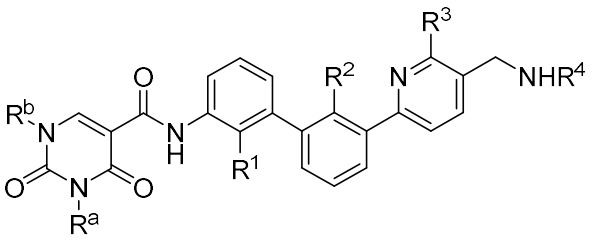
[0006] Agents that block the interaction of PD-L1 with either PD-1 or CD80 are desired. Some antibodies have been developed and commercialized. A few patent applications disclosing non-peptidic small molecules have been published (WO 2015/160641, WO 2015/034820, and WO 2017/066227 and WO2018/009505 from 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 use in slowing tumor growth, inhibiting tumor growth, and/or reducing tumor size in a subject suffering from 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:

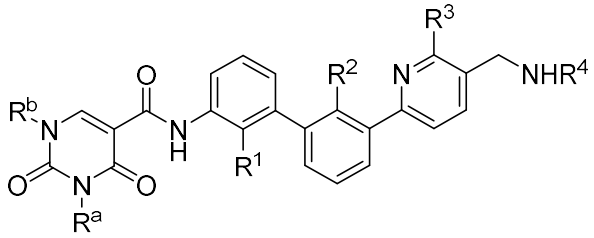
R^1 and R^2 are each independently selected from the group consisting of F, Cl, CH_3, and CF_3;

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

WHAT IS CLAIMED IS:

1. 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 use in slowing tumor growth, inhibiting tumor growth, and/or reducing tumor size in a subject suffering from 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.

2. The use of claim 1, wherein the effective amount is to be administered orally.

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

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

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

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

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

9. The 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 use of any one of claims 1 to 8, wherein R^3 is $–O–CH_3$.

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

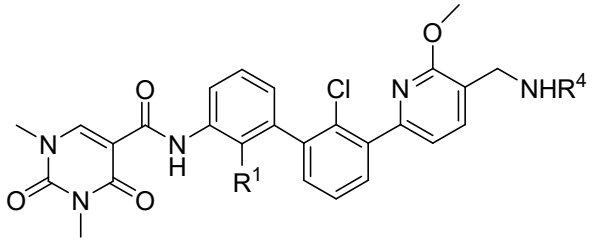
12. The use of any one of claims 1 to 11, wherein R^a is selected from the group consisting of H, CH_3, and CF_3.

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

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

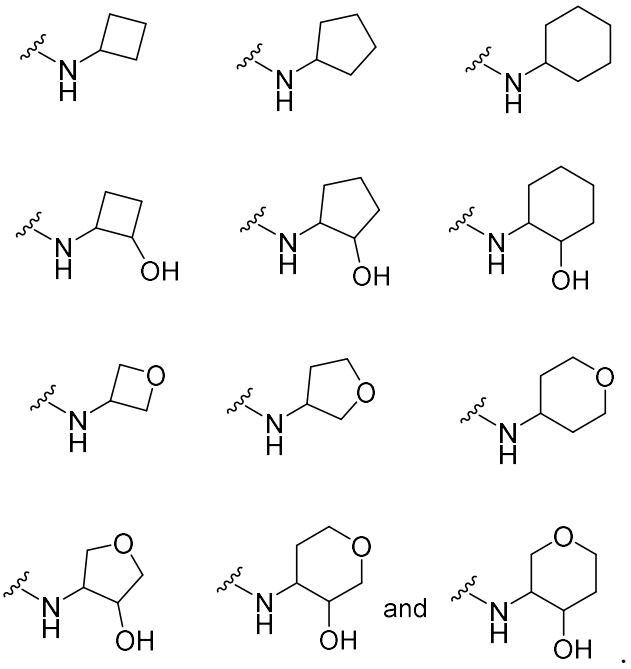
16. The use of any one of claims 1 to 5, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a compound of Formula (Ia):



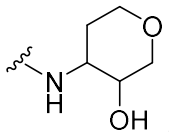
(Ia)

or a pharmaceutically acceptable salt thereof.

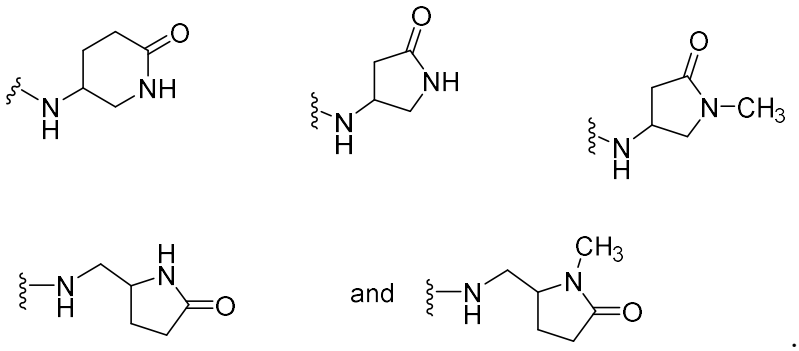
17. The use of any one of claims 1 to 16, wherein –NH(R^4) is selected from the group consisting of:



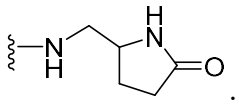
18. The use of any one of claims 1 to 16, wherein –NH(R^4) is selected from the group consisting of:



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



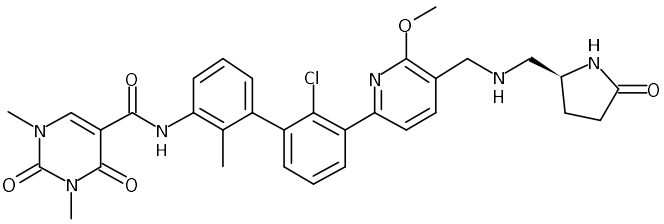
20. The use of any one of claims 1 to 16, wherein $-NHR^4$ is



.

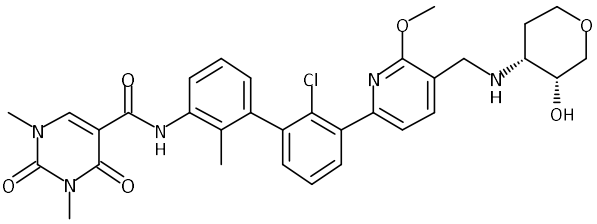
21. The use of any one of claims 1 to 20, wherein the compound of Formula (I) is an optically pure or enriched isomer.

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



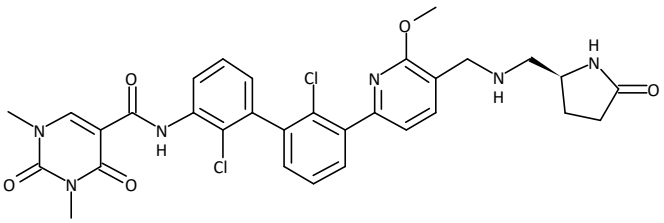
or a pharmaceutically acceptable salt thereof.

23. 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.

25. The use of any one of claims 1 to 24, wherein the effective amountmaintains a trough blood plasma concentration from 2 ng/mL to 1,000 ng/mL.

26. The use of any one of claims 1 to 24, wherein the effective amount maintains a trough blood plasma concentration from 5 ng/mL to 500 ng/mL.

27. The use of any one of claims 1 to 24, wherein the effective amount maintains a trough blood plasma concentration from 20 ng/mL to 300 ng/mL.

28. The use of any one of claims 1 to 24, wherein the effective amount maintains a trough blood plasma concentration from 30 ng/mL to 200 ng/mL.

29. The use of any one of claims 1 to 28, wherein the cancer is colon cancer.

30. The use of any one of claims 1 to 28, wherein the cancer is colorectal cancer.

31. The use of any one of claims 1 to 28, wherein the cancer is breast cancer.

32. The use of any one of claims 1 to 28, wherein the cancer is liver cancer.

33. The use of any one of claims 1 to 28, wherein the cancer is melanoma.

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

35. The use of claim 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.