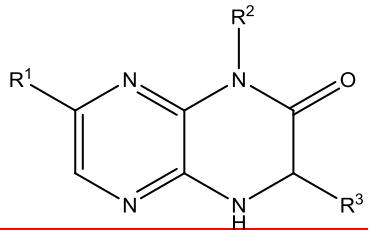
CLAIMS

What is claimed is:

~~1. A method for treating glioblastoma multiforme characterized by MGMT protein expression and/or promoter methylation status, comprising administering an effective amount of a~~Use of therapeutically effective dose of 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one ~~Dihydropyrazino-Pyrazine Compound~~ in the manufacture of a medicament for the treatment of ~~to a patient having~~ glioblastoma multiforme characterized by MGMT protein expression or promoter hypomethylation ~~methylation~~ status~~, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):~~



~~(I)~~

~~and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:~~

~~R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;~~

~~R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;~~

~~R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,~~

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1. ~~provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one~~.

2. The ~~method~~ use of claim 1, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

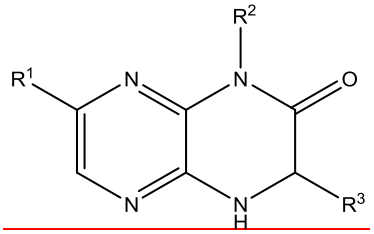
3. The ~~method~~ use of claim 2, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification, or a combination thereof.

4. The ~~method~~ use of claim 1, wherein ~~said patient is administered about~~the dose is 0.5 mg/day to ~~about~~ 45 mg/day of a 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof~~Dihydropyrazino-Pyrazine Compound~~.

5. The ~~method~~ use of claim 1, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

6. The ~~method~~ use of claim 1, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

~~7. A method for achieving a Response Assessment for Neuro-Oncology (RANO) Working Group for glioblastoma multiforme of complete response, partial response or stable disease in a patient having glioblastoma multiforme characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):~~



~~(I)~~

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~~and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:~~

~~R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;~~

~~R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;~~

~~R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,~~

~~provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.~~

~~8. The method of claim 7, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.~~

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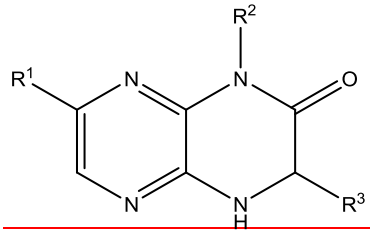
~~9. The method of claim 8, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.~~

~~10. The method of claim 7, wherein the glioblastoma multiforme is characterized by MGMT protein expression.~~

~~11. The method of claim 7, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.~~

~~12. A method for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient obtained prior to and after administration of said Dihydropyrazino-Pyrazine Compound, wherein less phosphorylated S6RP, 4E-BP1~~

and/or AKT in said biological sample obtained after administration of said Dihydropyrazino-Pyrazine Compound relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said Dihydropyrazino-Pyrazine Compound indicates inhibition, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

13. The method of claim 10, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

14. The method of claim 13, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

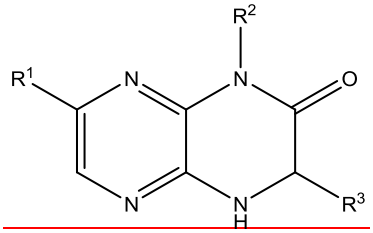
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15. The method of claim 10, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

16. The method of claim 10, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

17. A method for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of said patient obtained prior to and after administration of said Dihydropyrazino-Pyrazine Compound, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said Dihydropyrazino-Pyrazine Compound relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said Dihydropyrazino-Pyrazine Compound indicates inhibition, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

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~~provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.~~

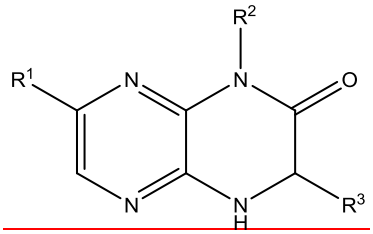
~~18. The method of claim 17, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.~~

~~19. The method of claim 18, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.~~

~~20. The method of claim 17, wherein the glioblastoma multiforme is characterized by MGMT protein expression.~~

~~21. The method of claim 17, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.~~

~~22. A method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of a Dihydropyrazino-Pyrazine Compound, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):~~



~~(I)~~

~~and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:~~

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~~R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;~~

~~R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;~~

~~R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,~~

~~provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.~~

~~23. The method of claim 22, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.~~

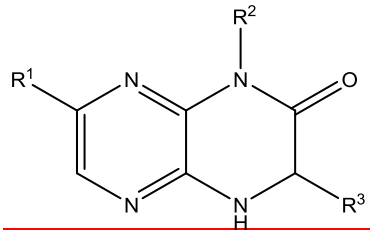
~~24. The method of claim 23, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.~~

~~25. The method of claim 22, wherein the glioblastoma multiforme is characterized by MGMT protein expression.~~

~~26. The method of claim 22, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.~~

~~27. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a Dihydropyrazino-Pyrazine Compound, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):~~

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(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

28. The method of claim 27, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

29. The method of claim 28, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

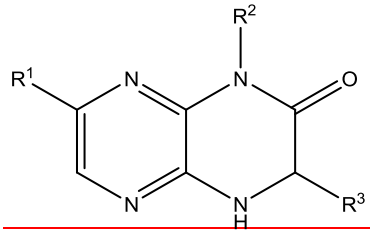
30. The method of claim 27, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

31. The method of claim 27, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

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32. A kit comprising a Dihydropyrazino-Pyrazine Compound and means for monitoring patient response to administration of said Dihydropyrazino-Pyrazine Compound, wherein said patient has glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

33. The kit of claim 32, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

34. The kit of claim 32, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

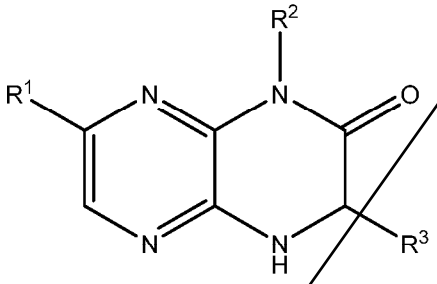
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CLAIMS

What is claimed is:

1. A method for treating glioblastoma multiforme characterized by MGMT protein expression and/or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to a patient having glioblastoma multiforme characterized by MGMT protein expression or promoter methylation status, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

2. The method of claim 1, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

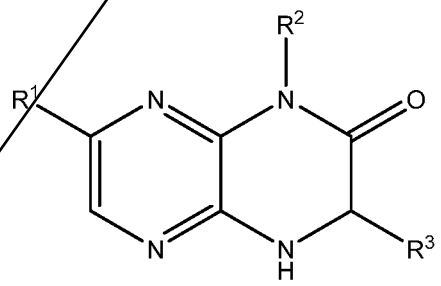
3. The method of claim 2, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification, or a combination thereof.

4. The method of claim 1, wherein said patient is administered about 0.5 mg/day to about 45 mg/day of a Dihydropyrazino-Pyrazine Compound.

5. The method of claim 1, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

6. The method of claim 1, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

7. A method for achieving a Response Assessment for Neuro-Oncology (RANO) Working Group for glioblastoma multiforme of complete response, partial response or stable disease in a patient having glioblastoma multiforme characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

8. The method of claim 7, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

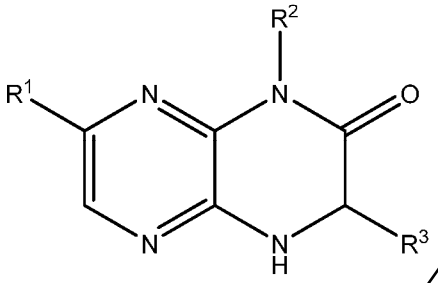
9. The method of claim 8, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

10. The method of claim 7, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

11. The method of claim 7, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

12. A method for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient obtained prior to and after administration of said Dihydropyrazino-Pyrazine Compound, wherein less

phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said Dihydropyrazino-Pyrazine Compound relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said Dihydropyrazino-Pyrazine Compound indicates inhibition, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

13. The method of claim 10, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

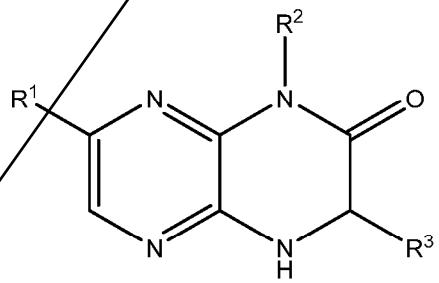
14. The method of claim 13, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due ERBB2 mutation, PTEN mutation or loss, NF1 mutation

or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

15. The method of claim 10, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

16. The method of claim 10, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

17. A method for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of said patient obtained prior to and after administration of said Dihydropyrazino-Pyrazine Compound, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said Dihydropyrazino-Pyrazine Compound relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said Dihydropyrazino-Pyrazine Compound indicates inhibition, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

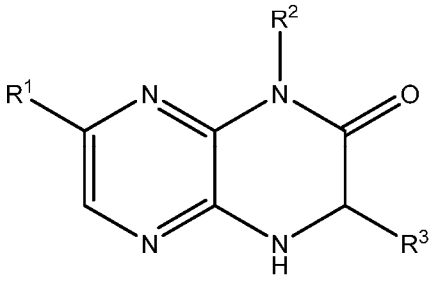
18. The method of claim 17, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

19. The method of claim 18, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

20. The method of claim 17, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

21. The method of claim 17, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

22. A method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of a Dihydropyrazino-Pyrazine Compound, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

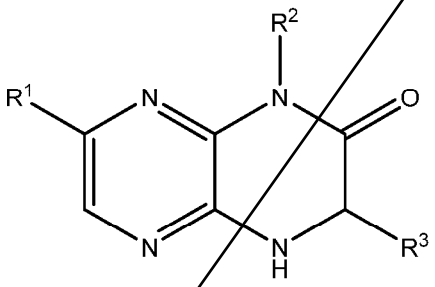
23. The method of claim 22, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

24. The method of claim 23, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

25. The method of claim 22, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

26. The method of claim 22, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

27. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a Dihydropyrazino-Pyrazine Compound, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

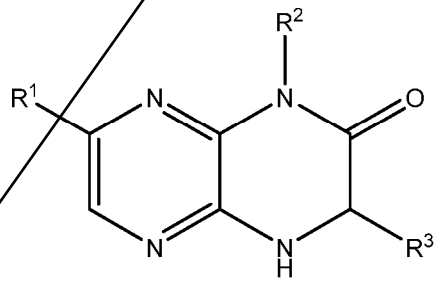
28. The method of claim 27, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

29. The method of claim 28, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification,, or a combination thereof.

30. The method of claim 27, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

31. The method of claim 27, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

32. A kit comprising a Dihydropyrazino-Pyrazine Compound and means for monitoring patient response to administration of said Dihydropyrazino-Pyrazine Compound, wherein said patient has glioblastoma multiforme (GBM) characterized by MGMT protein expression or promoter methylation status, wherein the Dihydropyrazino-Pyrazine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, prodrugs, metabolites and isotopologues thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

provided the Dihydropyrazino-Pyrazine Compounds is not 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

33. The kit of claim 32, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

34. The kit of claim 32, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.

CLAIMS

What is claimed is:

1. Use of therapeutically effective dose of 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one in the manufacture of a medicament for the treatment of glioblastoma multiforme characterized by MGMT protein expression or promoter hypomethylation status.

2. The use of claim 1, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated.

3. The use of claim 2, wherein the glioblastoma multiforme is that in which the PI3K/mTOR pathway is activated due to ERBB2 mutation, PTEN mutation or loss, NF1 mutation or loss, PIK3Ca mutation, EGFR mutation or overexpression, Met amplification, PDGFRa activation or amplification, AKT amplification, or a combination thereof.

4. The use of claim 1, wherein the dose is 0.5 mg/day to 45 mg/day of a 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

5. The use of claim 1, wherein the glioblastoma multiforme is characterized by MGMT protein expression.

6. The use of claim 1, wherein the glioblastoma multiforme is characterized by MGMT promoter hypomethylation.