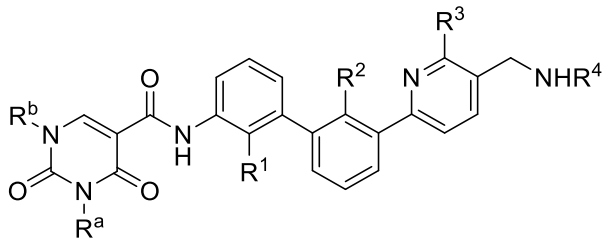
[0006] Agents that block the interaction of PD-L1 with either PD-1 or CD80 are desired. Some antibodies have been developed and commercialized. A few patent applications disclosing non-peptidic small molecules have been published (WO 2015/160641, WO 2015/034820, and WO 2017/066227 and WO2018/009505 from BMS; WO 2015/033299 and WO 2015/033301 from Aurigene; WO 2017/070089, US 2017/0145025, WO 2017/106634,US2017/0174679, WO2017/192961, WO2017/222976, WO2017/205464, WO2017/112730, WO2017/041899 and WO2018/013789 from Incyte, WO2018/006795 from Maxinovel and WO2018/005374 from us, ChemoCentryx). However there is still a need for alternative compounds such as small molecules as inhibitors of PD-L1, and which may have advantageous characteristics in term of oral administration, increased tumor penetration, stability, bioavailability, therapeutic index, and toxicity.

BRIEF SUMMARY OF THE DISCLOSURE

[0006a] In an aspect, there is provided a use of an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a cancer selected from the group consisting of colon cancer, renal cancer, colorectal cancer, gastric cancer, bladder cancer, melanoma, non-small cell lung cancer, Merkel cell carcinoma, liver cancer, breast cancer, and cancer of the head or neck, wherein:

R^1 and R^2 are each independently selected from the group consisting of F, Cl, CH_3, and CF_3;

R^3 is selected from the group consisting of F, Cl, CH_3, CF_3, –O–CH_3, and –O–CF_3;

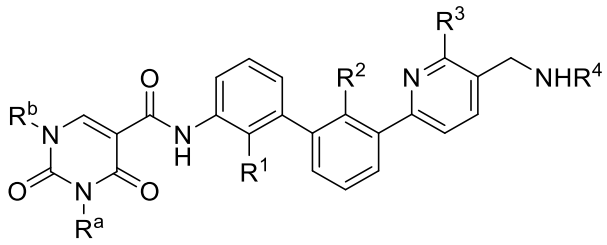
R^4 is selected from the group consisting of –Y and –X^1–Y, wherein each X^1 is C_{1-4} alkylene, and

Y is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl having 1 to 3 heteroatom ring vertices independently selected from the group consisting of N, O, and S, and 5- to 6-membered heteroaryl having 1 to 3 heteroatom ring vertices independently selected from the group consisting of N, O, and S, each of which is

unsubstituted or substituted with one to two substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and C_{1-4} hydroxyalkoxy; and

R^a and R^b are independently selected from the group consisting of H, C_{1-3} alkyl, and C_{1-4} haloalkyl.

[0007] In some ~~aspects~~examples, provided herein are methods of treating a cancer comprising administering to a subject in need thereof an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^a, and R^b are as described herein.

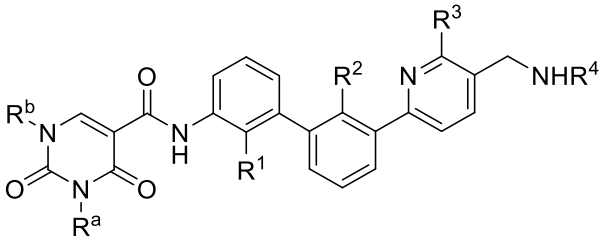
[0008] In some ~~embodiments~~ examples the cancer is selected from the group consisting of colon cancer, renal cancer, colorectal cancer, gastric cancer, bladder cancer, melanoma, non-small cell lung cancer, Merkel cell carcinoma, liver cancer, breast cancer, and cancer of the head or neck.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1A-B** plots the PD1/PD-L1 binding ELISA data (upper panel) and PD-1/PD-L1 Blockade Cell-based assay data (lower panel) for Compounds 2.001 (**A**) and 2.002 (**B**).

WHAT IS CLAIMED IS:

1. ~~A method of treating a cancer selected from the group consisting of colon cancer, renal cancer, colorectal cancer, gastric cancer, bladder cancer, melanoma, non-small cell lung cancer, Merkel cell carcinoma, liver cancer, breast cancer, and cancer of the head or neck comprising administering to a subject in need thereof~~ Use of an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a cancer selected from the group consisting of colon cancer, renal cancer, colorectal cancer, gastric cancer, bladder cancer, melanoma, non-small cell lung cancer, Merkel cell carcinoma, liver cancer, breast cancer, and cancer of the head or neck, wherein:

R^1 and R^2 are each independently selected from the group consisting of F, Cl, CH_3, and CF_3;

R^3 is selected from the group consisting of F, Cl, CH_3, CF_3, –O–CH_3, and –O–CF_3;

R^4 is selected from the group consisting of –Y and –X^1–Y, wherein each X^1 is C_{1-4} alkylene ~~and~~, and Y is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl having 1 to 3 heteroatom ring vertices independently selected from the group consisting of N, O, and S, and 5- to 6-membered heteroaryl having 1 to 3 heteroatom ring vertices independently selected from the group consisting of N, O, and S, each of which is unsubstituted or substituted with one to two substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and C_{1-4} hydroxyalkoxy; and

R^a and R^b are independently selected from the group consisting of H, C_{1-3} alkyl, and C_{1-4} haloalkyl.

2. The ~~method~~ use of claim 1, wherein the effective amount ~~of a compound of Formula (I)~~ is to be administered orally.

3. The ~~method~~ use of claim 1 or claim 2, wherein R^1 is selected from the group consisting of Cl and CH_3.

4. The ~~method~~ use of claim 1 or claim 2, wherein R^1 is Cl.

5. The ~~method~~ use of claim 1 or claim 2, wherein R^1 is CH_3.

6. The ~~method~~ use of any one of claims 1 to 5, wherein R^2 is selected from the group consisting of Cl and CH_3.

7. The ~~method~~ use of any one of claims 1 to 5, wherein R^2 is Cl.

8. The ~~method~~ use of any one of claims 1 to 5, wherein R^2 is CH_3.

9. The ~~method~~ use of any one of claims 1 to 8, wherein R^3 is selected from the group consisting of –O–CH_3 and –O–CF_3.

10. The ~~method~~ use of any one of claims 1 to 8, wherein R^3 is –O–CH_3.

11. The ~~method~~ use of any one of claims 1 to 8, wherein R^3 is –O–CF_3.

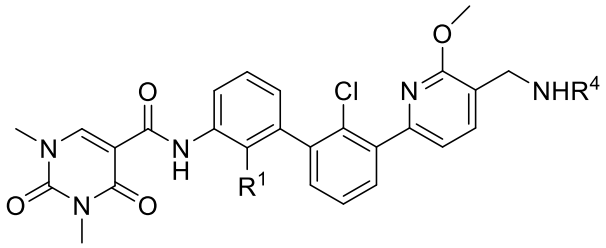
12. The ~~method~~ use of any one of claims 1 to 11, wherein R^a is selected from the group consisting of H, CH_3, and CF_3.

13. The ~~method~~ use of any one of claims 1 to 11, wherein R^a is CH_3.

14. The ~~method~~ use of any one of claims 1 to 13, wherein R^b is selected from the group consisting of H, CH_3, and CF_3.

15. The ~~method~~ use of any one of claims 1 to 13, wherein R^b is CH_3.

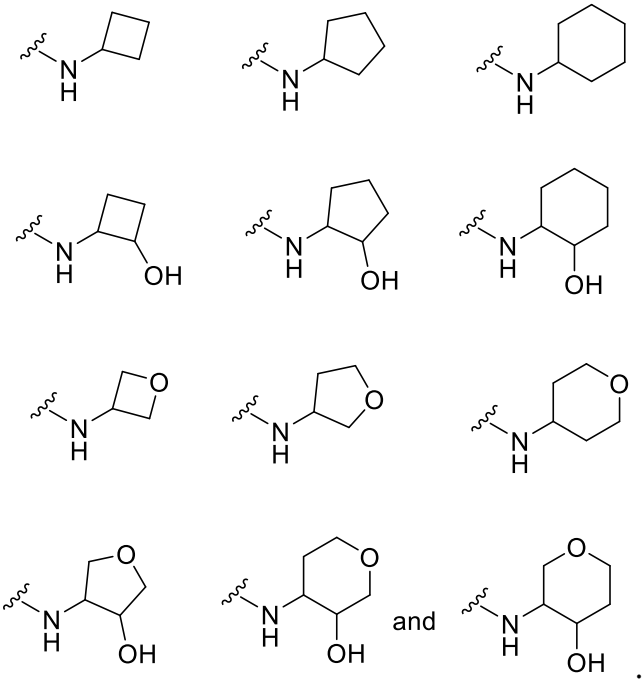
16. The ~~method~~ use of any one of claims 1 to 5, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a compound of~~has the~~ Formula (Ia):



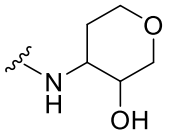
(Ia)

or a pharmaceutically acceptable salt thereof.

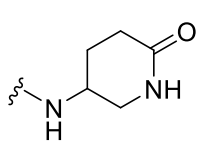
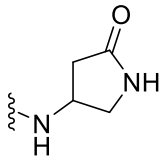
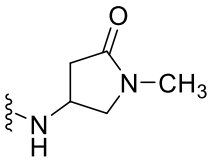
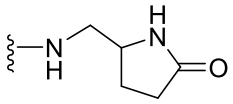
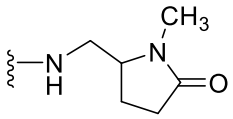
17. The ~~method~~ use of any one of claims ~~-~~1 to 16, wherein –NH(R^4) is selected from the group consisting of:



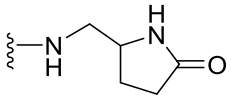
18. The ~~method~~ use of any one of claims ~~-~~1 to 16, wherein –NH(R^4) is selected from the group consisting of:



19. The ~~method~~ use of any one of claims ~~-~~1 to 16, wherein –NHR^4 is selected from the group consisting of:

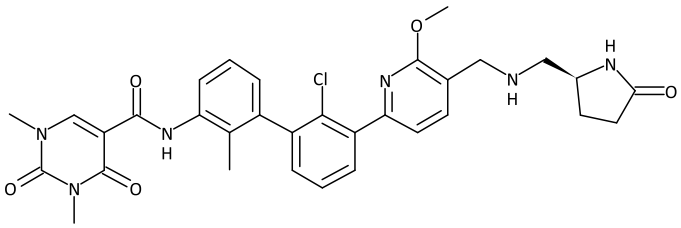




and

.

20. The ~~method~~ use of any one of claims 1 to 16, wherein –NHR^4 is

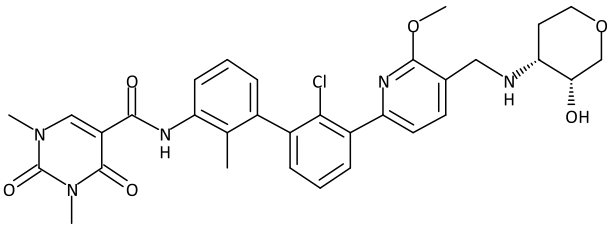

.

21. The ~~method~~ use of any one of claims 1 to 20, wherein the compound of Formula (I) is an optically pure or enriched isomer.

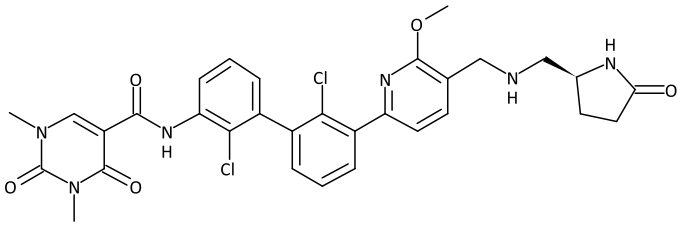
22. The ~~method~~ use of claim 1, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is


or a pharmaceutically acceptable salt thereof.~~is selected from a compound in Table 1.~~

23. The use of claim 1, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is


or a pharmaceutically acceptable salt thereof.

24. The use of claim 1, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is



or a pharmaceutically acceptable salt thereof.

~~23.~~25. The ~~method~~ use of any one of claims 1 to ~~22~~24, wherein the effective amount ~~of Formula (I)~~ maintains a trough blood plasma concentration from about 2 ng/mL to about 1,000 ng/mL.

~~24.~~26. The ~~method~~ use of any one of claims 1 to ~~22~~24, wherein the effective amount ~~of Formula (I)~~ maintains a trough blood plasma concentration from about 5 ng/mL to about 500 ng/mL.

~~25.~~27. The ~~method~~ use of any one of claims 1 to ~~22~~24, wherein the effective amount ~~of Formula (I)~~ maintains a trough blood plasma concentration from about 20 ng/mL to about 300 ng/mL.

~~26.~~28. The ~~method~~ use of any one of claims 1 to ~~22~~24, wherein the effective amount ~~of Formula (I)~~ maintains a trough blood plasma concentration from about 30 ng/mL to about 200 ng/mL.

~~27.~~29. The ~~method~~ use of any one of claims 1 to ~~26~~28, wherein the ~~disease or disorder~~cancer is colon cancer.

~~28.~~30. The ~~method~~ use of any one of claims 1 to ~~26~~28, wherein the ~~disease or disorder~~cancer is colorectal cancer.

~~29.~~31. The ~~method~~ use of any one of claims 1 to ~~26~~28, wherein the ~~disease or disorder~~cancer is breast cancer.

~~30.~~32. The ~~method~~ use of any one of claims 1 to ~~26~~28, wherein the ~~disease or disorder~~cancer is liver cancer.

~~31.~~33. The ~~method~~ use of any one of claims 1 to ~~26~~28, wherein the ~~disease or disorder~~cancer is melanoma.

~~32.~~34. The ~~method~~ use of any one of claims 1 to ~~31~~33, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered with~~further comprising administering to the subject~~ an effective amount of one or more additional therapeutic agent(s).

~~33.~~35. The ~~method~~ use of claim ~~32~~34, wherein the one or more additional therapeutic agent(s) is selected from the group consisting of a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-proliferation agent.