METHODS AND COMPOSITIONS FOR TREATING ADVANCED STAGE NON-SMALL CELL LUNG CANCER

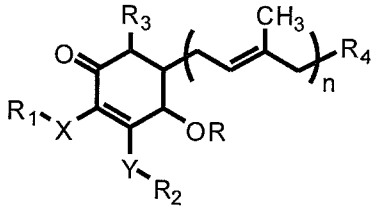
BACKGROUND OF THE INVENTION

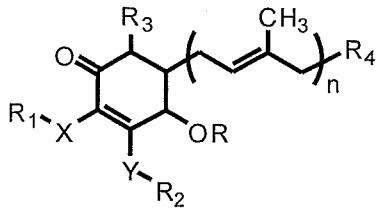
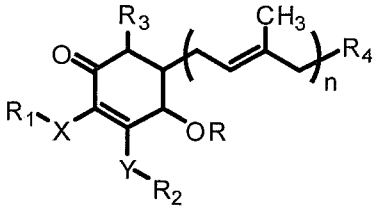
[0001] Lung cancer is the most frequently diagnosed major cancer in the world and leading cause of cancer mortality worldwide. In the United States of America (USA), it was estimated that 219,440 new cases of lung cancer (116,090 men and 103,350 women) were diagnosed and 159,390 deaths were related to this malignancy in 2009. In Taiwan, 8,748 new cases of lung cancer were diagnosed in 2006, accounting for 11.94% of cancer diagnoses, and 7,479 patients died of this disease, contributing to 19.68% cancer deaths. The mortality was 44.42 and 20.65 per 100,000 men and women, respectively.

[0002] Lung cancers are categorized on the basis of important prognostic and therapeutic implications as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). Non-small cell lung cancer contributed to about 80% of new cases diagnosed each year. NSCLC typically proliferates slower with lower doubling time than SCLC and can be characterized as three primary histologic types: adenocarcinoma, squamous cell, and large cell carcinoma. Adenocarcinoma has become the dominant histologic type of NSCLC and is the most common type in women and non-smokers. It typically arises in the periphery with glandular differentiation or mucin production, forms tubular or papillary structures, and metastasizes widely and early, compared to squamous carcinoma.

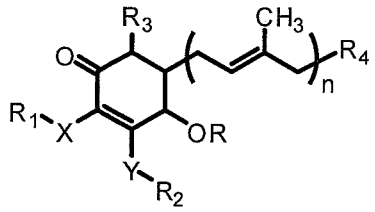
[0003] About 70% of NSCLC patients are diagnosed with advanced, poor-prognosis stage III or IV disease (approximately 50% for stage IV). The majority of these advanced tumors are considered inoperable due to disseminated (multiple sites) metastatic disease or metastatic sites that are not amendable to local therapy.

SUMMARY OF THE INVENTION

[0003a] In one aspect of the present invention, there is provided use of a therapeutically effective amount of a cyclohexenone compound having the structure:  in the manufacture of a medicament for treating a subject with advanced stage lung cancer, wherein each of X and Y is oxygen; 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 hydrogen; m=1-12, n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof. In another aspect of the present invention, there is provided use of a therapeutically effective amount of a cyclohexenone

compound having the structure:  in the manufacture of a medicament for treating an individual with non-small cell lung cancer stage IV, wherein each of X and Y is oxygen; 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 hydrogen; m=1-12, n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof. In yet another aspect of the present invention, there is provided use of a therapeutically effective amount of a cyclohexenone compound having the structure:  in the manufacture of a medicament for improving or maintaining the quality of life of an individual diagnosed with non-small cell lung cancer stage IV, wherein each of X and Y is oxygen; 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 hydrogen; m=1-12, n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof.

[0004] In one example, described herein is the treatment of advanced stage non-small cell lung cancer comprising administering to an individual a therapeutically effective amount of a cyclohexenone compound having the structure:



wherein each of X and Y is oxygen;

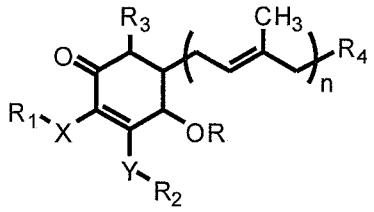
R is a hydrogen or $C(=O)C_1$-C_8alkyl;

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

R_4 is hydrogen; m=1-12,

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

[0005] In another example, described herein are methods of treating an individual with non-small cell lung cancer stage IV comprising administering to a subject in need a therapeutically effective amount of a cyclohexenone compound having the structure:



wherein each of X and Y is oxygen;

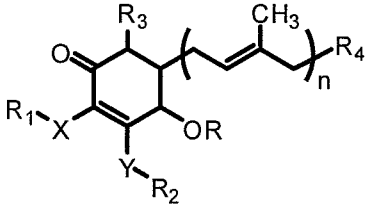
R is a hydrogen or $C(=O)C_1$-C_8alkyl;

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

R_4 is hydrogen; m=1-12,

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

[0006] In another example, described herein are methods for improving or maintaining the quality of life of an individual diagnosed with non-small cell lung cancer stage IV comprising administering to said individual a therapeutically effective amount of a cyclohexenone compound having the structure:



wherein each of X and Y is oxygen;

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 hydrogen; m=1-12,

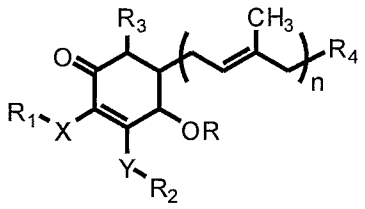
n=1-12; or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof.

INCORPORATION BY REFERENCE

[0007] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of a cyclohexenone compound having the structure:  in the manufacture of a medicament for treating a subject with advanced stage lung cancer,

wherein each of X and Y is oxygen;

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

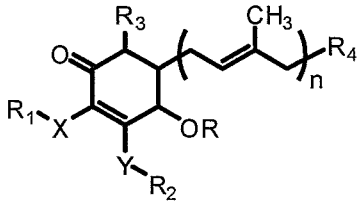
each of R_1, R_2 and R_3 independently is a hydrogen, methyl or $(CH_2)_m$—CH_3;

R_4 is hydrogen; m=1-12,

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

2. The use of claim 1, wherein said advanced stage lung cancer is non-small cell lung cancer stage IV.

3. Use of a therapeutically effective amount of a cyclohexenone compound having the structure:

 in the manufacture of a medicament for treating an individual with non-small cell lung cancer stage IV,

wherein each of X and Y is oxygen;

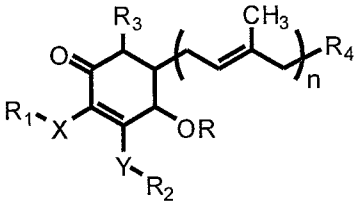
R is a hydrogen or $C(=O)C_1$-C_8alkyl;

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

R_4 is hydrogen; m=1-12,

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

4. The use of claim 3, wherein the treatment further comprises selecting an individual who has non-small cell lung cancer stage IV.

5. Use of a therapeutically effective amount of a cyclohexenone compound having the structure:  in the manufacture of a medicament for improving or maintaining the quality of life of an individual diagnosed with non-small cell lung cancer stage IV,

wherein each of X and Y is oxygen;

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 hydrogen; m=1-12,

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

6. The use of claims 1-5, wherein said individual is KRAS positive.

7. The use of claims 1-5, wherein said individual is a patient who has failed at least two lines of anti-cancer therapy.

8. The use of any one of claims 1-7, wherein said cyclohexenone compound, or a pharmaceutically acceptable salt, metabolite, solvate or prodrug thereof, is used parenterally, intravenously, orally, or by injection.

9. The use of claim 8, wherein the dose of said cyclohexenone compound is about 600 mg per day.

10. The use of any one of claims 1-9, wherein said individual is cancer free after 12 weeks of administration of said compound.

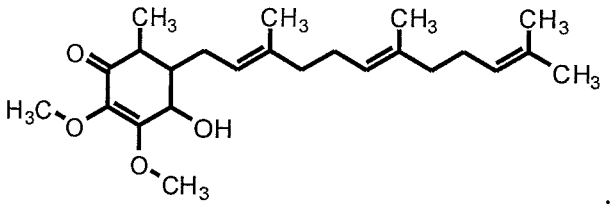
11. The use of any one of claims 1-10, wherein said compound is isolated from *Antrodia camphorata.*

12. The use of any one of claims 1-11, wherein R is a hydrogen or $C(=O)CH_3$.

13. The use of any one of claims 1-12, wherein R_1 is a hydrogen or methyl.

14. The use of any one of claims 1-13, wherein R_2 is a hydrogen or methyl.

15. The use of any one of claims 1-14, wherein said compound is



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