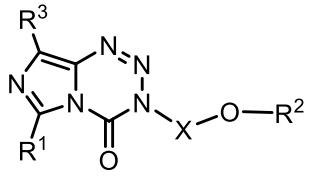
[0005] Certain imidazotetrazinone compounds are described in international patent applications WO 2023/049806 and WO 2009/077741, U.S. Patent 5,266,291, and by Moody *et al.* in *Pharmaceuticals* (2014) vol. 7, pages 797-838. Temozolomide, described in U.S. Patent 5,266,291, is marketed for the treatment of newly diagnosed glioblastoma multiforme cancers and refractory anaplastic astrocytoma in patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. Additional new compounds are needed to provide therapies that have superior efficacy and/or reduced adverse side effects.

[0006] Accordingly, the need exists for new compounds and therapeutic methods for treating cancer. The present invention addresses the foregoing needs and provides other related advantages.

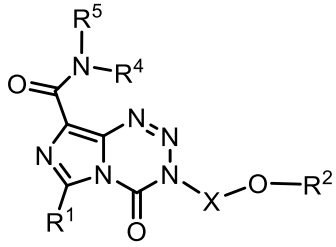
SUMMARY

[0007] The disclosure provides fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone compounds and related compounds, pharmaceutical compositions, and their use in treating cancer. In particular, the disclosure provides a collection of fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone compounds, such as a compound represented by Formula I:



(I)

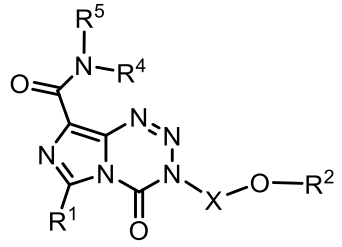
or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. In a more specific example, the compound of Formula I is a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

[0007a] In one aspect, there is provided a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen or methyl;

R^2 is C_{1-2} fluoroalkyl;

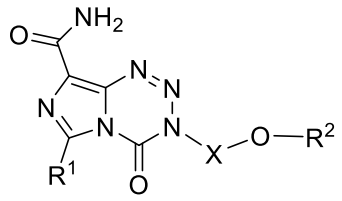
R^4 is hydrogen or C_{1-4} alkyl;

R^5 is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or 5-6 membered heteroaryl; wherein the phenyl is substituted with 0 or 1 occurrence of R^9; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing the nitrogen atom and 0 or 1 additional nitrogen atom; wherein the additional nitrogen atom is optionally substituted with C_{1-4} alkyl;

R^9 is C_{1-4} alkyl, fluoro, chloro, -OH, or $-NH_2$; and

X is C_{1-3} alkylene.

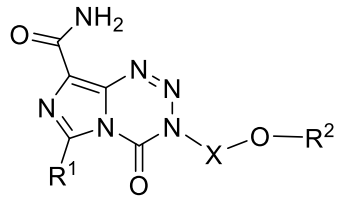
[0008] The disclosure also provides a collection of fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone compounds, such as a compound represented by Formula I-aa:



(I-aa)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

[0008a] Another aspect of the disclosure provides a compound represented by Formula I-aa:



(I-aa)

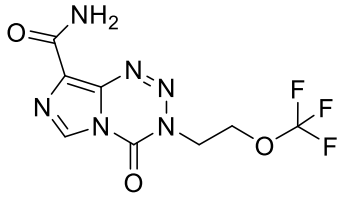
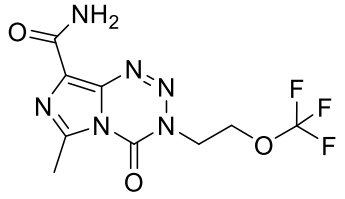
or a pharmaceutically acceptable salt thereof; wherein:

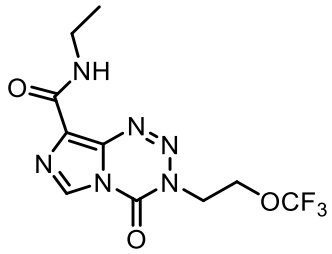
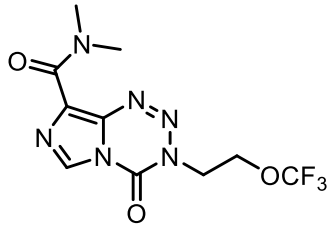
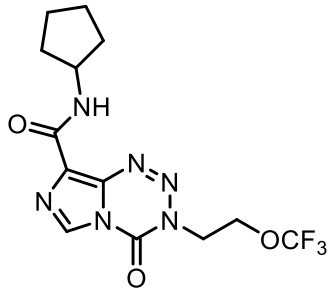
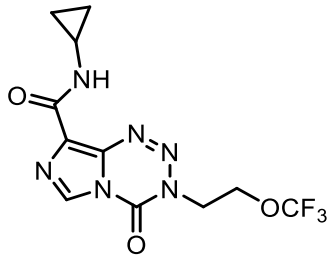
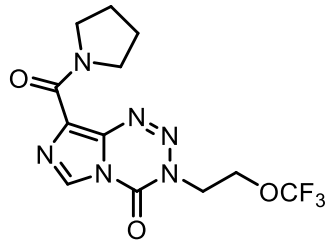
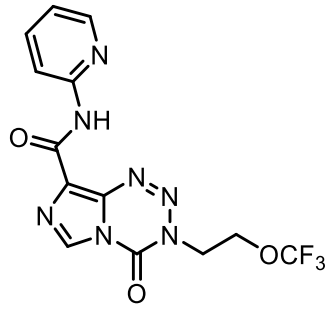
R^1 is hydrogen or methyl;

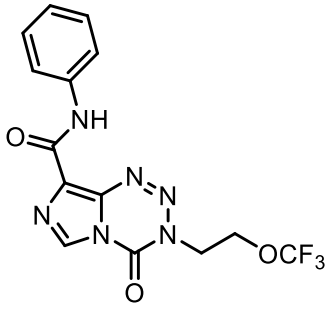
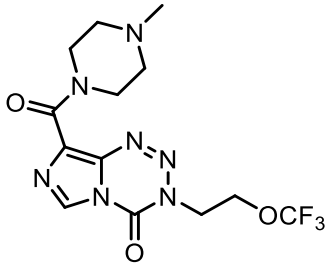
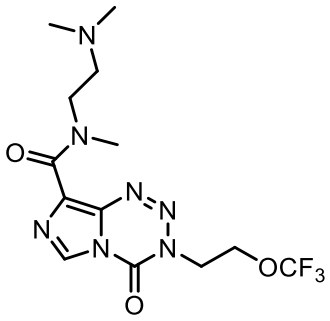
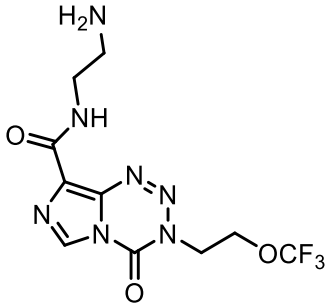
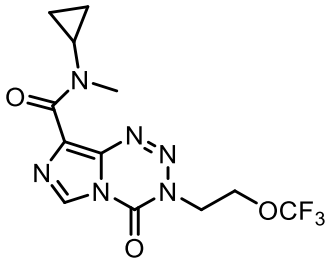
R^2 is C_{1-2} fluoroalkyl; and

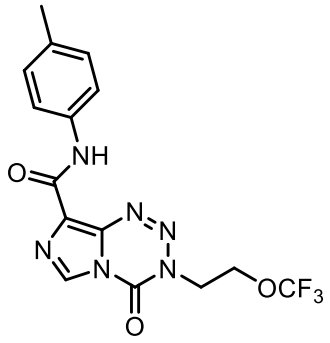
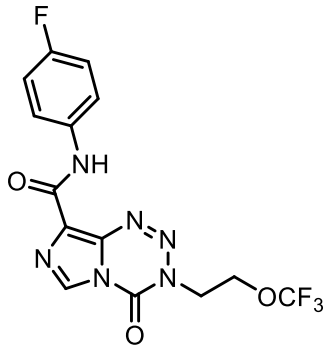
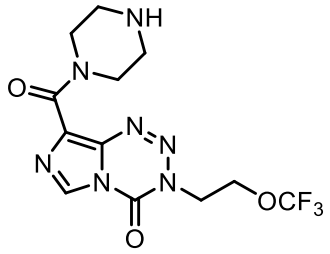
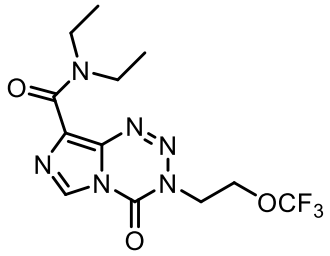
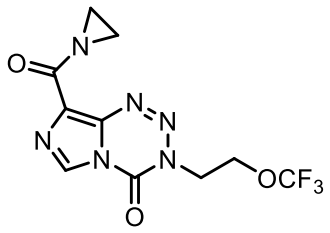
X is C_{1-3} alkylene.

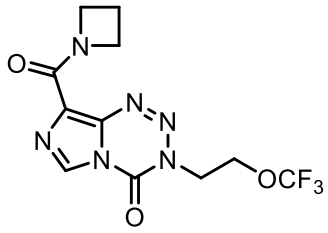
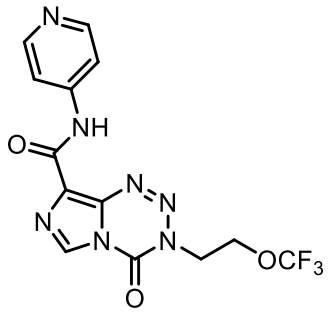
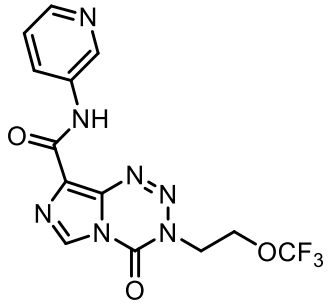
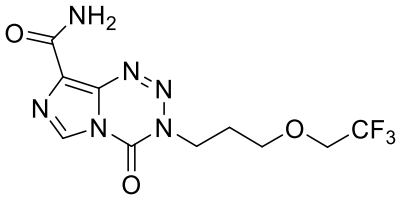
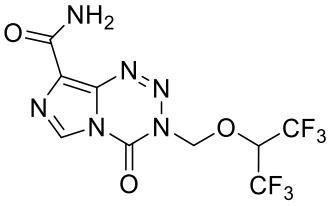
[0008b] Another aspect of the disclosure provides a compound selected from the following:

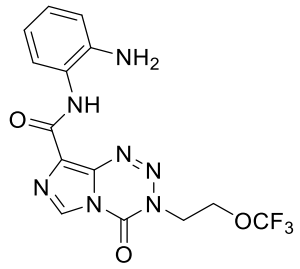
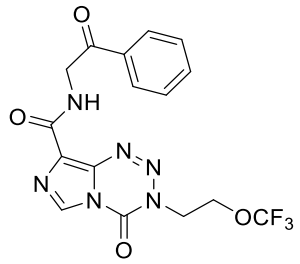
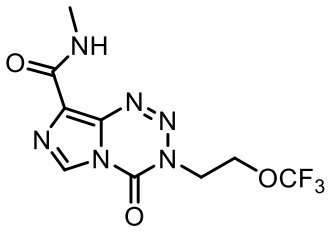
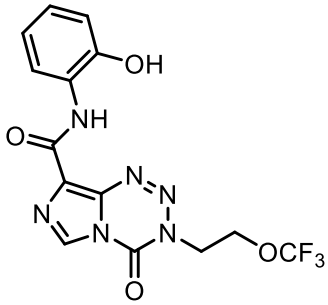
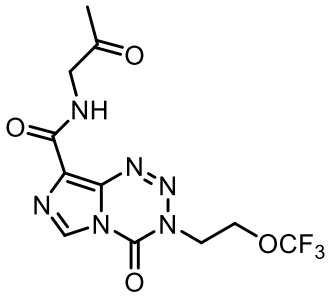
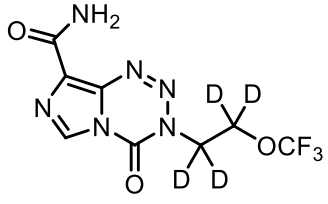
Compound No.	Chemical Structure
I-1	
I-2	

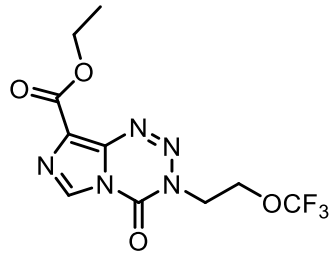
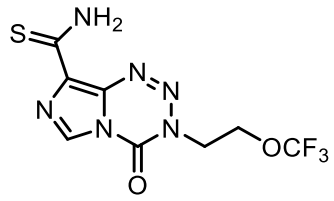
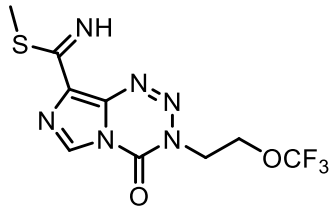
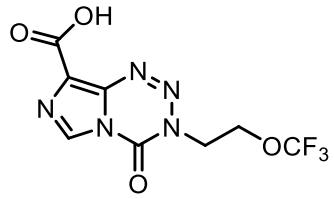
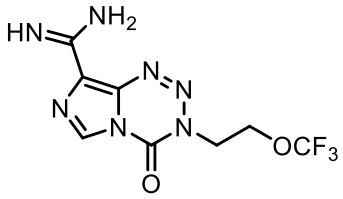
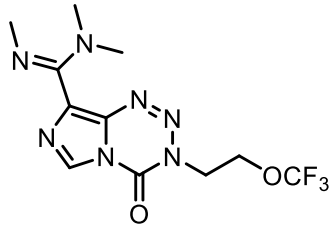
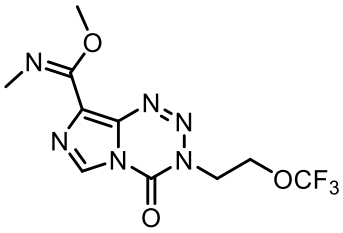
I-3	
I-4	
I-5	
I-6	
I-7	
I-8	

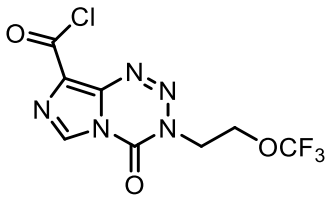
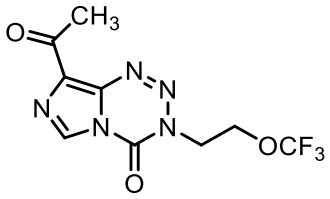
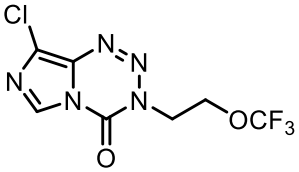
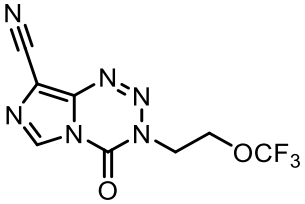
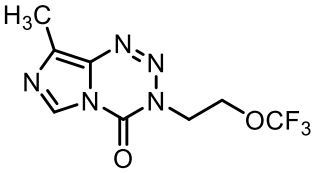
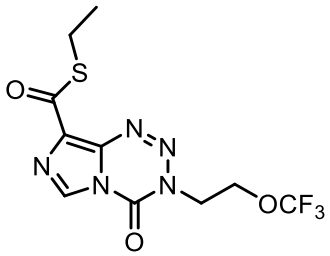
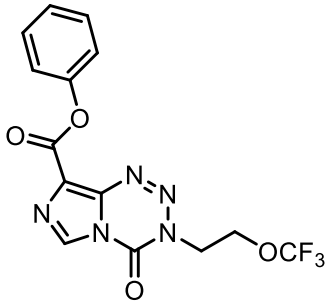
I-9	
I-10	
I-11	
I-12	
I-13	

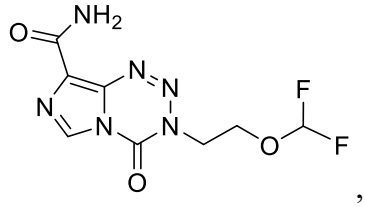
I-14	
I-15	
I-16	
I-17	
I-18	

I-19	
I-20	
I-21	
I-22	
I-23	

I-24	
I-25	
I-26	
I-27	
I-28	
I-29	

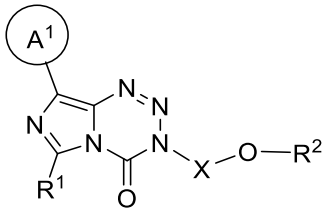
I-30	
I-31	
I-32	
I-33	
I-34	
I-35	
I-36	

I-37	
I-38	
I-39	
I-40	
I-41	
I-42	
I-43	

I-44	

or a pharmaceutically acceptable salt thereof.

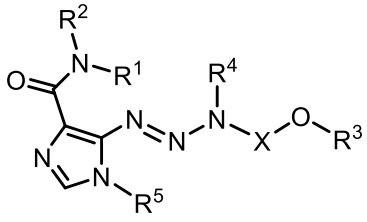
[0009] The disclosure also provides a collection of fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone compounds, such as a compound represented by Formula II:

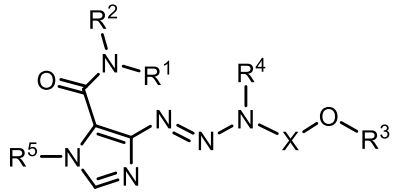


(II)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

[0010] The disclosure also provides a collection of fluoroalkoxyalkylene imidazotriazene compounds, such as a compound represented by Formula IIIa or Formula IIIb:

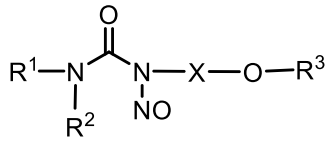




(IIIa) (IIIb)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

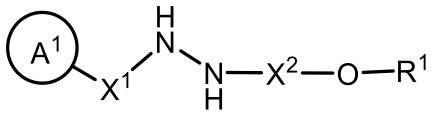
[0011] The disclosure also provides a collection of fluoroalkoxyalkylene nitrosourea compounds, such as a compound represented by Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

[0012] The disclosure also provides a collection of fluoroalkoxyalkylene hydrazine compounds, such as a compound represented by Formula V:



(V)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description.

[0013] Further description of additional collections of fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone and related compounds are described in the detailed description. All of the foregoing compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier. Another aspect of the disclosure provides a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

[0014] The disclosure also provides a method of treating cancer. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, I-A, I-aa, II, III, IV, or V, to treat the cancer, as further described in the detailed description. In certain examples, the cancer is MGMT deficient.

[0015] The disclosure also provides a method of producing a DNA lesion in a subject. The method comprises administering to a subject an effective amount of a compound described herein, such as a compound of Formula I, I-A, I-aa, II, III, IV, or V, to produce a DNA lesion in the subject, as further described in the detailed description. In certain examples, the subject has cancer.

[0016] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising exposing a MGMT-deficient cancer cell in the patient in need thereof to 2-(C_{1-4} fluoroalkoxy)ethane-1-diazonium, to thereby treat the MGMT-deficient cancer.

[0017] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising exposing a MGMT-deficient cancer cell in the patient in need thereof to 2-(trifluoromethoxy)ethane-1-diazonium, to thereby treat the MGMT-deficient cancer.

[0018] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising forming 2-(trifluoromethoxy)ethane-1-diazonium in a MGMT-deficient cancer cell in the patient in need of treatment, to thereby treat the MGMT-deficient cancer.

[0019] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising forming a 2-(C_{1-4} fluoroalkoxy)ethane-1-DNA adduct in a MGMT-deficient cancer cell in the patient in need thereof, to thereby treat the MGMT-deficient cancer.

[0020] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising forming a 2-(trifluoromethoxy)ethane-1-DNA adduct in a MGMT-deficient cancer cell in the patient in need thereof, to thereby treat the MGMT-deficient cancer.

[0021] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising exposing DNA to 2-(trifluoromethoxy)ethane-1-diazonium to thereby form a 2-(trifluoromethoxy)ethane-1-DNA adduct in a MGMT-deficient cancer cell in the patient in need thereof, to thereby treat the MGMT-deficient cancer.

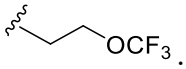
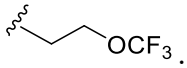
[0022] The disclosure also provides a method, comprising exposing DNA to 2-(trifluoromethoxy)ethane-1-diazonium in a cancer cell to thereby form a 2-(trifluoromethoxy)ethane-1-DNA adduct in the cancer cell.

[0023] The disclosure also provides a method of treating a MGMT-deficient cancer in a patient, comprising administering to the patient in need thereof a compound comprising a 2-

(trifluoromethoxy)ethanyl group, to thereby treat the patient, wherein said compound undergoes conversion *in vivo* to 2-(trifluoromethoxy)ethane-1-diazonium.

[0024] The disclosure also provides a method of forming a 2-(trifluoromethoxy)ethane-1-DNA adduct, comprising exposing DNA to a compound comprising a 2-(trifluoromethoxy)ethanyl group to thereby form a 2-(trifluoromethoxy)ethane-1-DNA adduct, wherein said compound undergoes conversion *in vivo* to 2-(trifluoromethoxy)ethane-1-diazonium.

[0025] The disclosure also provides a method of forming a 2-(trifluoromethoxy)ethane-1-DNA adduct, comprising exposing DNA to 2-(trifluoromethoxy)ethane-1-diazonium to thereby form a 2-(trifluoromethoxy)ethane-1-DNA adduct. In certain embodiments, the method comprises exposing DNA in a cancer patient to 2-(trifluoromethoxy)ethane-1-diazonium. In certain example, the cancer patient has a cancer that is MGMT-deficient.

[0026] The disclosure also provides a DNA adduct, comprising DNA covalently bonded to one or more occurrences of . In certain examples, the DNA adduct comprises DNA covalently bonded to 1 to 10 occurrences of .

[0026a] Another aspect of the disclosure provides a compound as defined herein or a pharmaceutical composition as defined herein for use in therapy.

[0026b] Another aspect of the disclosure provides use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of cancer in a subject.

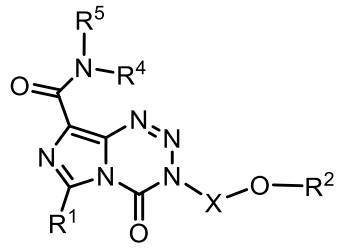
[0026c] Another aspect of the disclosure provides a compound as defined herein or the pharmaceutical composition as defined herein for use in producing a DNA lesion in a subject.

DETAILED DESCRIPTION

[0027] The invention provides fluoroalkoxyalkylene dihydroimidazo[5,1-*d*]tetrazinone compound and related compounds, pharmaceutical compositions, and their use in treating cancer. Compounds described herein provide advantages over compounds described in the literature. For example, the literature compound 3-(2-fluoroethyl)-N-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide (referred to as compound A1; structure shown below) has been found to have the adverse event of lethal toxicity in animal model testing. For example, compound A1 resulted in the death of 100% of rats when administered to the rats at a dose of 10 mg/kg. The compound A1 resulted in the death of 100% of dogs when administered to the dogs at a dose of 2 mg/kg.

Claims:

1. A compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen or methyl;

R^2 is C_{1-2} fluoroalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or 5-6 membered heteroaryl; wherein the phenyl is substituted with 0 or 1 occurrence of R^9; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring containing the nitrogen atom and 0 or 1 additional nitrogen atom; wherein the additional nitrogen atom is optionally substituted with C_{1-4} alkyl;

R^9 is C_{1-4} alkyl, fluoro, chloro, -OH, or $-NH_2$; and

X is C_{1-3} alkylene.

2. The compound of claim 1, wherein the compound is a compound of Formula I-A.

3. The compound of claim 1 or 2, wherein R^1 is hydrogen.

4. The compound of any one of claims 1-3, wherein R^2 is trifluoromethyl.

5. The compound of any one of claims 1-4, wherein R^4 is hydrogen.

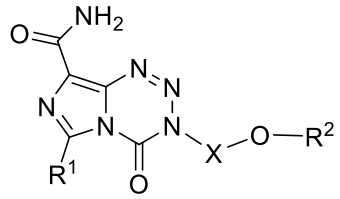
6. The compound of any one of claims 1-5, wherein R^5 is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, or phenyl.

7. The compound of any one of claims 1-6, wherein R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring

containing the nitrogen atom and 0 or 1 additional nitrogen atom; wherein the additional nitrogen atom is optionally substituted with C_{1-4} alkyl.

8. The compound of any one of claims 1-7, wherein X is $-CH_2CH_2-$.

9. A compound represented by Formula I-aa:



(I-aa)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen or methyl;

R^2 is C_{1-2} fluoroalkyl; and

X is C_{1-3} alkylene.

10. The compound of claim 9, wherein the compound is a compound of Formula I-aa.

11. The compound of claim 9 or 10, wherein X is $-CH_2CH_2-$.

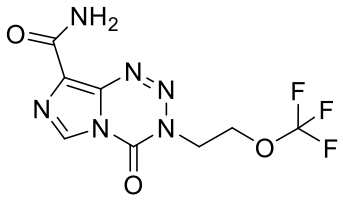
12. The compound of any one of claims 9-11, wherein R^1 is hydrogen.

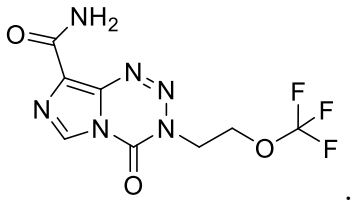
13. The compound of any one of claims 9-11, wherein R^1 is methyl.

14. The compound of any one of claims 9-13, wherein R^2 is trifluoromethyl.

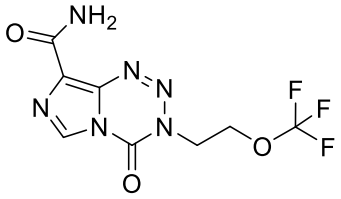
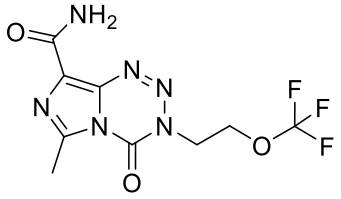
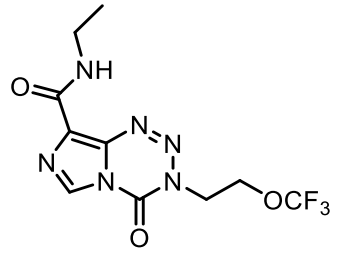
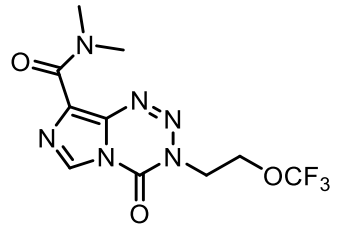
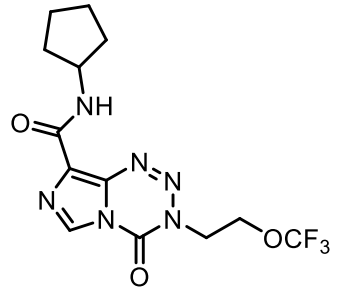
15. The compound of any one of claims 9-13, wherein R^2 is C_1 fluoroalkyl.

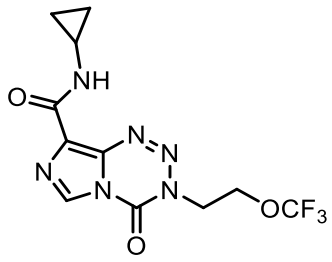
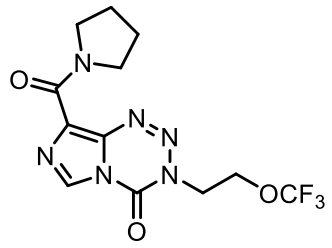
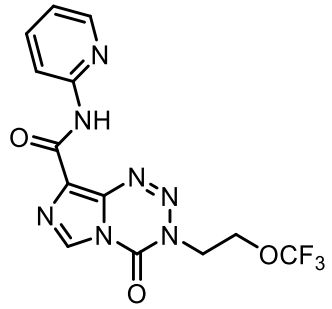
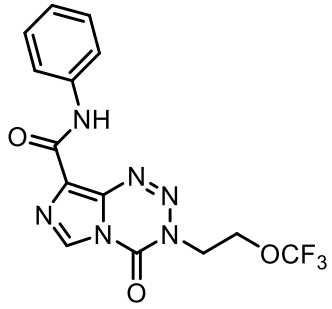
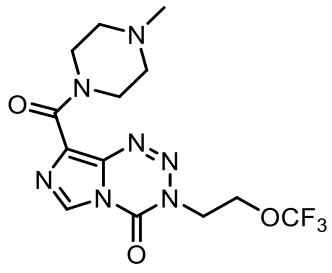
16. The compound of any one of claims 9-13, wherein R^2 is C_{1-2} trifluoroalkyl.

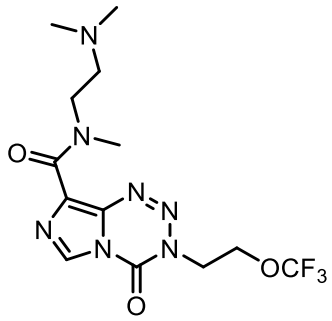
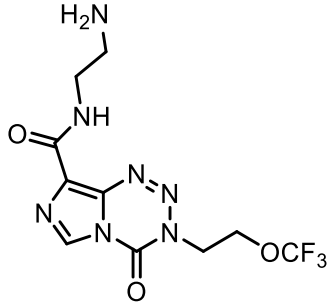
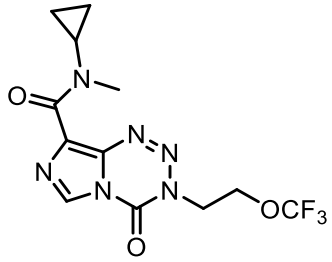
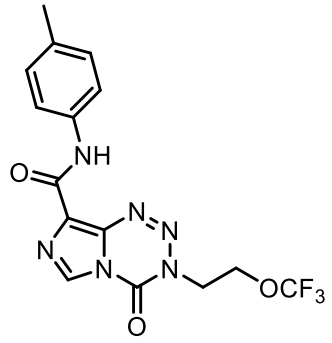
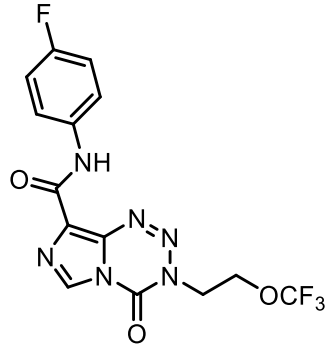
17. The compound of claim 9, wherein the compound is  or a pharmaceutically acceptable salt thereof.

18. The compound of claim 9, wherein the compound is .

19. A compound selected from the following:

Compound No.	Chemical Structure
I-1	
I-2	
I-3	
I-4	
I-5	

Compound No.	Chemical Structure
I-6	
I-7	
I-8	
I-9	
I-10	

Compound No.	Chemical Structure
I-11	
I-12	
I-13	
I-14	
I-15	

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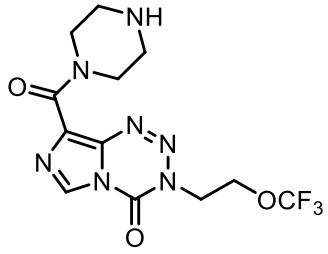
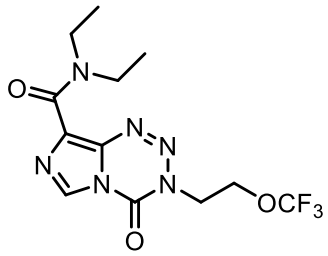
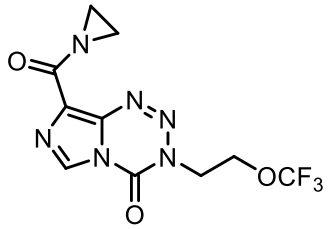
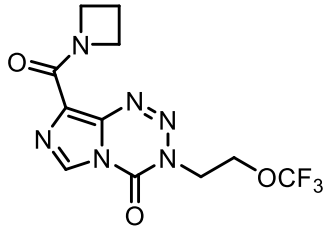
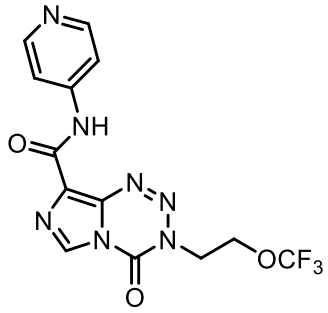
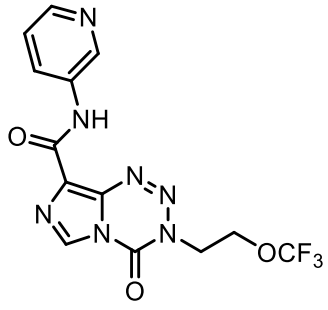
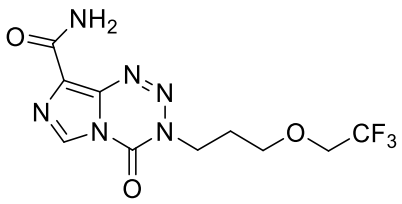
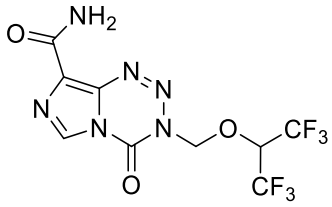
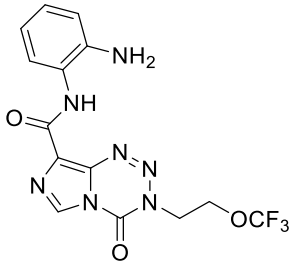
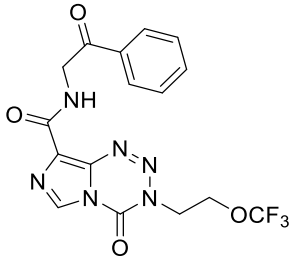
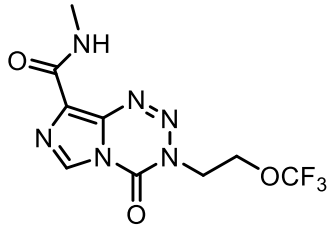
I-16	
I-17	
I-18	
I-19	
I-20	
I-21	

Compound No.	Chemical Structure
I-22	
I-23	
I-24	
I-25	
I-26	

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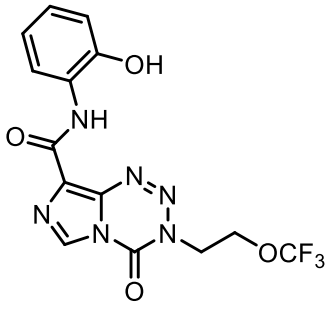
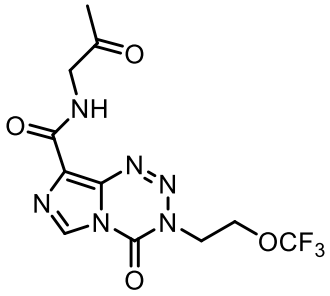
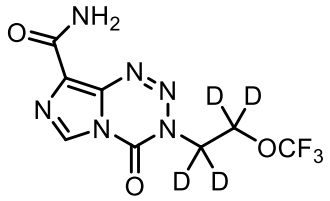
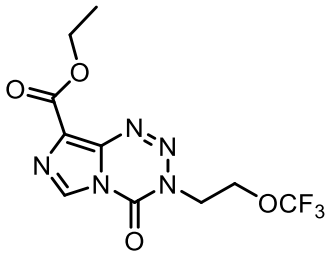
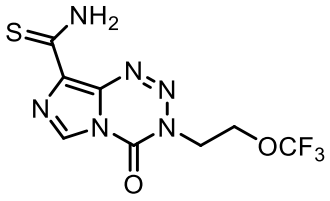
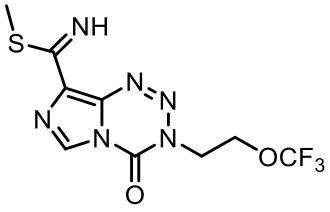
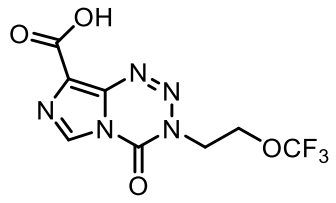
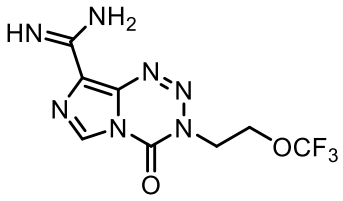
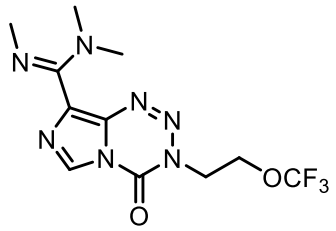
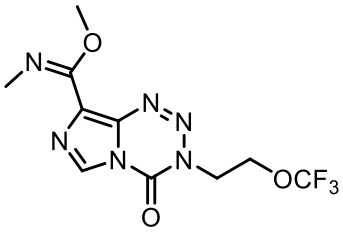
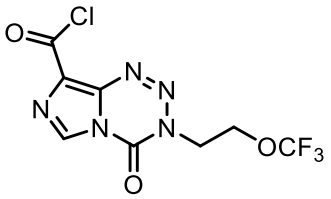
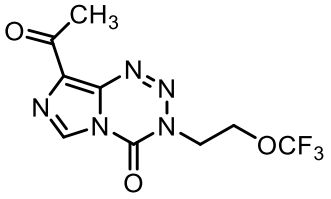
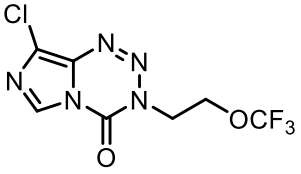
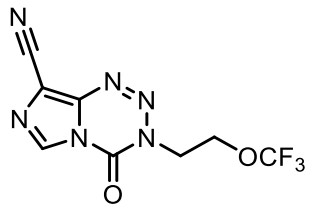
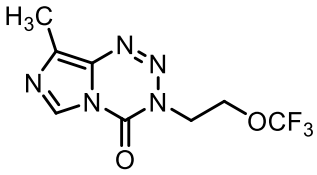
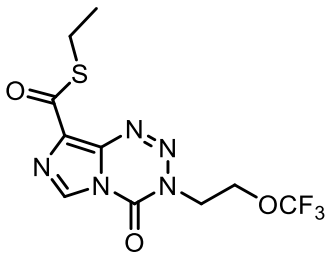
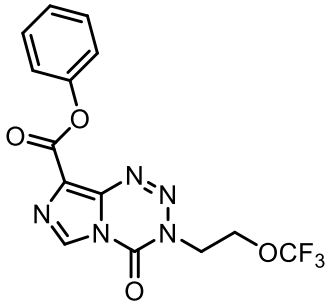
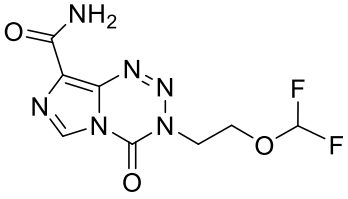
I-27	
I-28	
I-29	
I-30	
I-31	
I-32	

Compound No.	Chemical Structure
I-33	
I-34	
I-35	
I-36	
I-37	
I-38	
I-39	

Compound No.	Chemical Structure
I-40	
I-41	
I-42	
I-43	
I-44	

or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of any one of claims 1-8 or 19 and a pharmaceutically acceptable carrier.

21. A pharmaceutical composition comprising a compound of any one of claims 9-17 and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition comprising a compound of claim 18 and a pharmaceutically acceptable carrier.

23. A compound of any one of claims 1-19 or a pharmaceutical composition of claim 20 for use in therapy.

24. A compound of any one of claims 9-18 for use in therapy.

25. Use of a compound of claims 1-19 or a pharmaceutical composition of claim 20 in the manufacture of a medicament for the treatment of cancer in a subject.

26. Use of a compound of claims 9-18 in the manufacture of a medicament for the treatment of cancer in a subject.

27. A compound of any one of claims 1-19 or the pharmaceutical composition of claim 20 for use in producing a DNA lesion in a subject.

28. A compound of any one of claims 9-18 for use in producing a DNA lesion in a subject.

29. The compound or pharmaceutical composition for use of claim 29 or the compound for use of claim 30, wherein the subject has cancer.

30. The use of claim 25 or 26, the compound or pharmaceutical composition for use of claim 29 or the compound for use of claim 29, wherein the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct cancer, gallbladder cancer, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, leukemia, urothelial cancer, colorectal cancer, or glioblastoma multiforme.

31. The use of claim 25 or 26, the compound or pharmaceutical composition for use of claim 29 or the compound for use of claim 29, wherein the cancer is a breast invasive carcinoma, colon adenocarcinoma, head and neck cancer, lung adenocarcinoma, rectal adenocarcinoma, acute myeloid leukemia, glioblastoma multiforme, brain lower grade glioma, colorectal cancer, or metastatic melanoma.

32. The use of claim 25 or 26, the compound or pharmaceutical composition for use of claim 29 or the compound for use of claim 29, wherein the cancer is a glioblastoma multiforme.

33. The use of claim 25, 26 or 30-32, the compound or pharmaceutical composition for use of claim 29-32 or the compound for use of claim 29-32, wherein the cancer is MGMT deficient.

34. The use of claim 25, 26 or 30-33, the compound or pharmaceutical composition for use of claim 29-33 or the compound for use of claim 29-33, wherein the cancer is MMR deficient.

35. The use of claim 25, 26 or 30-34, the compound or pharmaceutical composition for use of claim 29-34 or the compound for use of claim 29-34, wherein the cancer is resistant to treatment using temozolomide.

36. The use of claim 25, 26 or 30-35, the compound or pharmaceutical composition for use of claim 29-35 or the compound for use of claim 29-35, wherein the subject is a human.