excellent therapeutic targets based on their intrinsic biochemical properties (Cheng Y, LeGall T, Oldfield CJ, *et al.*, Trends Biotechnol 2006;24(10):435-42).

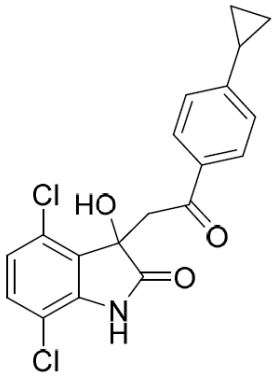
SUMMARY

[0004] Despite years of *in vitro* and xenograft studies with antisense and siRNA directed towards EWS-FLI1, none of these is heretofore practical as a human therapy based on inadequate delivery and stability. Accordingly, there is a need for improved therapies to treat disorders such as ESFTs.

[0005] FLI-1 is a member of the ETS family transcription factors which are normally active in the developing embryo, but not after birth. There are 29 members of this family of transcription factors, four of which, FLI-1, ETV1, ETV4 and ERG, have been associated with a wide range of cancers.

[0006] Therapeutic compounds targeting the inhibition of the binding of oncogenic fusion proteins of FLI1, ETV1, ETV4 or ERG or the transcription factors themselves will have utility in treatment of cancers including the Ewing's sarcoma family of tumors, pancreatic cancer, prostate cancer, glioblastoma, non-small cell lung cancer, and several other cancers. The preferred examples fulfill these needs, and provide other advantages as well.

[0006a] In one aspect of the present disclosure, there is provided a use of a compound having the structure :

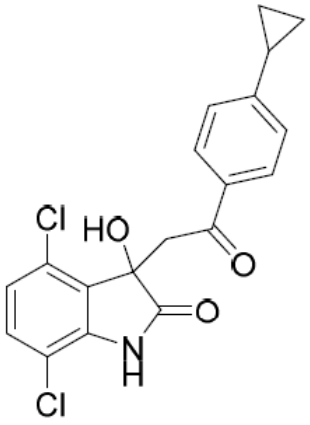


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

[0006b] In another aspect of the present disclosure, there is provided a use of a compound having the structure:

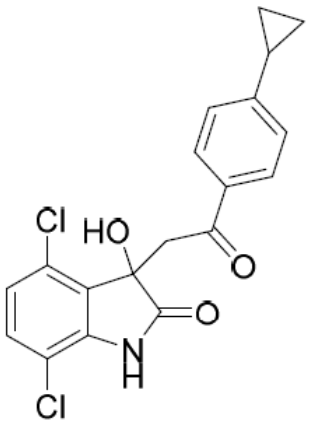


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

[0006c] In a further aspect of the present disclosure, there is provided a use of a combination comprising a compound having the structure:

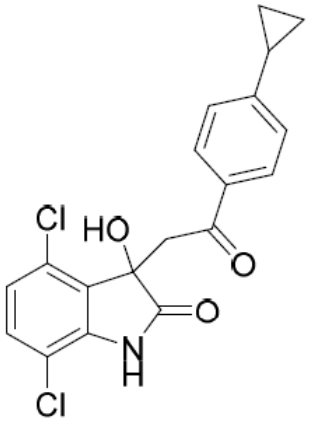


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

[0006d] In another aspect of the present disclosure, there is provided a use of a combination comprising a compound having the structure:



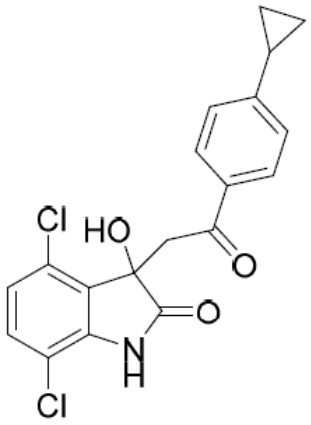
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

[0006e] In a further aspect of the present disclosure, there is provided an in vitro method for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with

a compound having a structure:

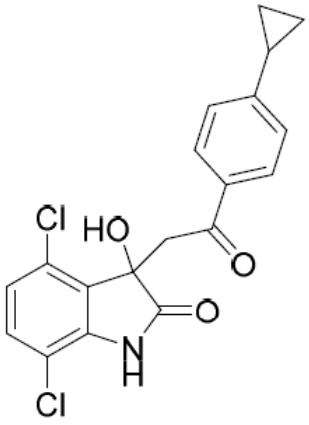


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax.

[0006f] In another aspect of the present disclosure, there is provided an in vitro method for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with a combination comprising

a compound having a structure:



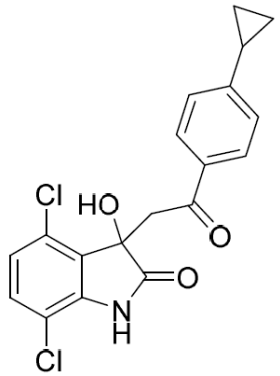
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax.

[0006g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising:

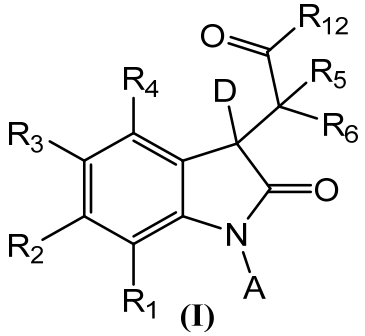
at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax; and

a compound having a structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof.

[0007] Some examples disclosed herein relate to a compound of Formula (I) including forms such as stereoisomers, free forms, pharmaceutically acceptable salts or esters thereof, solvates, or combinations of such forms, wherein A, D, R_1, R_2, R_3, R_4, R_5, R_6, and R_{12} are as defined herein.



(I)

[0008] Some examples disclosed herein relate to methods for treating cancer in a mammal, comprising administering to the mammal an effective amount of one or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one

or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof,. Other examples described herein relate to using one or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of cancer.

[0009] Still other examples described herein relate to a compound of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, for treatment of cancer wherein the cancer is selected from the group consisting of Ewing's sarcoma, glioblastoma, acute myeloid leukemia, breast cancer, head & neck cancer, melanoma, non-small cell lung cancer, ovarian cancer, prostate cancer, and uterine cancer. These and other examples are described in greater detail below.

DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 is a diagram illustrating that TK216 (also referred to herein as TK-216, which is 4,7-Dichloro-3-(2-(4-cyclopropylphenyl)-2-oxoethyl)-3-hydroxyindolin-2-one) is active in oncogenesis and inhibits aptosis.

[0011] FIG. 2 shows TK216 treatment inhibited EWS-FLI1 protein interactions, leading to a decrease in transcription and proliferation.

[0012] FIG. 3 shows TK216 reduced transcriptional activity in COS7 cells co-transfected with EWS-FLI1 and NROB1 reporter-luciferase plasmids which contain EWS-FLI1 DNA-binding sites.

[0013] FIG. 4 shows treatment with TK216 resulted in a dose-dependent inhibition of proliferation in Ewing Sarcoma A4573 cell line.

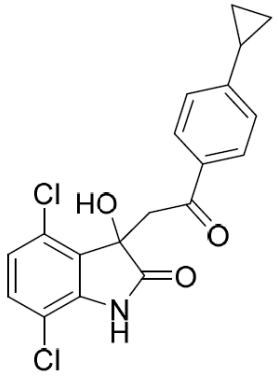
[0014] FIG. 5 shows TK216 displayed anti-proliferative activity in AML cell lines.

[0015] FIG. 6 shows TK216 displayed anti-proliferative activity in DLBCL cell lines.

[0016] FIG. 7 and FIG. 8 show TK216 induced apoptosis in DLBCL cell lines, with the amount of cleaved-Caspase 3 normalized to b-actin and presented as fold over control.

CLAIMS

1. Use of a compound having the structure :

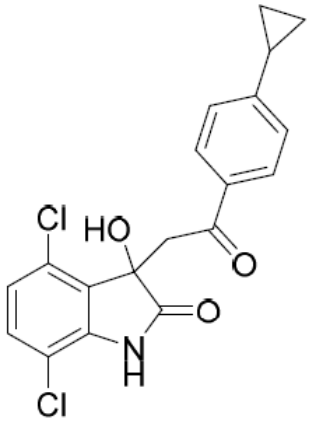


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

2. The use of claim 1, wherein the cell is mammalian.
3. The use of any one of Claims 1-2, wherein the cell is human.
4. Use of a compound having the structure:

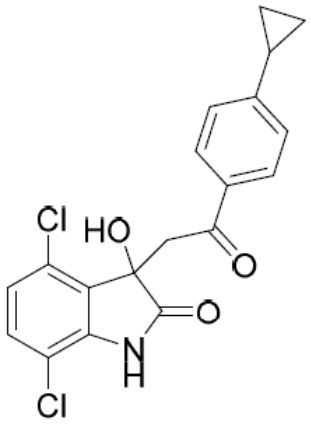


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

5. Use of a combination comprising a compound having the structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

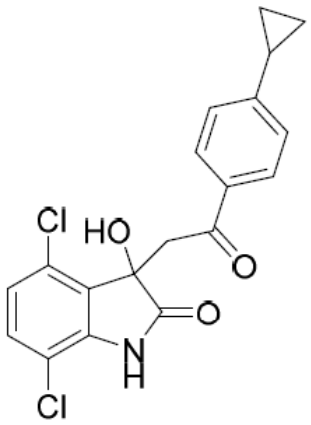
at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

6. The use of claim 1, wherein the cell is mammalian.

7. The use of anyone of claims 1-2, wherein the cell is human.

8. Use of a combination comprising a compound having the structure:



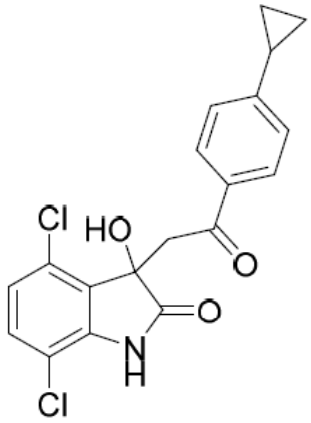
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

9. An in vitro method for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with

a compound having a structure:

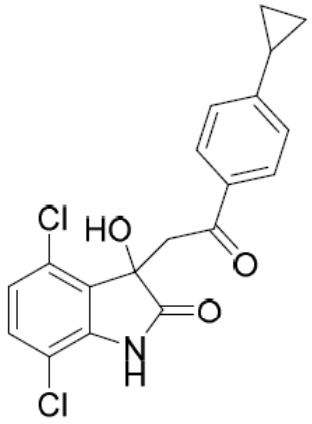


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax.

10. An in vitro method for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with a combination comprising

a compound having a structure:



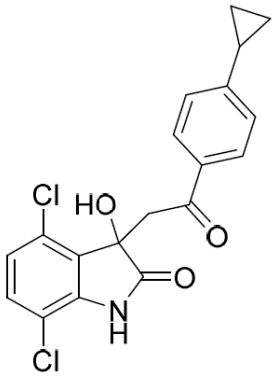
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax.

11. A pharmaceutical composition, comprising:

at least one therapeutic agent selected from the group consisting of lenalidomide and venetoclax; and

a compound having a structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof.