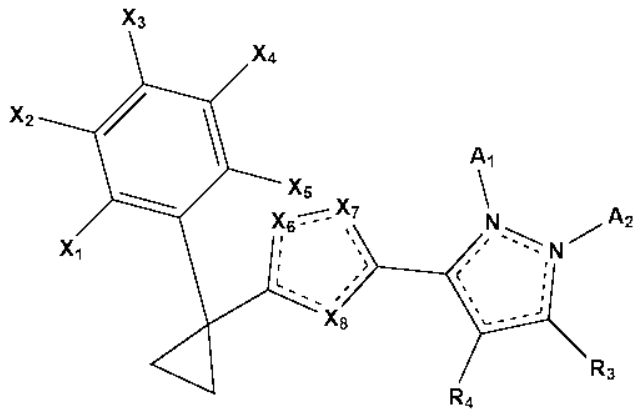
and the development of disease. Regulation of metabolic mechanisms, including oxidative phosphorylation, with POLRMT modulators affords an opportunity for intervention in complex disorders. In view of the numerous and varied roles of POLRMT, the need exists for potent and specific modulators of POLRMT.

SUMMARY

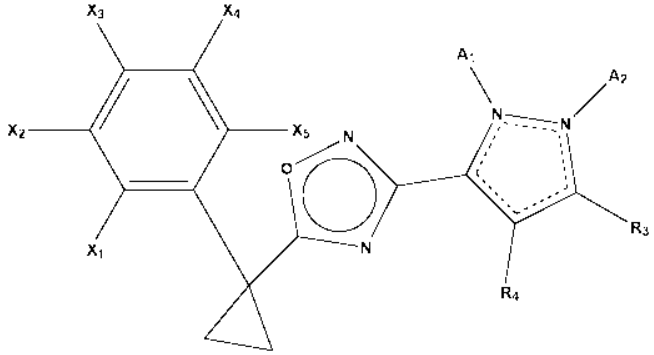
[0005] Briefly, therefore, the present disclosure is directed to compounds, pharmaceutically acceptable salts of the compounds, and methods of using the compounds, salts of the compounds to treat various neurodegenerative and metabolic disorders, cancer, and also disorders related to aging and mitochondrial diseases.

[0006] In an example of the present disclosure, the present disclosure provides a compound, which, according to an example of the present disclosure is a compound represented by Formula (I),



Formula (I).

[0006a] In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (III):



wherein

X_1-X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1-C_6 alkyl, a substituted C_1-C_6 alkyl, a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, a C_1-C_6 alkoxy, optionally substituted with an aryl, a C_3-C_{10} cycloalkyl, -$C(O)NH_2$, -$C(O)NHY^1$, -$C(O)NY^1Y^2$, -COOH, -$C(O)OY^1$, -Y^1COOH, or -Y^1OY^2;

Y^1 and Y^2 are each independently a C_1-C_6 alkyl optionally substituted with one or more halogen or hydroxy;

A_1 and A_2 are each independently a hydrogen, a C_1-C_6 alkyl, a substituted C_1-C_6 alkyl, an aryl, substituted aryl, a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, a C_3-C_6 heterocyclyl, substituted C_3-C_6 heterocyclyl, or absent;

wherein A_1 and A_2 may be optionally substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, -$C(O)NH_2$, -$CS(O)_2Y^3$, a -$CY^1S(O)_2Y^3$;

Y^3 is independently a hydrogen or a C_1-C_4 alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C_1-C_4 haloalkoxyl, and a C_1-C_4 alkoxyl;

R_3 is a halogen, a hydrogen, a C_1-C_6 alkyl, a C_1-C_6 alkyl substituted with one or more halogen, or a C_3-C_6 cycloalkyl; and

R_4 is a hydrogen, a C_1-C_6 alkyl, or a C_1-C_6 alkyl substituted with one or more halogen;

if R_3 and R_4 are optionally interconnected they form a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

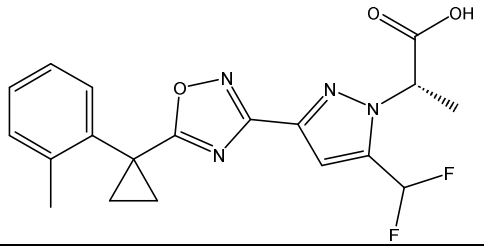
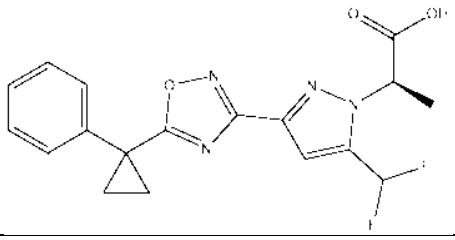
[0007] In some examples, X_1-X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1-C_6 alkyl, a substituted C_1-C_6 alkyl, a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, a C_1-C_6 alkoxy, optionally substituted with an aryl, a C_3-C_{10} cycloalkyl, -$C(O)NH_2$, -$C(O)NHY^1$, -$C(O)NY^1Y^2$, -COOH, -$C(O)OY^1$, -Y^1COOH, or -Y^1OY^2.

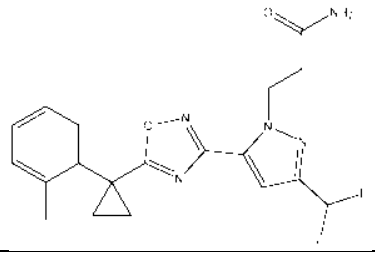
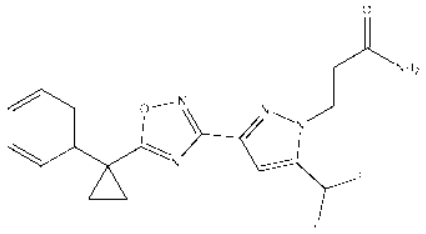
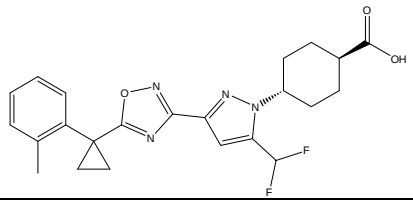
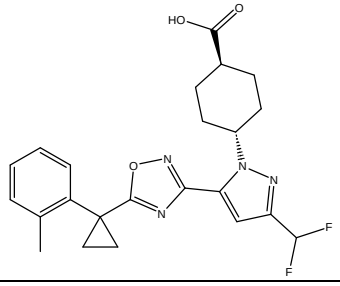
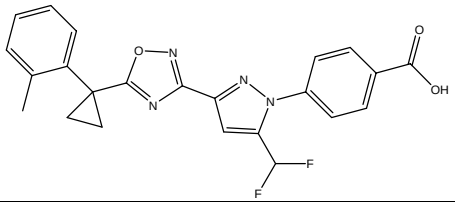
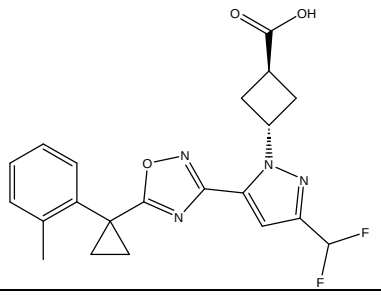
[0008] In some examples, Y^1 and Y^2 are each independently a C_1-C_6 alkyl optionally substituted with one or more halogen or hydroxy.

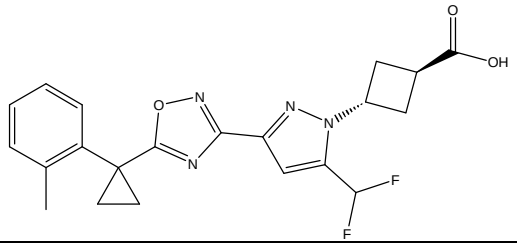
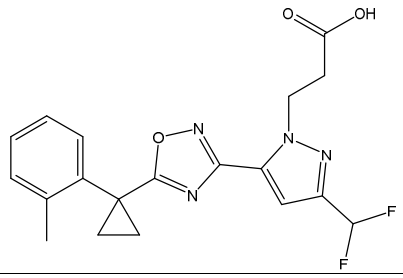
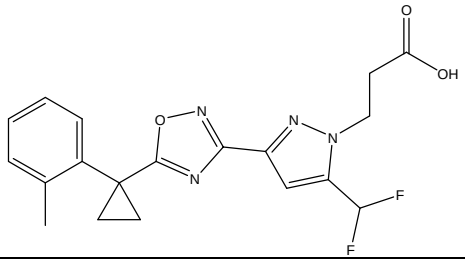
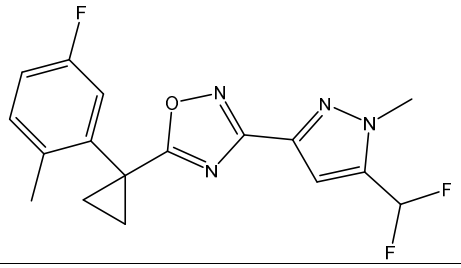
[0009] In some examples, X_6-X_8 are each independently a C, N, S, or O.

[0010] In some examples, R_3 is a halogen, a hydrogen, a C_1-C_6 alkyl, a C_1-C_6 alkyl substituted with one or more halogen, or a C_3-C_6 cycloalkyl.

[0011] In some examples, R_4 is a hydrogen, a C_1-C_6 alkyl, or a C_1-C_6 alkyl substituted with one or more halogen.
[0012] In some examples, if R_3 and R_4 are optionally interconnected they form a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.
[0013] In some examples, A_1 and A_2 are each independently a hydrogen, a C_1-C_6 alkyl, a substituted C_1-C_6 alkyl, an aryl, substituted aryl, a C_3-C_6 cycloalkyl, a substituted C_3-C_6 cycloalkyl, a C_3-C_6 heterocyclyl, substituted C_3-C_6 heterocyclyl, or absent.
[0014] In some examples, A_1 and A_2 may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$.
[0015] In some examples, Y^3 is independently hydrogen or C_1-C_4 alkyl optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, C_1-C_4 haloalkoxyl, and C_1-C_4 alkoxyl.
[0016] Some examples of the present disclosure include compounds described above, wherein the compound has a POLRMT IC_{50} of 200 nM or less.
[0017] Some examples of the present disclosure include a pharmaceutical composition comprising a compound according to any of the previous claims.
[0017a] In one aspect, the present disclosure refers to a composition comprising one of the following compounds:

Compound	**Structure**
Compound 318	
Compound 321	

Compound 322	
Compound 323	
Compound 339	
Compound 340	
Compound 341	
Compound 342	

Compound 343	
Compound 344	
Compound 345	
Compound 287	

[0018] Some examples of the present disclosure are directed towards a method of inhibiting the activity of POLRMT comprising administering a compound of any of the previous claims to a subject in need thereof.
[0019] Other examples and iterations of the present disclosure are detailed below.

DETAILED DESCRIPTION OF THE INVENTION
[0020] Modulators of POLRMT are useful in compositions and methods suitable for treating many disorders, such as cancer, neurodegenerative disorders, metabolic disorders, as well as diseases related to aging and mitochondrial diseases. Provided herein are novel compositions, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. Provided herein are compounds of Formulae (I), (IIa), (IIa-2), (IIb-1), (IIb-2)a, (IIc), (IIc-1), (IIc-2a), (IIc-2b), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), (Va), (Va-1), (Vb), and (Vb-1) pharmaceutically acceptable salts thereof, prodrugs thereof, and pharmaceutical compositions comprising such compounds, their salts, or their prodrugs that are useful as inhibitors of POLRMT.