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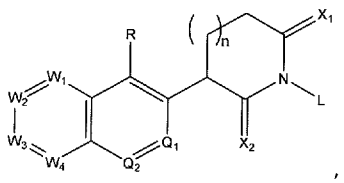
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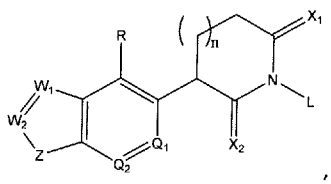
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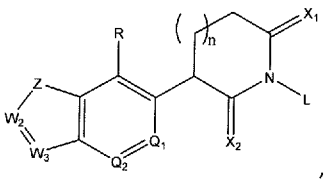
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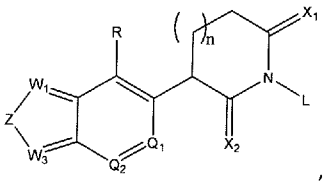
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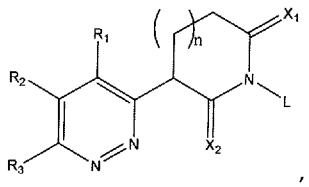
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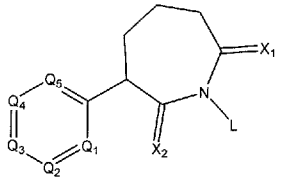
(IV)

(57) **Abstract:** The present invention discloses novel compounds which bind to cereblon, and methods of use thereof. The compounds are represented by Formulas (I), (IIa)-(IIc), (III) and (IV).

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NOVEL COMPOUNDS WHICH BIND TO CEREBLON, AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates to novel compounds which bind to the protein cereblon and modulate the substrate specificity of CUL4-DDB1-RBX1-CRBN ubiquitin ligase complex ($CRL4^{CRBN}$). Cereblon is a substrate recognition component of $CRL4^{CRBN}$. Chemical modulation of cereblon may induce association of novel substrate proteins, followed by their ubiquitination and degradation.

BACKGROUND

Cereblon (CRBN) is a protein which associates with DDB1 (damaged DNA binding protein 1), CUL4 (Cullin-4), and RBX1 (RING-Box Protein 1). Collectively, the proteins form a ubiquitin ligase complex, which belongs to Cullin RING Ligase (CRL) protein family and is referred to as $CRL4^{CRBN}$. Cereblon became of particular interest to the scientific community after it was confirmed to be a direct protein target of thalidomide, which mediates the biological activity of cereblon. Thalidomide, a drug approved for treatment of multiple myeloma in the late 1990s, binds to cereblon and modulates the substrate specificity of the $CRL4^{CRBN}$ ubiquitin ligase complex. This mechanism underlies the pleiotropic effect of thalidomide on both immune cells and cancer cells (*see* Lu G et al.: The Myeloma Drug Lenalidomide Promotes the Cereblon-Dependent Destruction of Ikaros Proteins. Science. 2014 Jan 17; 343(6168): 305-9).

Thalidomide's success in cancer therapy stimulated efforts towards development of analogues with higher potency and fewer detrimental side effects. As a results, various drug candidates were produced: lenalidomide, pomalidomide, CC-220, CC-122, CC-885, and TD-106. These compounds are collectively called Cereblon Modulating Agents (CMAs). For discussions of these compounds, see - for example - US 5635517(B2), WO2008039489 (A2), WO2017197055 (A1), WO2018237026 (A1), WO2017197051 (A1), US 8518972 (B2), EP 2057143 (B1), WO2019014100 (A1), WO2004103274 (A2), and Kim SA et al.: A novel cereblon modulator for targeted protein degradation. Eur J Med Chem. 2019 Mar 15; 166: 65-74.

The clinical applicability of CMAs in numerous hematologic malignancies, such as multiple myeloma, myelodysplastic syndromes lymphomas and leukemia, has been demonstrated (*see* Le Roy A et al.:

Immunomodulatory Drugs Exert Anti-Leukemia Effects in Acute Myeloid Leukemia by Direct and Immunostimulatory Activities. Front Immunol. 2018; 9: 977).

The antitumor activity of cereblon modulators is mediated by:

1) inhibition of cancer cell proliferation and induction of apoptosis,

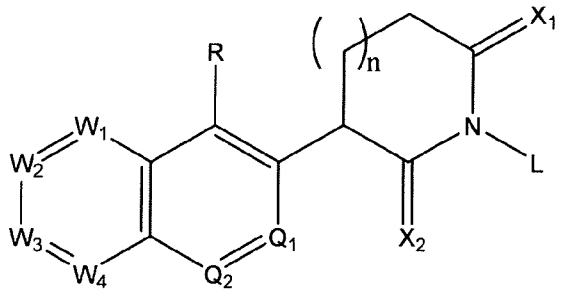
2) disruption of trophic support from tumor stroma,

3) stimulation of immune cells, resulting in proliferation of T-cells, cytokine production and activation of NK (natural killer) cells (*see* Le Roy A et al.: Immunomodulatory Drugs Exert Anti-Leukemia Effects in Acute Myeloid Leukemia by Direct and Immunostimulatory Activities. Front Immunol. 2018; 9: 977).

It has been demonstrated that chemically-modified thalidomide-based derivatives can significantly modify the substrate specificity of $CRL4^{CRBN}$ ubiquitin ligase. Thus, it is desired to progress development of cereblon modulating agents in order to achieve desired substrate specificity in the CMA-bound $CRL4^{CRBN}$ ubiquitin ligase complex (*see* Sievers QL et al.: Defining the human C_2H_2 zinc finger degrome targeted by thalidomide analogues through CRBN. Science. 2018 Nov 2; 362(6414)) to reach a desired safety profile. There is thus a continuing need to provide novel cereblon-binding compounds which have pharmaceutically relevant properties.

SUMMARY OF INVENTION

In accordance with a first aspect of the invention, there is provided a compound of Formula (I):



(I)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR, wherein at least one of Q_1 and Q_2 is N;

each of W_1, W_2, W_3 and W_4 is independently N or CR';

n is 0, 1 or 2;

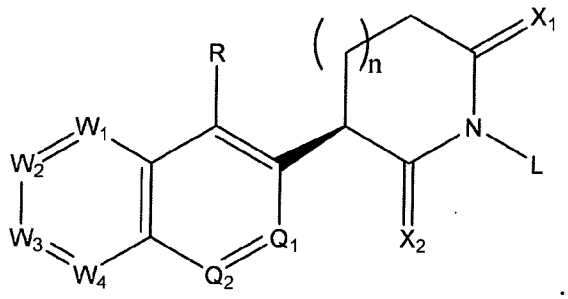
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -NR''_2, or -$S(O)_2$R'';

each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -OC(O)R'', -OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SR'', -$S(O)_2$R'', -$S(O)_2$OR'', -$S(O)_2NH_2$, -$S(O)_2$NHR'', or -$S(O)_2NR''_2$;

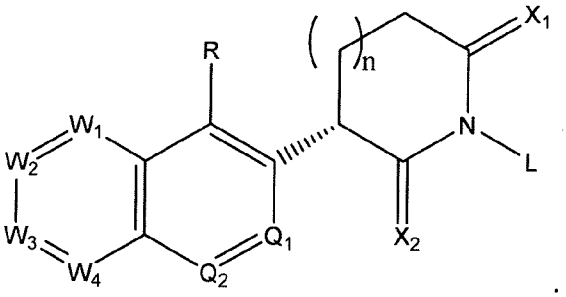
each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -OC(O)R'', -OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SR'', -$S(O)_2$R'', -$S(O)_2$OR'', -$S(O)_2NH_2$, -$S(O)_2$NHR'', or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

In certain embodiments, the compound of Formula (I) has the structure:



In other embodiments, the compound of Formula (I) has the structure:



In some embodiments, one of W_1, W_2, W_3 and W_4 is N, and the remaining three of W_1, W_2, W_3 and W_4 are each CR'. In some such embodiments, W_1 is N, and W_2, W_3 and W_4 are CR'. In other embodiments, W_2 is N, and W_1, W_3 and W_4 are CR'. In yet other embodiments, W_3 is N, and W_1, W_2 and W_4 are CR'. In other embodiments, W_4 is N, and W_1, W_2 and W_3 are CR'.

In some embodiments, W_1, W_2, W_3 and W_4 are each CR'. In some such embodiments, W_2, W_3 and W_4 are each CH. In other embodiments, W_1 is C-NH_2, C-NHR'' or C-NR''_2. In certain embodiments, W_1 is C-NH_2.

In other embodiments, two of W_1, W_2, W_3 and W_4 are N, and the remaining two of W_1, W_2, W_3 and W_4 are each CR'. In some such embodiments, W_1 and W_2 are each N, and W_3 and W_4 are each CR'. In other such embodiments, W_1 and W_3 are each N, and W_2 and W_4 are each CR'. In other such embodiments, W_1 and W_4 are each N, and W_2 and W_3 are each CR'. In other such embodiments, W_2 and W_3 are each N, and W_1 and W_4 are each CR'. In other such embodiments, W_2 and W_4 are each N, and W_1 and W_3 are each CR'. In other such embodiments, W_3 and W_4 are each N, and W_1 and W_2 are each CR'.

In yet other embodiments, three of W_1, W_2, W_3 and W_4 are N, and the remaining one of W_1, W_2, W_3 and W_4 is CR'. In some such embodiments, W_1, W_2 and W_3 are N, and W_4 is CR'. In other such embodiments, W_1, W_2 and W_4 are N, and W_3 is CR'. In other such embodiments, W_1, W_3 and W_4 are N, and W_2 is CR'. In other such embodiments, W_2, W_3 and W_4 are N, and W_1 is CR'.

In some embodiments of the compound of Formula (I), Q_1 is N and Q_2 is CR. In some embodiments of the compound of Formula (I), Q_1 is CR and Q_2 is N. In some embodiments of the compound of Formula (I), Q_1 is N and Q_2 is N.

In some embodiments of the compound of Formula (I), each R is independently hydrogen or alkyl. In some such embodiments, each R is independently hydrogen or C_1-C_4 alkyl. In some embodiments, the C_1-C_4 alkyl is methyl, ethyl, n-propyl or n-butyl. In some embodiments, the C_1-C_4 alkyl is methyl or ethyl. In some embodiments, each R is independently hydrogen or methyl.

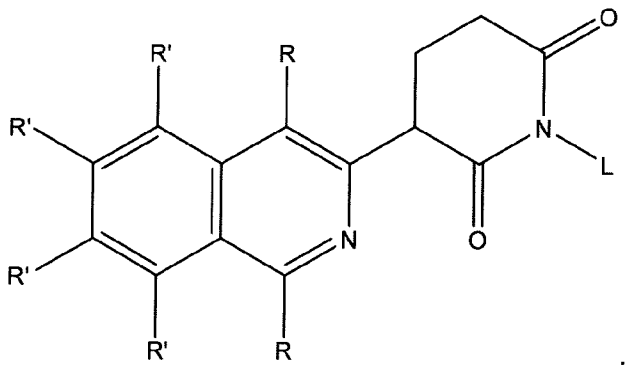
In some embodiments of the compound of Formula (I), each R' is independently hydrogen, -NH_2, -NHR'' or -NR''_2. In some such embodiments, each R' is independently hydrogen or -NH_2. In some such embodiments, each R' is hydrogen.

In some embodiments of the compound of Formula (I), X_1 and X_2 are O. In other embodiments, X_1 is O and X_2 is S. In other embodiments, X_1 is S and X_2 is O. In other embodiments, X_1 and X_2 are S.

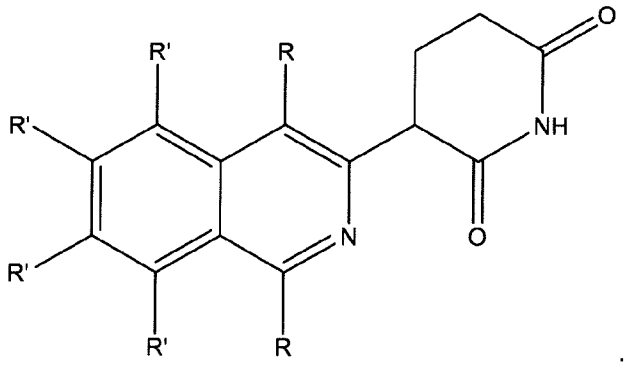
In some embodiments of the compound of Formula (I), n is 0. In other embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2.

In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In other embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH$_2$, -C(O)NHR'', or -C(O)NR''$_2$. In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, or haloalkenyl. In other embodiments of the compound of Formula (I), L is -OR'', -NR''$_2$, or -S(O)$_2$R'' In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl. In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, alkenyl, or aryl. In some embodiments of the compound of Formula (I), L is hydrogen, alkyl, or alkenyl. In some embodiments of the compound of Formula (I), L is hydrogen or alkyl. In some embodiments of the compound of Formula (I), L is hydrogen.

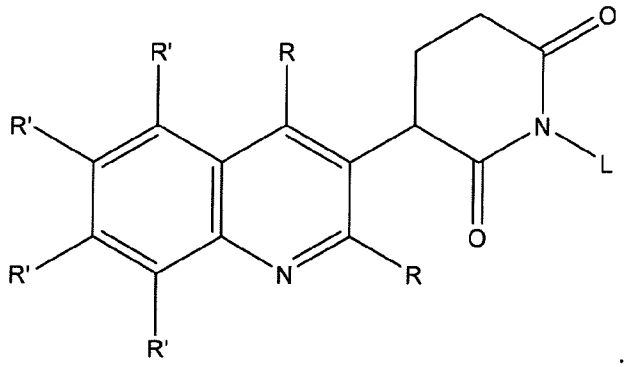
In some embodiments, the compound of Formula (I) is:



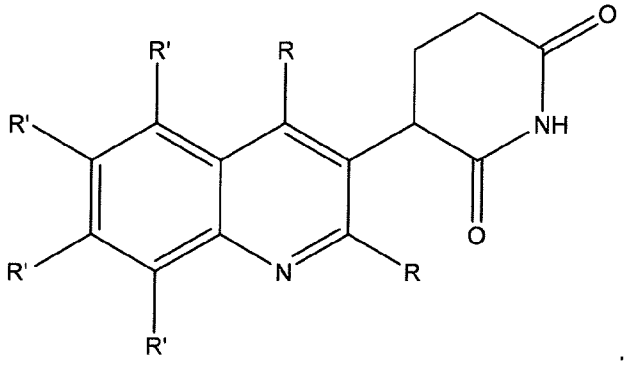
In some such embodiments, the compound of Formula (I) is:



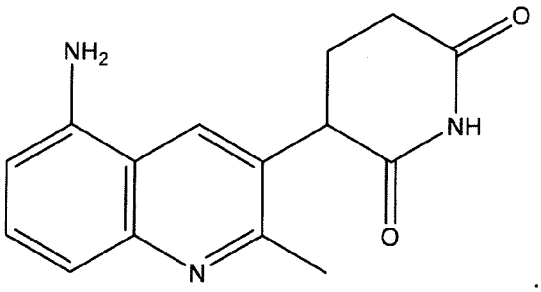
In other embodiments, the compound of Formula (I) is:



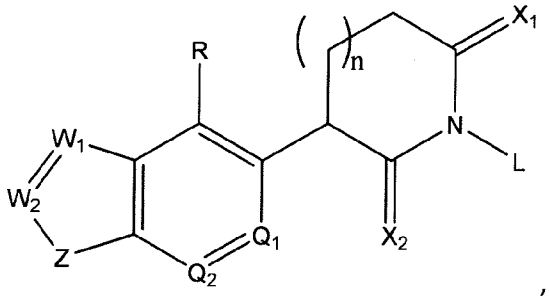
In some such embodiments, the compound of Formula (I) is:



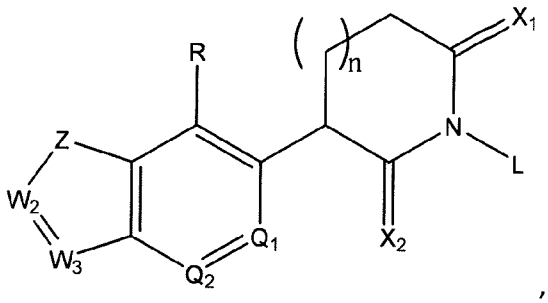
In one embodiment, the compound of Formula (I) is:



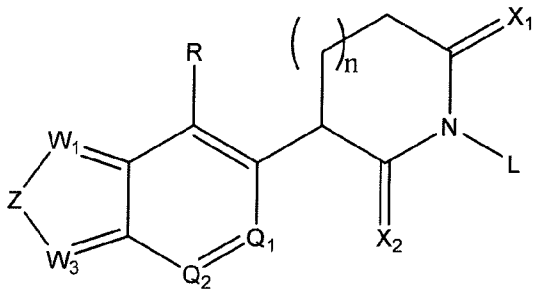
In accordance with a second aspect of the invention, there is provided a compound of Formula (IIa), (IIb), or (IIc):



(IIa)



(IIb)



(IIc)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR, wherein at least one of Q_1 and Q_2 is N;

each of W_1, W_2 and W_3 is independently N or CR';

Z is O, S, or NH;

n is 0, 1 or 2;

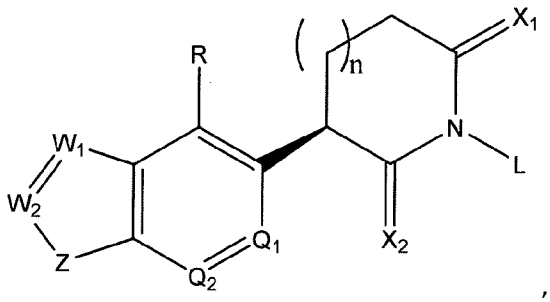
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -NR''_2, or -$S(O)_2R''$;

each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$;

each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

In some embodiments, the compound of Formula (IIa), (IIb), or (IIc) has the structure:



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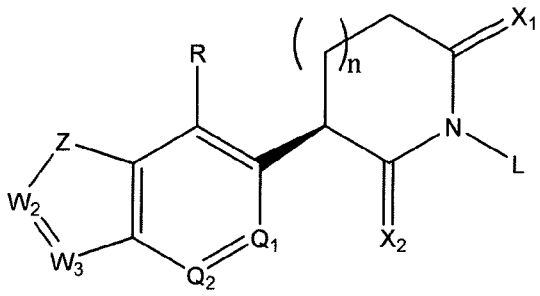

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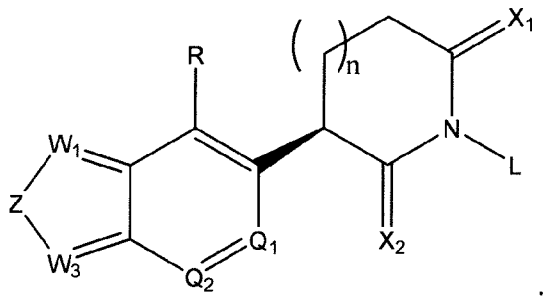

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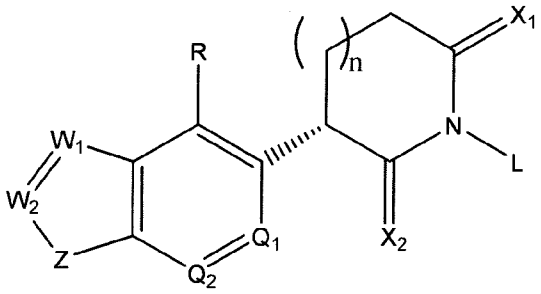
In other embodiments, the compound of Formula (IIa), (IIb), or (IIc) has the structure:



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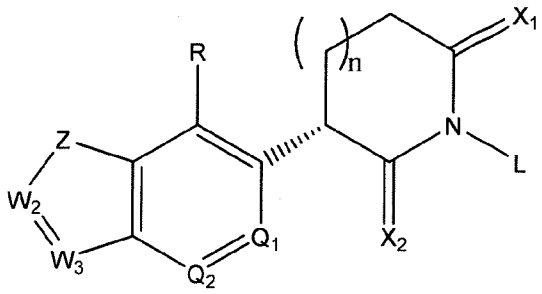

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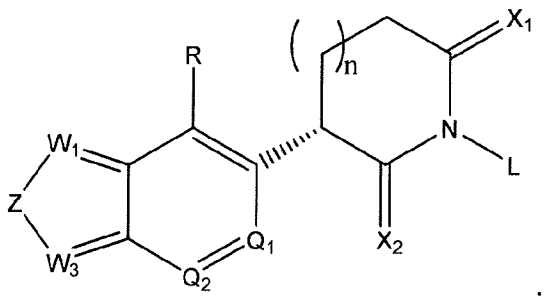

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In some embodiments of the compound of Formula (IIa) or (IIc), W_1 is N. In some embodiments of the compound of Formula (IIa) or (IIb), W_2 is N. In some embodiments of the compound of Formula (IIb) or (IIc), W_3 is N.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), one of W_1, W_2 and W_3 is N, and the other of W_1, W_2 and W_3 is CR'. In some such embodiments, one of W_1, W_2 and W_3 is N, and the other of W_1, W_2 and W_3 is CH.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), W_1, W_2 and W_3 are each CR'.

In some embodiments of the compound of Formula (IIa) or (IIc), W_1 is C-NH_2, C-NHR'' or C-NR''_2. In some such embodiments, W_1 is C-NH_2.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), W_1, W_2 and W_3 are each N.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), Z is O. In other embodiments of the compound of Formula (IIa), (IIb) or (IIc), Z is S. In other embodiments of the compound of Formula (IIa), (IIb) or (IIc), Z is NH.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), Q_1 is N and Q_2 is CR. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc) Q_1 is CR and Q_2 is N. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc) Q_1 is N and Q_2 is N.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), each R is independently hydrogen or alkyl. In some such embodiments, each R is independently hydrogen or C_1-C_4 alkyl. In some embodiments, C_1-C_4 alkyl is methyl, ethyl, n-propyl or n-butyl. In some embodiments, C_1-C_4 alkyl is methyl or ethyl. In some embodiments, each R is independently hydrogen or methyl.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), each R' is independently hydrogen, $-NH_2$, -NHR'' or $-NR''_2$. In some such embodiments, each R' is independently hydrogen or $-NH_2$. In some such embodiments, each R' is hydrogen.

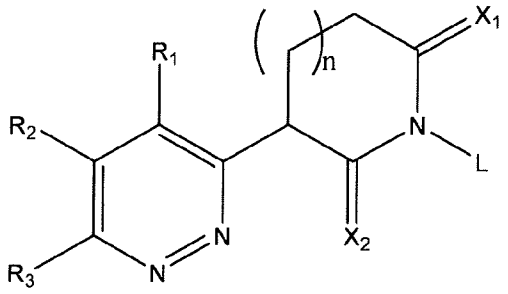
In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), X_1 and X_2 are O. In other embodiments, X_1 is O and X_2 is S. In other embodiments, X_1 is S and X_2 is O. In other embodiments, X_1 and X_2 are S.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), n is 0. In other embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2.

In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', $-NR''_2$, or $-S(O)_2R''$. In other embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', or $-C(O)NR''_2$. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', $-NR''_2$, or $-S(O)_2R''$. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, or haloalkenyl. In other embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is -OR'', $-NR''_2$, or $-S(O)_2R''$ In some

embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, alkenyl, or aryl. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen, alkyl, or alkenyl. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen or alkyl. In some embodiments of the compound of Formula (IIa), (IIb) or (IIc), L is hydrogen.

In accordance with a third aspect of the invention, there is provided a compound of Formula (III):



(III)

wherein

each of X_1 and X_2 is independently O or S;

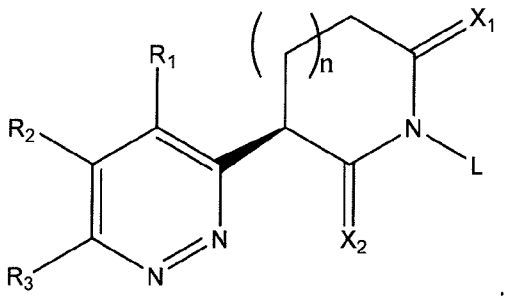
n is 0, 1 or 2;

L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -NR''_2, or -$S(O)_2$R'';

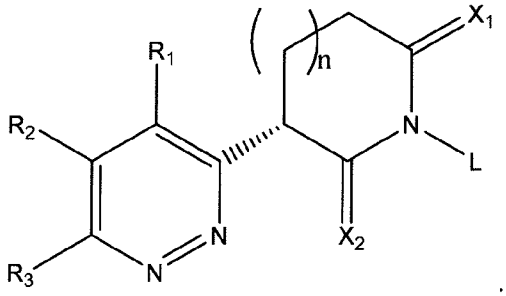
each of R_1, R_2 and R_3 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -OC(O)R'', -OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SR'' , $S(O)_2$R'', -$S(O)_2$OR'', -$S(O)_2NH_2$, -$S(O)_2$NHR'', or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

In some embodiments, the compound of Formula (III) has the structure:



In other embodiments, the compound of Formula (III) has the structure:

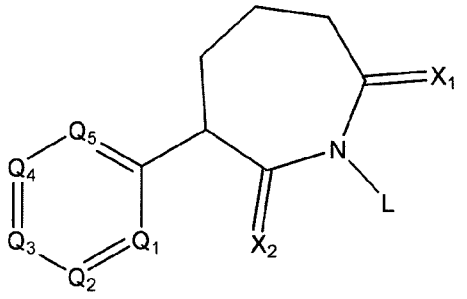


In some embodiments of the compound of Formula (III), X_1 and X_2 are O. In other embodiments, X_1 is O and X_2 is S. In other embodiments, X_1 is S and X_2 is O. In other embodiments, X_1 and X_2 are S.

In some embodiments of the compound of Formula (III), n is 0. In other embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2.

In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In other embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH$_2$, -C(O)NHR'', or -C(O)NR''$_2$. In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, or haloalkenyl. In other embodiments of the compound of Formula (III), L is -OR'', -NR''$_2$, or -S(O)$_2$R'' In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl. In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, alkenyl, or aryl. In some embodiments of the compound of Formula (III), L is hydrogen, alkyl, or alkenyl. In some embodiments of the compound of Formula (III), L is hydrogen or alkyl. In some embodiments of the compound of Formula (III), L is hydrogen.

In accordance with a fourth aspect of the invention, there is provided a compound of formula (IV):



(IV)

wherein

each of X_1 and X_2 is independently O or S;

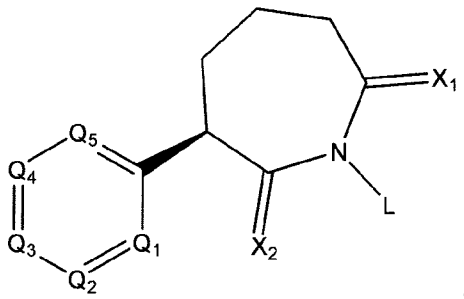
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -NR''_2, or -$S(O)_2$R'';

each of Q_1, Q_2, Q_3, Q_4 and Q_5 is independently N or CR, wherein at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N;

each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -OC(O)R'', -OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SR'', -$S(O)_2$R'', -$S(O)_2$OR'', -$S(O)_2NH_2$, -$S(O)_2$NHR'', or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

In some embodiments, the compound of Formula (IV) has the structure:



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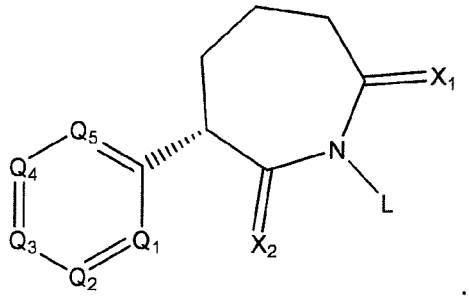
In some embodiments, the compound of Formula (IV) has the structure:



In some embodiments of the compound of Formula (IV), X_1 and X_2 are O. In other embodiments, X_1 is O and X_2 is S. In other embodiments, X_1 is S and X_2 is O. In other embodiments, X_1 and X_2 are S.

In some embodiments of the compound of Formula (IV), one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N, and the remaining four of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR. In some such embodiments, Q_1 is N. In other such embodiments, Q_2 is N. In other such embodiments, Q_3 is N. In other such embodiments, Q_4 is N. In other such embodiments, Q_5 is N.

In some embodiments of the compound of Formula (IV), two of Q_1, Q_2, Q_3, Q_4 and Q_5 are N, and the remaining three of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR. In some such embodiments, Q_1 and Q_2 are N, and Q_3, Q_4 and Q_5 are each CR. In other such embodiments, Q_2 and Q_3 are N, and Q_1, Q_4 and Q_5 are each CR. In other such embodiments, Q_1 and Q_3 are N, and Q_2, Q_4 and Q_5 are each CR. In other such embodiments, Q_2 and Q_4 are N, and Q_1, Q_3 and Q_5 are each CR. In other such embodiments, Q_1 and Q_4 are N, and Q_2, Q_3 and Q_5 are each CR.

In some embodiments of the compound of Formula (IV), three of Q_1, Q_2, Q_3, Q_4 and Q_5 are N, and the remaining two of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR.

In some embodiments of the compound of Formula (IV), each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NR''C(O)R'', -NR''C(O)OR'', $-NO_2$, -CN, -C(O)R'', -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SR'', $S(O)_2R''$. In some embodiments, each R is independently hydrogen or $-NH_2$. In some embodiments, each R is hydrogen.

In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In other embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH$_2$, -C(O)NHR'', or -C(O)NR''$_2$. In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''$_2$, or -S(O)$_2$R''. In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, or haloalkenyl. In other embodiments of the compound of Formula (IV), L is -OR'', -NR''$_2$, or -S(O)$_2$R'' In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl. In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, alkenyl, or aryl. In some embodiments of the compound of Formula (IV), L is hydrogen, alkyl, or alkenyl. In some embodiments of the compound of Formula (IV), L is hydrogen or alkyl. In some embodiments of the compound of Formula (IV), L is hydrogen.

In accordance with a fifth aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to any of the above aspects of the present invention.

The invention also provides a compound according to any of the above aspects of the present invention for use as a cereblon binder.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in medicine.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in immune-oncology.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders.

The present invention also provides a method for the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders; wherein the method comprises administering to a patient in need thereof an effective amount of a compound or composition according to any of the above aspects of the present invention.

In some embodiments of the method, the method further comprises administering at least one additional active agent to the patient. In some embodiments, the at least one additional active agent is an anti-cancer agent or an agent for the treatment of an autoimmune disease. In some embodiments, the at least one additional active agent is a small molecule, a peptide, an antibody, a corticosteroid, or a combination thereof. In some embodiments, the at least one additional active agent is at least one of bortezomib, dexamethasone, and rituximab.

The present invention also provides a combined preparation of a compound of any one of the first to fourth aspects of the present invention and at least one additional active agent, for simultaneous, separate or sequential use in therapy.

In some embodiments of the combined preparation, the at least one additional active agent is an anti-cancer agent or an agent for the treatment of an autoimmune disease. In some embodiments, the at least one additional active agent is a peptide, an antibody, a corticosteroid, or a combination thereof. In some embodiments, the at least one additional active agent is at least one of bortezomib, dexamethasone, and rituximab. In some embodiments, the therapy is the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders.

As used herein the term "alkyl" is intended to include both unsubstituted alkyl groups, and alkyl groups which are substituted by one or more additional groups – for example -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, -

SO_2R'', -C(O)R'', -CN, or $-NO_2$. In some embodiments, the alkyl group is an unsubstituted alkyl group. In some embodiments, the alkyl group is a C_1-C_{12} alkyl, a C_1-C_{10} alkyl, a C_1-C_8 alkyl, a C_1-C_6 alkyl, or a C_1-C_4 alkyl group.

As used herein the term "alkenyl" is intended to include both unsubstituted alkenyl groups, and alkenyl groups which are substituted by one or more additional groups – for example -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-SO_2R''$, -C(O)R'', -CN, or $-NO_2$. In some embodiments, the alkenyl group is an unsubstituted alkenyl group. In some embodiments, the alkenyl group is a C_2-C_{12} alkenyl, a C_2-C_{10} alkenyl, a C_2-C_8 alkenyl, a C_2-C_6 alkenyl, or a C_2-C_4 alkenyl group.

As used herein the term "alkynyl" is intended to include both unsubstituted alkynyl groups, and alkynyl groups which are substituted by one or more additional groups – for example -OH, -OR'', halogen, $-NH_2$, -NHR'', $-NR''_2$, $-SO_2R''$, -C(O)R'', -CN, or $-NO_2$. In some embodiments, the alkynyl group is an unsubstituted alkynyl group. In some embodiments, the alkynyl group is a C_2-C_{12} alkynyl, a C_2-C_{10} alkynyl, a C_2-C_8 alkynyl, a C_2-C_6 alkynyl, or a C_2-C_4 alkynyl group.

As used herein the term "aryl" is intended to include both unsubstituted aryl groups, and aryl groups which are substituted by one or more additional groups – for example -OH, -OR'', halogen, $-NH_2$, -NHR'', $-NR''_2$, $-SO_2R''$, -C(O)R'', -CN, or $-NO_2$. In some embodiments, the aryl group is an unsubstituted aryl group. In some embodiments, the aryl group is a C_6-C_{10} aryl, a C_6-C_8 aryl, or a C_6 aryl.

As used herein the term "heteroaryl" is intended to include both unsubstituted heteroaryl groups, and heteroaryl groups which are substituted by one or more additional groups – for example -OH, -OR'', halogen, $-NH_2$, -NHR'', $-NR''_2$, $-SO_2R''$, -C(O)R'', -CN, or $-NO_2$. In some embodiments, the heteroaryl group is an unsubstituted heteroaryl group. In some embodiments, the heteroaryl group is a C_6-C_{10} heteroaryl, a C_6-C_9 heteroaryl, a C_6-C_8 heteroaryl, or a C_6 heteroaryl.

As used herein the term "benzyl" is intended to include both unsubstituted benzyl groups, and benzyl groups which are substituted by one or more additional groups – for example -OH, -OR'', halogen, $-NH_2$, -NHR'', $-NR''_2$, $-SO_2R''$, -C(O)R'', -CN, or $-NO_2$. In some embodiments, the benzyl group is an unsubstituted benzyl group.

BRIEF DESCRIPTION OF THE DRAWINGS

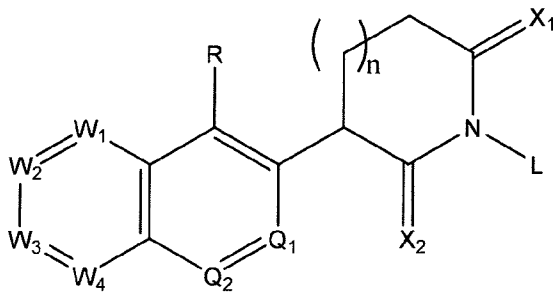
Figure 1 is an assay showing the effect of various compounds of the invention and various reference compounds on SALL4 degradation in the Kelly cell line.

Figure 2 is an assay showing the effect of various compounds of the invention and various reference compounds on IKZF1 degradation in the H929 cell line.

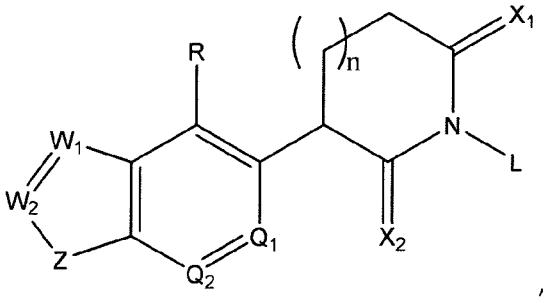
Figure 3 is an assay showing the effect of various compounds of the invention and various reference compounds on IKZF3 degradation in the H929 cell line.

DETAILED DESCRIPTION OF THE INVENTION

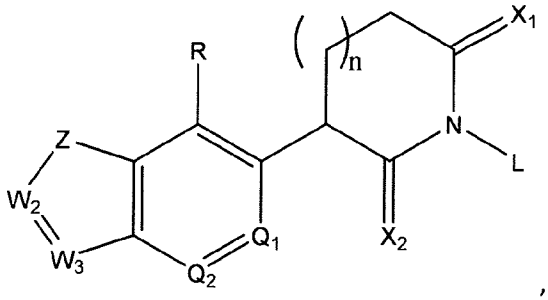
As discussed above, the present invention provides compounds of Formulas (I), (IIa)-(IIc), (III) and (IV):



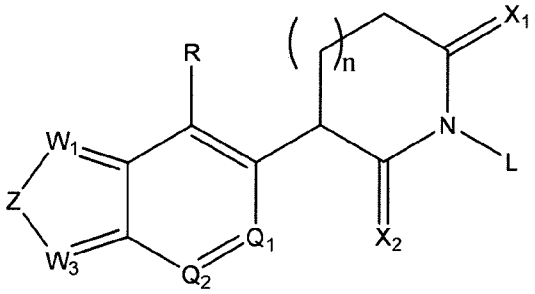
(I)



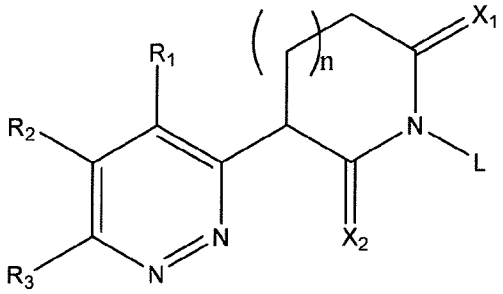
(IIa)



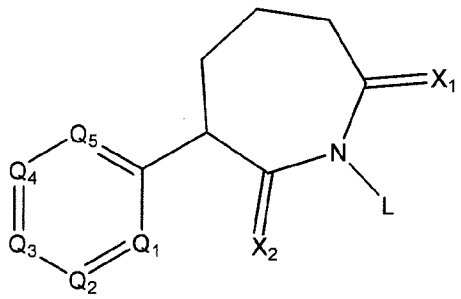
(IIb)



(IIc)



(III)



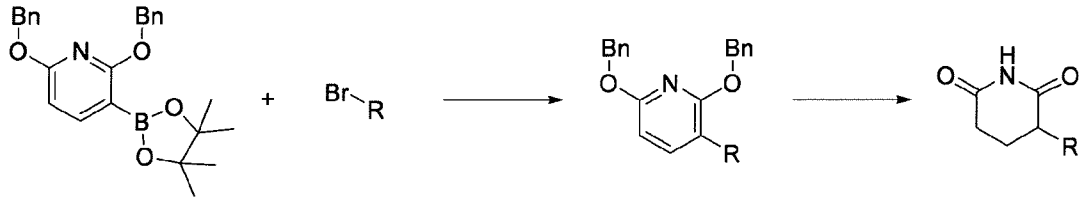
(IV)

wherein L, X_1, X_2, Q_1, Q_2, Q_3, Q_4, Q_5, W_1, W_2, W_3, W_4, R, R_1, R_2, R_3 and Z are as defined above.

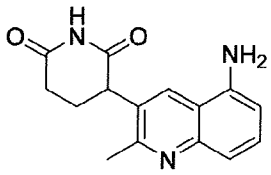
Binding of the above compounds to cereblon may alter the specificity of the $CRL4^{CRBN}$ complexes, and induce association of novel substrate proteins, followed by their ubiquitination and degradation. Examples of such proteins include, but are not limited to, IKZF1 and IKZF3.

The above compounds may modulate cereblon in a unique way allowing $CRL4^{CRBN}$ ubiquitin ligase complex to recognise different substrates to those which it would otherwise recognise, and target them for degradation. Consequently, the compounds of the present invention are expected to broaden/modify CRBN's antiproliferative activity, thus extending the range of cancer types sensitive to treatment with CMAs.

The compounds of the present invention are advantageous in terms of their synthetic feasibility. The synthesis of the compounds can be summarized as follows:

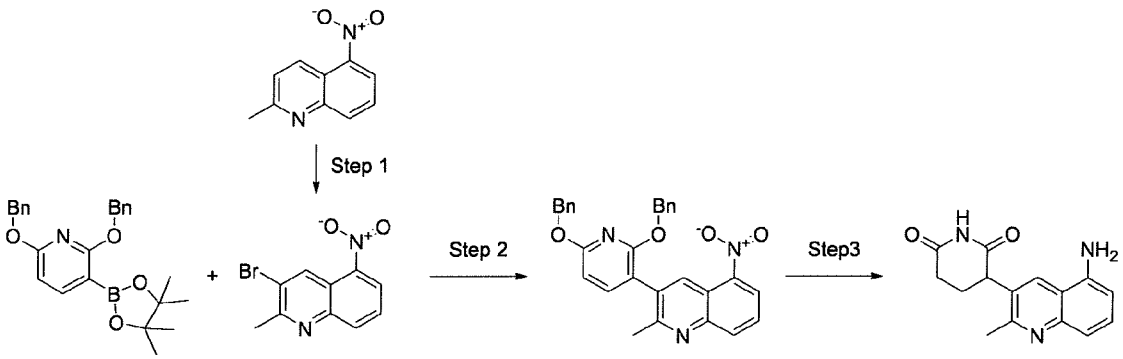


One example of a compound of the present invention is 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (Compound 1):



Compound 1

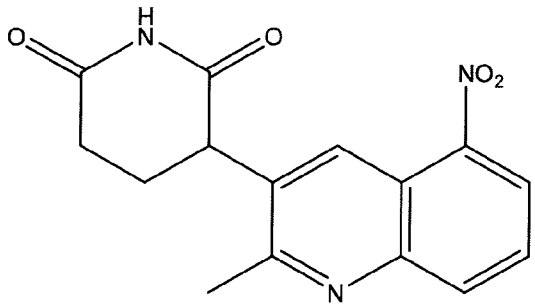
3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (Compound 1) can be synthesised as follows:

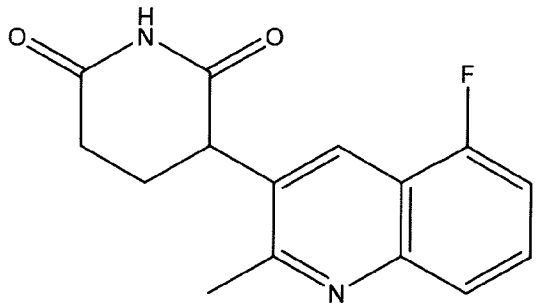


Compound 1

wherein Step 1 involves reaction with m-CPBA and phosphoryl bromide; Step 2 involves reaction with 2,6-Bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, tripotassium phosphate and $Pd(dppf)Cl_2$ CH_2Cl_2; and Step 3 involves reaction with H_2 gas in the presence of Pd on activated charcoal. Full experimental details for the synthesis of 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione are given in the "Examples" section, below.

Other examples of compounds of the present invention are shown below:





As also discussed in the Examples section, the present inventors have found that the compound 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (Compound 1) exhibits a similar cereblon binding capability to that of the known CMA, CC-122. Despite the pharmaceutical activity of the known CMAs such as CC-122, patients often develop resistance to these compounds. The use of novel compounds – such as those of the present invention, as described above - may help to overcome this clinical obstacle.

One of the serious disadvantages of the currently available CMAs is their safety profile. For example, the teratogenicity of the CMAs is dependent upon the extent to which the CMAs induce degradation of SALL4 transcription factor. Known CMAs induce degradation of several proteins (including SALL4) which bind to $CRL4^{CRBN}$ ligase only in presence of the CMA. SALL4 degradation, observed under treatment with CMAs, is responsible (at least partly) for the teratogenicity of the CMAs. Compounds with diminished capability to induce SALL4 degradation may demonstrate an improved safety profile.

The compounds of the present invention may also possess pharmaceutically advantageous properties, such as increased stability and improved ADMET (absorption, distribution, metabolism, excretion, and/or toxicity) properties.

The compounds of the present invention may be useful in the treatment of various diseases and disorders, including (but not limited to):

1) Cancer. The compounds provided herein can be used for treating, preventing or managing either primary or metastatic tumors. Specific examples of cancer include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages, and AIDS-related cancers and hematological malignancies.

   a) Hematological malignancies include leukemia, lymphoma, multiple myeloma or smoldering myeloma.

      - Leukemia can be selected from: acute leukemia, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia, acute myeloid leukemia (AML), adult acute basophilic leukemia, adult acute eosinophilic leukemia, adult acute megakaryoblastic leukemia, adult acute minimally differentiated myeloid leukemia, adult acute monoblastic leukemia, adult acute monocytic leukemia, adult acute myeloblastic leukemia with maturation, adult acute myeloblastic leukemia without maturation, adult acute myeloid leukemia with abnormalities, adult acute myelomonocytic leukemia, adult erythroleukemia, adult pure erythroid leukemia, secondary acute myeloid leukemia, untreated adult acute myeloid leukemia, adult acute myeloid leukemia in remission, adult acute promyelocytic leukemia with PML-RARA, alkylating agent-related acute myeloid leukemia, prolymphocytic leukemia, and chronic myelomonocytic leukemia, refractory hairy cell leukemia, T-cell large granular lymphocyte leukemia, relapsed or refractory chronic lymphocytic leukemia.

      - Lymphoma can be selected from the group consisting of: adult grade III lymphomatoid granulomatosis, adult nasal type extranodal NK/T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, cutaneous B-Cell non- Hodgkin lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, hepatosplenic T-cell lymphoma, intraocular lymphoma, lymphomatous involvement of non- cutaneous extranodal site, mature T-cell and K-

cell non-Hodgkin lymphoma, nodal marginal zone lymphoma, post-transplant lymphoproliferative disorder, recurrent adult Burkitt lymphoma, recurrent adult diffuse large cell lymphoma, recurrent adult diffuse mixed cell lymphoma, recurrent adult diffuse small cleaved cell lymphoma, recurrent adult grade III lymphomatoid granulomatosis, recurrent adult immunoblastic lymphoma, recurrent adult lymphoblastic lymphoma, recurrent adult T-cell leukemia/lymphoma, recurrent cutaneous T-cell non-Hodgkin lymphoma, recurrent grade 1 follicular lymphoma, recurrent grade 2 follicular lymphoma, recurrent grade 3 follicular lymphoma, recurrent mantle cell lymphoma, recurrent marginal zone lymphoma, recurrent mycosis fungoides and Sezary syndrome, recurrent small lymphocytic lymphoma, Richter syndrome, small intestinal lymphoma, splenic marginal zone lymphoma, testicular lymphoma, Waldenstrom macroglobulinemia, adult T-cell leukemia-lymphoma, peripheral T-cell lymphoma, B-cell lymphoma, Hodgkin's disease, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma, MALT lymphoma, mantle cell lymphoma, non-Hodgkins lymphoma, central nervous system lymphoma, refractory primary- cutaneous large B-cell lymphoma (Leg-type), refractory anemia, refractory anemia with excess blasts, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, secondary myelodysplastic syndromes, myelodysplastic syndrome, and myeloproliferative disease.

2) Autoimmune diseases, such as: Acute disseminated encephalomyelitis, acute motor axonal neuropathy, Addison's disease, adiposis dolorosa, adult-onset Still's disease, alopecia areata, ankylosing spondylitis, anti-glomerular basement membrane nephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis, anti-N-methyl-D-aspartate receptor encephalitis, antiphospholipid syndrome, antisynthetase syndrome, aplastic anemia, autoimmune angioedema, autoimmune encephalitis, autoimmune enteropathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune polyendocrine syndrome type 2, autoimmune polyendocrine syndrome type 3, autoimmune progesterone dermatitis, autoimmune retinopathy, autoimmune thrombocytopenic purpura, autoimmune thyroiditis, autoimmune urticaria, autoimmune

uveitis, balo concentric sclerosis, Behçet's disease, Bickerstaff's encephalitis, bullous pemphigoid, celiac disease, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy, churg-Strauss syndrome, cicatricial pemphigoid, cogan syndrome, cold agglutinin disease, complex regional pain syndrome, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, diabetes mellitus type 1, discoid lupus erythematosus, endometriosis, enthesitis, enthesitis-related arthritis, eosinophilic esophagitis, eosinophilic fasciitis, epidermolysis bullosa acquisita, erythema nodosum. essential mixed cryoglobulinemia, evans syndrome, felty syndrome, fibromyalgia, gastritis, gestational pemphigoid, giant cell arteritis, goodpasture syndrome, Graves' disease, graves ophthalmopathy, Guillain–Barré syndrome, hashimoto's encephalopathy, hashimoto thyroiditis, Henoch-Schonlein purpura, hidradenitis suppurativa, idiopathic inflammatory demyelinating diseases, igG4-related systemic disease, inclusion body myositis, inflamatory bowel disease (IBD), intermediate uveitis, interstitial cystitis, juvenile arthritis, kawasaki's disease, Lambert-Eaton myasthenic syndrome, leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus nephritis, lupus vasculitis, lyme disease (Chronic), Ménière's disease, microscopic colitis, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, morphea, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myocarditis, myositis, neuromyelitis optica, neuromyotonia, opsoclonus myoclonus syndrome, optic neuritis, Ord's thyroiditis, palindromic rheumatism, paraneoplastic cerebellar degeneration, Parry Romberg syndrome, Parsonage-Turner syndrome, pediatric autoimmune neuropsychiatric disorder associated with streptococcus, pemphigus vulgaris, pernicious anemia, pityriasis lichenoides et varioliformis acuta, POEMS syndrome, polyarteritis nodosa, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary immunodeficiency, primary sclerosing cholangitis, progressive inflammatory neuropathy, psoriasis, psoriatic arthritis, pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, relapsing polychondritis, restless leg syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, rheumatoid vasculitis, sarcoidosis, Schnitzler syndrome, scleroderma, Sjogren's syndrome, stiff person syndrome, subacute bacterial endocarditis, Susac's syndrome, Sydenham chorea, sympathetic ophthalmia, systemic lupus erythematosus, systemic scleroderma, thrombocytopenia,

Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, urticaria, urticarial vasculitis, vasculitis and vitiligo;

3) Diseases and disorders associated with, or characterized by, undesired angiogenesis, including inflammatory diseases, autoimmune diseases, pain, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to: arthritis, endometriosis, Crohn's disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, and 5q-deletion syndrome, nociceptive pain, neuropathic pain, mixed pain of nociceptive and neuropathic pain, visceral pain, migraine, headache and postoperative pain. Examples of nociceptive pain include, but are not limited to, pain associated with chemical or thermal burns, cuts of the skin, contusions of the skin, osteoarthritis, rheumatoid arthritis, tendonitis, and myofascial pain. Examples of neuropathic pain include, but are not limited to, CRPS type I, CRPS type II, reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, reflex dystrophy, sympathetically maintained pain syndrome, causalgia, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, trigeminal neuralgia, post herpetic neuralgia, cancer related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, spinal cord injury pain, central post-stroke pain, radiculopathy, diabetic neuropathy, post-stroke pain, luetic neuropathy, and other painful neuropathic conditions such as those induced by drugs such as vincristine and velcade;

4) Macular Degeneration ("MD") and related syndromes, such as: atrophic (dry) MD, exudative (wet) MD, age-related maculopathy (ARM), choroidal neovascularisation (CNVM), retinal pigment epithelium detachment (PED), and atrophy of retinal pigment epithelium (RPE);

5) Skin diseases such as: keratoses and related symptoms, skin diseases or disorders characterized with overgrowths of the epidermis, acne, and wrinkles. Examples of skin diseases or disorders characterized with overgrowths of the epidermis include, but are not

limited to, any conditions, diseases or disorders marked by the presence of overgrowths of the epidermis, including but not limited to, infections associated with papilloma virus, arsenical keratoses, sign of Leser-Trélat, warty dyskeratoma (WD), trichostasis spinulosa (TS), erythrokeratodermia variabilis (EKV), ichthyosis fetalis (harlequin ichthyosis), knuckle pads, cutaneous melanoacanthoma, porokeratosis, psoriasis, squamous cell carcinoma, confluent and reticulated papillomatosis (CRP), acrochordons, cutaneous horn, cowden disease (multiple hamartoma syndrome), dermatosis papulosa nigra (DPN), epidermal nevus syndrome (ENS), ichthyosis vulgaris, molluscum contagiosum, prurigo nodularis, and acanthosis nigricans (AN);

6) Pulmonary disorders, such as pulmonary hypertension and related disorders. Examples of pulmonary hypertension and related disorders include, but are not limited to: primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vasular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus including systemic and cutaneous lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis;

7) Asbestos-related disorders, such as: mesothelioma, asbestosis, malignant pleural effusion, benign exudative effusion, pleural plaques, pleural calcification, diffuse pleural thickening, rounded atelectasis, fibrotic masses, and lung cancer;

8) Parasitic diseases and disorders caused by human intracellular parasites such as, but not limited to, P. falcifarium, P. ovale, P. vivax, P. malariae, L. donovari, L. infanium, L. aethiopica,

L. major, L. tropica, L mexicana, L braziliensis, T. Gondii, B. microti, B. divergens, B. coli, C. parvum, C. cayetanensis, E. histolytica, I. belli, S. monsonii, S. haemolobium, Trypanosoma ssp., Toxoplasma ssp.,andO. volvulus.Other diseases and disorders caused by non-human intracellular parasites such as, but not limited to,Babesia bovis, Babesia canis, Banesia Gibsoni, Besnoitia darlingi, Cytauxzoon felis, Eimeria ssp., Hammondia ssp.,andTheileria ssp.,are also encompassed. Specific examples include, but are not limited to, malaria, babesiosis, trypanosomiasis, leishmaniasis, toxoplasmosis, meningoencephalitis, keratitis, amebiasis, giardiasis, cryptosporidiosis, isosporiasis, cyclosporiasis, microsporidiosis, ascariasis, trichuriasis, ancylostomiasis, strongyloidiasis, toxocariasis, trichinosis, lymphatic filariasis, onchocerciasis, filariasis, schistosomiasis, and dermatitis caused by animal schistosomes;

9) Immunodeficiency disorders, which include, but are not limited to, adenosine deaminase deficiency, antibody deficiency with normal or elevated Igs, ataxia-tenlangiectasia, bare lymphocyte syndrome, common variable immunodeficiency, Ig deficiency with hyper-IgM, Ig heavy chain deletions, IgA deficiency, immunodeficiency with thymoma, reticular dysgenesis, Nezelof syndrome, selective IgG subclass deficiency, transient hypogammaglobulinemia of infancy, Wistcott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency;

10) Atherosclerosis and related conditions, such as: all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting;

11) Hemoglobinopathy and related disorders, such as sickle cell anemia, and any other disorders related to the differentiation of CD34+ cells;

12) TNFα related disorders, such as: endotoxemia or toxic shock syndrome; cachexia; adult respiratory distress syndrome; bone resorption diseases such as arthritis; hypercalcemia; Graft versus Host Reaction; cerebral malaria; inflammation; tumor growth; chronic pulmonary inflammatory diseases; reperfusion injury; myocardial infarction; stroke; circulatory shock; rheumatoid arthritis; Crohn's disease; HIV infection and AIDS; other disorders such as rheumatoid arthritis, rheumatoid .spondylitis, osteoarthritis, psoriatic arthritis and other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting,

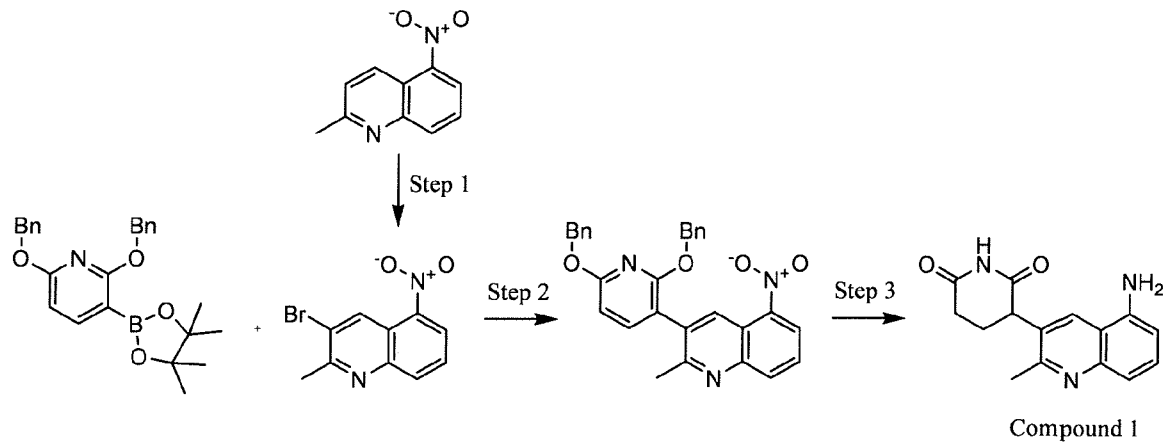
Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythromatosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS; disorders such as septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, radiation damages, and hyperoxic alveolar injury; viral infections, such as those caused by the herpes viruses; viral conjunctivitis; or atopic dermatitis;

The compounds of the present invention may also be useful in preventing, treating, or reducing the risk of developing graft versus host disease (GVHD) or transplant rejection.

The compounds of the present invention may also inhibit the production of certain cytokines including, but not limited to, TNF-α, IL-1β, IL-12, 1L-18, GM-CSF, IL-10, TGF-β and/or IL-6. The present compounds may stimulate the production of certain cytokines, and also act as a costimulatory signal for T cell activation, resulting in increased production of cytokines such as, but not limited to, IL-12, IL-2, IL-10, TGF-β and/or IFN-γ. In addition, compounds provided herein can enhance the effects of NK cells and antibody-mediated cellular cytotoxicity (ADCC). Further, compounds provided herein may be immunomodulatory and/or cytotoxic, and thus may be useful as chemotherapeutic agents.

EXAMPLES

Example 1: Synthesis of 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (Compound 1)



Step 1: Synthesis of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline

2-Methyl-5-nitro-8,8a-dihydroquinoline (19.8 g, 105.3 mmol) was dissolved in dichloromethane (250 mL) and cooled to 5°C in an ice bath. m-CPBA (32.9 g, 133.4 mmol, 70%) was added in portions thereto and the reaction mixture was stirred at room temperature (20-25°C) for 12 hrs. The mixture was washed with 2M NaOH solution (2×150 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to afford a yellow solid (22 g). The solid was dissolved in $CHCl_3$ (200 mL), the obtained solution was cooled to 5°C in the ice-bath, and phosphoryl bromide (62.6 g, 218.3 mmol) in $CHCl_3$ (300 mL) was added dropwise to the reaction mixture. The mixture was stirred at room temperature (20-25°C) for 12 hrs, poured into ice-water, basified to pH=12 with solid potassium carbonate, and extracted with $CHCl_3$ (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by flash column chromatography (eluent Hexane-MTBE 0-100%) to afford 2.9 g of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline (10% yield) as a brown solid.

Step 2: Synthesis of 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline

2,6-Bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4.55 g, 10.9 mmol), tripotassium phosphate (4.8 g, 22.6 mmol), and $Pd(dppf)Cl_2$ CH_2Cl_2 (0.86 g, 1 mmol) were added sequentially to a solution of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline (2.9 g, 10.86 mmol) in 1,4-

dioxane (50 mL) and water (5 mL). The obtained mixture was stirred at 100°C for 12 hrs under an argon atmosphere. The solvents were removed under vacuum, the residue was diluted with EtOAc (100 mL) and filtered through a pad of silica gel. The filtrate was evaporated under vacuum and recrystallized from EtOAc to afford 2.05 g 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline (4.3 mmol, 39% yield) as a pale yellow solid.

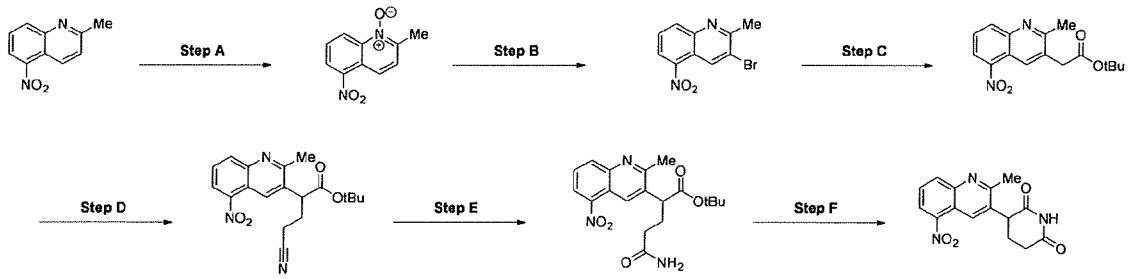
Step 4: Synthesis of 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione

Pd on activated charcoal (1.2 g) was added to a solution of 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline (2.05 g, 4.29 mmol) in THF/methanol (5:1, 300 mL). The reaction mixture was stirred under H_2 atmosphere for 96 hrs. The catalyst was removed by filtration and the filtrate was evaporated under vacuum. The obtained crude product was purified by HPLC (eluent water-acetonitrile) to afford 0.05 g of the target compound 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (4% yield) as a white solid.

^{1}H NMR: (500MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.25 (s, 1H), 7.33 (t, *J*= 7.9 Hz, 1H) 7.07 (d, *J*= 8.2 Hz, 1H), 6.61 (d, *J*= 7.5 Hz, 1H), 5.86 (brs, 2H), 4.25 – 4.17 (m, 1H), 2.89 – 2.79 (m, 1H), 2.69 – 2.61 (m, 1H), 2.59 (s, 3H), 2.46 – 2.36 (m, 1H), 2.15 – 2.08 (m, 1H)

LCMS (m/z $[M+H]^+$): 270.2

Example 2: Synthesis of 3-(2-methyl-5-nitroquinolin-3-yl)piperidine-2,6-dione



Step A: To an ice cold solution of 5-nitro-2-methyl quinoline (2.3 g, 12.22 mmol) in DCM (25 mL) was added *m*-CPBA (2.3 g, 13.67 mmol). The reaction mixture was warmed to RT and stirred for 16

h. The mixture was filtered and filtrates were washed with 1 M KOH solution, dried over Na_2SO_4, and concentrated under reduced pressure to give 2-methyl-5-nitroquinoline 1-oxide (88% yield).

Step B: To an ice cold solution of 2-methyl-5-nitroquinoline 1-oxide (500.0 mg, 2.44 mmol) in DCM (5 mL) was added $POBr_3$ (1.4 g, 4.9 mmol) in DCM (5 mL). The reaction mixture warmed to RT and stirred for 48 h. Ice water was added, the solution was neutralized with 10% NH_3 solution, extracted with DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give 2-methyl-3-bromo-5-nitroquinoline (14% yield).

Step C: To a solution of 2-methyl-3-bromo-5-nitroquinoline (600 mg, 2.24 mmol) in dioxane (8 mL) was added KOAc (441 mg, 4.49 mmol) followed by 1-(*tert*-butyldimethylsilyloxy)-1-*tert*-butoxyethylene (2.07 g, 8.98 mmol) and the reaction mixture was degassed for 15 min under N_2. $Pd[P(o\text{-}Tol)_3]_2Cl_2$ (353.2 mg, 0.449 mmol) was added and the reaction mixture was stirred at 130 °C for 48 h, diluted with ethyl acetate, filtered through celite bed, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 2-(2-methyl-5-nitroquinolin-3-yl)acetate (58% yield).

Step D: To a solution of *tert*-butyl 2-(2-methyl-5-nitroquinolin-3-yl)acetate (200 mg, 0.662 mmol) in DMF (10 mL) were added K_2CO_3 (150.6 mg, 0.662 mmol), benzyltriethylammonium chloride (91.4 mg, 0.662mmol) and acrylonitrile (0.043 mL, 0.662 mmol) and the reaction mixture was stirred at RT for 16h. The reaction mixture was diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give tert-butyl 4-cyano-2-(2-methyl-5-nitroquinolin-3-yl)butanoate (40% yield).

Step E: To an ice cold solution of tert-butyl 4-cyano-2-(2-methyl-5-nitroquinolin-3-yl)butanoate (120.0 mg, 0.338 mmol) in DMSO (5 mL) were added H_2O_2 (0.052 mL,1.688 mmol) and K_2CO_3 (6.533 mg, 0.047 mmol). The reaction mixture warmed to RT and stirred for 16h, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by SFC to give *tert*-butyl 5-amino-2-(2-methyl-5-nitroquinolin-3-yl)-5-oxopentanoate (51% yield).

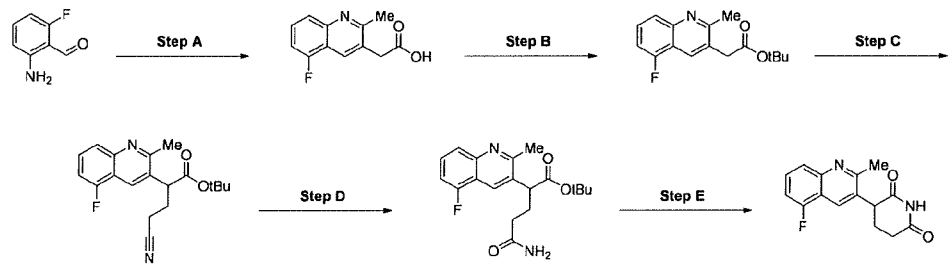
Step F: In a vial were placed *tert*-butyl 5-amino-2-(2-methyl-5-nitroquinolin-3-yl)-5-oxopentanoate (5.0 mg, 0.013 mmol, 1.000 eq), p-toluenesulfonic acid (25.5 mg, 0.134 mmol, 10.000 eq) and acetonitrile (0.5 mL) and the reaction mixture was stirred at 80°C for 2h. The mixture was

concentrated under reduced pressure and purified by HPLC to give 3-(2-methyl-5-nitroquinolin-3-yl)piperidine-2,6-dione (77% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.98 (s, 1H), 8.60 (s, 1H), 8.40 – 8.30 (m, 2H), 7.89 (dd, *J* = 8.5, 7.7 Hz, 1H), 4.42 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.82 (ddd, *J* = 17.8, 12.8, 5.3 Hz, 1H), 2.71 (s, 3H), 2.66 – 2.61 (m, 1H), 2.44 (dd, *J* = 12.8, 4.3 Hz, 1H), 2.14 (ddt, *J* = 10.0, 7.8, 3.9 Hz, 1H).

LCMS (m/z [M+H]$^+$): 299.9

Example 3: Synthesis of 3-(5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione



Step A: To a solution of 2-amino-6-fluorobenzaldehyde (1.0 g, 7.19 mmol) in MeOH (20 mL) was added 4-oxopentanoic acid (0.739 mL, 7.194 mmol) followed by 2M NaOH (5.0 mL). The reaction mixture was refluxed for 18 h, concentrated under reduced pressure, neutralized with acetic acid, the solids were filtered and washed with ether and pentane to give 2-(5-fluoro-2-methylquinolin-3-yl)acetic acid (38%).

Step B: To a solution of DCC (1.036 g, 5.023 mmol) in DCM (5.0 mL) were added DMAP (446 mg, 3.653 mmol) and 2-(5-fluoro-2-methylquinolin-3-yl)acetic acid (1.0 g, 4.566 mmol). *Tert*-butanol (0.406 mL, 13.7 mmol) was added and the reaction mixture was warmed to RT and stirred for 12 h. The reaction mixture was diluted water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 2-(5-fluoro-2-methylquinolin-3-yl)acetate (35% yield).

Step C: To a solution of *tert*-butyl 2-(5-fluoro-2-methylquinolin-3-yl)acetate (500 mg, 1.816 mmol) in DMF (10 mL) were added K_2CO_3 (251 mg, 1.816 mmol), benzyltriethylammonium chloride (413.6 mg, 1.816 mmol) and acrylonitrile (0.119 mL, 1.816 mmol) and the reaction mixture was stirred at RT for 16h. The reaction mixture was diluted with water, extracted with ethyl acetate, dried over

Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 4-cyano-2-(5-fluoro-2-methylquinolin-3-yl)butanoate (50% yield).

Step D: To an ice cold solution of *tert*-butyl 4-cyano-2-(5-fluoro-2-methylquinolin-3-yl)butanoate (500 mg, 1.524 mmol) in DMSO (5 mL) were added H_2O_2 (0.238 mL, 7.77 mmol) and K_2CO_3 (29.5 mg, 0.14 mmol). The reaction mixture warmed to RT and stirred for 16h, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 5-amino-2-(5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (45% yield).

Step E: In a vial were placed *tert*-butyl 5-amino-2-(5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (5.0 mg, 0.014 mmol, 1.000 eq), p-toluenesulfonic acid (27.5 mg, 0.144 mmol, 10.000 eq) and acetonitrile (0.5 mL) and the reaction mixture was stirred at 80°C for 2h. The mixture was concentrated under reduced pressure and purified by HPLC to give 3-(5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (84% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.94 (s, 1H), 8.24 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.70 (td, *J* = 8.2, 6.2 Hz, 1H), 7.37 (dd, *J* = 10.0, 7.6 Hz, 1H), 4.36 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.82 (ddd, *J* = 17.8, 13.2, 5.4 Hz, 1H), 2.68 (s, 3H), 2.61 (dd, *J* = 17.4, 3.5 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.12 (dtd, *J* = 12.8, 5.1, 2.6 Hz, 1H).

LCMS (m/z $[M+H]^+$): 272.9

Example 4: Fluorescence Polarization (FP) Assays

CRBN-DDB1 protein complex was mixed with Cy5-labelled thalidomide and a compound to be tested (the "test compound"). The test solution contained 50 mM Tris pH=7.0, 200 mM NaCl, 0.02 % v/v Tween-20, 2 mM DTT, 5 nM Cy5-labelled thalidomide (the tracer), 25 nM CRBN-DDB1 protein, 2% v/v DMSO. The test solution was added to a 384-well assay plate.

The plate was spun-down (1 min, 1000 rpm, 22°C) and then shaken using a VibroTurbulator for 10 min at room temperature (20-25°C), with the frequency set to level 3. The assay plate with protein and the tracer was incubated for 60 min at room temperature (20-25°C) prior to read-out with a plate reader. Read-out

(fluorescence polarization) was performed by a Pherastar plate reader, using a Cy5 FP Filterset (590nm/675nm).

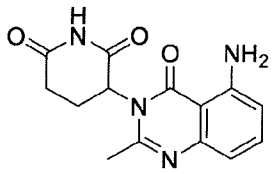
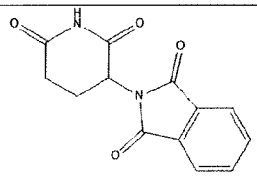
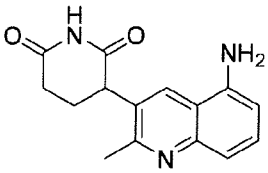
The FP experiment was carried out with various concentrations of the test compounds in order to measure K_i values.

The K_i values of competitive inhibitors were calculated using the equation based on the IC_{50} values of relationship between compound concentration and measured fluorescence polarization, the K_d value of the Cy5-T and CRBN/DDB1 complex, and the concentrations of the protein and the tracer in the displacement assay (as described by Z. Nikolovska-Coleska et al., *Analytical Biochemistry* 332 (2004) 261-273).

Fluorescence Polarization (FP) Assay – Results

Compounds are categorized based on their activity to CRBN defined as Ki:

Table 1: FP assay results for Compound 1 and control compounds CC-122 and Thalidomide

Test compound structure	Test compound name	CRBN binding (Ki)
	CC-122	<5μM
	Thalidomide	<5μM
	Compound 1	<5μM

As can be seen from Table 1, above, compound Compound 1 of the present invention exhibited similar CRBN binding affinity (Ki in the same concentration range) as the reference compounds, CC-122 and Thalidomide.

Example 5: SALL4 degradation assay – Kelly cell line

The effect of various compounds of the invention and various reference compounds on SALL4 degradation in the Kelly cell line was investigated, using the degradation assay protocol below.

Kelly cells were maintained in RPMI-1640 medium, supplemented with penicillin/streptomycin and 10% Fetal Bovine Serum (FBS). Cells were seeded on 6-well plates, and the compounds to be tested were added at the desired concentration range. Final DMSO concentration was 0.25%. After 24h incubation (37°C, 5% CO_2), cells were washed and cell lysates were prepared using RIPA lysis buffer. The amount of protein was determined via BCA assay, and the appropriate quantity was then loaded on the precast gel for the protein separation. After primary and secondary antibody staining, the membranes were washed and signals developed. The densitometry analysis was implemented to obtain the numeric values used later in the protein level evaluation process.

The compounds tested in this assay were Thalidomide, CC-122 and compound 1 of the present invention, at concentrations of 1-20μM for 24h. The results are shown in Figure 1. Densitometry values are normalized to the loading control (β-ACTIN) and presented as % of DMSO control in Table 2, below, using the following labels:

≤ 25% for 0-25% of SALL4 protein reduction,

>25% for 26-74% of SALL4 protein reduction,

≥ 75% for 75-100% of SALL4 protein reduction.

As illustrated in Figure 1, the compounds of the invention induce degradation of SALL4 protein in the Kelly (neuroblastoma) cell line with lower potency than the reference compounds CC-122 and Thalidomide. The compounds of the present invention may therefore be more useful in circumstances where degradation of SALL4 protein is not desired.

TABLE 2: % OF SALL4 PROTEIN REDUCTION IN KELLY CELLS, AFTER 24H			
	At 1μM	At 10μM	At 20μM
CC-122	≥ 75%	≥ 75%	≥ 75%
Compound 1	≤ 25%	> 25%	> 25%
Thalidomide	> 25%	> 25%	≥ 75%

Example 6: IKZF1 degradation assay – H929 cell line

The effect of various compounds of the invention and various reference compounds on IKZF1 degradation in the H929 cell line was investigated, using the degradation assay protocol below.

H929 cells were maintained in RPMI-1640 medium, supplemented with penicillin/streptomycin, 10% Fetal Bovine Serum (FBS) and 0.05 mM 2-Mercaptoethanol. Cells were seeded on 6- or 12-well plates, and the compounds to be tested were added at the desired concentration range. Final DMSO concentration was 0.25%. After 24h incubation (37°C, 5% CO_2), cells were harvested, washed and cell lysates were prepared using RIPA lysis buffer. The amount of protein was determined via BCA assay, and the appropriate quantity was then loaded on the precast gel for the protein separation. After primary and secondary Ab staining, the membranes were washed and signals developed. The densitometry analysis was implemented to obtain the numeric values used later in the protein level evaluation process.

The compounds tested in this assay were Thalidomide, and compound 1 of the present invention, at concentrations of 1-20μM for 24h. The results are shown in Figure 2. Densitometry values are normalized to the loading control (β-ACTIN) and presented as % of DMSO control in Table 3, below, using the following labels:

≤ 25% for 0-25% of IKZF1 protein reduction,

>25% for 26-74% of IKZF1 protein reduction,

≥ 75% for 75-100% of IKZF1 protein reduction.

As illustrated in Figure 2, the compounds of the invention induce degradation of IKZF1 protein in the H929 cell line with higher potency than the reference compound Thalidomide. The compounds of the present invention may therefore be useful as anti-cancer compounds.

TABLE 3: % OF IKZF1 PROTEIN REDUCTION IN H929 CELLS, AFTER 24H			
	At 1μM	At 10μM	At 20μM
Compound 1	> 25%	≥ 75%	≥ 75%
Thalidomide	≤ 25%	≤ 25%	> 25%

Example 7: IKZF3 degradation assay – H929 cell line

The effect of various compounds of the invention and various reference compounds on IKZF3 degradation in the H929 cell line was investigated, using the degradation assay protocol below.

H929 cells were maintained in RPMI-1640 medium, supplemented with penicillin/streptomycin and 10% Fetal Bovine Serum (FBS) and 0.05 mM 2-Mercaptoethanol. Cells were seeded on 6- or 12-well plates, and the compounds to be tested were added at the desired concentration range. Final DMSO concentration was 0.25%. After 24h incubation (37°C, 5% CO_2), cells were harvested, washed and cell lysates were prepared using RIPA lysis buffer. The amount of protein was determined via BCA assay, and the appropriate quantity was then loaded on the precast gel for the protein separation. After primary and secondary Ab staining, the membranes were washed and signals developed. The densitometry analysis was implemented to obtain the numeric values used later in the protein level evaluation process.

The compounds tested in this assay were Thalidomide, and compound 1 of the present invention, at concentrations of 1-20μM for 24h. The results are shown in Figure 3. Densitometry values are normalized to the loading control (β-ACTIN) and presented as % of DMSO control in Tables 4A and 4B, below, using the following labels:

≤ 25% for 0-25% of IKZF3 protein reduction,

>25% for 26-74% of IKZF3 protein reduction,

≥ 75% for 75-100% of IKZF3 protein reduction.

As illustrated in Figure 3, the compounds of the invention induce degradation of IKZF3 protein in the H929 cell line with higher potency than the reference compound Thalidomide. The compounds of the present invention may therefore be useful as anti-cancer compounds.

TABLE 4A: % OF IKZF3 (UPPER BAND) PROTEIN REDUCTION IN H929 CELLS, AFTER 24H			
	At 1μM	At 10μM	At 20μM
Compound 1	> 25%	≥ 75%	≥ 75%
Thalidomide	≤ 25%	≤ 25%	> 25%

TABLE 4B: % OF IKZF3 (BOTTOM BAND) PROTEIN REDUCTION IN H929 CELLS, AFTER 24H			
	At 1μM	At 10μM	At 20μM
Compound 1	> 25%	≥ 75%	≥ 75%
Thalidomide	≤ 25%	≤ 25%	> 25%

Example 8: Viability – CTG assay

The effect of compound 1 of the invention on the viability of H929 (myeloma) was investigated, using the CTG assay protocol below.

Three thousand cells in 50 μL of culture medium were plated in 384-well plate, and incubated with 50, 13, and 2 μM of each compound for 72 hours. ATP content in the remaining cells after the treatment was quantitated with the CellTiter-Glo Luminescent Viability Assay Kit (Promega). The activity of the compound at each concentration was shown as percentage viability; 100% viability was the ATP content in the cells incubated with DMSO, the carrier of the compounds. The results are presented in Table 5.

As can be seen from Table 5, the compounds of the invention may be useful in the treatment of cancer.

TABLE 5: AVERAGE OF % VIABILITY OF QUADRUPLICATE			
	At 2μM	At 13μM	At 50μM
Compound 1	61.2	47.5	32.9

ABBREVIATIONS AND DEFINITIONS

A list of the abbreviations used in the present application is shown in Table 6, below:

Table 6: Abbreviations

Abbreviation	Meaning
CRBN	Cereblon
CRL	Cullin RING Ligase
CMA	Cereblon Modulating Agent
Cy5-T	Cy5-labelled thalidomide
DDB1	damaged DNA binding protein 1
CUL4	Cullin-4
RBX1	RING-Box Protein 1
Bn	benzyl
Tris	Tris(hydroxymethyl)aminomethane
DMSO	Dimethylsulfoxide
THF	tetrahydrofuran
m-CPBA	*meta*-chloroperbenzoic acid
MTBE	methyl tert butyl ether
$Pd(dppf)Cl_2$ CH_2Cl_2	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
DTT	dithiothreitol
NK cells	Natural killer cells
ADCC	antibody-mediated cellular cytotoxicity
GVHD	Graft versus host disease
HPLC	High performance liquid chromatography

BCA	Bicinchoninic acid
RIPA	Radioimmunoprecipitation assay
Ab	Antibody
CTG	CellTiter-Glo
ATP	Adenosine triphosphate

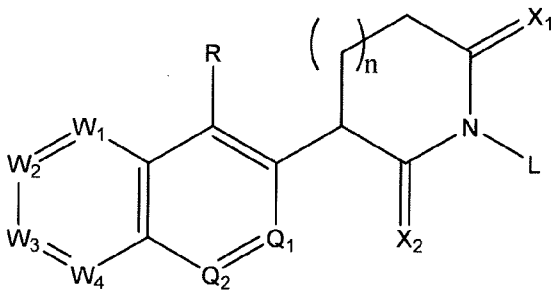
As used herein, the term "room temperature" means a temperature of between 20°C and 25°C.

As used herein, the term "small molecule" means an organic compound with a molecular weight of less than 900 Daltons.

5

CLAIMS

1. A compound of Formula (I):



(I)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR, wherein at least one of Q_1 and Q_2 is N;

each of W_1, W_2, W_3 and W_4 is independently N or CR';

n is 0, 1 or 2;

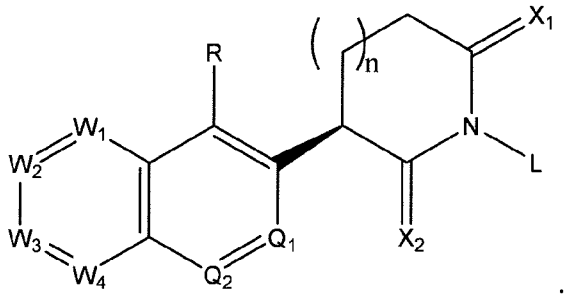
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -NR''_2, or -$S(O)_2R''$;

each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$;

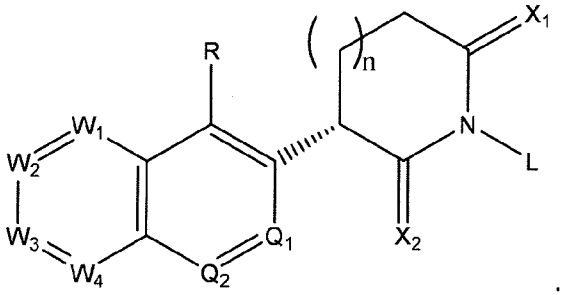
each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

2. The compound of claim 1, having the structure:



3. The compound of claim 1, having the structure:



4. The compound of any preceding claim, wherein one of W_1, W_2, W_3 and W_4 is N, and the remaining three of W_1, W_2, W_3 and W_4 are each CR'.

5. The compound of claim 4, wherein W_1 is N, and W_2, W_3 and W_4 are CR'.

6. The compound of claim 4, wherein W_2 is N, and W_1, W_3 and W_4 are CR'.

7. The compound of claim 4, wherein W_3 is N, and W_1, W_2 and W_4 are CR'.

8. The compound of claim 4, wherein W_4 is N, and W_1, W_2 and W_3 are CR'.

9. The compound of any one of claims 1-3, wherein W_1, W_2, W_3 and W_4 are each CR'.

10. The compound of claim 9, wherein W_2, W_3 and W_4 are each CH.

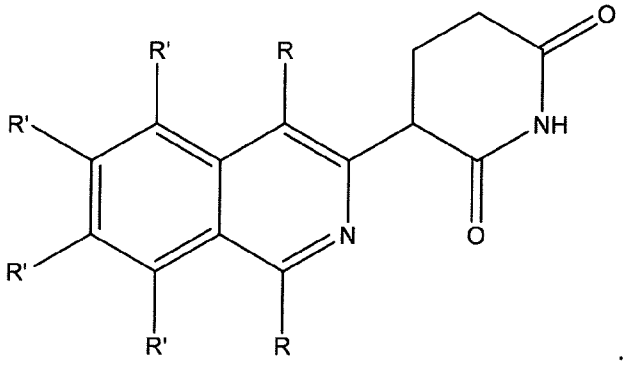
11. The compound of claim 9 or claim 10, wherein W_1 is C-NH_2, C-NHR'' or C-NR''_2; optionally C-NH_2.

12. The compound of any one of claims 1-3, wherein two of W_1, W_2, W_3 and W_4 are N, and the remaining two of W_1, W_2, W_3 and W_4 are each CR'.

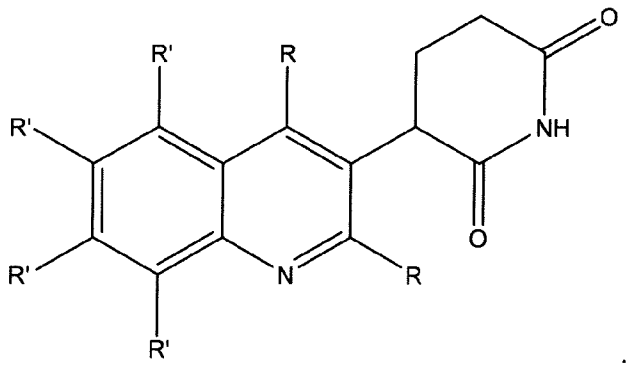
13. The compound of any one of claims 1-3, wherein three of W_1, W_2, W_3 and W_4 are N, and the remaining one of W_1, W_2, W_3 and W_4 is CR'.

14. The compound of any preceding claim, wherein L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', -NR''_2, or -$S(O)_2R''$; optionally wherein L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl; further optionally wherein L is hydrogen.

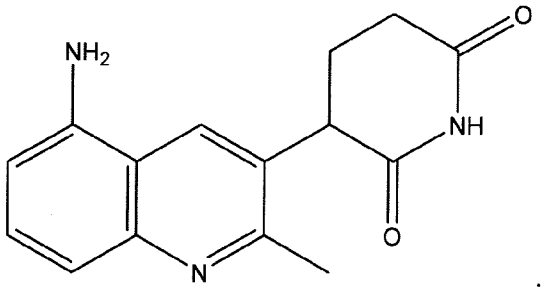
15. The compound of any one of claims 1-3, wherein the compound is:



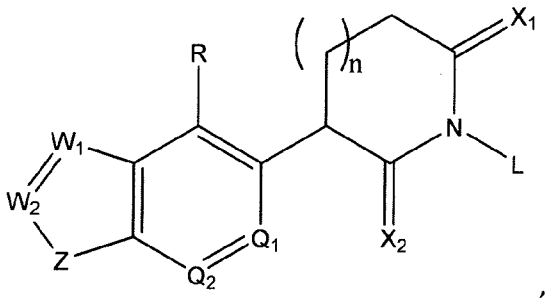
16. The compound of any one of claims 1-3, wherein the compound is:



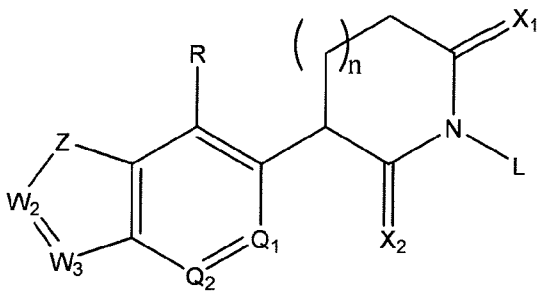
17. The compound of claim 16, wherein the compound is:



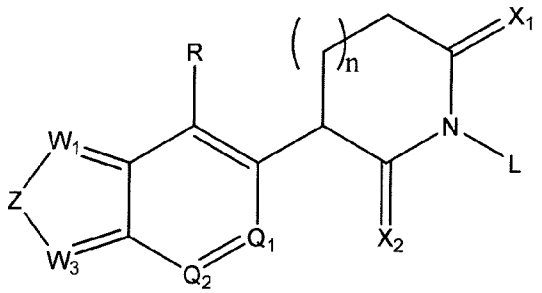
18. A compound of Formula (IIa), (IIb), or (IIc):



(IIa)



(IIb), or



(IIc)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR, wherein at least one of Q_1 and Q_2 is N;

each of W_1, W_2 and W_3 is independently N or CR';

Z is O, S, or NH;

n is 0, 1 or 2;

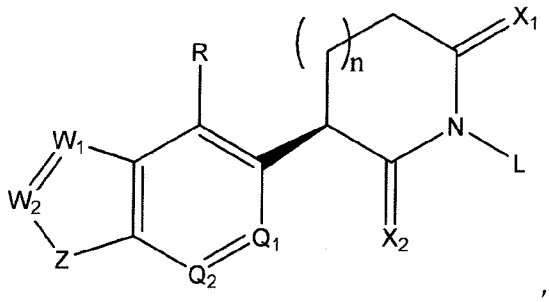
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -NR''_2, or -$S(O)_2R''$;

each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$;

each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

19. The compound of claim 18, having the structure:



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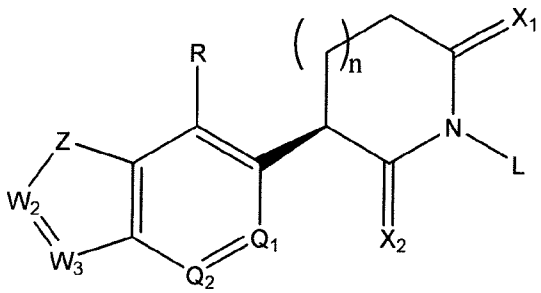
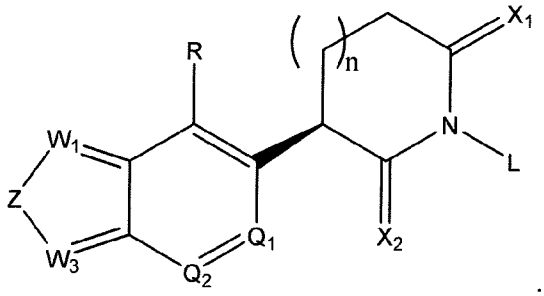
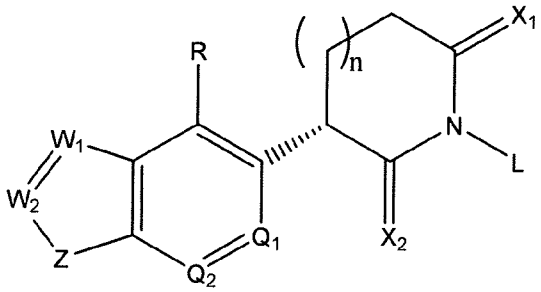


, or

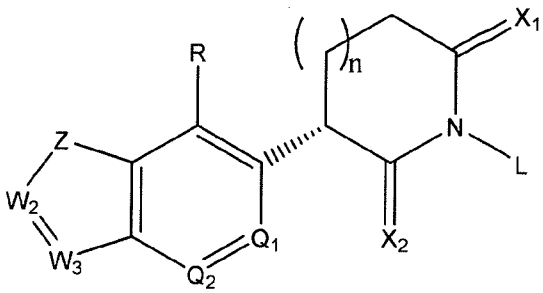


.

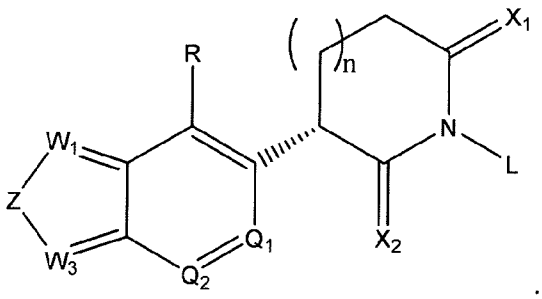
20. The compound of claim 18, having the structure:



,



, or



.

21. The compound of any one of claims 18-20, wherein W_1 is N.

22. The compound of any one of claims 18-21, wherein W_2 is N.

23. The compound of any one of claims 18-22, wherein W_3 is N.

24. The compound of any one of claims 18-23, wherein one of W_1, W_2 and W_3 is N, and the other of W_1, W_2 and W_3 is CR'.

25. The compound of claim 24, wherein one of W_1, W_2 and W_3 is N, and the other of W_1, W_2 and W_3 is CH.

26. The compound of any one of claims 18-25, wherein W_1, W_2 and W_3 are each CR'.

27. The compound of any one of claims 18-25, wherein W_1 is C-NH_2, C-NHR'' or C-NR''_2; optionally C-NH_2.

28. The compound of any one of claims 18-23, wherein W_1, W_2 and W_3 are each N.

29. The compound of any one of claims 18-28, wherein Z is O.

30. The compound of any one of claims 18-28, wherein Z is S.

31. The compound of any one of claims 18-28, wherein Z is NH.

32. The compound of any preceding claim, wherein Q_1 is N and Q_2 is CR.

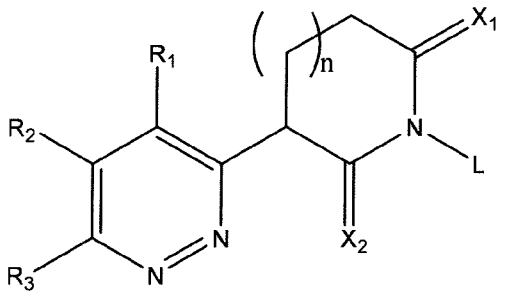
33. The compound of any one of claims 1-31, wherein Q_1 is CR and Q_2 is N.

34. The compound of any one of claims 1-31, wherein Q_1 is N and Q_2 is N.

35. The compound of any preceding claim, wherein each R is independently hydrogen or alkyl; optionally hydrogen or C_1-C_4 alkyl; further optionally wherein the C_1-C_4 alkyl is methyl or ethyl; further optionally wherein each R is independently hydrogen or methyl.

36. The compound of any preceding claim, wherein each R' is independently hydrogen, $-NH_2$, -NHR'' or $-NR''_2$; optionally hydrogen or $-NH_2$.

37. A compound of Formula (III):



(III)

wherein

each of X_1 and X_2 is independently O or S;

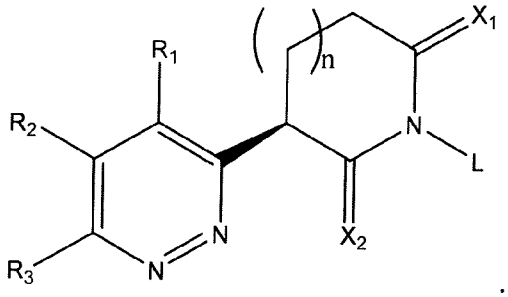
n is 0, 1 or 2;

L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -NR''_2, or -$S(O)_2R''$;

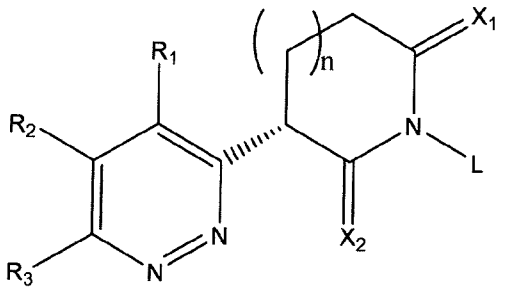
each of R_1, R_2 and R_3 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OR'', -OC(O)R'', -OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SR'' , $S(O)_2R''$, -$S(O)_2OR''$, -$S(O)_2NH_2$, -$S(O)_2NHR''$, or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

38. The compound of claim 37, having the structure:



39. The compound of claim 37, having the structure:



40. The compound of any preceding claim, wherein X_1 and X_2 are O.

41. The compound of any one of claims 1-39, wherein X_1 is O and X_2 is S.

42. The compound of any one of claims 1-39, wherein X_1 is S and X_2 is O.

43. The compound of any one of claims 1-39, wherein X_1 and X_2 are S.

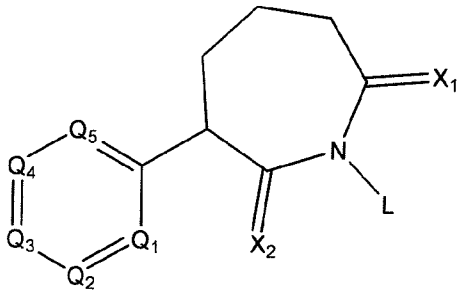
44. The compound of any preceding claim, wherein n is 0.

45. The compound of any one of claims 1-43, wherein n is 1 or 2.

46. The compound of any one of claims 1-43, wherein n is 1.

47. The compound of any one of claims 1-43, wherein n is 2.

48. A compound of formula (IV):



(IV)

wherein

each of X_1 and X_2 is independently O or S;

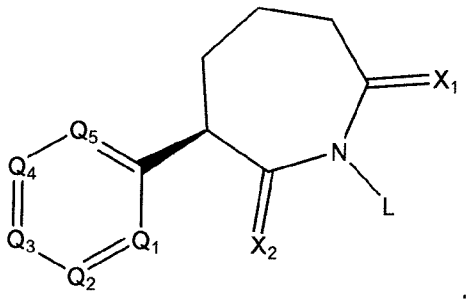
L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -NR''_2, or -$S(O)_2$R'';

each of Q_1, Q_2, Q_3, Q_4 and Q_5 is independently N or CR, wherein at least one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N;

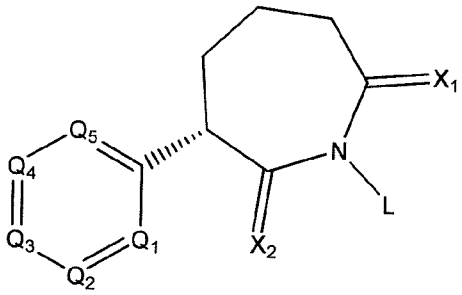
each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NR''C(O)R'', -NR''C(O)OR'', -NO_2, -CN, -C(O)R'', -C(O)OR'', -$C(O)NH_2$, -C(O)NHR'', -$C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', -$OC(O)NH_2$, -OC(O)NHR'', -$OC(O)NR''_2$, -SR'', -$S(O)_2$R'', -$S(O)_2$OR'', -$S(O)_2NH_2$, -$S(O)_2$NHR'', or -$S(O)_2NR''_2$; and

each R'' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

49. The compound of claim 48, having the structure:



50. The compound of claim 48, having the structure:



51. The compound of any one of claims 48-50, wherein X_1 and X_2 are O.

52. The compound of any one of claims 48-50, wherein X_1 is O and X_2 is S.

53. The compound of any one of claims 48-50, wherein X_1 is S and X_2 is O.

54. The compound of any one of claims 48-50, wherein X_1 and X_2 are S.

55. The compound of any one of claims 48-54, wherein one of Q_1, Q_2, Q_3, Q_4 and Q_5 is N, and the remaining four of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR.

56. The compound of claim 55, wherein Q_1 is N.

57. The compound of claim 55, wherein Q_2 is N.

58. The compound of claim 55, wherein Q_3 is N.

59. The compound of any one of claims 48-54, wherein two of Q_1, Q_2, Q_3, Q_4 and Q_5 are N, and the remaining three of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR.

60. The compound of claim 59, wherein Q_1 and Q_2 are N, and Q_3, Q_4 and Q_5 are each CR.

61. The compound of claim 59, wherein Q_2 and Q_3 are N, and Q_1, Q_4 and Q_5 are each CR.

62. The compound of claim 59, wherein Q_1 and Q_3 are N, and Q_2, Q_4 and Q_5 are each CR.

63. The compound of claim 59, wherein Q_2 and Q_4 are N, and Q_1, Q_3 and Q_5 are each CR.

64. The compound of claim 59, wherein Q_1 and Q_4 are N, and Q_2, Q_3 and Q_5 are each CR.

65. The compound of any one of claims 48-54, wherein three of Q_1, Q_2, Q_3, Q_4 and Q_5 are N, and the remaining two of Q_1, Q_2, Q_3, Q_4 and Q_5 are each CR.

66. The compound of any one of claims 48-65, wherein each R is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NR''C(O)R'', -NR''C(O)OR'', $-NO_2$, -CN, -C(O)R'', -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OR'', -OC(O)R'', -OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SR'', $S(O)_2R''$; optionally wherein each R is hydrogen or alkyl, further optionally wherein each R is hydrogen.

67. The compound of any one of claims 18-66, wherein L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -OR'', $-NR''_2$, or $-S(O)_2R''$; optionally wherein L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl.

68. The compound of claim 67, wherein L is hydrogen.

69. A compound of any one of the preceding claims, for use as a cereblon binder.

70. A pharmaceutical composition comprising a compound of any one of claims 1-68.

71. A compound of any one of claims 1-68, or a composition according to claim 70, for use in medicine.

72. A compound of any one of claims 1-68, or a composition according to claim 70, for use in immune-oncology.

73. A compound of any one of claims 1-68, or a composition according to claim 70, for use in the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders.

74. A method for the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders;

wherein the method comprises administering to a patient in need thereof an effective amount of compound of any one of claims 1-68 or a composition according to claim 70.

75. The method of claim 74, further comprising administering at least one additional active agent to the patient.

76. A combined preparation of a compound of any one of claims 1-68 and at least one additional active agent, for simultaneous, separate or sequential use in therapy.

77. The combined preparation of claim 76, or the method of claim 75, wherein the at least one additional active agent is an anti-cancer agent or an agent for the treatment of an autoimmune disease.

78. The combined preparation of any one of claims 76-77, or the method of claim 75 or 77, wherein the at least one additional active agent is a small molecule, peptide, an antibody, a corticosteroid, or a combination thereof.

79. The combined preparation or method of claim 78, wherein the at least one additional active agent is at least one of bortezomib, dexamethasone, and rituximab.

80. The combined preparation of any one of claims 76-79, wherein the therapy is the treatment of cancer, autoimmune diseases, macular degeneration (MD) and related disorders, diseases and disorders associated with undesired angiogenesis, skin diseases, pulmonary disorders, asbestos-related disorders, parasitic diseases and disorders, immunodeficiency disorders, atherosclerosis and related conditions, hemoglobinopathy and related disorders, or TNFα related disorders.

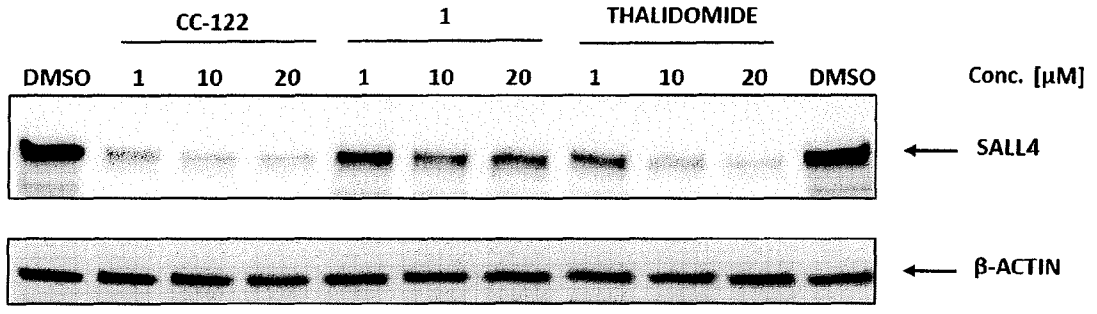

CC-122
1
THALIDOMIDE
DMSO
1
10
20
1
10
20
1
10
20
DMSO
Conc. [µM]
SALL4
β-ACTIN

FIGURE 1

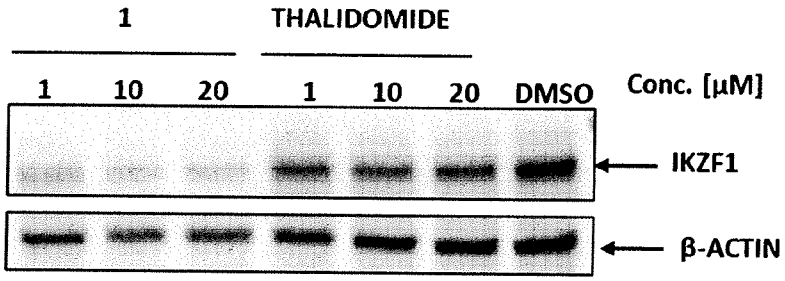


FIGURE 2

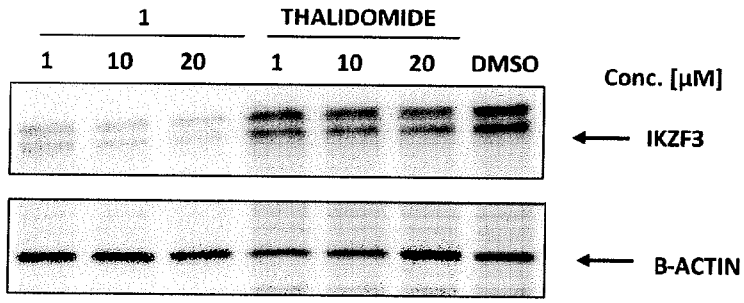


FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2020/000099

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/4709 A61P35/00 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/197046 A1 (C4 THERAPEUTICS INC [US]) 16 November 2017 (2017-11-16) pages 298-352; compounds 26-43, 46-49, 51-59, 61-64, especially compounds 34, 35, 40, 48, 56, 57; pages 109-115; page 14, line 24 - page 17, line 11; claims 3, 4, 13, 14; compounds III, IV, VI -----	1-80
A	WO 2015/200795 A1 (CELGENE CORP [US]) 30 December 2015 (2015-12-30) the whole document compound A -----	1-80

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2021	11/11/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

International application No.
PCT/PL2020/000099

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17(completely); 32-36, 40-47, 69-80(partially)

   concerning compounds of formula I

   ---

2. claims: 18-31(completely); 32-36, 40-47, 67-80(partially)

   concerning compounds of formulae IIa, IIb and IIc

   ---

3. claims: 37-39(completely); 40-47, 67-80(partially)

   concerning compounds of formula III

   ---

4. claims: 48-66(completely); 67-80(partially)

   concerning compounds of formula IV

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2020/000099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017197046 A1	16-11-2017	CN 109641874 A	16-04-2019
		EP 3455218 A1	20-03-2019
		US 2019076542 A1	14-03-2019
		WO 2017197046 A1	16-11-2017
WO 2015200795 A1	30-12-2015	EP 3160486 A1	03-05-2017
		EP 3827836 A1	02-06-2021
		ES 2843973 T3	21-07-2021
		JP 6640126 B2	05-02-2020
		JP 2017528690 A	28-09-2017
		US 2015374678 A1	31-12-2015
		US 2019030019 A1	31-01-2019
		US 2021000813 A1	07-01-2021
		WO 2015200795 A1	30-12-2015