METHODS AND COMPOSITIONS FOR TREATING CANCER METASTASIS

CROSS REFERENCE

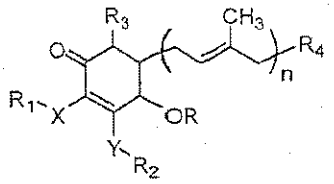
[0001] This application claims the benefit of U.S. provisional application Ser. No. 61/602,489, filed February 23, 2012, which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Cancer metastasis is the primary cause of post-operation or post-therapy recurrence in cancer patients. For example, bone metastases, or metastatic bone disease, a class of cancer metastases that results from primary tumor invasion to bone among cancer metastasis, is one of the most common ones of metastasis of various types of human cancers (e.g., breast, lung, prostate and thyroid cancers). The occurrence of bone metastases causes serious morbidity due to intractable pain, high susceptibility to fracture, nerve compression and hypercalcemia. Cancer metastasis remains substantially refractory to therapy despite intensive efforts to develop treatments.

SUMMARY OF THE DISCLOSUREINVENTION

[0002a] In one aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for treating a disease or condition associated with bone metastasis in a subject, wherein said medicament comprises a therapeutically effective amount



of a compound having the structure:

wherein each of X and Y independently is oxygen, NR_5 or sulfur;

R is a hydrogen or $C(=O)C_1$-C_8alkyl;

each of R_1, R_2 and R_3 independently is a hydrogen, methyl or $(CH_2)_m$—CH_3;

R_4 is NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

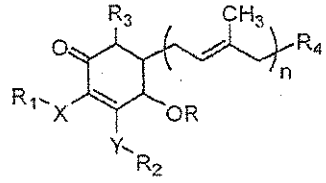
each of R_5 and R_6 is independently a hydrogen or C_1-C_8alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

m=1-12; and

n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof.

[0002b] In another aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for inhibiting hypercalcemia of malignancy, or inhibiting bone resorption, or treating osteolytic lesions in a subject, wherein said medicament comprises a therapeutically effective amount of a compound having the structure:



wherein each of X and Y independently is oxygen, NR_5 or sulfur;

R is a hydrogen or $C(=O)C_1$-C_8alkyl;

each of R_1, R_2 and R_3 independently is a hydrogen, methyl or $(CH_2)_m$—CH_3;

R_4 is NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents selected from NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, and C_1-C_8 haloalkyl;

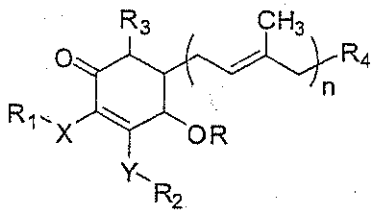
each of R_5 and R_6 is independently a hydrogen or C_1-C_8 alkyl;

R_7 is a C_1-C_8alkyl, OR_5 or NR_5R_6;

m=1-12; and

n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof.

[0003] In one aspect provides herein for treating a disease or condition associated with bone metastasis in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a cyclohexenone compound having the structure:



wherein each of X and Y independently is oxygen, NR_5 or sulfur;

R is a hydrogen or $C(=O)C_1$-C_8alkyl;

each of R_1, R_2 and R_3 independently is a hydrogen, methyl or $(CH_2)_m$—CH_3;

R_4 is NR_5R_6, OR_5, $OC(=O)R_7$, $C(=O)OR_5$, $C(=O)R_5$, $C(=O)NR_5R_6$, halogen, 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, glucosyl, wherein the 5 or 6-membered lactone, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, aryl, and glucosyl are optionally substituted with one or more substituents