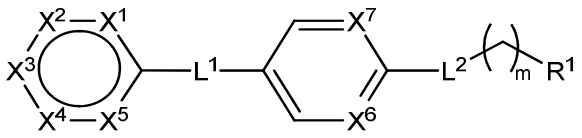
CLAIMS

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 represents -N=, -CH=, or -O-;

X^2 represents -CH=, -C(R^2)=, or a covalent bond;

X^3 represents -CH=, -C(R^2)=, or a covalent bond;

X^4 represents -O-, -C(R^3)=, -N=, or -S-; and

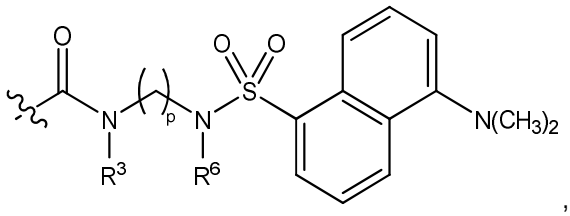
X^5 represents a covalent bond, -C(R^3)=, or -O-;

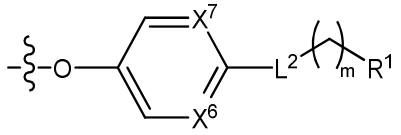
provided that one of X^2 and X^3 is -C(R^2)= and the other of X^2 and X^3 is -CH= or a covalent bond, and provided that at most only one of X^2, X^3, and X^5 represents a covalent bond;

R^2 represents ArylC(R^3)=C(H)-, HeteroarylC(R^3)=C(H)-, ArylN(R^3)C(O)-, HeteroarylN(R^3)C(O)-, Arylcyclopropyl-, Heteroarylcyclopropyl-, R^3OC(O)C(H)=C(H)-, R^3OC(O)-, Aryl-C≡C-, Heteroaryl-C≡C-, Aryl-, Heteroaryl-, Aryl-CH(R^3)-CH(R^3)-, or Heteroaryl-CH(R^3)-CH(R^3)-, wherein the Aryl group and the Heteroaryl group are substituted with one to three, preferably one or two, R^4 groups, each being the same or different;

R^3 independently in each occurrence represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl, the alkyl, alkenyl, alkynyl, and cycloalkyl being optionally substituted with –OR^6, -N(R^6)$_2$, -C(O)OR^6, -CN or –C(O)N(R^6)$_2$;

R^4 independently in each occurrence represents -F, -Cl, -Br, -I, -SR^3, -SOR^5, -S(O)$_2$$R^5$, -S(O)$_2$N($R^3$)$_2$, -triazolyl, -CN, -C(O)$OR^3$, -C(O)$R^3$, -$NO_2$, -C(O)N($R^3$)$_2$, -$OR^3$, -C($R^3$)$_2$OH, -N($R^3$)$_2$, -N($R^3$)C(O)$R^3$, -N($R^3$)C(O)$OR^5$, -OC(O)N($R^3$)$_2$, -$N_3$, -$R^3$,



, or ;

R^5 independently in each occurrence represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl, the alkyl, alkenyl, alkynyl, and cycloalkyl being optionally substituted with –OR^6, -$N(R^6)_2$, -$C(O)OR^6$, -CN or –$C(O)N(R^6)_2$;

R^6 independently represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl;

L^1 represents –CHR^3-O-, –CH_2-NH-, –C(O)NH-, -C(O)-CHR^6, -CR^6=CR^6-, -CH_2-S-, -CH_2-, or –CH_2-O-CH_2-;

X^6 and X^7 independently represent -CR^3=, or -N=;

L^2 represents a covalent bond, -C(O)-, -$C(R^3)$(OH)-, -O-, -S-, -CHR^3-, -$CH(R^3)$-S-, or -$CH(R^3)$-O-;

m independently in each occurrence represents an integer from 1 to 4;

p represents an integer from 1 to 6; and

R^1 represents heteroaryl, aryl, -N_3, -OH, -$OC(O)N(R^7)_2$, -$C(O)N(R^7)_2$, -$N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)OR^8$, -$N(R^7)C(O)$-L^3-OR^7, or -$N(R^7)C(O)$-L^3-$OC(O)N(R^7)_2$, the heteroaryl and aryl being optionally substituted with one or more R^9, which are the same or different, wherein:

L^3 represents C_1-C_5alkylene, C_2-C_5alkenylene, C_2-C_5alkynylene, or C_1-C_4fluoroalkylene, the alkylene, alkenylene, and alkynylene being optionally substituted with one or more R^9, which are the same or different;

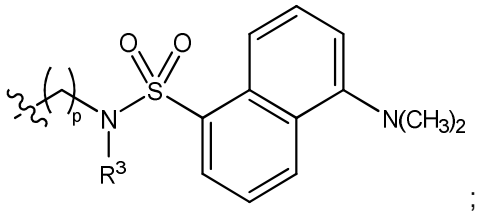
R^7 independently represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl; the alkyl, alkenyl, alkynyl, and cycloalkyl being optionally substituted with one or more R^9, which are the same or different,

or when two R^7 groups are attached to a same nitrogen atom, the two R^7 groups together with the nitrogen atom to which they are attached optionally form a 5-7-membered heterocycloalkyl, the heterocycloalkyl optionally comprising one or more further heteroatom independently selected from -O-, -$N(R^3)$-, -S-, -S(O)- and -SO_2-, the heterocycloalkyl being optionally substituted with one or more R^9, which are the same or different;

R^8 independently represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl; the alkyl, alkenyl, alkynyl, and cycloalkyl being optionally substituted with one or more R^9, which are the same or different; and

R^9 independently represents -C_1-C_6alkyl, -C_0-C_6alkyl-OR^{11}, -C_3-C_6cycloalkyl, -C_3-C_6cycloalkyl-OR^{11}, -C_1-C_6alkyl-$OC(O)R^{11}$, -C_1-C_6alkyl-$OC(O)N(R^{11})_2$, -C_1-C_6alkyl-$OC(O)N(R^{11})$-L^4-OR^{11}, -C_0-C_6alkyl-$C(O)OR^{11}$, -C_0-C_6alkyl-$C(O)N(R^{11})_2$, -C_1-C_6alkyl-$N(R^{11})_2$, -C_1-C_6alkyl-$N(R^{11})C(O)R^{11}$, -C_1-C_6alkyl-$N(R^{11})C(O)$-L^4-$N(R^{11})$-$C(O)R^{11}$, -C_1-C_6alkyl-$N(R^{11})S(O)_2R^{10}$, -C_1-C_6alkyl-$N(R^{11})S(O)_2$-L^4-$N(R^{11})$-$C(O)OR^{10}$, -$Si(C_1$-C_5alkyl$)_3$, -C(O)-O-C_1-C_6alkyl, phenyl optionally

substituted with R^4, benzyl optionally substituted with R^4, pyridinyl optionally substituted with R^4, or



;

wherein:

L^4 represents C_1-C_5alkylene, C_2-C_5alkenylene, C_2-C_5alkynylene, or C_1-C_4fluoroalkylene; and

R^{10} independently represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl, the alkyl, alkenyl, alkylnyl, and cycloalkyl being optionally substituted with –OR^6, -$N(R^6)_2$, -C(O)OR^6, -CN or –C(O)$N(R^6)_2$;

R^{11} independently represents -H, -C_1-C_5alkyl, -C_2-C_5alkenyl, -C_2-C_5alkynyl, -C_1-C_4fluoroalkyl, or -C_3-C_7cycloalkyl, the alkyl, alkenyl, alkylnyl, and cycloalkyl being optionally substituted with –OR^6, -$N(R^6)_2$, -C(O)OR^6, -CN or –C(O)$N(R^6)_2$, or

when two R^{11} groups are attached to a same nitrogen atom, the two R^{11} groups together with the nitrogen atom to which they are attached optionally form a 5-7-membered heterocycloalkyl, the heterocycloalkyl optionally comprising one or more further heteroatom independently selected from -O-, -$N(R^3)$-, -S-, -S(O)- and -SO_2-.

2. The compound of claim 1, wherein R^5, R^8 and R^{10} are other than -H.

3. The compound of claim 1 or 2, wherein one of X^2 and X^3 represents a covalent bond, the other of X^2 and X^3 represents -$C(R^2)$=, and X^5 represents -$C(R^3)$= or -O-.

4. The compound of claim 3, wherein X^1 represents -N=, X^4 represents -O- or -S-, and/or X^5 represents -$C(R^3)$=, preferably -CH=.

5. The compound of claim 4, wherein X^4 represents -O-.

6. The compound of claim 4, wherein X^4 represents -S-.

7. The compounds of claim 1 or 2, wherein one of X^2 and X^3 is -$C(R^2)$= and the other of X^2 and X^3 is -CH=, and X^5 represents -$C(R^3)$= or -O-.

8. The compound of claim 7, wherein X^3 represents -CH= and X^2 represents -$C(R^2)$=.

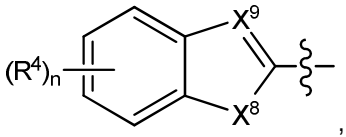
9. The compound of claim 7, wherein X^3 represents -$C(R^2)$= and X^2 represents -CH=.

10. The compound of any one of claims 1, 2, and 7 to 9, wherein X^5 represents -C(R^3)=, preferably -CH=; X^1 represents -C(R^3)=, preferably -CH=; and/or X^4 represents -C(R^3)=, preferably -CH=.

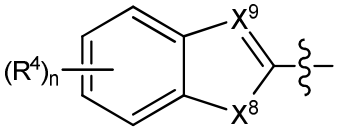
11. The compound of any one of claims 1 to 10, wherein R^2 represents ArylC(R^3)=C(H)-, HeteroarylC(R^3)=C(H)-, ArylN(R^3)C(O)-, Arylcyclopropyl-, R^3OC(O)C(H)=C(H)-, R^3OC(O)-, Aryl-, Heteroaryl-, or Aryl-CH(R^3)-CH(R^3)-, preferably ArylC(R^3)=C(H)- or Heteroaryl, and more preferably ArylC(R^3)=C(H)-.

12. The compound of any one of claims 1 to 11, wherein the Aryl group in R^2 is phenyl or naphthyl, more preferably phenyl, the Aryl group being optionally substituted with one to three R^4 groups, which are the same or different.

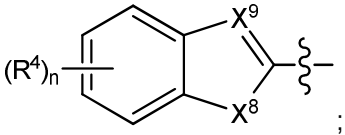
13. The compound of any one of claims 1 to 11, wherein the Heteroaryl group in R^2 is selected from:



, pyridyl, pyrimidinyl, thienyl, isoxazolyl, quinolyl, isoquinolyl, indolyl, indolinyl, benzo[b]thienyl, benzimidazolyl, benzoxalolyl, benzofuranyl, isobenzofuranyl and benzothiazolyl, preferably



or pyridyl, more preferably



;

wherein n represents an integer from 0 to 3, X^8 represents -NH-, -O-, or -S-, preferably -NH-, and X^9 is -N= or -CH=, preferably -CH=; and

the Heteroaryl group being optionally substituted with one to three R^4 groups, which are the same or different.

14. The compound of claim 1, selected from Compounds 1, 2, 3A, 3B, 4 to 147, or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, selected from Compounds 65, 122, 124, 127, 128, 129, 130, 138, 141, 144, and 147, or a pharmaceutically acceptable salt thereof.

16. Use of a compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating acute myeloid leukemia (*AML*), wherein an effective amount of the compound or the pharmaceutically acceptable salt thereof is to be administered to a subject in need thereof.

17. The use of claim 16, wherein said *AML* is poor prognosis *AML*.

18. The use of claim 16, wherein said *AML* comprises at least one of the following features: (a) high level of expression of one or more homeobox (*HOX*)-network genes; (b) high level of expression of one or more of the genes depicted in Table 1; (c) low level of expression of one or more of the genes depicted in Table 2; (d) one or more of the following cytogenetic or molecular risk factor: intermediate cytogenetic risk, Normal Karyotype (NK), mutated *NPM1*, mutated *CEBPA*, mutated *FLT3*, mutated DNA methylation genes, mutated *RUNX1*, mutated *WT1*, mutated *SRSF2*, intermediate cytogenetic risk with abnormal karyotype (intern(abnK)), trisomy 8 (+8) and abnormal chr(5/7); and (e) a leukemic stem cell (LSC) frequency of at least about 1 LSC per $1x10^6$ total cells.

19. The use claim 18, wherein said *AML* comprises high level of expression of one or more *HOX*-network genes.

20. The use of claim 19, wherein said one or more HOX-network genes are *HOXB1, HOXB2, HOXB3, HOXB5, HOXB6, HOXB7, HOXB9, HOXB-AS3, HOXA1, HOXA2, HOXA3, HOXA4, HOXA5, HOXA6, HOXA7, HOXA9, HOXA10, HOXA10-AS, HOXA11, HOXA11-AS, MEIS1* and/or *PBX3*.

21. The use of any one of claims 18 to 20, wherein said *AML* comprises high level of expression of one or more of the genes depicted in Table 1.

22. The use of claim 21, wherein said *AML* comprises high level of expression of the PRDM16 genes.

23. The use of any one of claims 18 to 22, wherein said *AML* comprises low level of expression of one or more of the genes depicted in Table 2.

24. The use of any one of claims 18 to 23, wherein said *AML* comprises one or more of the cytogenetic or molecular risk factor defined in item (d) of claim 18.

25. The use of claim 24, wherein said *AML* is intermediate cytogenetic risk *AML* and/or NK-*AML*.

26. The use of claim 24 or 25, wherein said *AML* comprises at least two of said cytogenetic or molecular risk factors.

27. The use of any one of claims 21 to 26, wherein said *AML* comprises a mutated *NPM1*, a mutated *FLT3* and/or a mutated DNA methylation gene.

28. The use of claim 27, wherein said DNA methylation gene is *DNMT3A* or *IDH1*.

29. The use of claim 27 or 28, wherein said mutated *FLT3* is *FLT3* with internal tandem duplication (*FLT3*-ITD).

30. The use of any one of claims 21 to 29, wherein said *AML* comprises at least two of features (a) to (e).

31. The use of any one of claims 21 to 30, wherein said *AML* is NK-*AML* with mutated *NPM1*.

32. The use of any one of claims 16 to 31, wherein the compound or pharmaceutically acceptable salt thereof is present in a pharmaceutical composition.

33. The use of any one of claims 16 to 32, wherein the subject is a pediatric subject.

34. The use of any one of claims 16 to 32, wherein the subject is an adult subject.

35. A method for determining the likelihood that a subject suffering from acute myeloid leukemia (*AML*) responds to a treatment with the compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 15, said method comprising determining whether *AML* cells from said subject is *AML*, wherein the presence of *AML* as claimed in any one of claims 17 to 31 is indicative that the subject has a high likelihood of responding to said treatment.

36. Use of a compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting tumor growth and/or inducing tumor cell death and/or treating cancer in a subject, wherein said inhibiting growth and/or inducing tumor cell death and/or treating cancer comprises inhibiting mitochondrial activity/respiration in a cancer cell.

37. A compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, for use in inhibiting tumor growth and/or inducing tumor cell death and/or treating cancer, wherein said inhibiting growth and/or inducing tumor cell death and/or treating cancer comprises inhibiting mitochondrial activity/respiration in a cancer cell.

38. Use of a compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting mitochondrial activity/respiration in a cancer cell.

39. The use of any one of claims 35 to 38, wherein said mitochondrial activity inhibition comprises blocking ETC or oxidative phosphorylation leading to production of Reactive Oxygen Species (ROS).

40. The use of claim 39, wherein said mitochondrial activity inhibition comprises inhibition of complex I inducing production of ROS.

41. The use of any one of claims 35 to 40, wherein cancer cell is selected from lymphoma, leukemia, glioblastoma, sarcoma, lung, and breast cancers.