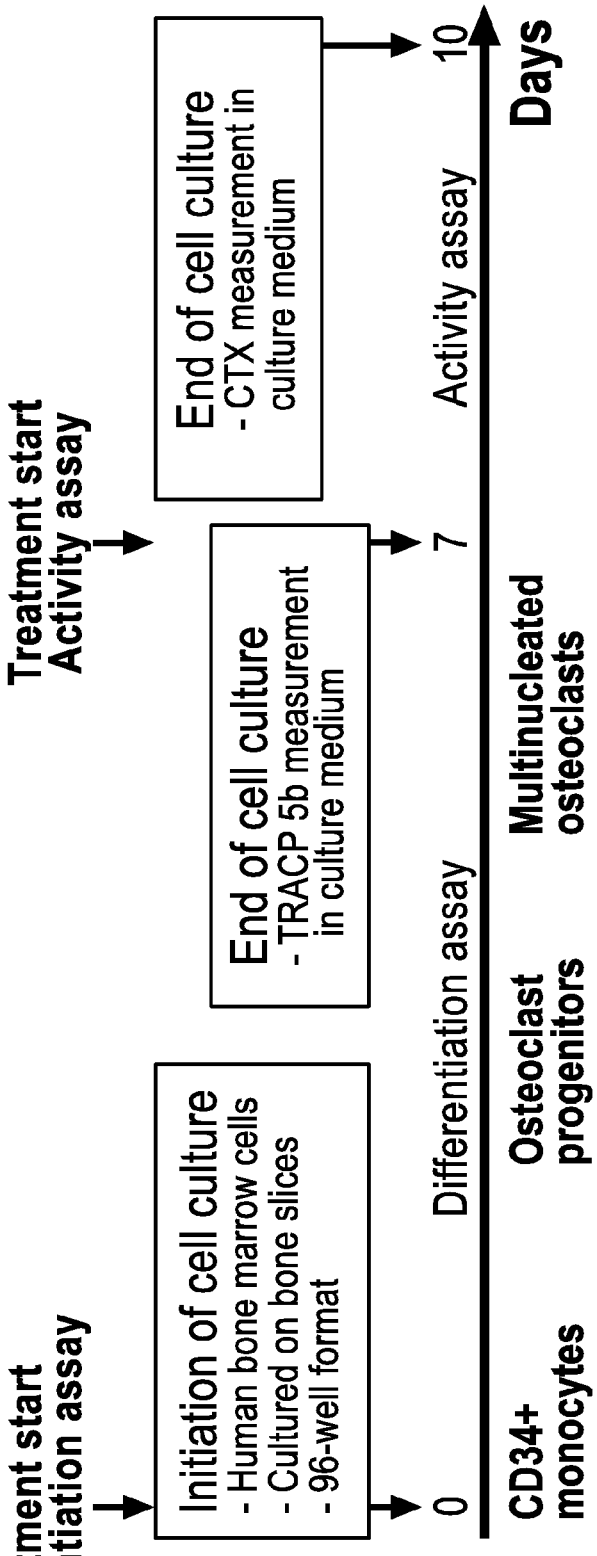

Treatment start
Differentiation assay
Initiation of cell culture
- Human bone marrow cells
- Cultured on bone slices
- 96-well format
End of cell culture
- TRACP 5b measurement
in culture medium
Treatment start
Activity assay
End of cell culture
- CTX measurement in
culture medium
0
7
10
Days
Differentiation assay
Activity assay
CD34+
monocytes
Osteoclast
progenitors
Multinucleated
osteoclasts

FIG. 3

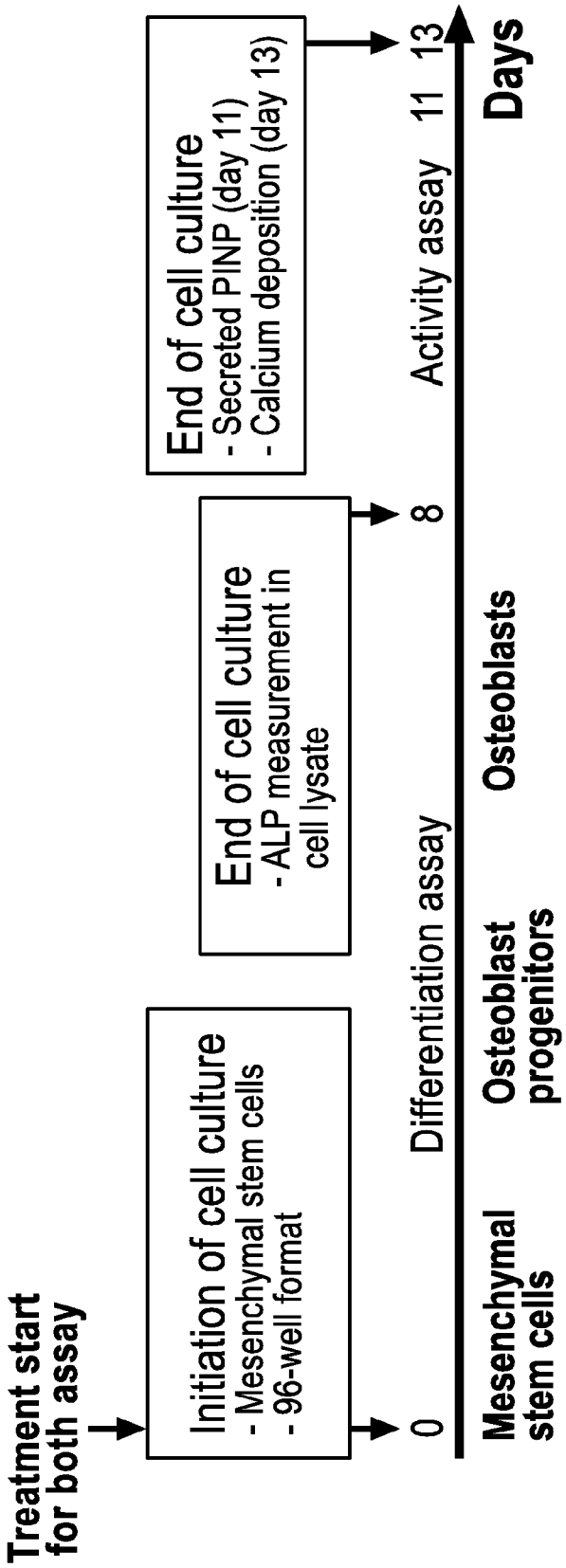

Treatment start for both assay
Initiation of cell culture
- Mesenchymal stem cells
- 96-well format
End of cell culture
- ALP measurement in cell lysate
End of cell culture
- Secreted PINP (day 11)
- Calcium deposition (day 13)
0
Differentiation assay
8
Activity assay
11
13
Days
Mesenchymal stem cells
Osteoblast progenitors
Osteoblasts

FIG. 4

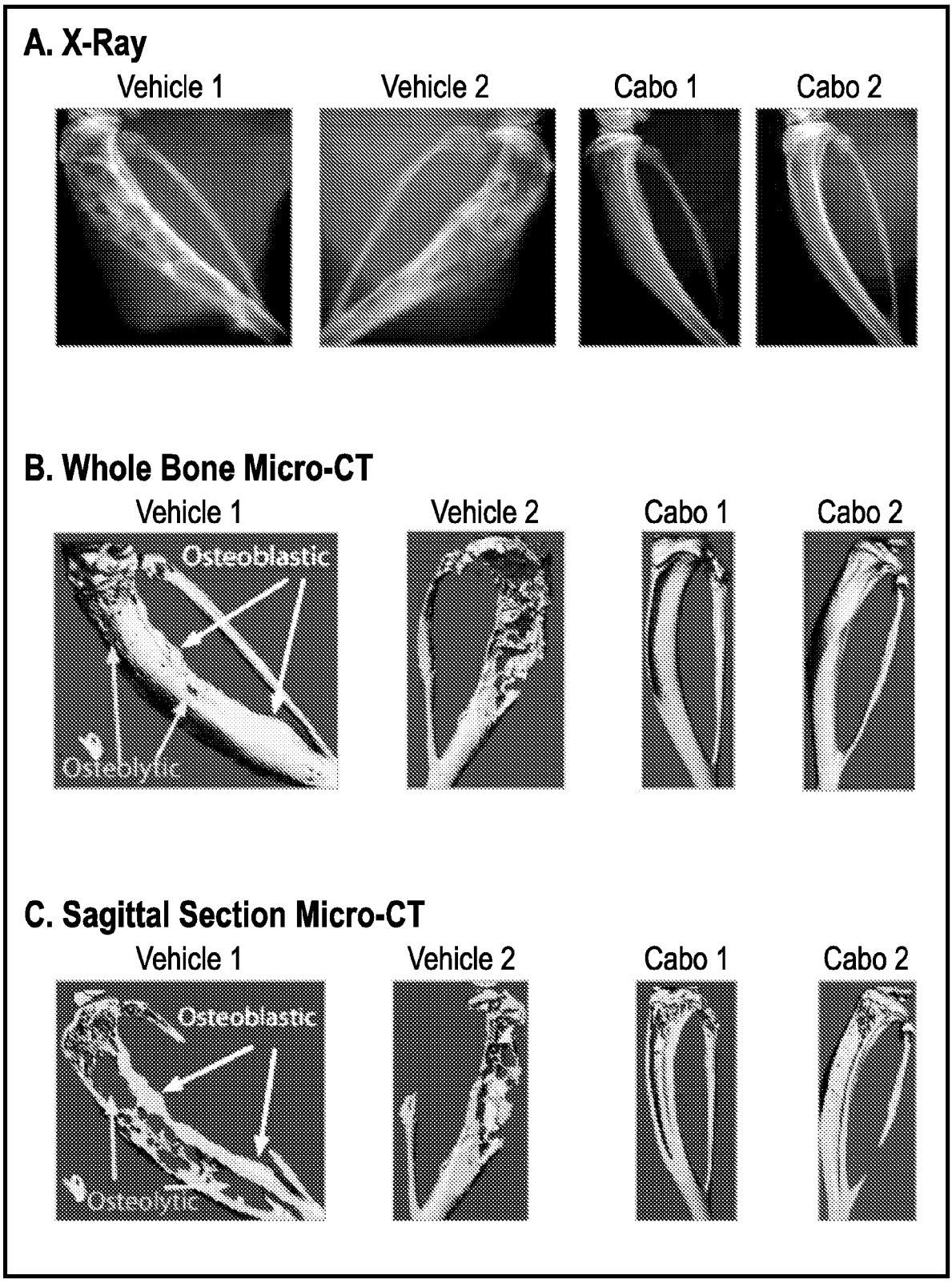
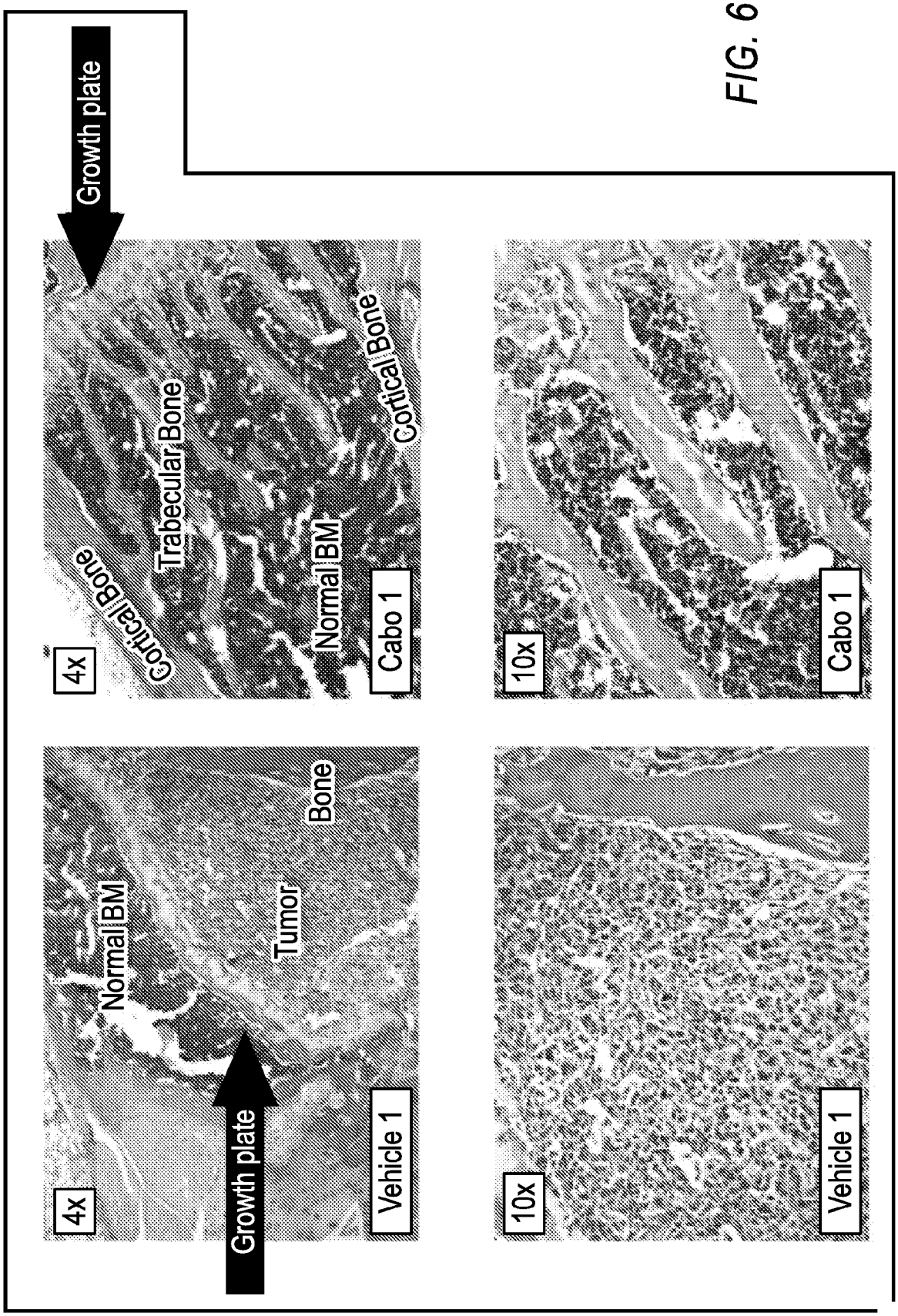

A. X-Ray
Vehicle 1
Vehicle 2
Cabo 1
Cabo 2
B. Whole Bone Micro-CT
Vehicle 1
Vehicle 2
Cabo 1
Cabo 2
Osteoblastic
Osteolytic
C. Sagittal Section Micro-CT
Vehicle 1
Vehicle 2
Cabo 1
Cabo 2
Osteoblastic
Osteolytic

FIG. 5

FIG. 6


Growth plate
Cortical Bone
Trabecular Bone
Normal BM
Cortical Bone
4x
Cabo 1
10x
Cabo 1
Normal BM
Tumor
Bone
Growth plate
4x
Vehicle 1
10x
Vehicle 1

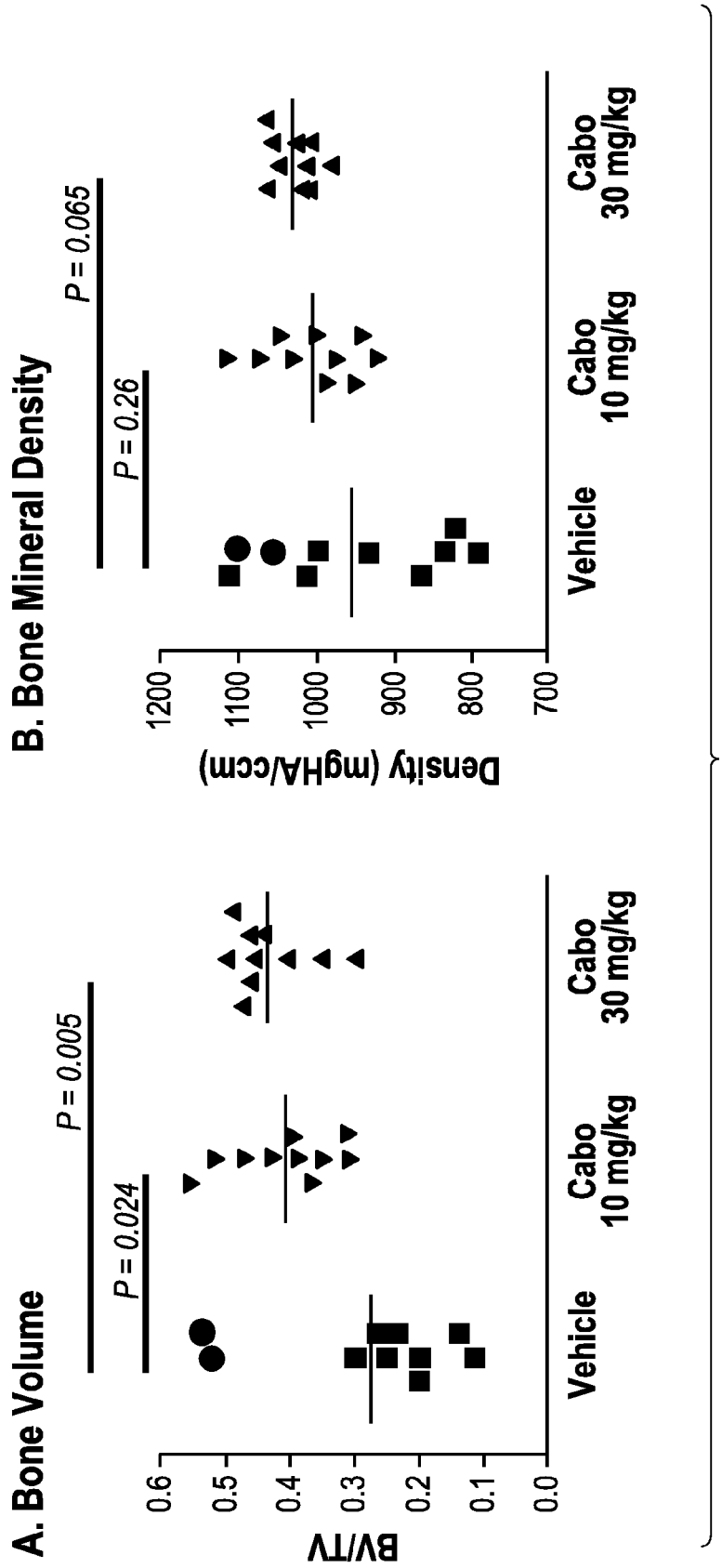

A. Bone Volume
P = 0.005
P = 0.024
BV/TV
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg
B. Bone Mineral Density
P = 0.065
P = 0.26
Density (mgHA/ccm)
1200
1100
1000
900
800
700
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg

FIG. 7

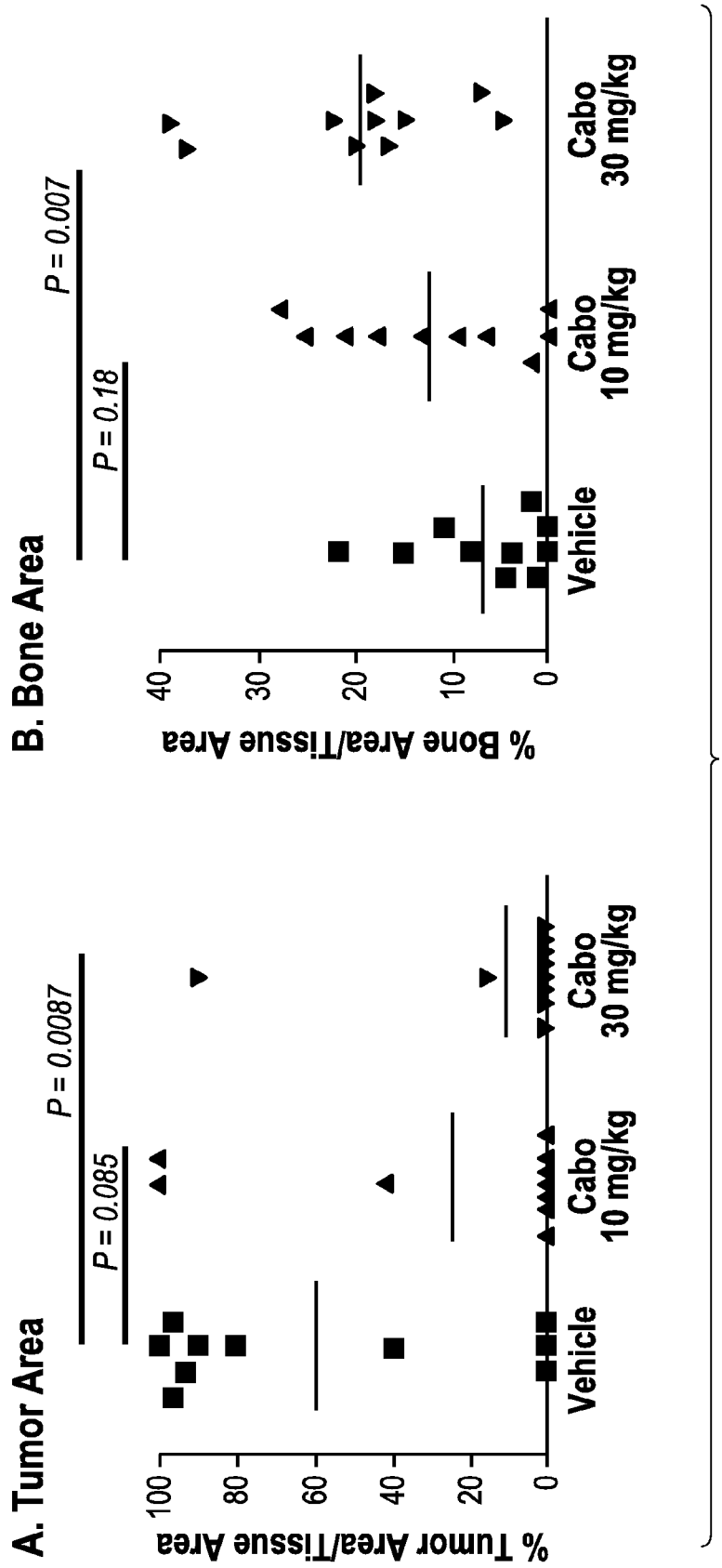

A. Tumor Area
P = 0.0087
P = 0.085
% Tumor Area/Tissue Area
100
80
60
40
20
0
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg
B. Bone Area
P = 0.007
P = 0.18
% Bone Area/Tissue Area
40
30
20
10
0
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg

FIG. 8

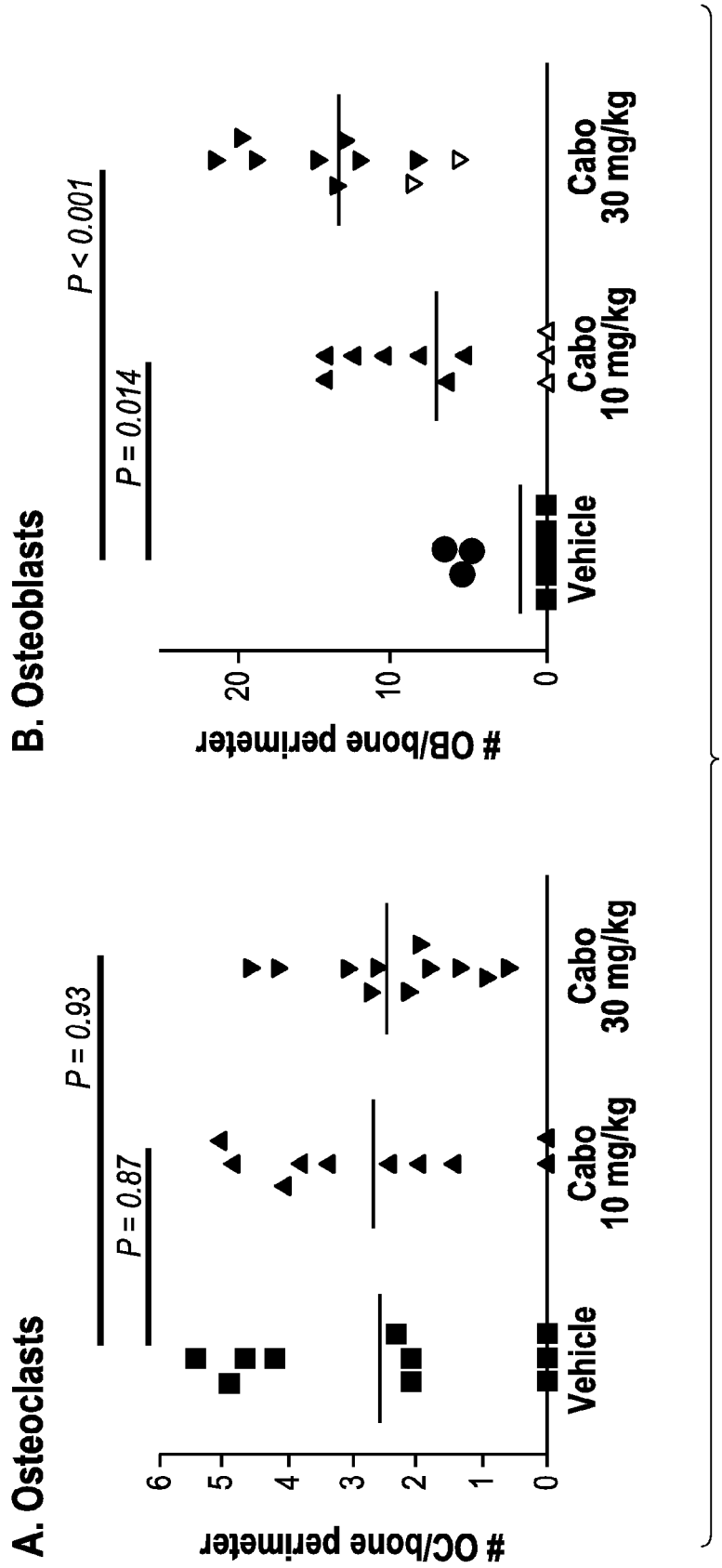

A. Osteoclasts
OC/bone perimeter
0
1
2
3
4
5
6
P = 0.87
P = 0.93
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg
B. Osteoblasts
OB/bone perimeter
0
10
20
P = 0.014
P < 0.001
Vehicle
Cabo 10 mg/kg
Cabo 30 mg/kg

FIG. 9

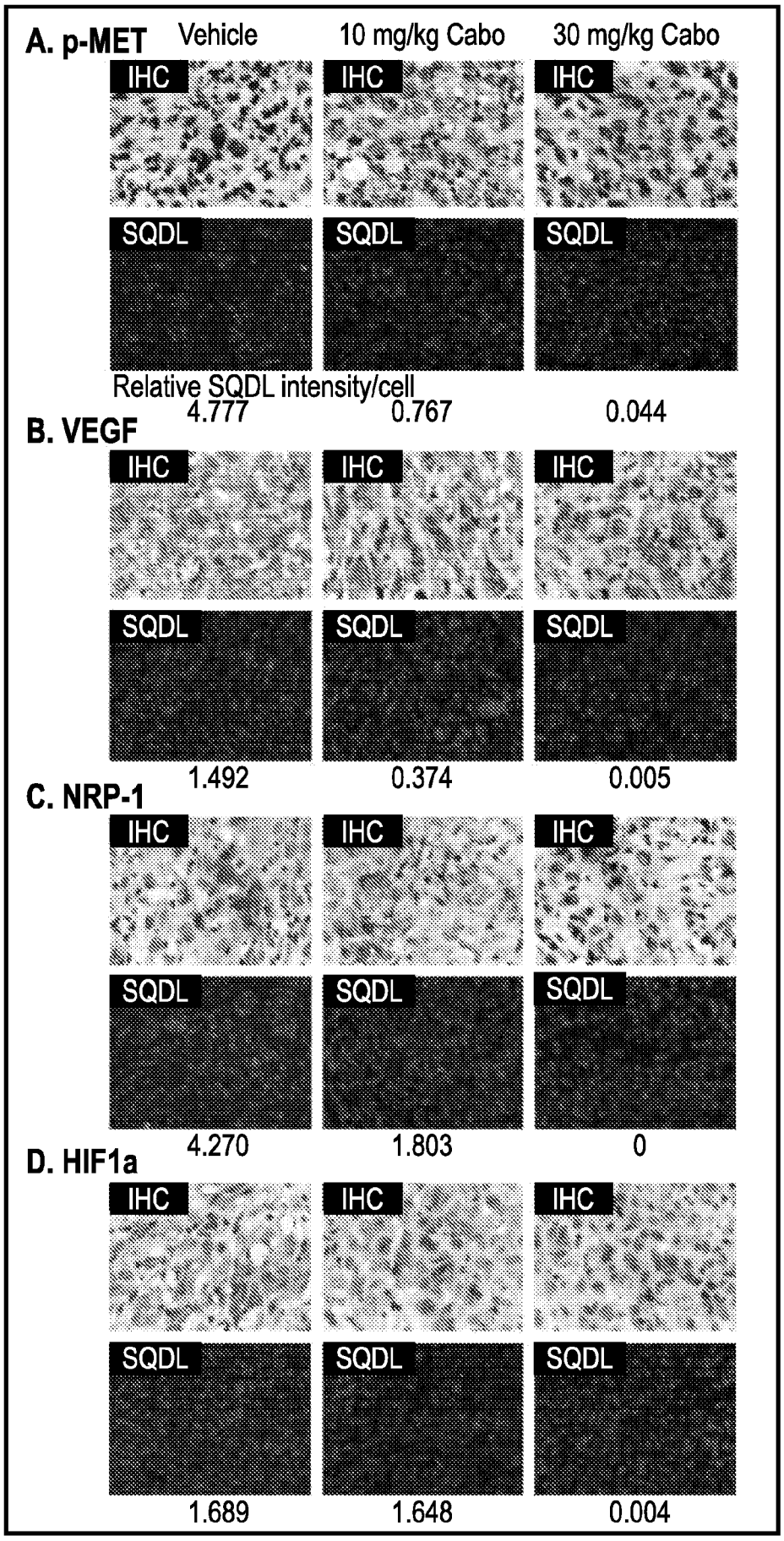

A. p-MET
Vehicle
10 mg/kg Cabo
30 mg/kg Cabo
IHC
SQDL
Relative SQDL intensity/cell
4.777
0.767
0.044
B. VEGF
1.492
0.374
0.005
C. NRP-1
4.270
1.803
0
D. HIF1a
1.689
1.648
0.004

FIG. 10

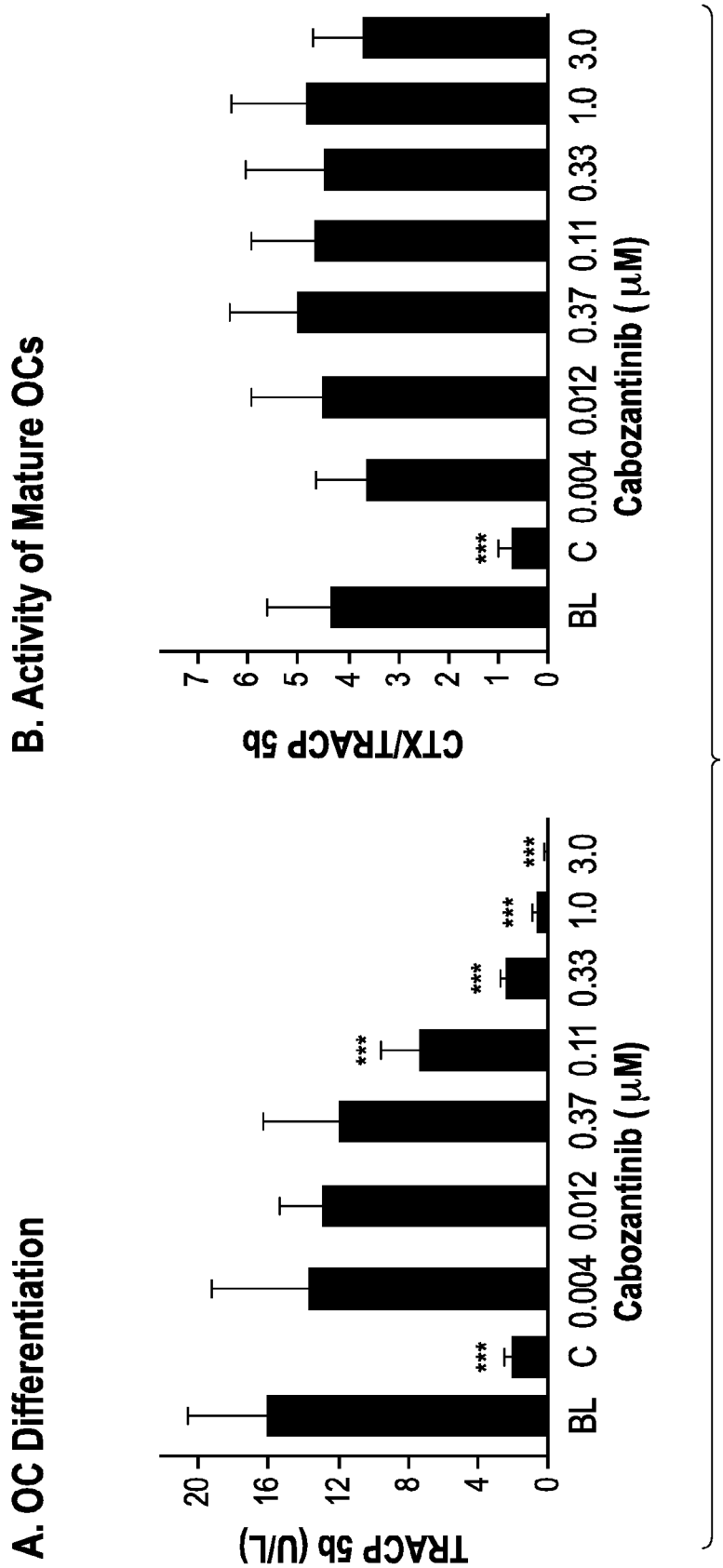

A. OC Differentiation
TRACP 5b (U/L)
0
4
8
12
16
20
***
***
***
***
BL C 0.004 0.012 0.37 0.11 0.33 1.0 3.0
Cabozantinib (μM)
B. Activity of Mature OCs
CTX/TRACP 5b
0
1
2
3
4
5
6
7
***
BL C 0.004 0.012 0.37 0.11 0.33 1.0 3.0
Cabozantinib (μM)

FIG. 11

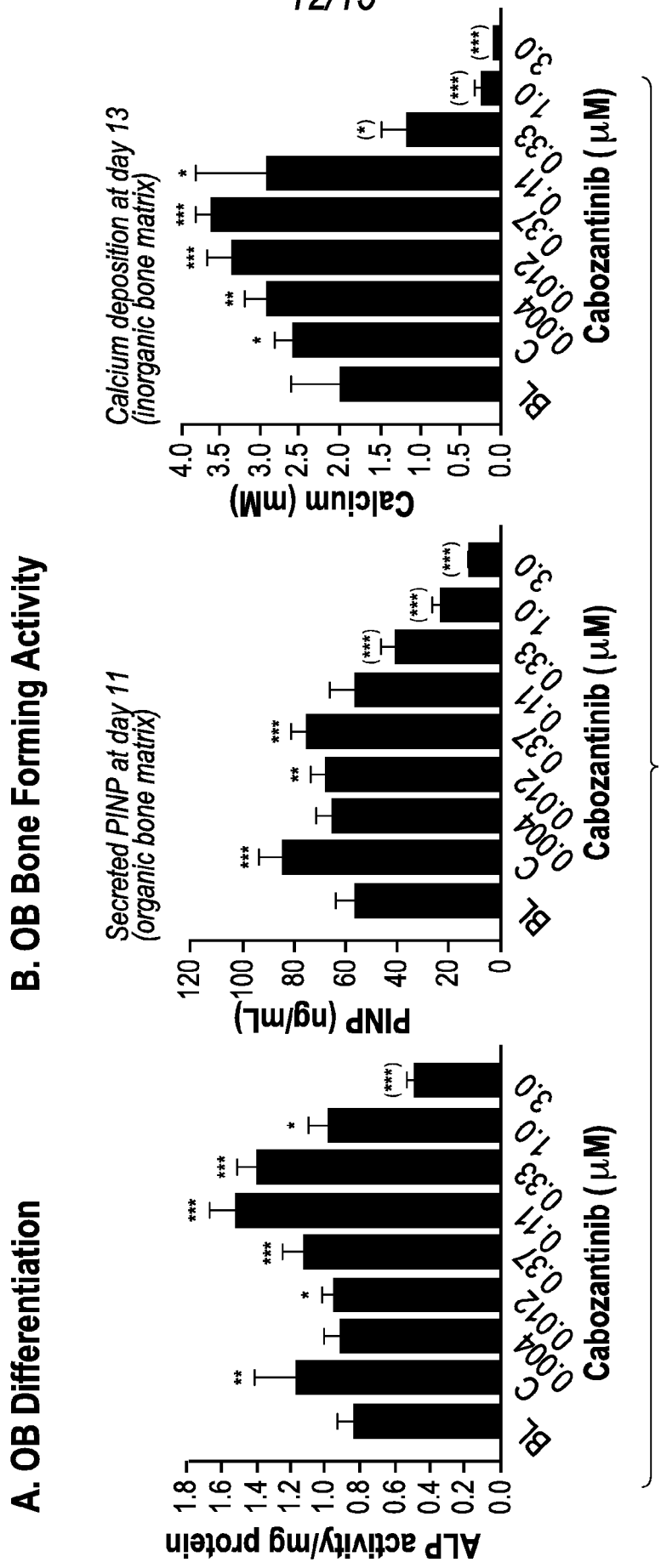

A. OB Differentiation
ALP activity/mg protein
Cabozantinib (μM)
BL
C
0.004
0.012
0.037
0.11
0.33
1.0
3.0
B. OB Bone Forming Activity
Secreted PINP at day 11
(organic bone matrix)
PINP (ng/mL)
Calcium deposition at day 13
(inorganic bone matrix)
Calcium (mM)

FIG. 12

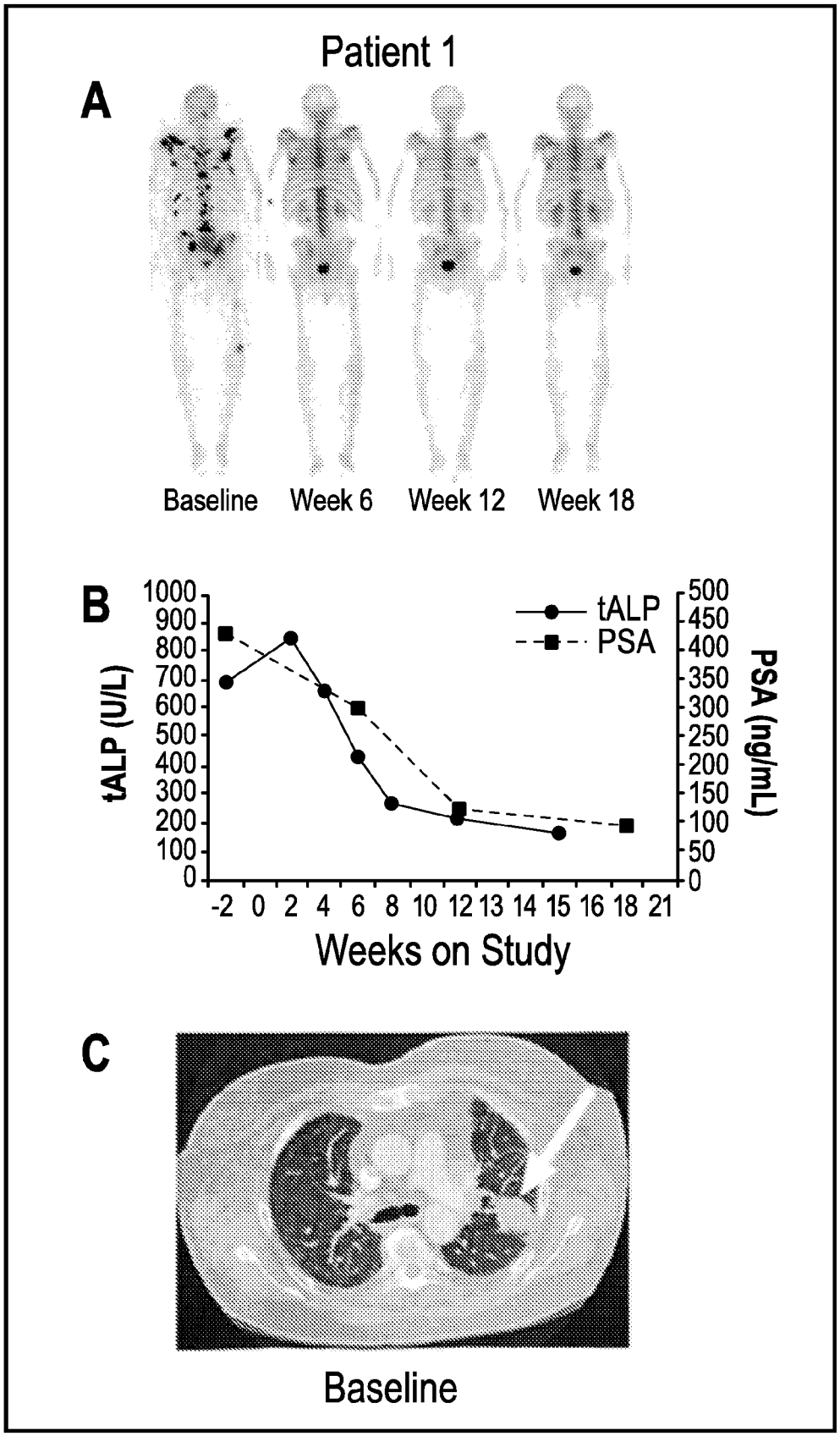

Patient 1
A
Baseline
Week 6
Week 12
Week 18
B
tALP
PSA
tALP (U/L)
PSA (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
500
450
400
350
300
250
200
150
100
50
0
-2 0 2 4 6 8 10 12 13 14 15 16 18 21
Weeks on Study
C
Baseline

FIG. 13

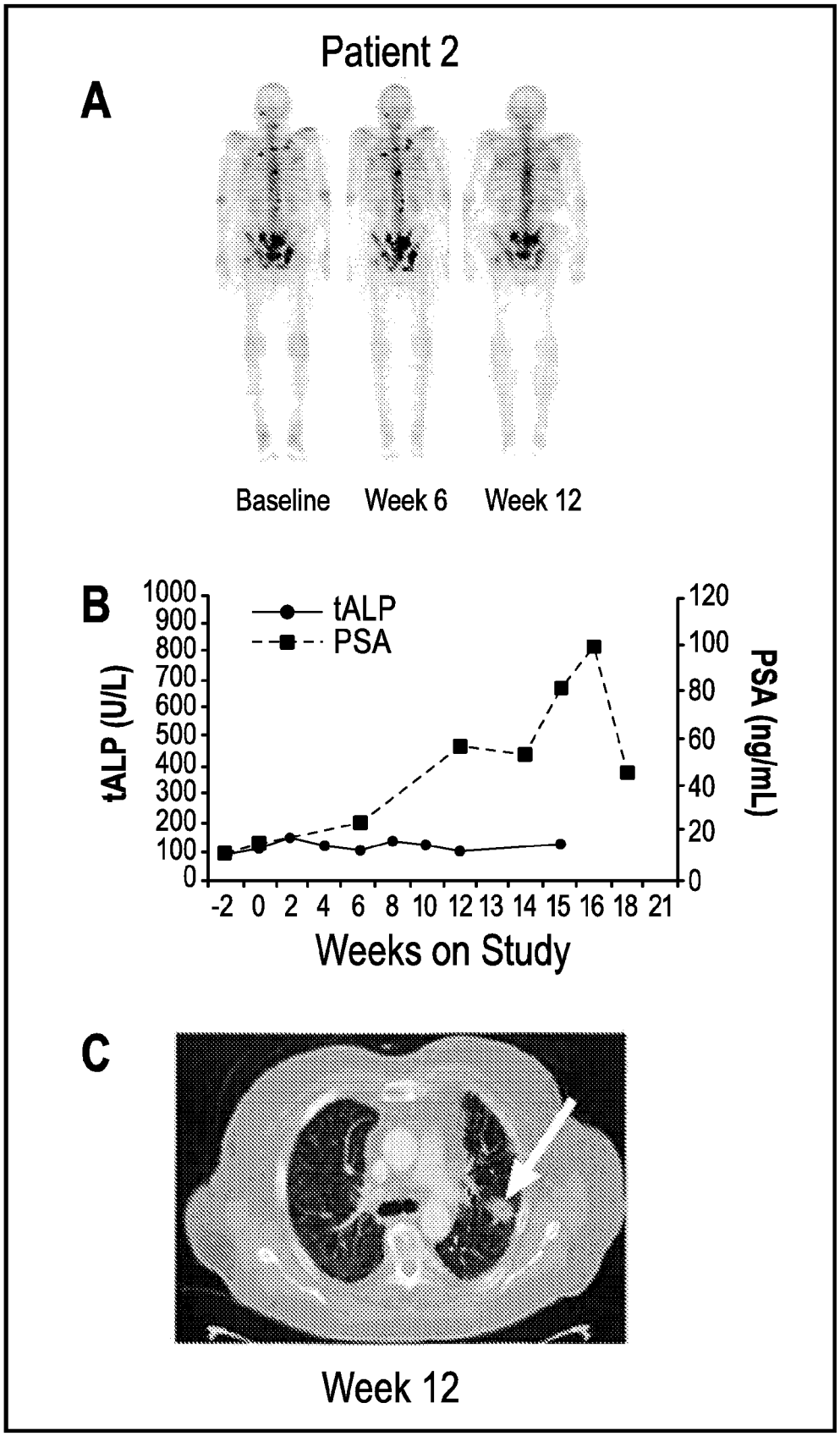

Patient 2
A
Baseline
Week 6
Week 12
B
tALP
PSA
tALP (U/L)
PSA (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
120
100
80
60
40
20
0
-2 0 2 4 6 8 10 12 13 14 15 16 18 21
Weeks on Study
C
Week 12

FIG. 14

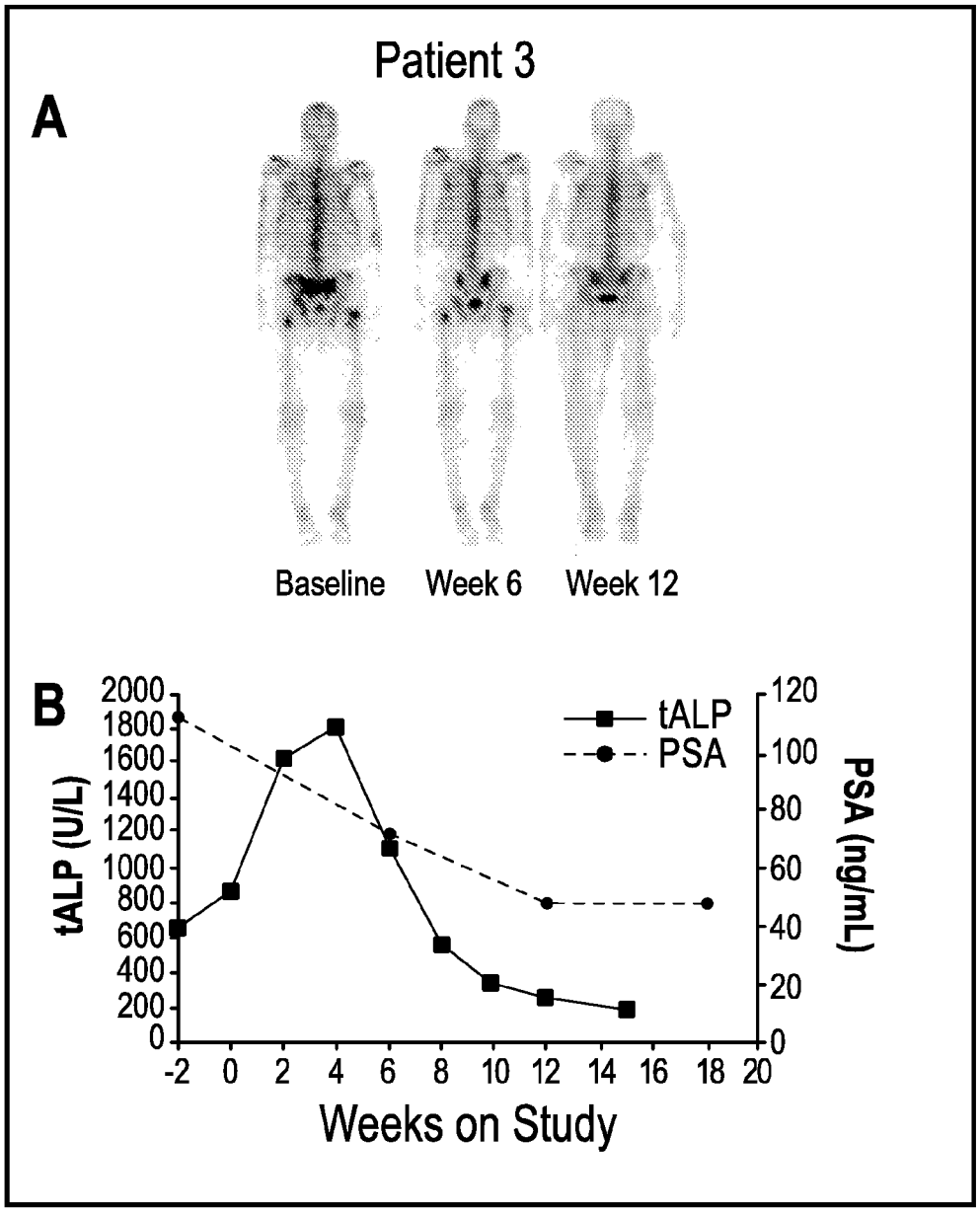

Patient 3
A
Baseline
Week 6
Week 12
B
tALP (U/L)
PSA (ng/mL)
tALP
PSA
Weeks on Study

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/064116

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/47 A61K31/517 A61P35/00 A61K35/04
ADD.

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2012/044572 A1 (EXELIXIS INC [US]; SMITH DAVID [US]; HUSSAIN MAHA [US]) 5 April 2012 (2012-04-05) page 34 - page 36; claims 1-11 page 1, paragraph 4 -----	1-10
X,P	WO 2012/044577 A1 (EXELIXIS INC [US]; SMITH DAVID [US]; HUSSAIN MAHA [US]) 5 April 2012 (2012-04-05) pages 17,18, paragraph 124 - paragraph 126 pages 57,58; claims 1-6 page 1, paragraph 4 -----	1-5,7-10

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2013	16/01/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Opravz, Petra

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/064116

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DANA T AFTAB ET AL: "MET and VEGF: synergistic targets in castration-resistant prostate cancer", CLINICAL AND TRANSLATIONAL ONCOLOGY, SPRINGER MILAN, MILAN, vol. 13, no. 10, 16 November 2011 (2011-11-16), pages 703-709, XP019977937, ISSN: 1699-3055, DOI: 10.1007/S12094-011-0719-5 page 706, left-hand column, paragraph 3rd -----	1-4,7-10
X	WO 2011/017639 A1 (EXELIXIS INC [US]; AFTAB DANA T [US]; MUELLER THOMAS [US]; WEITZMAN AA) 10 February 2011 (2011-02-10) page 4 - page 6, paragraph 12-18 page 10, line 7 - line 11 examples 1A,1B -----	1-5,7-10
A	SMITH D C ET AL: "406 Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease", EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 8, no. 7, 1 November 2010 (2010-11-01), page 129, XP027498096, ISSN: 1359-6349, DOI: 10.1016/S1359-6349(10)72113-3 [retrieved on 2010-11-01] abstract -----	1-10
A	YASUHIDE KITAGAWA ET AL: "Vascular endothelial growth factor contributes to prostate cancer-mediated osteoblastic activity", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 65, no. 23, 1 December 2005 (2005-12-01), pages 10921-10929, XP002662712, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-05-1809 page 10921 -----	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/064116

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012044572 A1	05-04-2012	NONE	
WO 2012044577 A1	05-04-2012	NONE	
WO 2011017639 A1	10-02-2011	AU 2010279234 A1	01-03-2012
		CA 2770100 A1	10-02-2011
		CN 102647985 A	22-08-2012
		EA 201270247 A1	30-11-2012
		EP 2461810 A1	13-06-2012
		KR 20120059540 A	08-06-2012
		US 2012282179 A1	08-11-2012
		WO 2011017639 A1	10-02-2011

摘要

本发明涉及用 MET 和 VEGF 的双重抑制剂来治疗癌症，具体是去势抵抗性前列腺癌和骨转移。