R^a is H or optionally substituted C_1-C_6 alkyl;

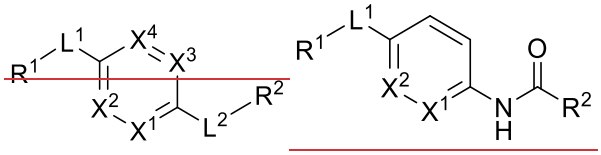
L^3 is optionally substituted C_2-C_9 heterocyclylene;

each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl, or a pharmaceutically acceptable salt thereof.

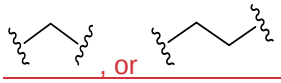
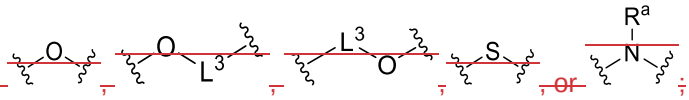
In an aspect, there is provided the use of a compound having the structure of **Formula Ia**:



Formula Ia,

wherein

R^1 is phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-di-fluoro-phenyl, 3,4-dichloro-phenyl, 3,5-di-fluoro-phenyl, 3,5-dichloro-phenyl, 3-chloro-4-fluoro-phenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-nitrile-phenyl, 3-nitrile-4-fluoro-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-bromo-phenyl, 3-cyclopropyl-phenyl, 3-cyano-5-fluoro-phenyl, 3-chloro-5-fluoro-phenyl, 3-chloro-5-cyano-phenyl, 3-chloro-5-methoxy-phenyl, 1,3-dihydroisobenzofuran, 5-chloropyridin-3-yl, 5-trifluoromethyl-pyridin-3-yl, 4-trifluoromethyl-pyridin-2-yl, or 5-fluoropyridin-3-yl;~~optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;~~

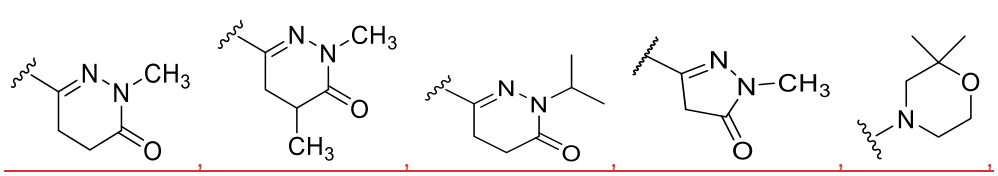
L^1 is ;~~optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,~~ ;

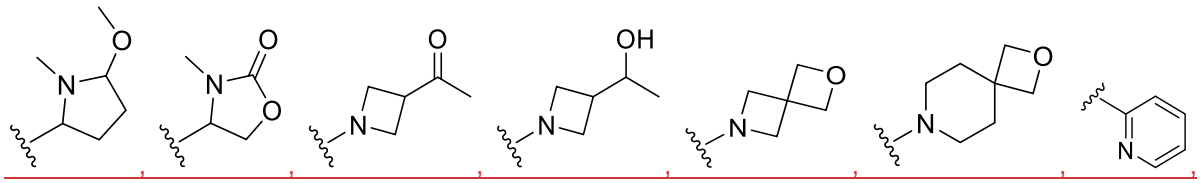
~~R^a is H or optionally substituted C_1-C_6 alkyl;~~

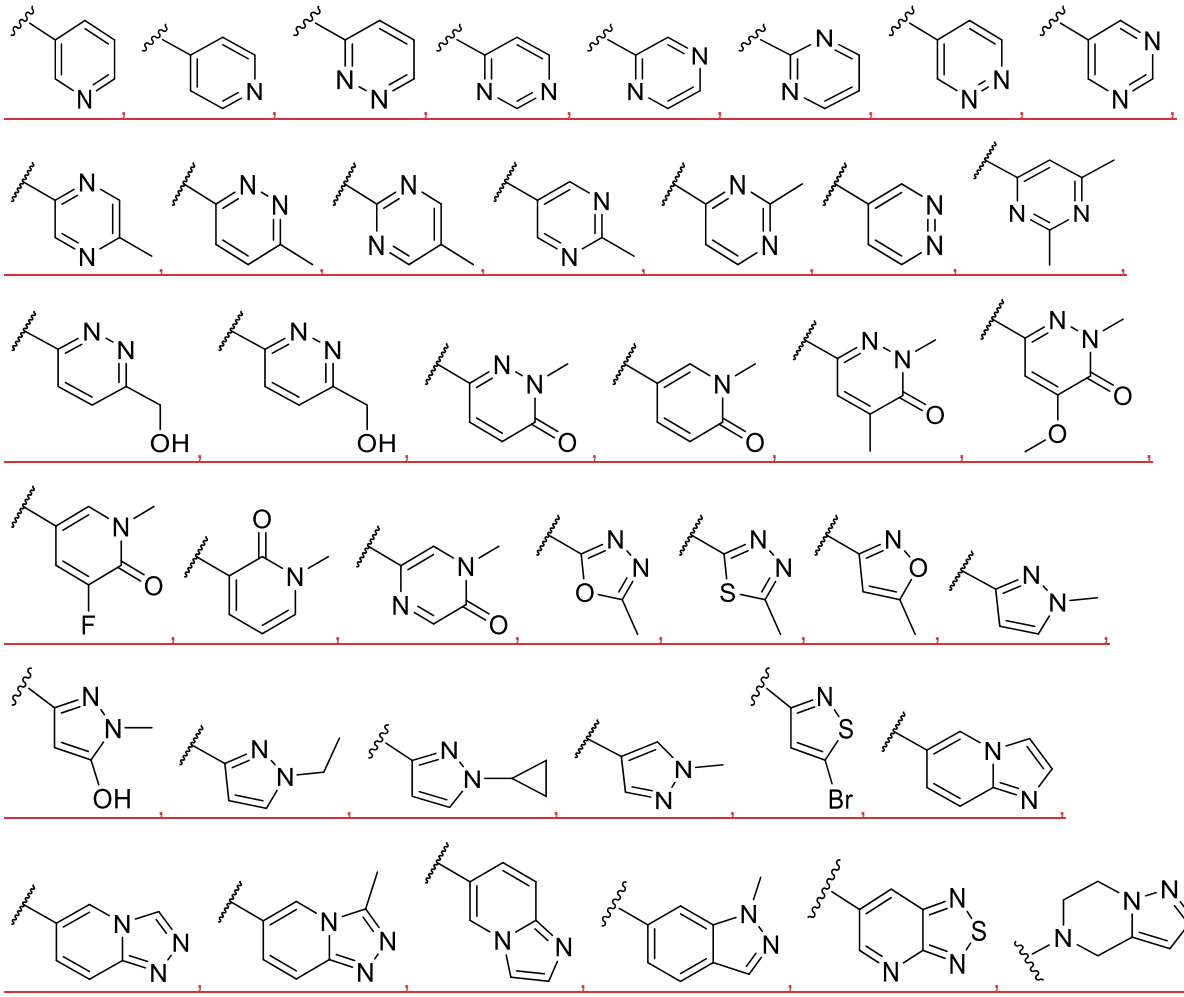
~~L^3 is optionally substituted C_2-C_9 heterocyclylene;~~

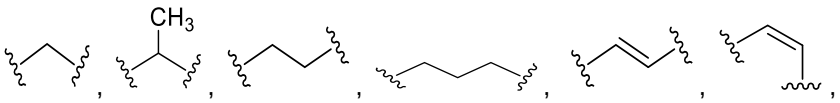
each of X^1, and X^2~~, X^3, and X^4~~ is, independently, N or CH;

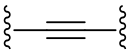
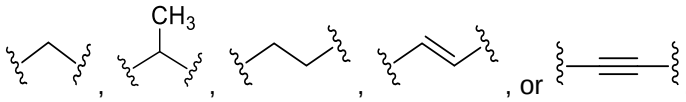
~~L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and~~

R^2 is 





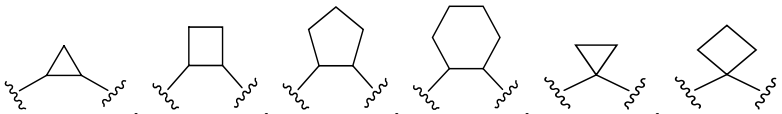
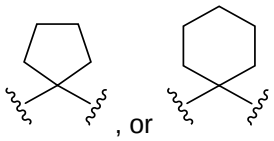
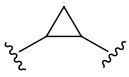
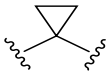
In some examples, L^1 is 

or . In some embodiments, L^1 is 

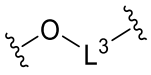
.

In some examples, L^1 is .

In some examples, L^1 is optionally substituted C_3-C_6 carbocyclylene.

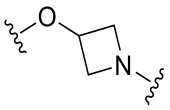
In some examples, L^1 is , . In some examples, L^1 is  or .

In some examples, L^1 is . In some examples, L^1 is 

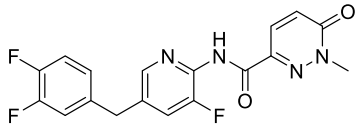
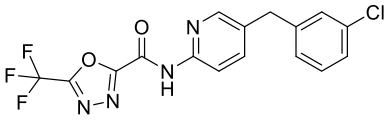
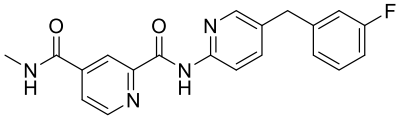
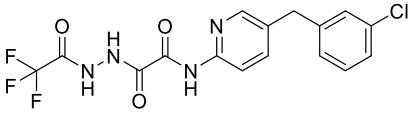
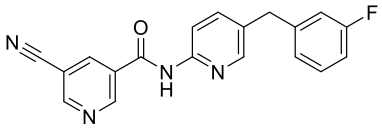
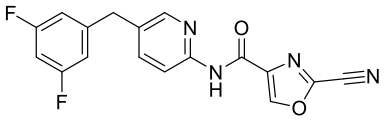
. In some examples, L^1 is 

.

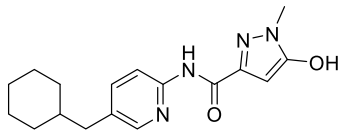
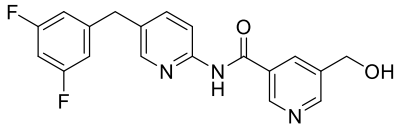
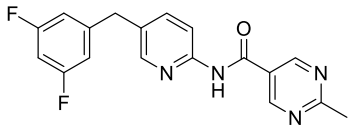
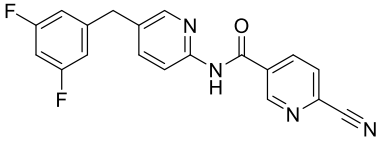
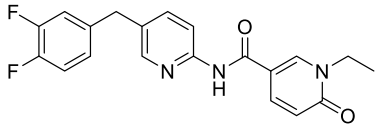
In some examples, L^1 is  or 

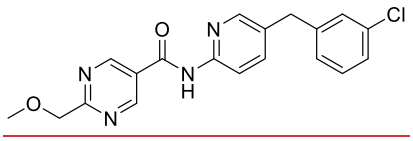
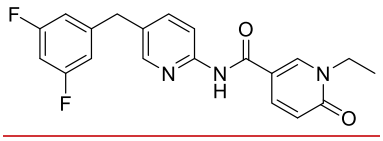
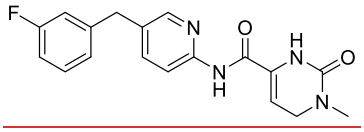
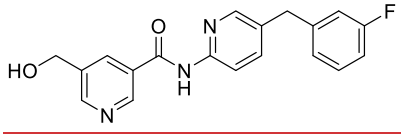
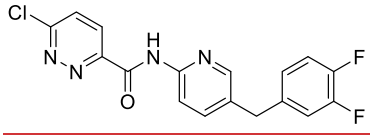
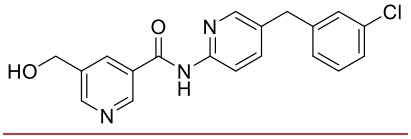
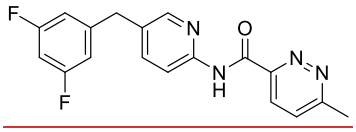
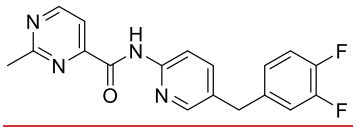
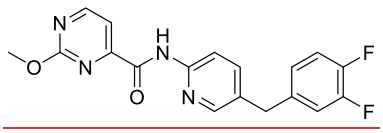
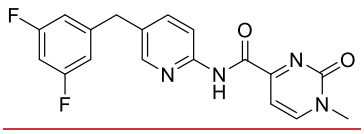
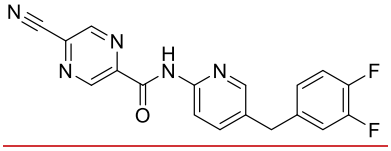
. In some examples, L^1 is .

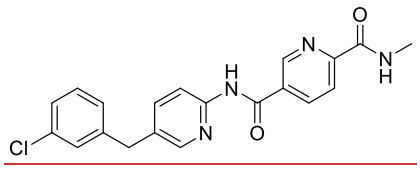
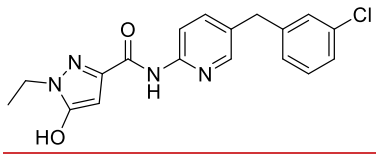
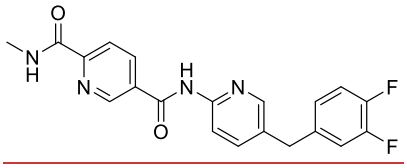
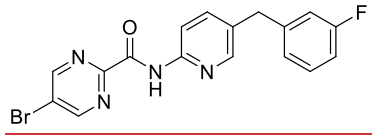
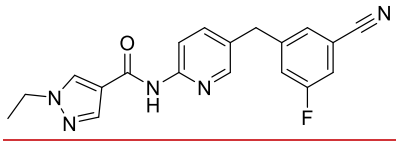
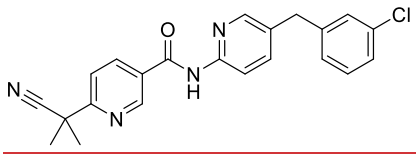
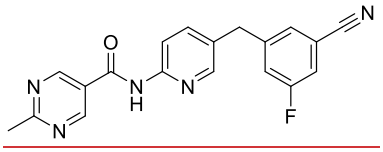
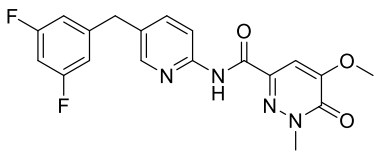
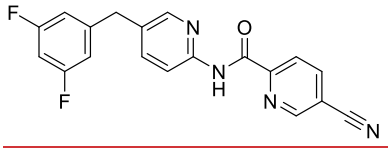
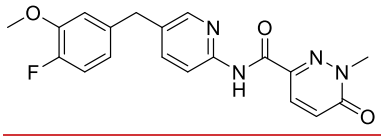
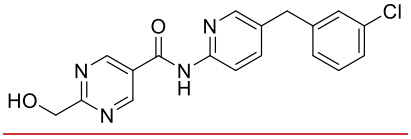
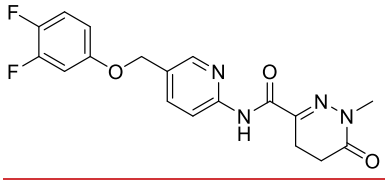
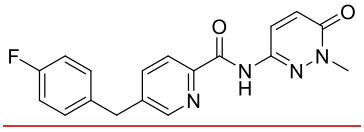
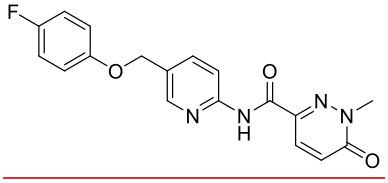
In some examples, L^1 is optionally substituted C_1-C_6 heteroalkylene.

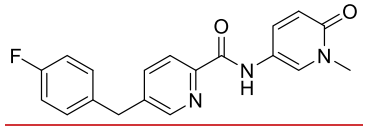
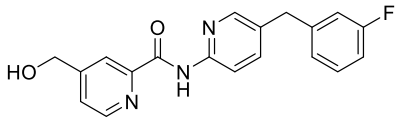
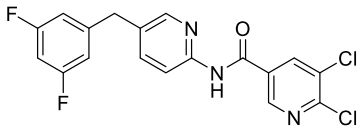
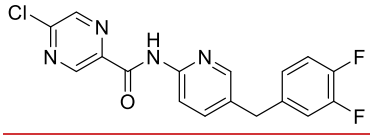
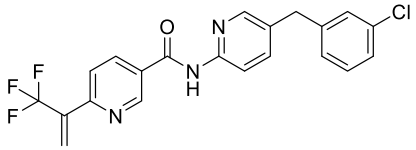
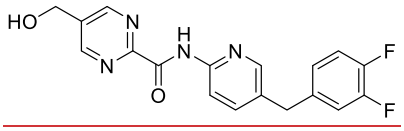
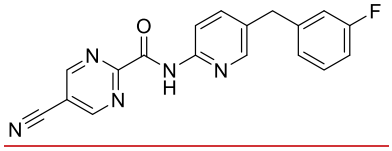
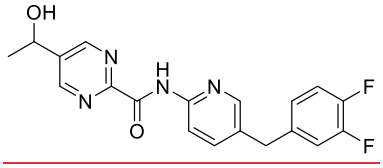
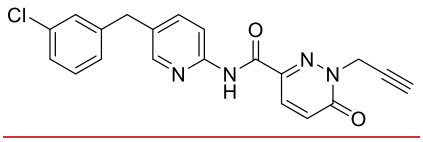
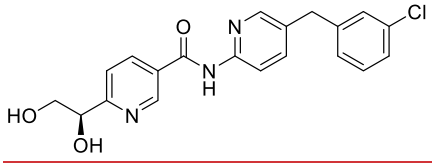
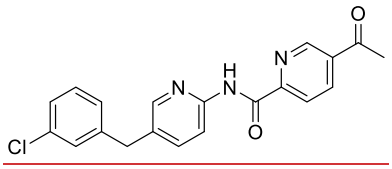
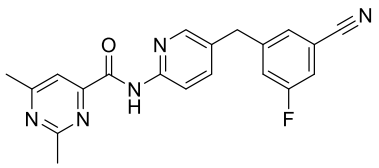
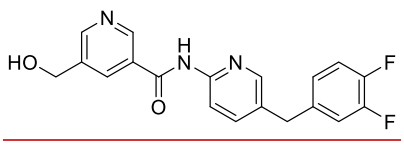
CMPD No.	Structure	CMPD No.	Structure
577		681	
578		682	
579		683	

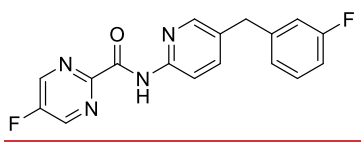
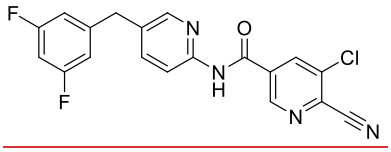
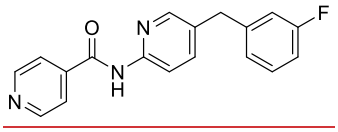
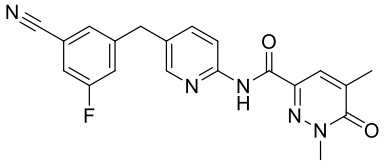
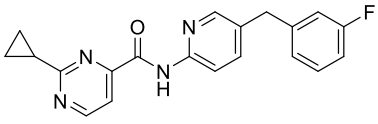
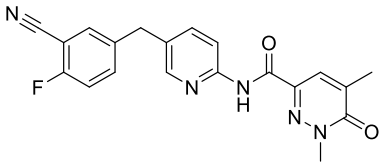
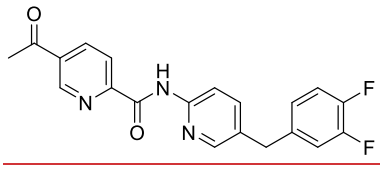
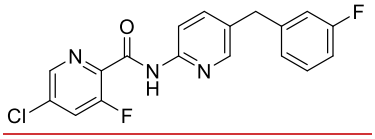
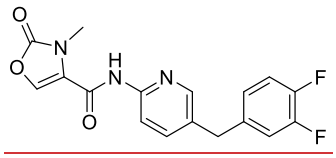
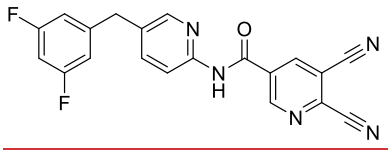
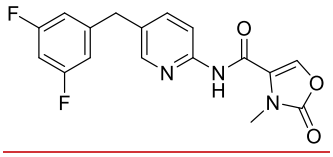
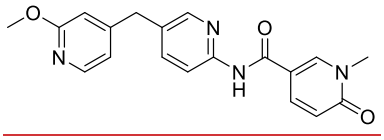
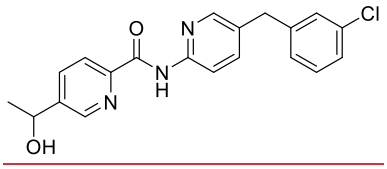
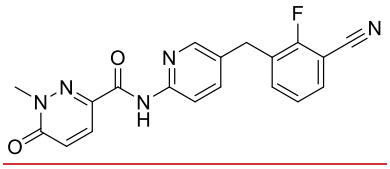
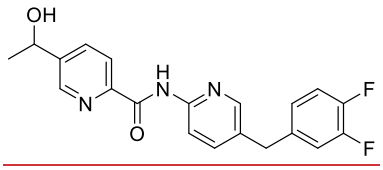
In an aspect, there is provided a compound, wherein the compound has ~~or pharmaceutically acceptable salt thereof, having~~ the structure ~~of any one of compounds 476-683 in Table 2.~~

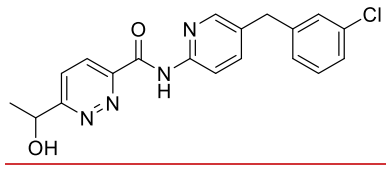
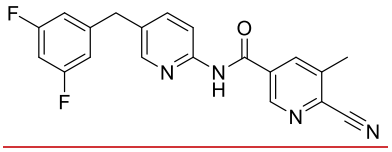
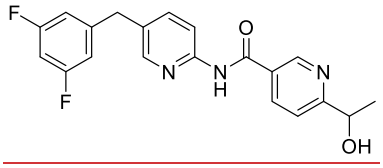
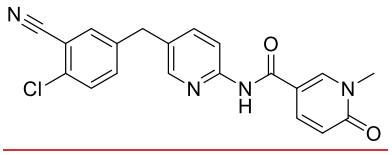
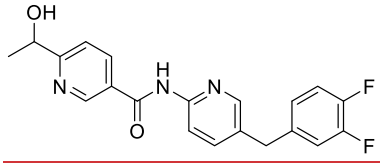
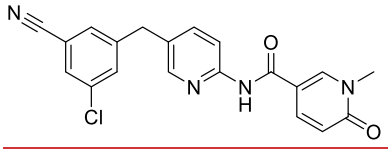
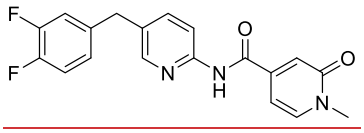
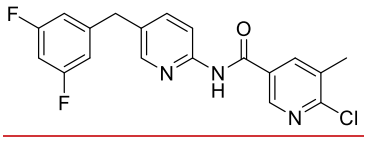
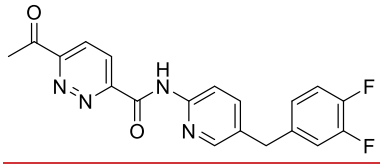
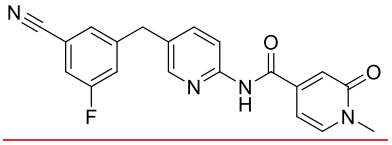
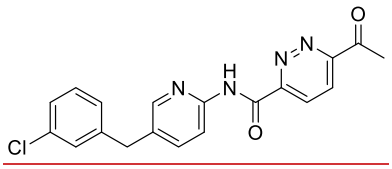
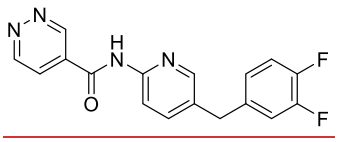
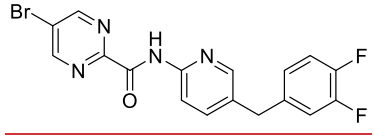
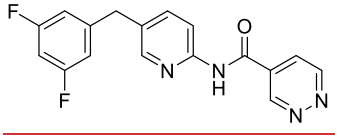
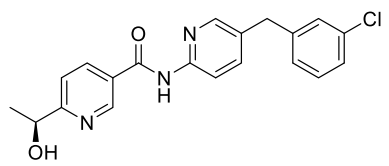
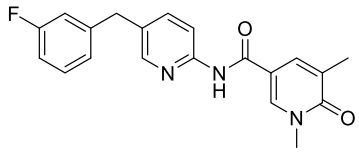
CMPD No.	Structure	CMPD No.	Structure
476		580	
		581	
478		582	

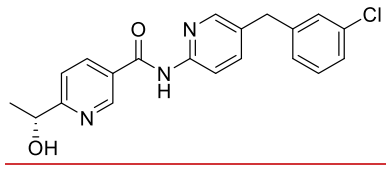
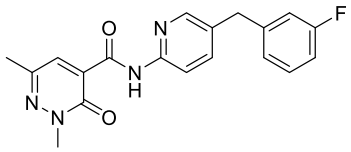
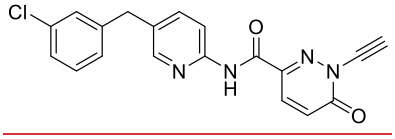
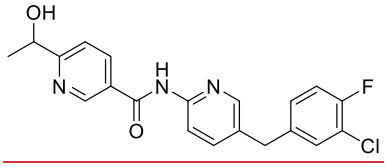
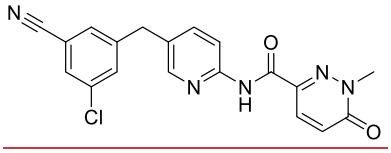
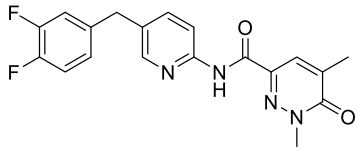
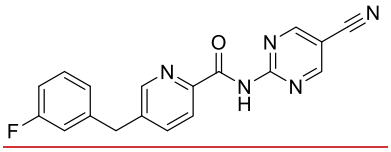
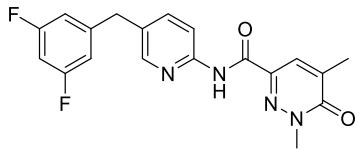
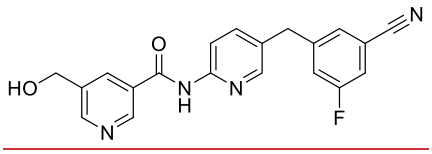
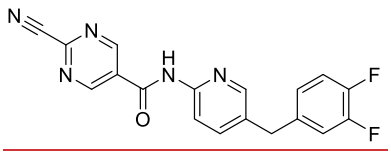
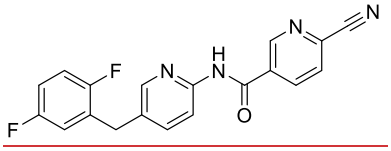
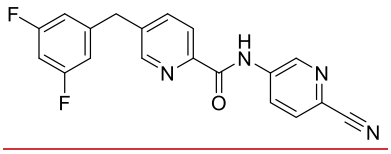
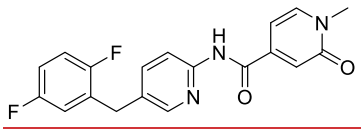
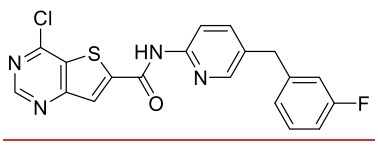
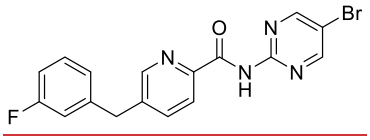
479		583	
480			
481		585	
483			
484			
485			
486		590	
		591	

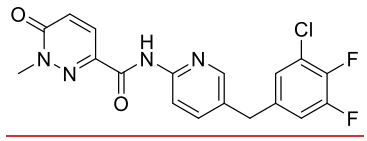
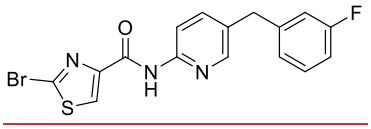
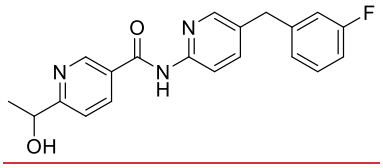
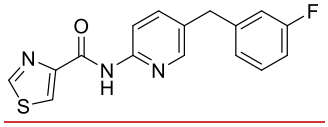
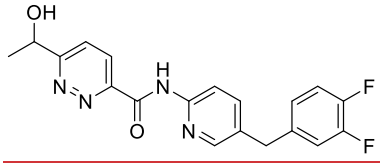
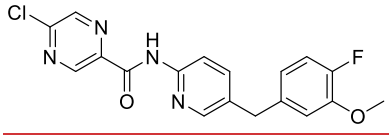
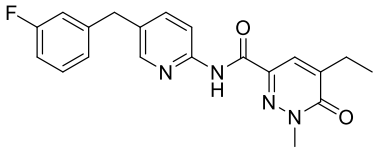
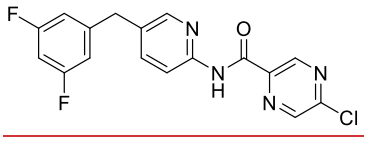
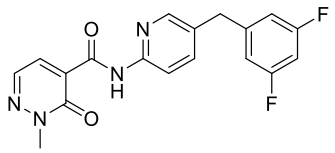
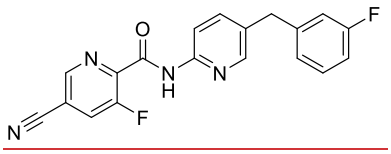
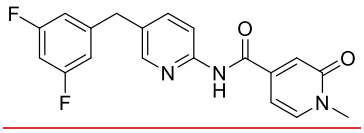
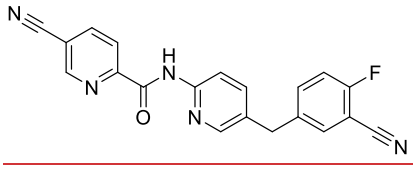
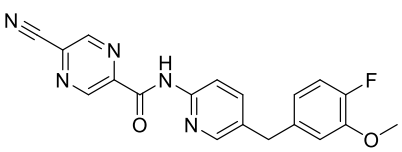
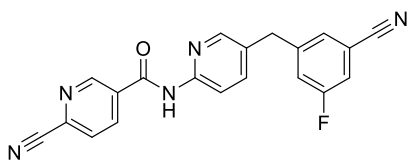
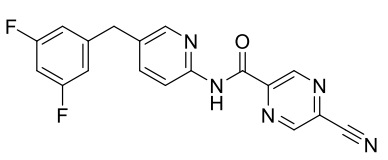
		592	
489		593	
490		594	
491		595	
		596	
493		597	
494		598	
495		599	

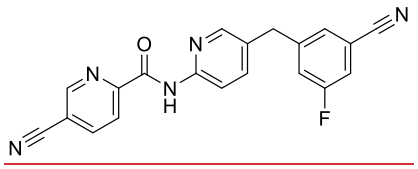
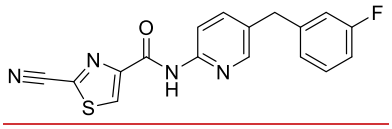
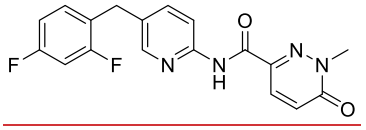
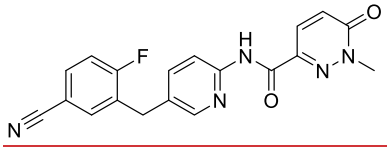
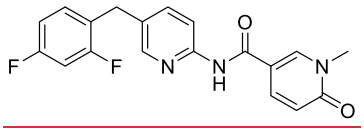
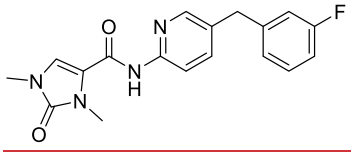
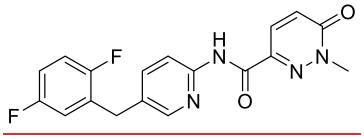
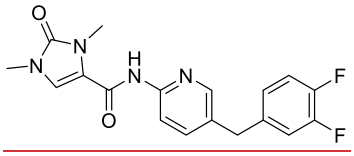
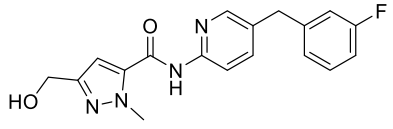
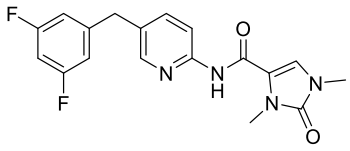
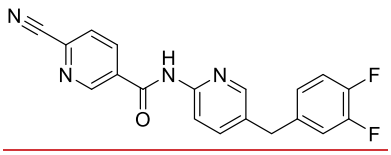
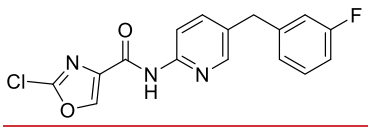
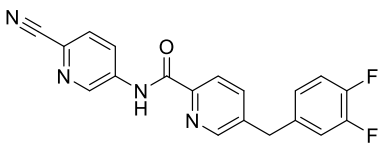
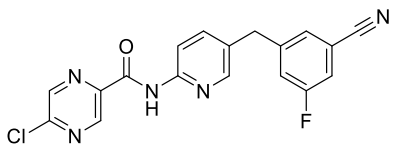
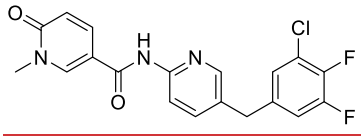
496			
497		601	
		602	
499		603	
500		604	
501		605	
502		606	
503			

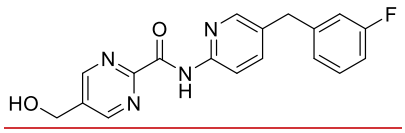
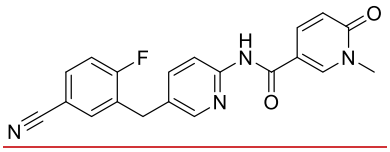
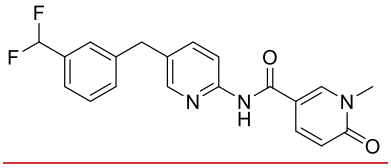
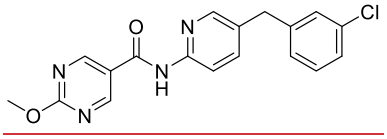
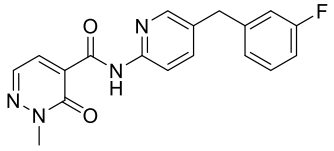
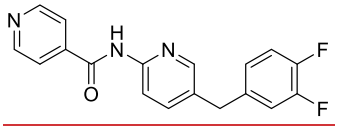
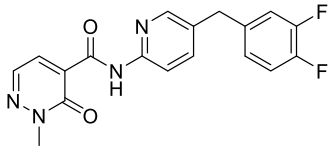
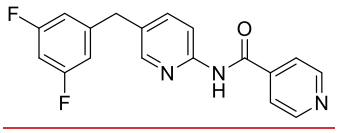
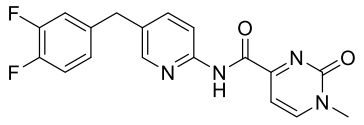
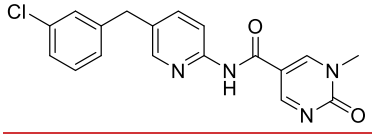
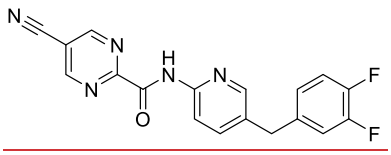
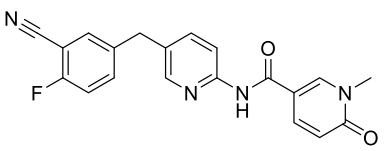
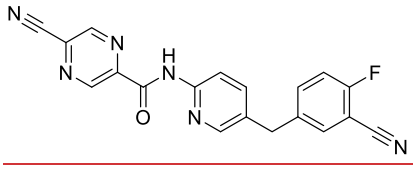
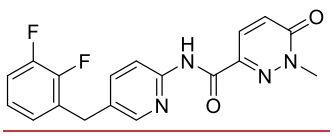
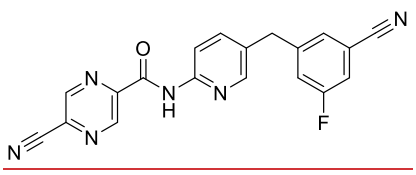
504		608	
505		609	
506		610	
507		611	
508		612	
509		613	
510		614	
511			

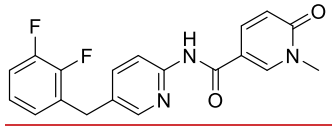
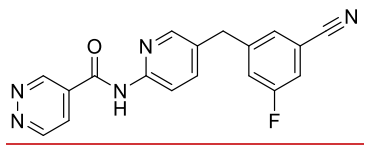
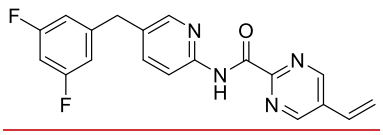
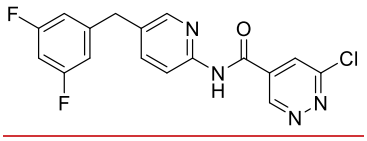
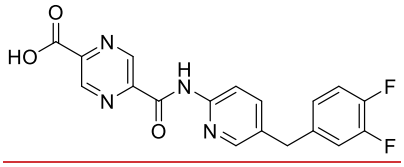
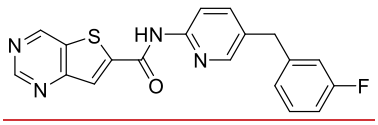
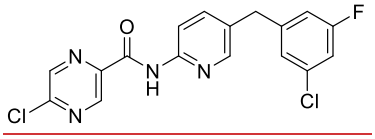
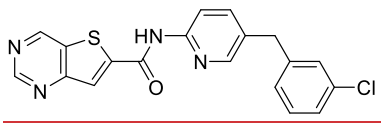
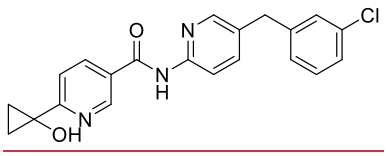
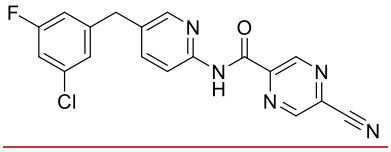
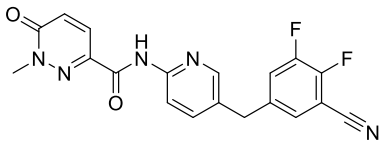
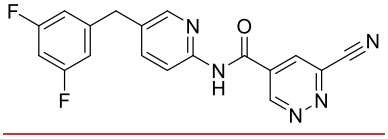
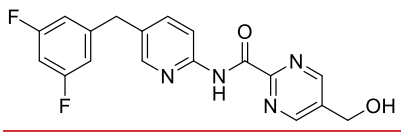
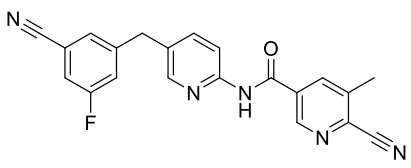
512		616	
513		617	
514		618	
515		619	
516		620	
517		621	
518		622	
519		623	

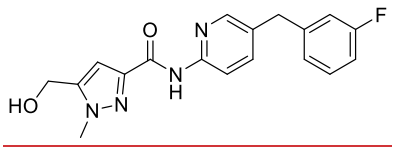
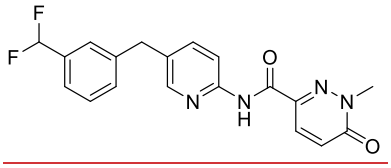
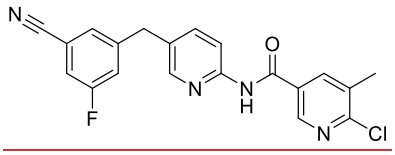
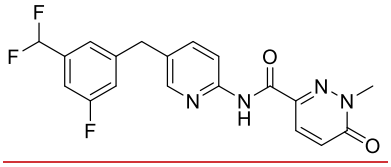
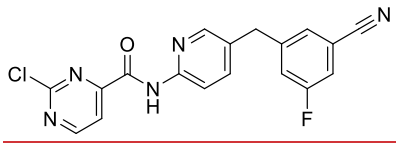
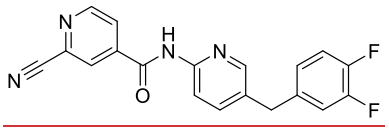
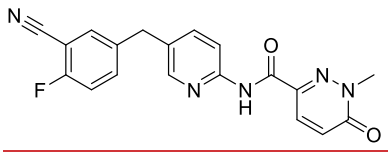
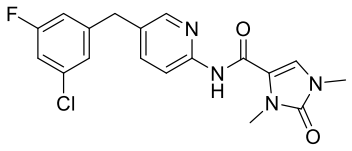
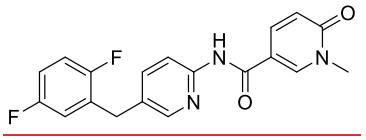
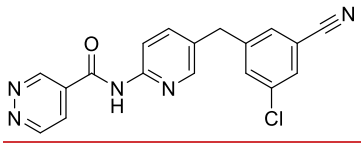
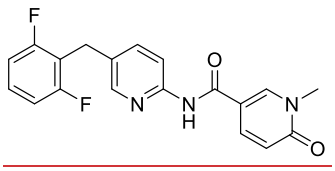
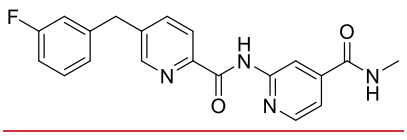
520		624	
521			
522		626	
523		627	
524		628	
525		629	
526		630	
527		631	

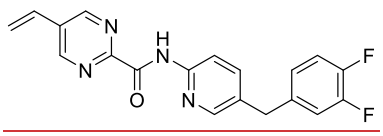
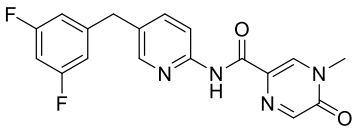
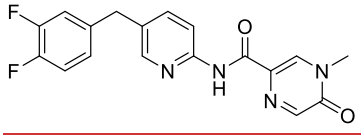
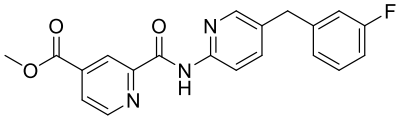
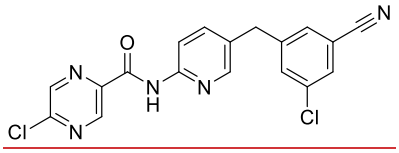
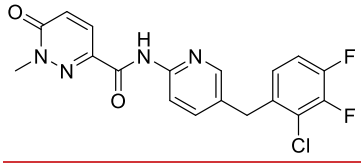
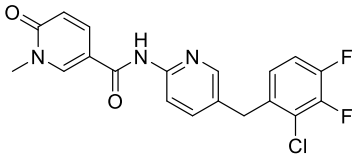
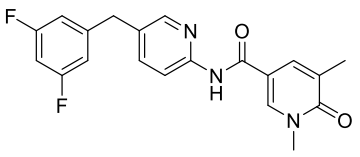
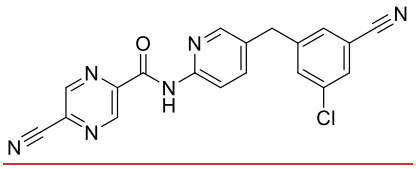
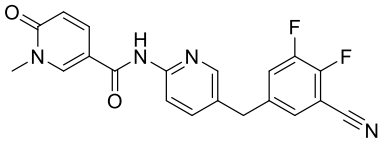
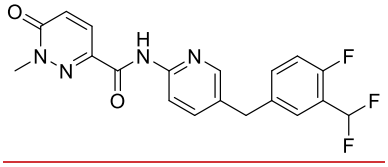
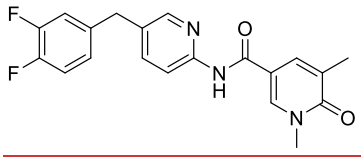
528		632	
529		633	
530		634	
531		635	
532		636	
533			
534		638	
535		639	

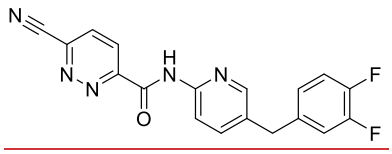
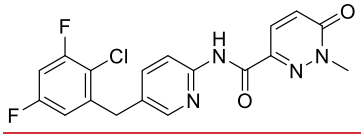
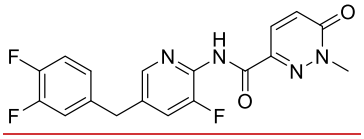
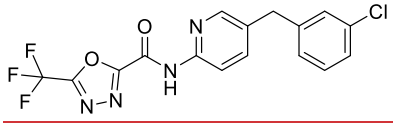
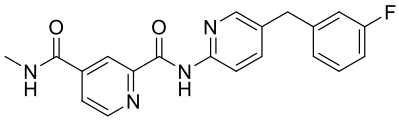
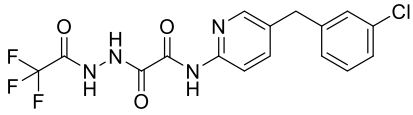
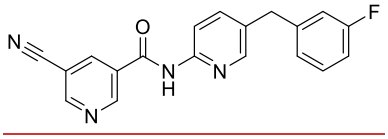
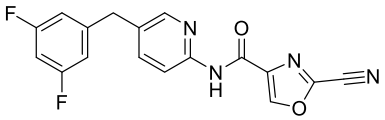
536		640	
537		641	
538		642	
539		643	
540		644	
541		645	
542		646	
543			

544		648	
545		649	
546		650	
547		651	
548		652	
549			
550		654	
551		655	

552		656	
553		657	
554			
555		659	
556			
557		661	
558		662	
559		663	

560			
561		665	
562		666	
563			
564		668	
565		669	
566			
567			

568		672	
		673	
570		674	
571			
572		676	
		677	
574			
575		679	

576		680	
577		681	
578		682	
579		683	

~~In an aspect, t~~This disclosure features a pharmaceutical composition comprising a compound of any of the foregoing compounds, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In an aspect, this disclosure features a pharmaceutical composition comprising a compound as defined above, and a pharmaceutically acceptable excipient.

In some examples, the pharmaceutical composition includes a compound of **Formula I** or **Formula II** and a pharmaceutically acceptable excipient.

In an example, this disclosure features a method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

~~In an aspect, there is provided the use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a neurological disorder in a subject in need thereof~~

In an example, this disclosure features a method of inhibiting toxicity in a cell related to a protein, the method comprising administering an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

~~In an aspect, there is provided the use of a compound, or pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for inhibiting toxicity in a cell related to a protein.~~

In some examples, the toxicity is α-synuclein-related toxicity. In some examples, the toxicity is ApoE4-related toxicity.

In some examples, the cell is a mammalian neural cell.

In an example, this disclosure features a method of treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

~~In an aspect, there is provided the use of an effective amount of a compound, or pharmaceutically acceptable salt as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof.~~

Non-limiting exemplary SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS)

disorders, dementia, multiple sclerosis, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome.

In some examples, the SCD-associated disorder is a SCD1-associated disorder.

In some examples, the SCD-associated disorder is a SCD5-associated disorder.

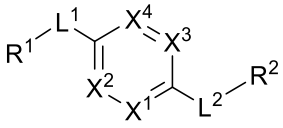
In an example, this disclosure features a method of inhibiting SCD5, the method comprising contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

~~In another aspect, there is provided the use of an effective amount of a compound as defineda bove or a pharmaceutical composition as defined above in the manufacture of a medicament for inhibiting SCD5.~~

In an example, this disclosure features a method of inhibiting SCD1, the method comprising contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In an aspect, there is provided the use of ~~an effective amount of~~ a compound as defined above ~~or a pharmaceutical composition as defined above~~ in the manufacture of a medicament for the treatment of brain cancer in a subject in need thereof~~inhibiting SCD1~~.

In an example, this disclosure features a method of treating a primary brain cancer in a subject in need thereof, the method comprising administering an effective amount of a compound having the structure of **Formula I**:

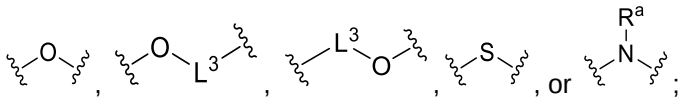


Formula I,

wherein

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,



;

R^a is H or optionally substituted C_1-C_6 alkyl;

L^3 is optionally substituted C_2-C_9 heterocyclylene;

each of X^1, X^2, X^3, and X^4 is, independently, N or CH;

L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and

R^2 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

or a pharmaceutically acceptable salt thereof.

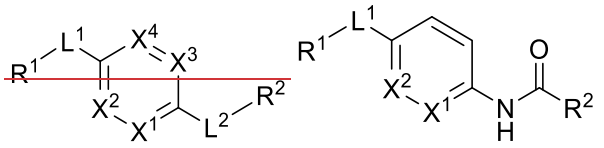
In some examples, the compound, or pharmaceutically acceptable salt thereof, has the structure of any one of compounds 1-475 in Table 1 or any one of compounds 476-683 in Table 2.

In some examples, the primary brain cancer is a glioma. In some examples, the glioma is an astrocytoma. In some examples, the astrocytoma is a glioblastoma.

In some examples, the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents.

Claims

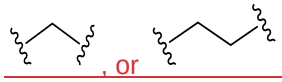
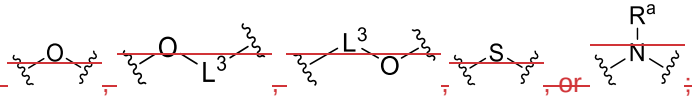
1. Use of a compound having the structure of **Formula Ia**:



Formula Ia,

wherein

R^1 is phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-di-fluoro-phenyl, 3,4-dichloro-phenyl, 3,5-di-fluoro-phenyl, 3,5-dichloro-phenyl, 3-chloro-4-fluoro-phenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-nitrile-phenyl, 3-nitrile-4-fluoro-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3-bromo-phenyl, 3-cyclopropyl-phenyl, 3-cyano-5-fluoro-phenyl, 3-chloro-5-fluoro-phenyl, 3-chloro-5-cyano-phenyl, 3-chloro-5-methoxy-phenyl, 1,3-dihydroisobenzofuran, 5-chloropyridin-3-yl, 5-trifluoromethyl-pyridin-3-yl, 4-trifluoromethyl-pyridin-2-yl, or 5-fluoropyridin-3-yl;~~optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocyclyl~~;

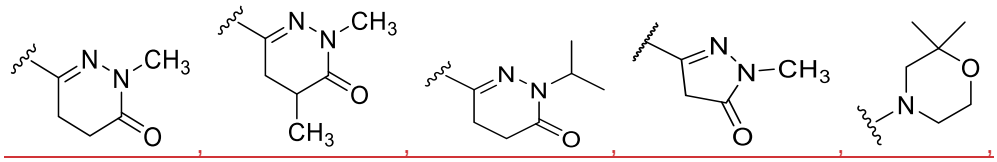
L^1 is , or ;~~optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_3-C_6 carbocyclylene,~~ 

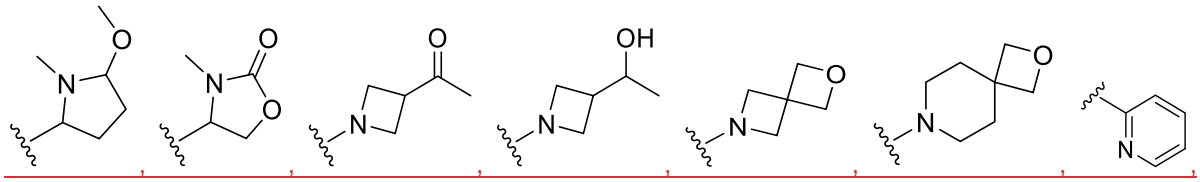
~~R^a is H or optionally substituted C_1-C_6 alkyl;~~

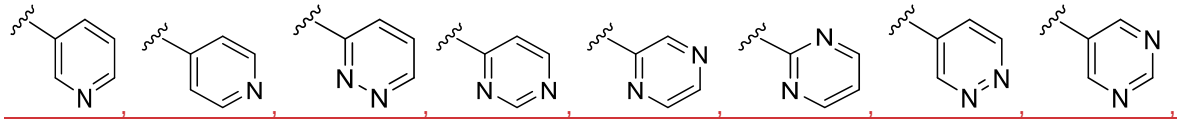
~~L^3 is optionally substituted C_2-C_9 heterocyclylene;~~

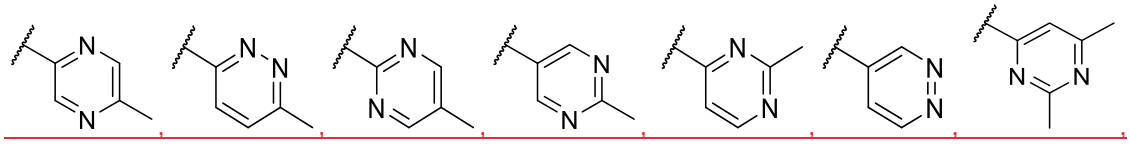
each of X^1, and X^2~~, X^3, and X^4~~ is, independently, N or CH;

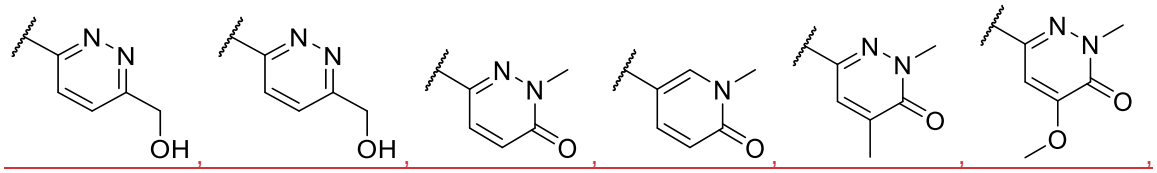
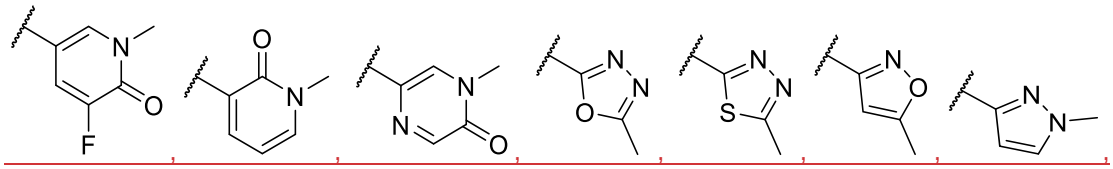
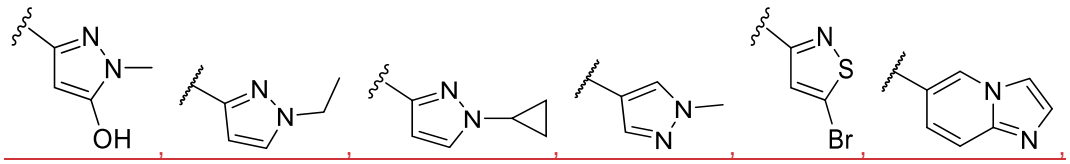
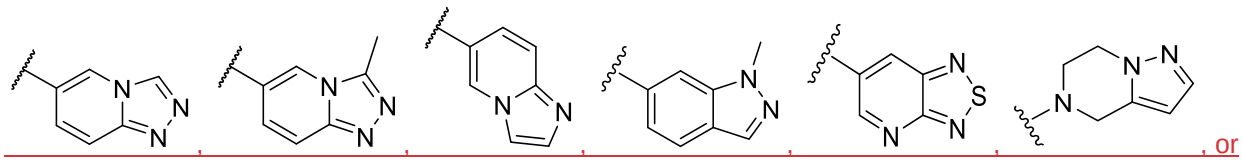
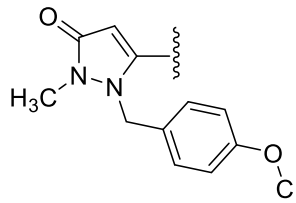
~~L^2 is optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene; and~~

R^2 is 







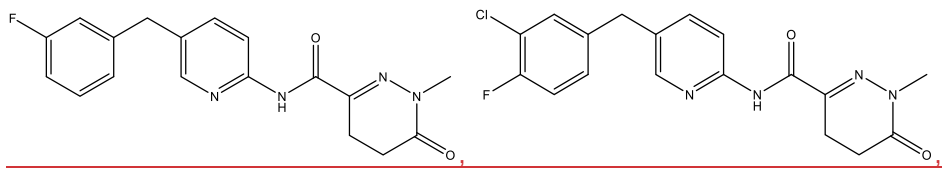
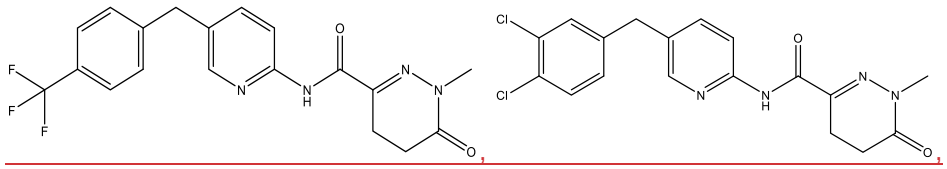
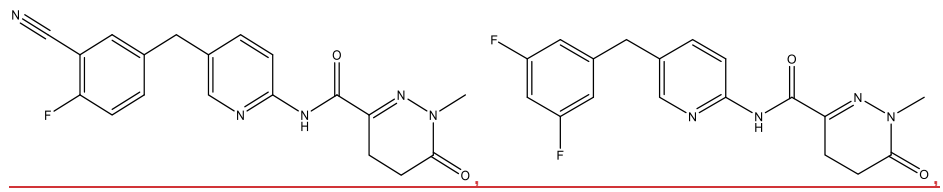






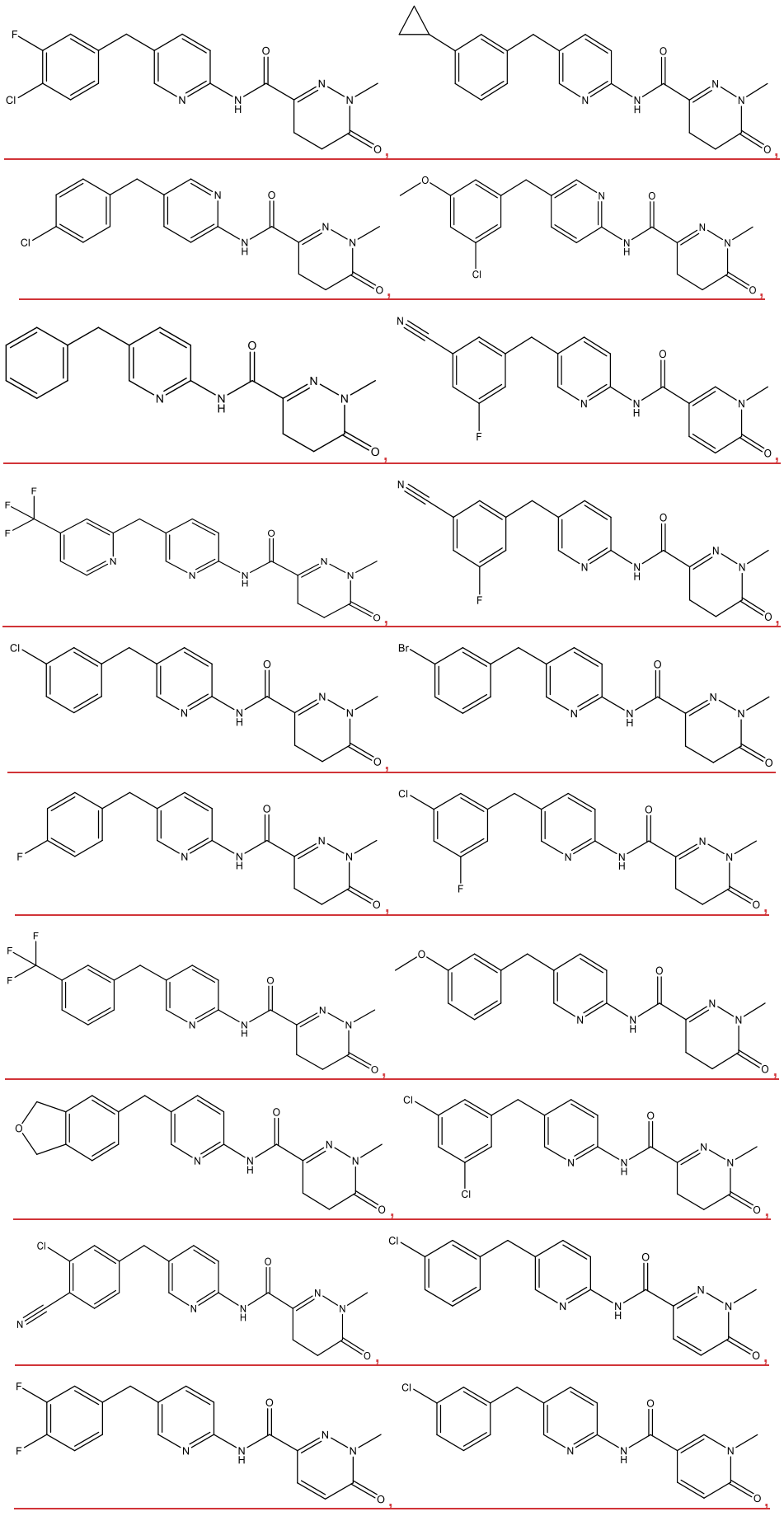
optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

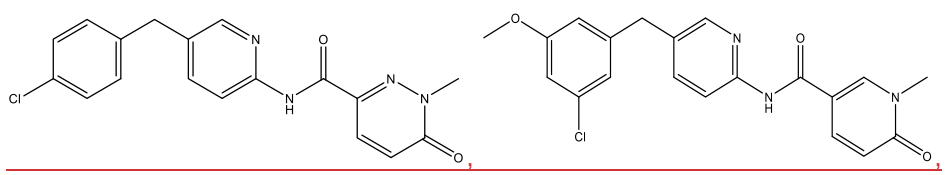
or a pharmaceutically acceptable salt thereof,

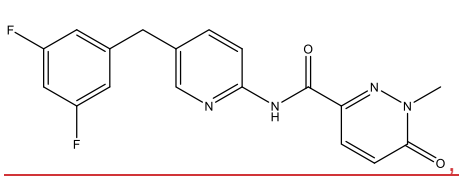
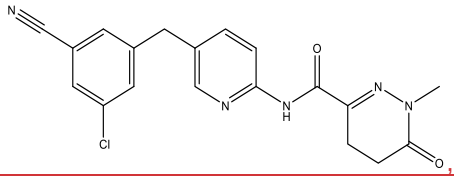
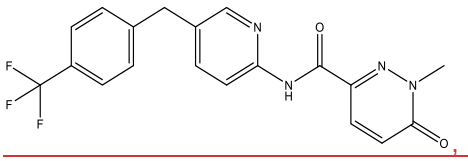
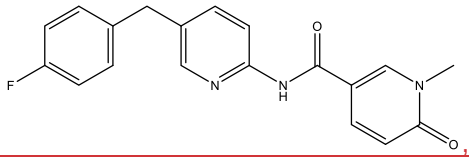
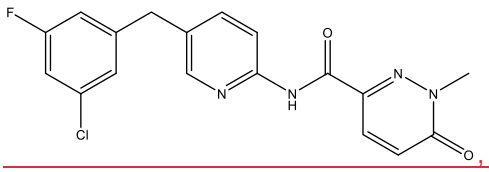
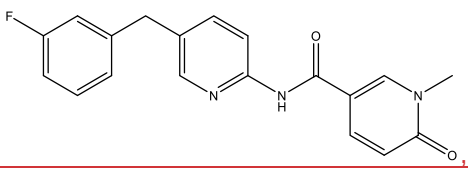
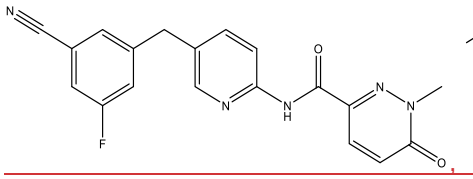
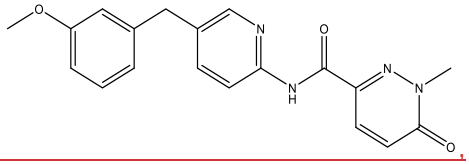
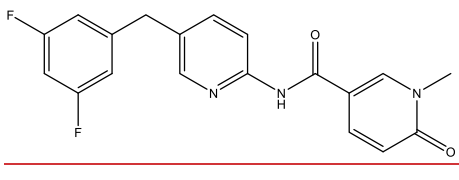
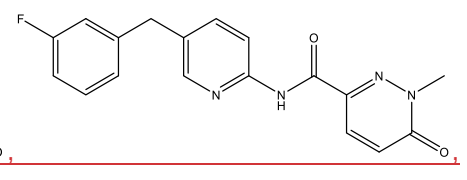
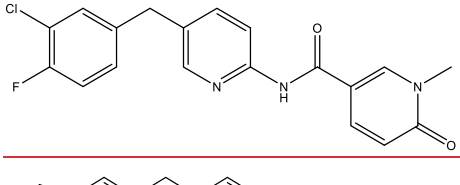
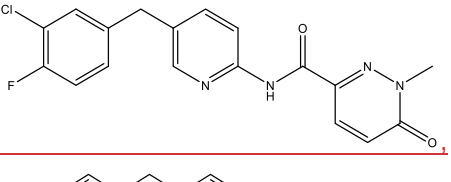
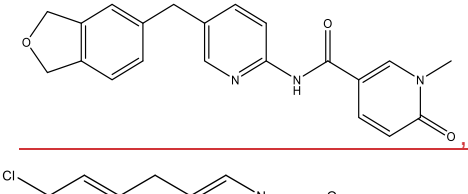
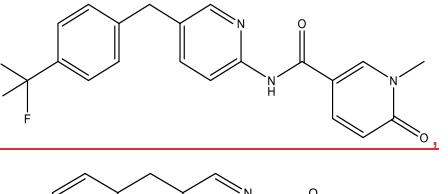
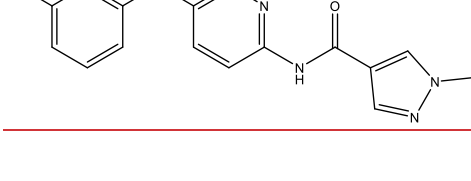
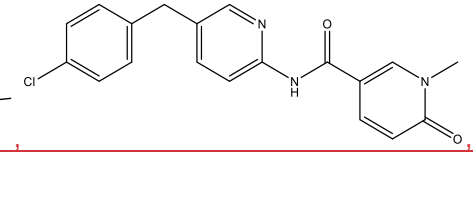
in the manufacture of a medicament for the treatment of a primary brain cancer in a subject in need thereof.

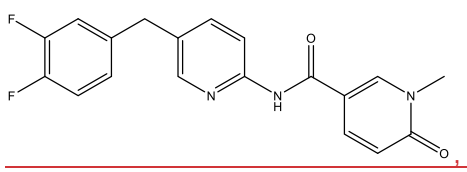
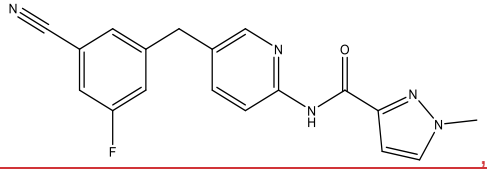
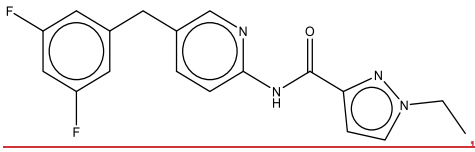
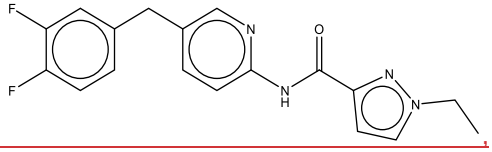
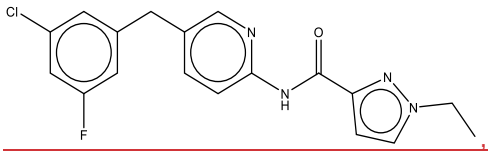
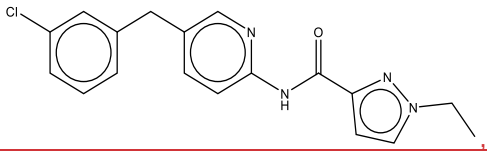
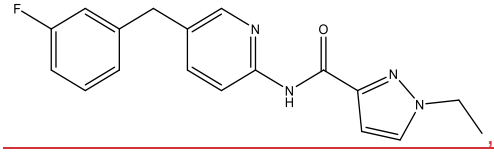
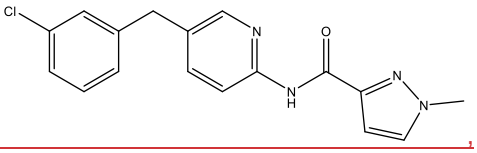
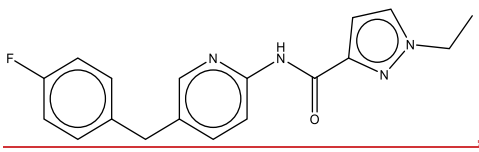
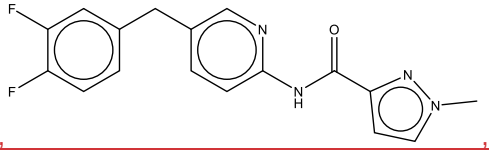
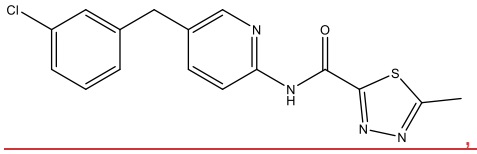
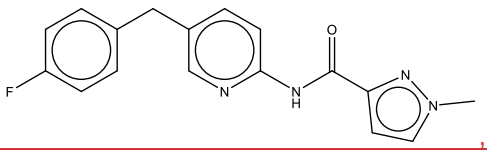
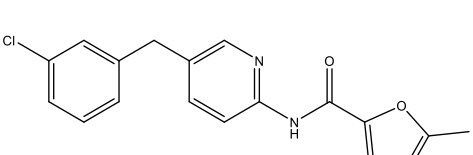
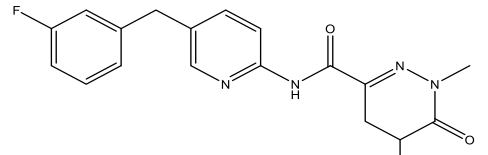
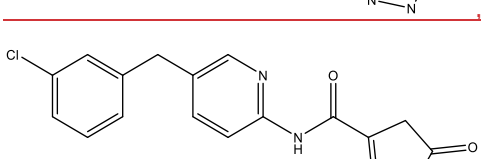
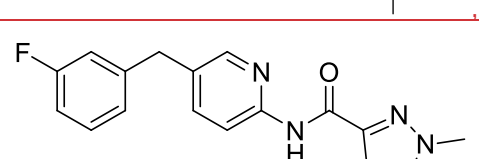
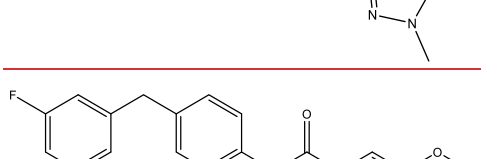
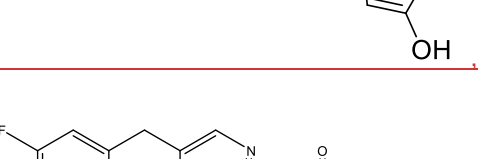
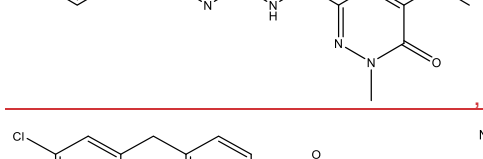
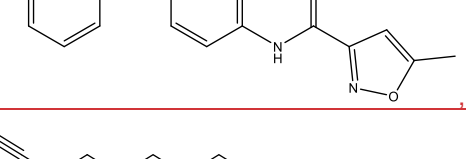
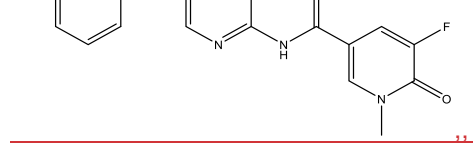
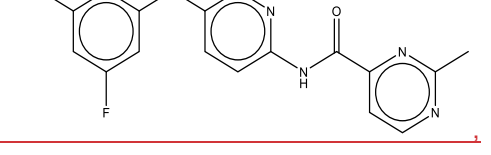
2. The use of claim 1, wherein the compound, or pharmaceutically acceptable salt thereof, has the structure of any one of compounds 1-475 in Table 1 or any one of compounds 476-683 in Table 2 is

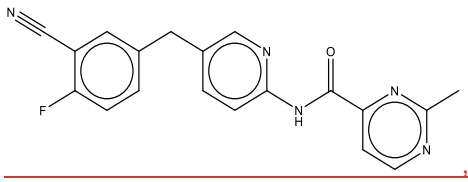
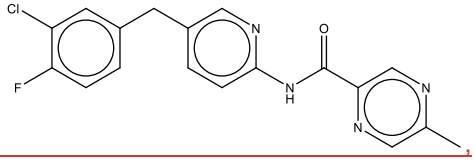
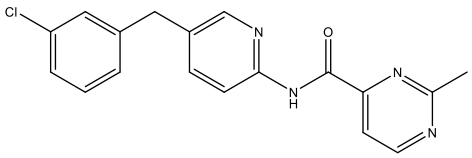
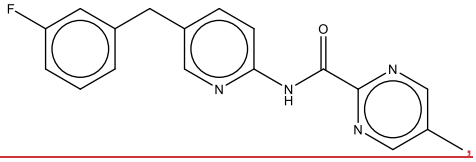
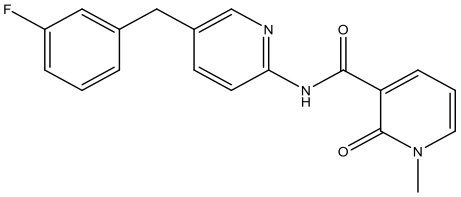
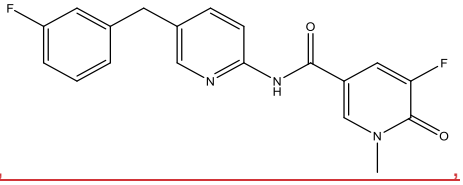
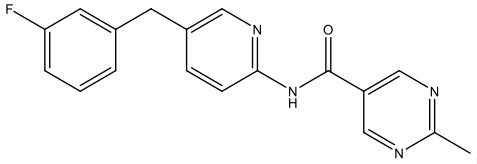
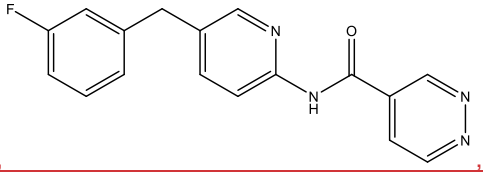
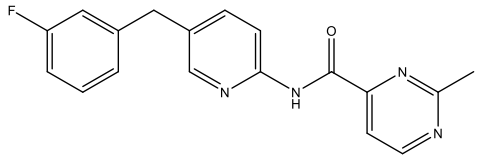
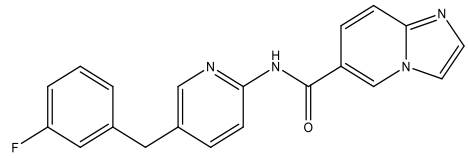
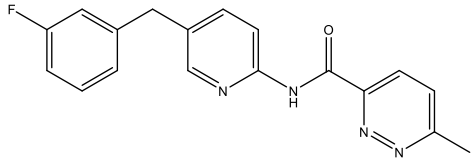
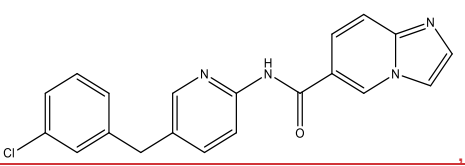
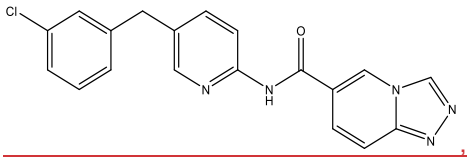
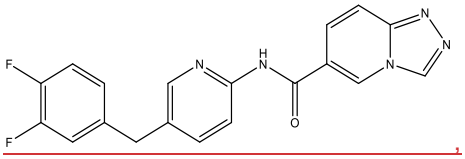
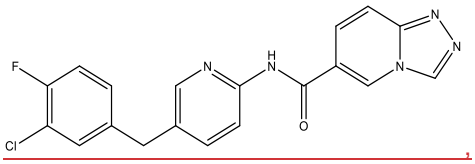
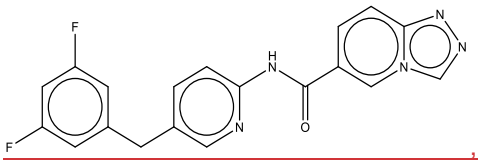


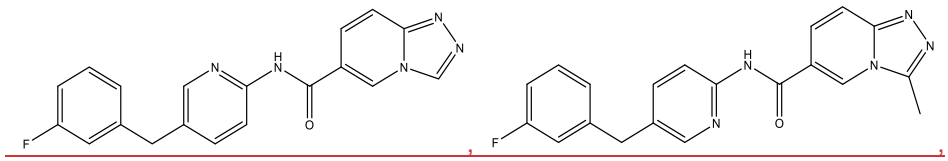


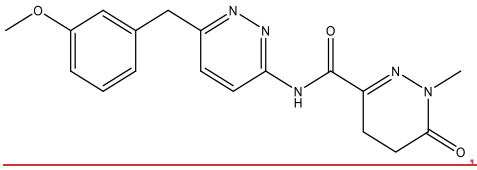
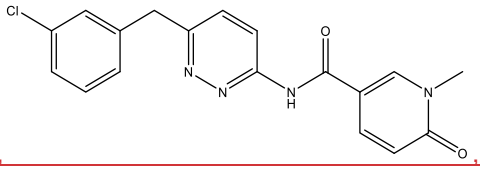
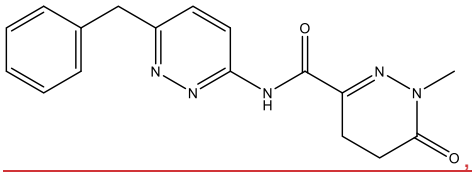
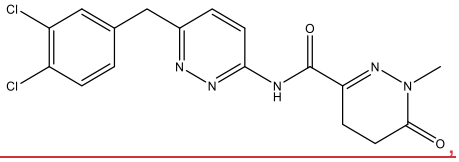
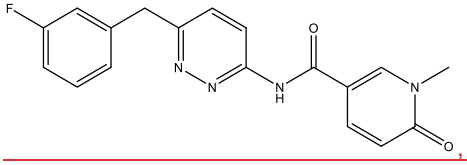
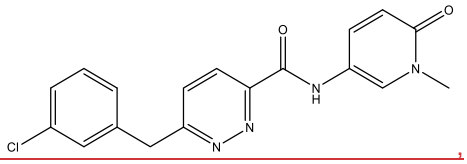
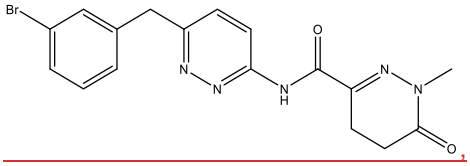
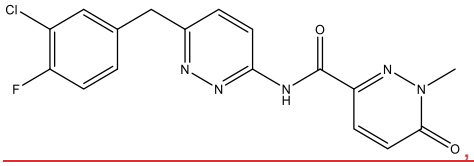
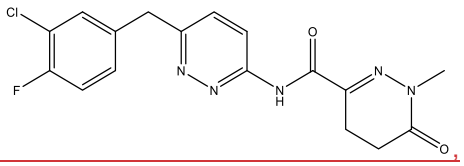
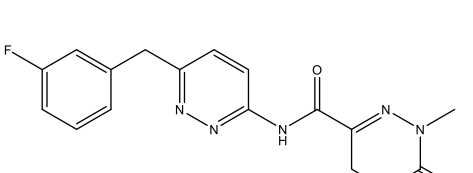
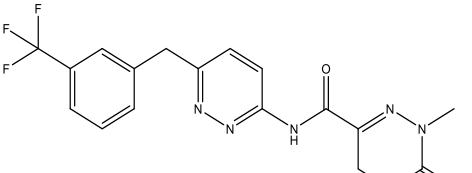
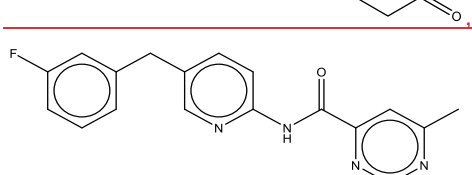
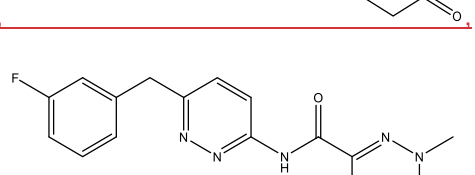

















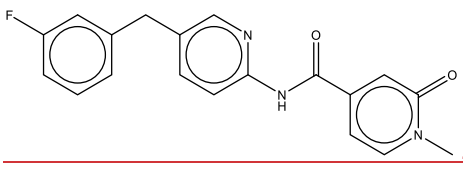
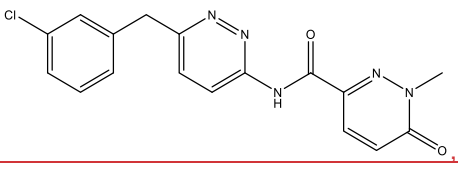
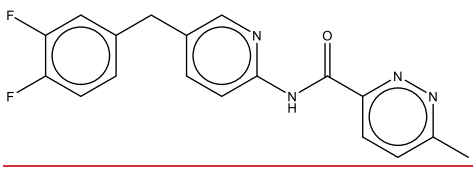
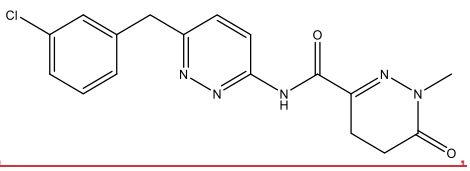























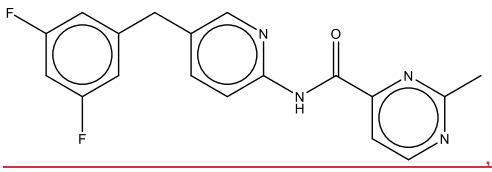


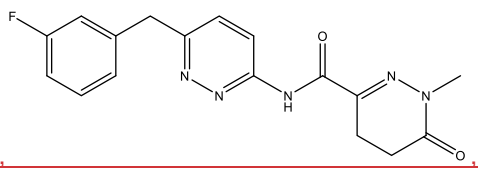

















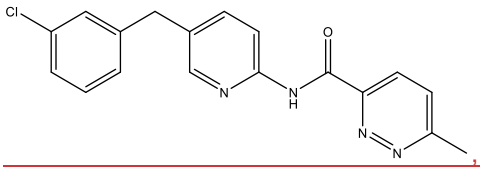


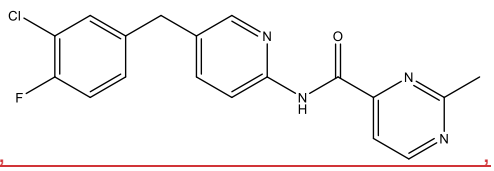














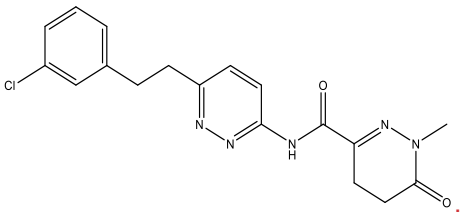





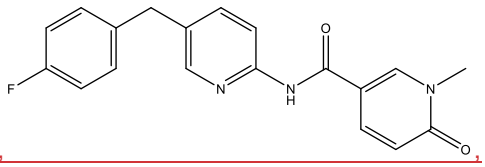


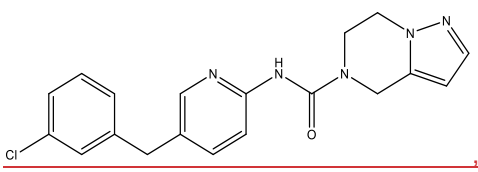


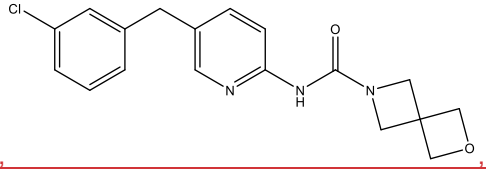


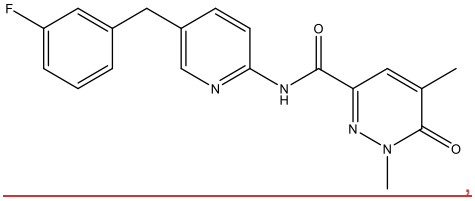


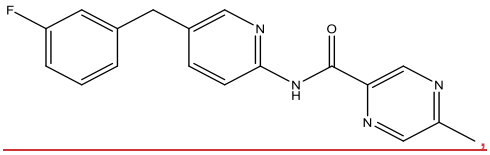


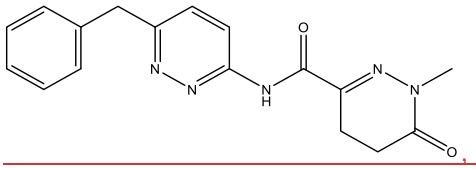


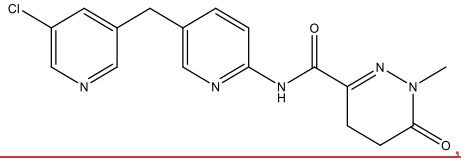


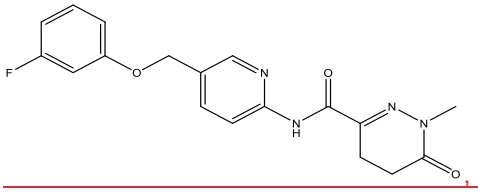


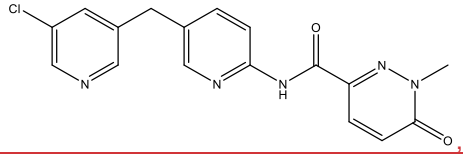


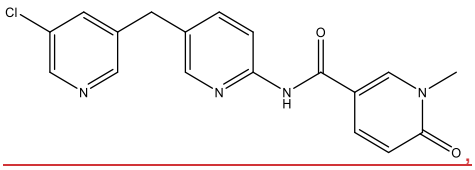


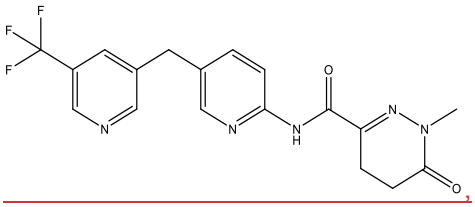


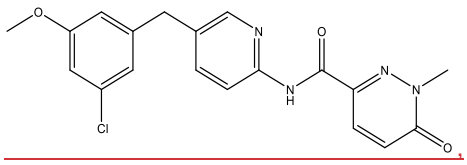


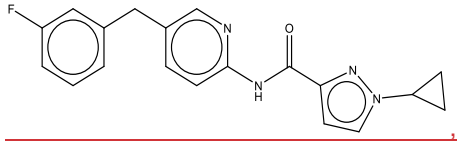


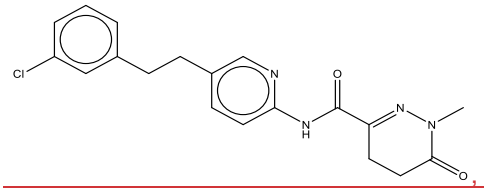


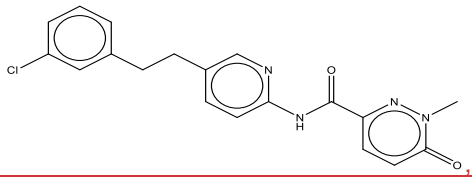


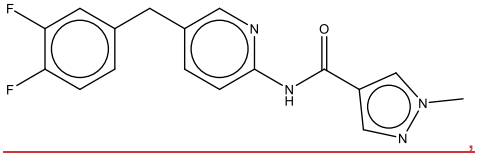


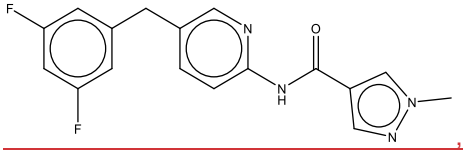


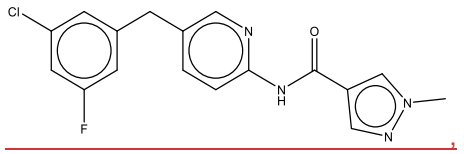


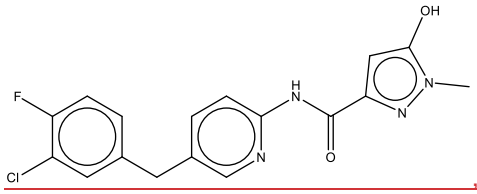


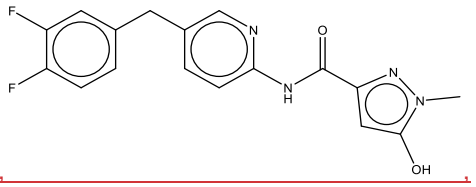


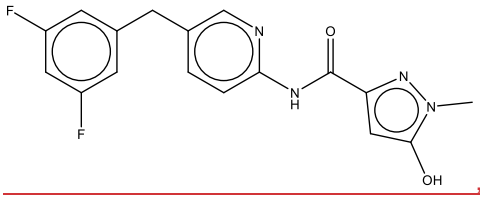


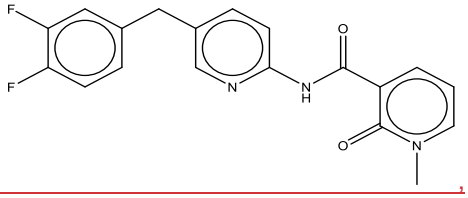


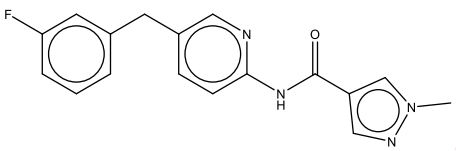


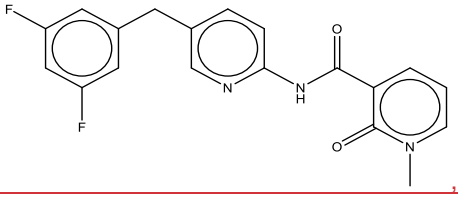


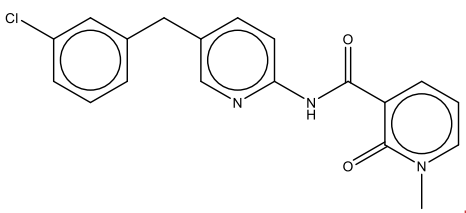


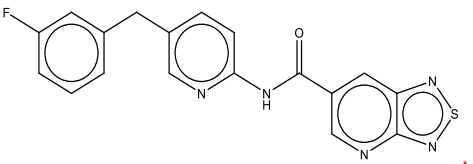


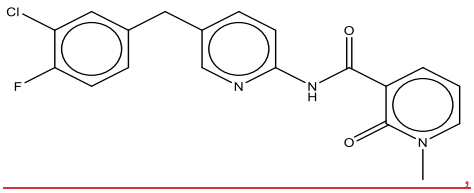


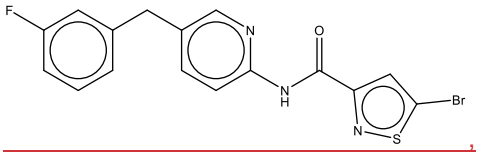


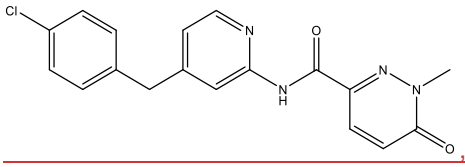


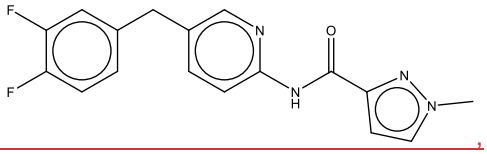


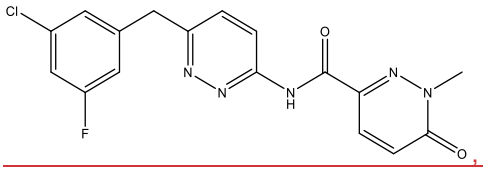


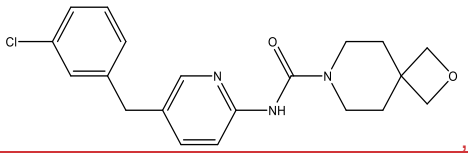


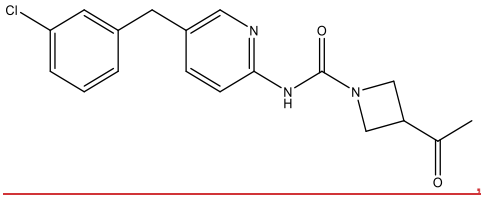


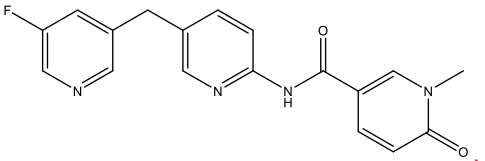


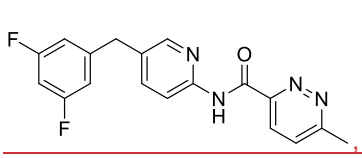


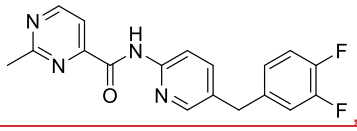


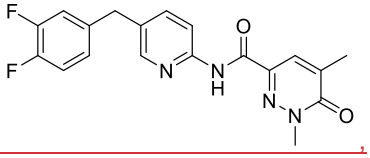


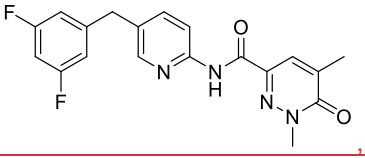


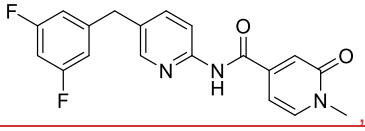


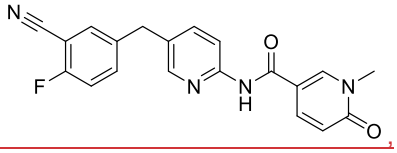


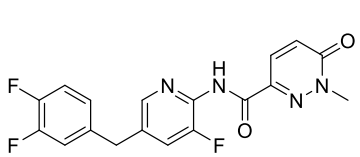


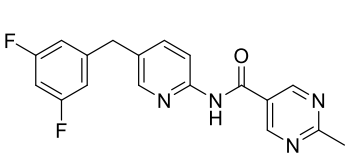


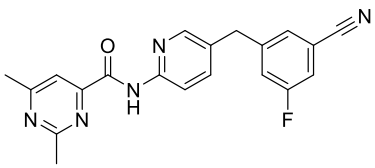


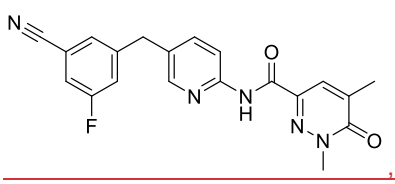


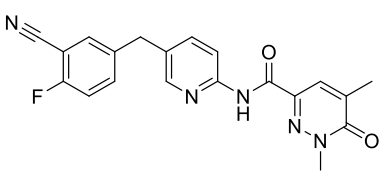


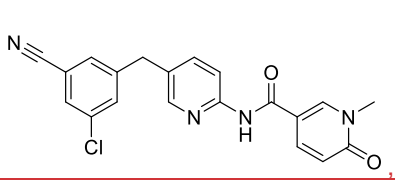


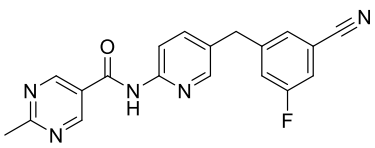


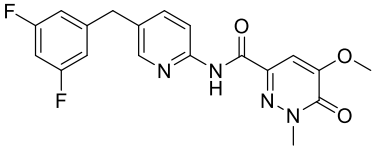


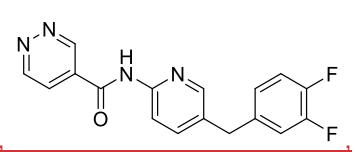


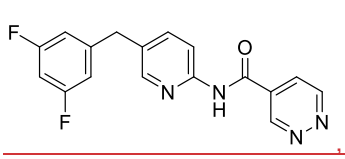
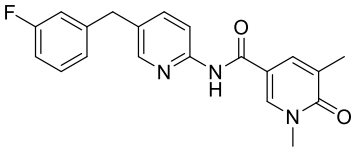
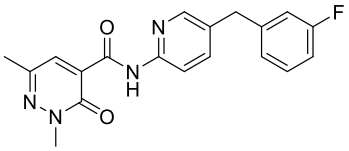
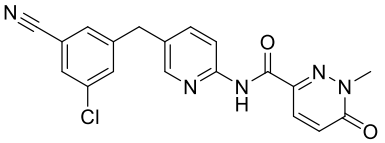
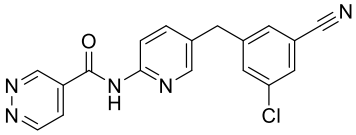
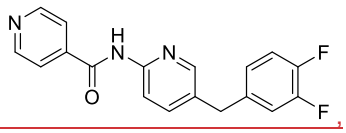
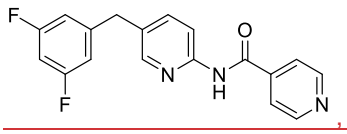
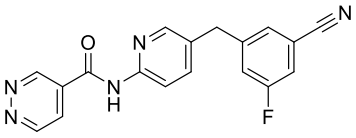
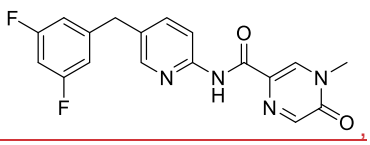
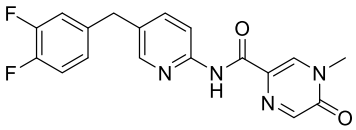
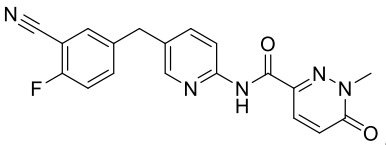








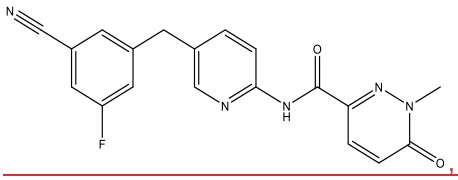
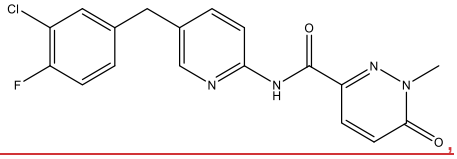
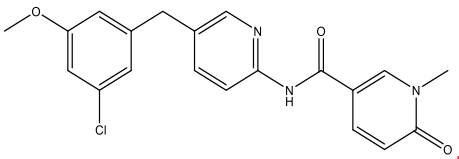
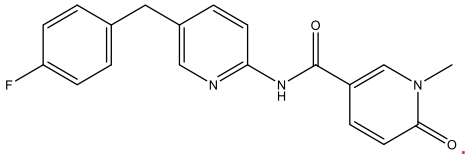
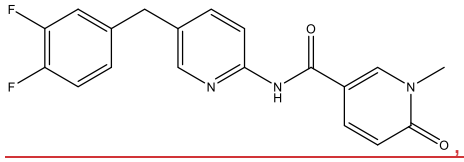
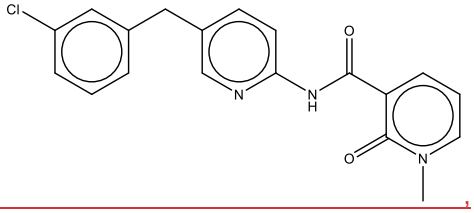
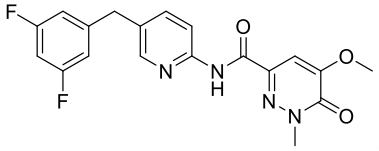
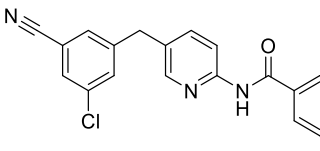


, or .

5

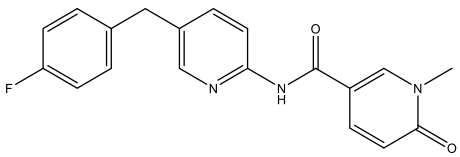
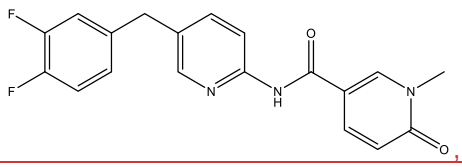
3. The use according to claim 1 or 2, wherein the compound is:

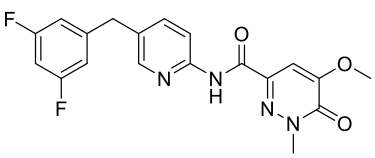
, or .

10

4. The use according to claim 1 or 2, wherein the compound is:

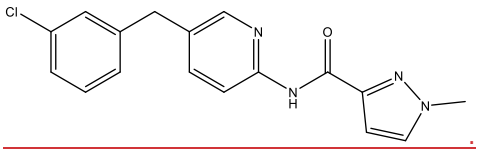



, or



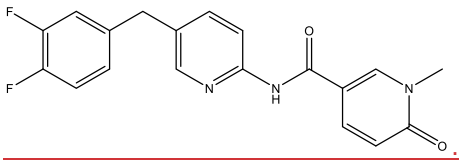
.

5. The use according to claim 1 or 2, wherein the compound is:



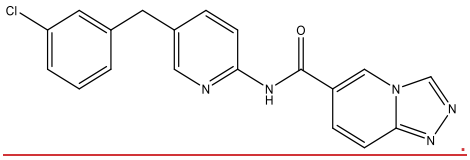
.

6. The use according to claim 1 or 2, wherein the compound is:



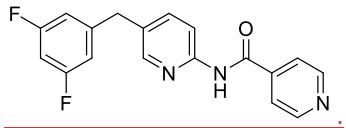
.

7. The use according to claim 1 or 2, wherein the compound is:



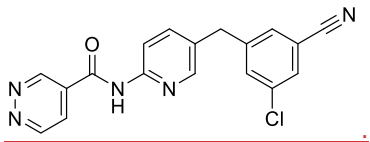
.

8. The use according to claim 1 or 2, wherein the compound is:



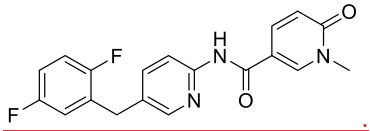
.

9. The use according to claim 1 or 2, wherein the compound is:



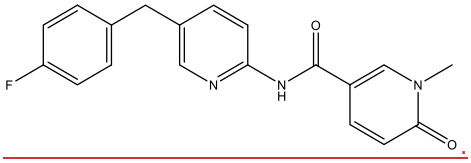
.

10. The use according to claim 1 or 2, wherein the compound is:



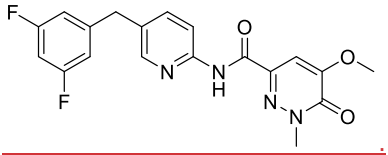
.

11. The use according to claim 1 or 2, wherein the compound is:



.

12. The use according to claim 1 or 2, wherein the compound is:



.

13. The use of any one of claims 1 to 12, wherein the brain cancer is primary brain cancer.

~~3~~14. The use of claim ~~1 or 2~~13, wherein the primary brain cancer is a glioma.

~~4~~15. The use of claim ~~3~~14, wherein the glioma is an astrocytoma.

~~5~~16. The use of claim ~~4~~15, wherein the astrocytoma is a glioblastoma.

~~6~~17. The use of any one of claims 1-~~5~~16, wherein the cancer is determined or predicted to be resistant to one or more chemotherapeutic agents.

18~~7~~. The use of any one of claims 1-~~6~~17, wherein the cancer has failed to respond to one or more chemotherapeutic agents.

~~8~~19. The use of claim ~~6~~ 17 or ~~7~~18, wherein one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

~~9~~20. The use of claim ~~8~~19, wherein one or more chemotherapeutic agents is temozolomide.

~~10~~21. The use of any one of claims 1-~~9~~20, wherein one or more additional therapeutic interventions is to be administered to the subject.

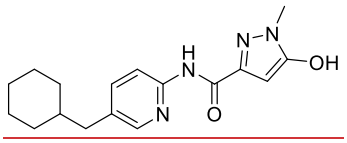
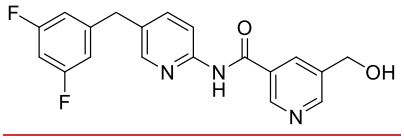
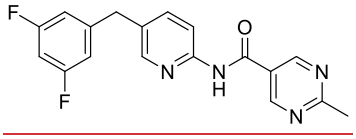
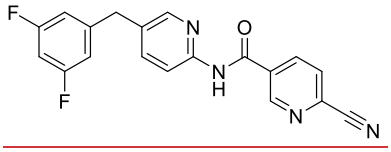
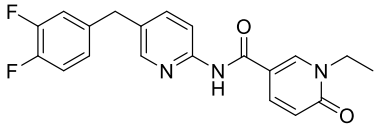
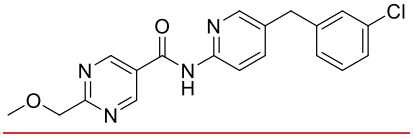
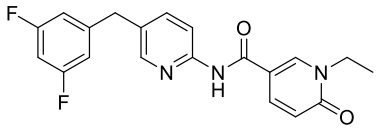
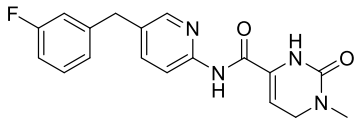
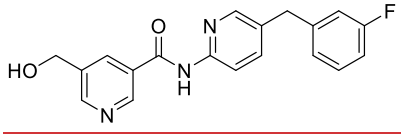
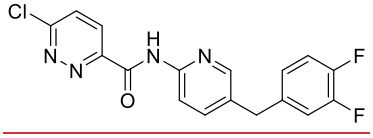
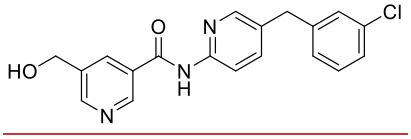
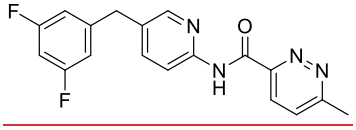
~~11~~22. The use of claim ~~10~~21, wherein one or more additional therapeutic interventions comprises surgery, radiation, and/or one or more additional chemotherapeutic agents.

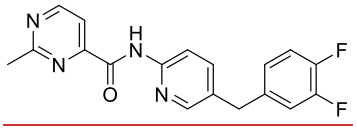
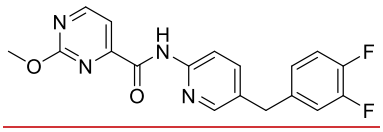
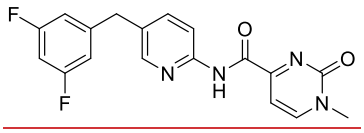
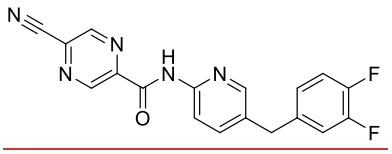
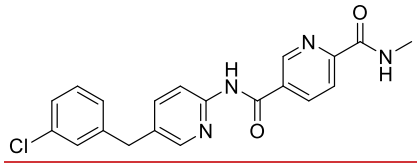
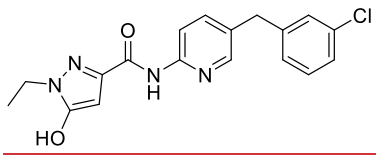
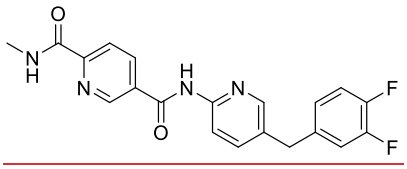
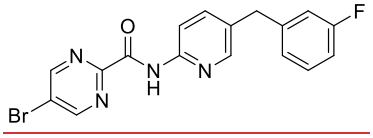
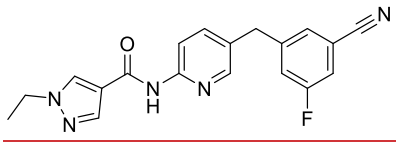
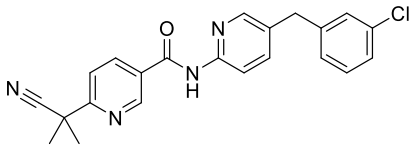
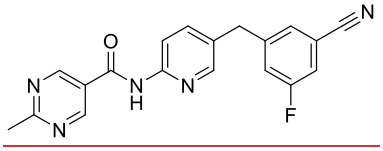
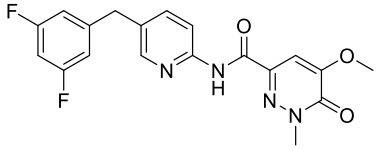
~~12~~23. The use of claim ~~11~~22, wherein one or more additional therapeutic interventions is one or more chemotherapeutic agents.

~~13~~24. The use of claim ~~12~~23, wherein one or more chemotherapeutic agents is selected from the group of temozolomide, carmustine, bevacizumab, lomustine, everolimus, vincristine, or procarbazine.

~~14~~25. The use of claim ~~13~~24, wherein one or more chemotherapeutic agents is temozolomide.

~~15~~26. A compound, ~~or pharmaceutically acceptable salt thereof, having~~ wherein the compound has the structure ~~of any one of compounds 476-683 in Table 2.~~

CMPD No.	Structure	CMPD No.	Structure
476		580	
		581	
478		582	
479		583	
480			
481		585	
483			
484			

CMPD No.	Structure	CMPD No.	Structure
485			
486		590	
		591	
		592	
489		593	
490		594	
491		595	
		596	

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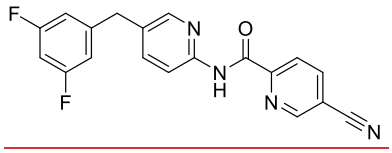
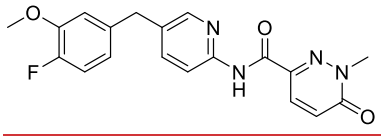
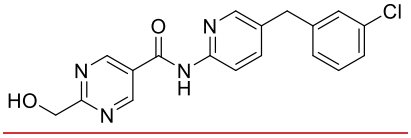
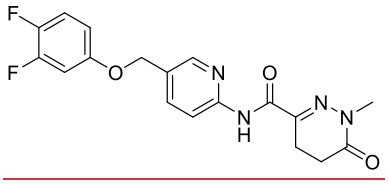
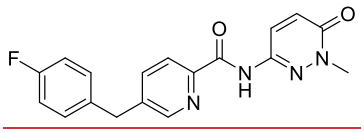
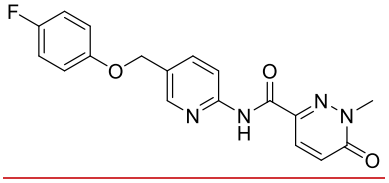
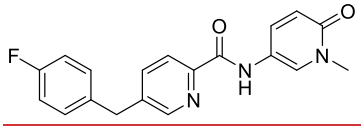
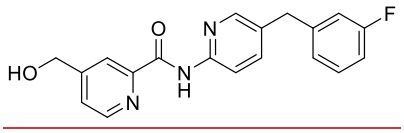
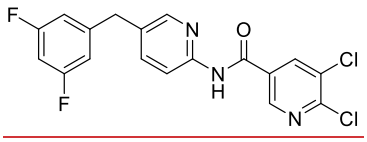
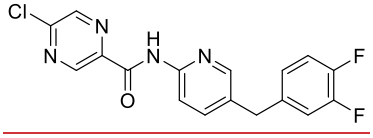
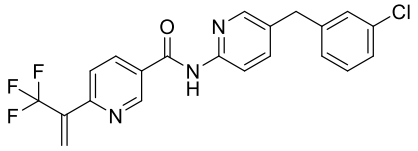
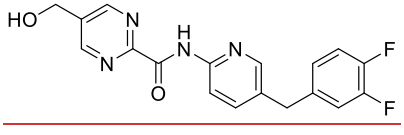
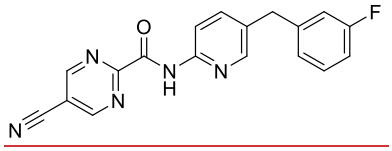
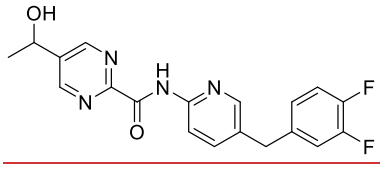
493		597	
494		598	
495		599	
496			
497		601	
		602	
499		603	
500		604	

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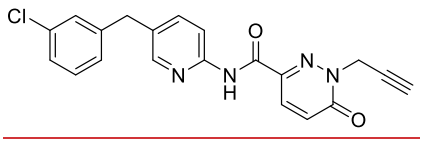
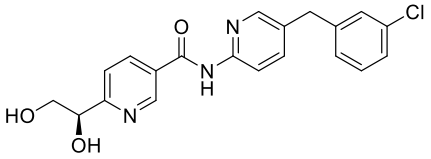
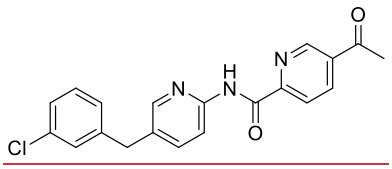
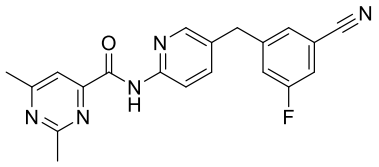
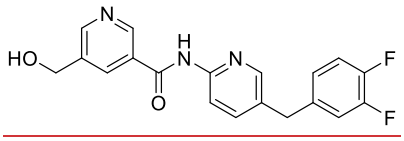
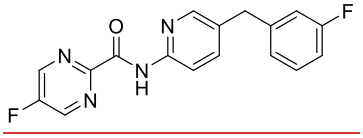
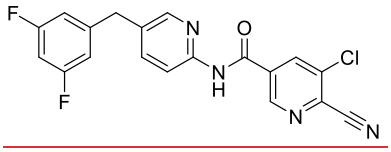
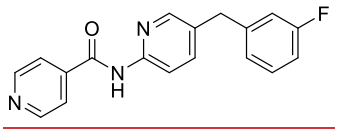
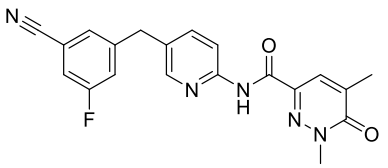
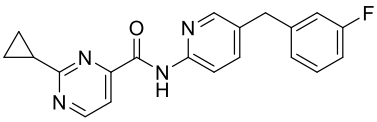
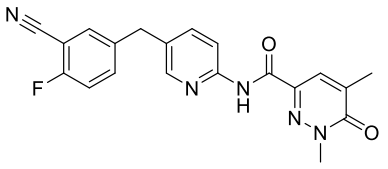
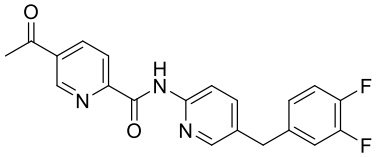
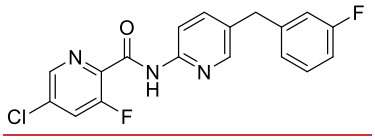
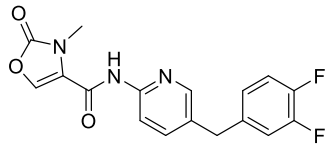
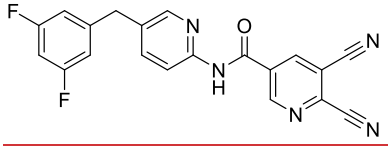
501		605	
502		606	
503			
504		608	
505		609	
506		610	
507		611	
508		612	

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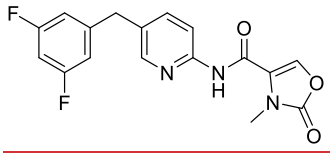
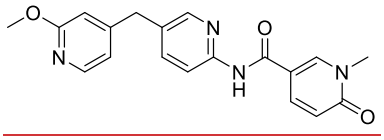
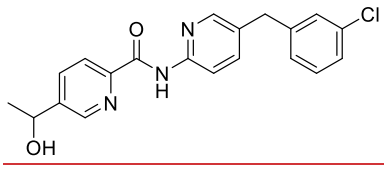
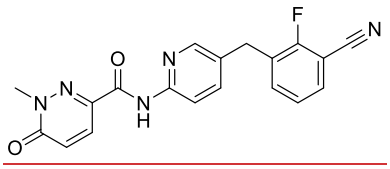
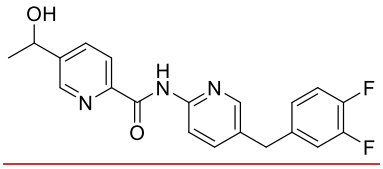
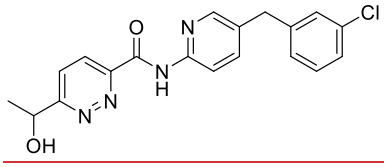
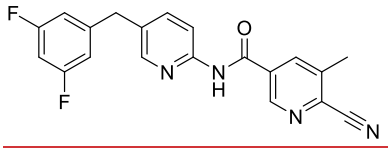
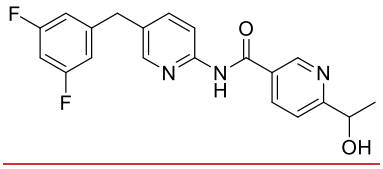
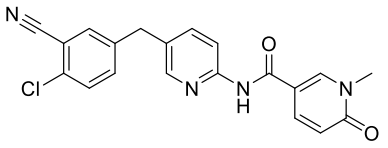
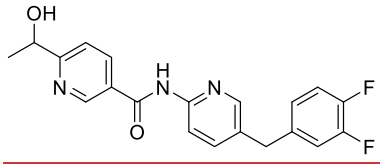
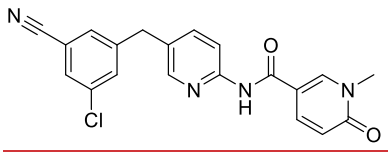
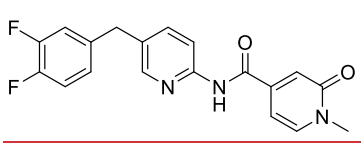
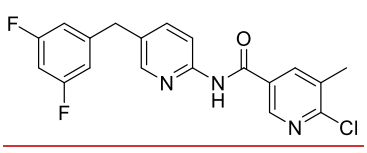
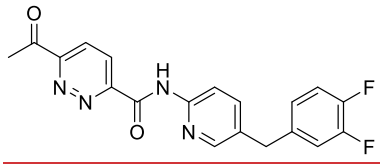
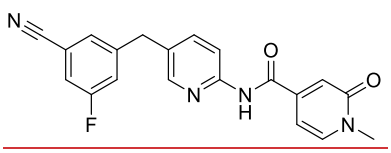
509		613	
510		614	
511			
512		616	
513		617	
514		618	
515		619	
516		620	

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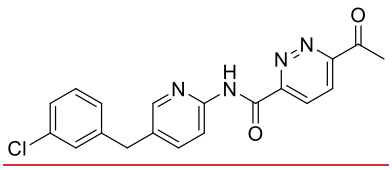
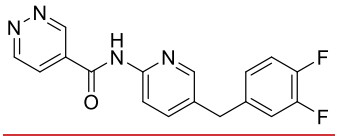
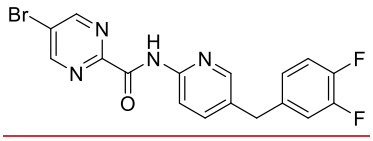
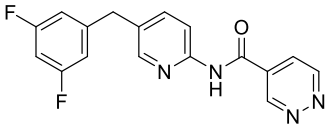
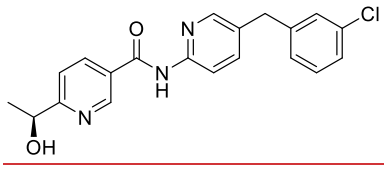
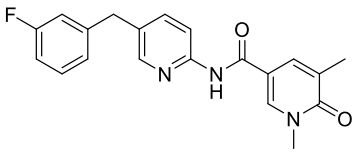
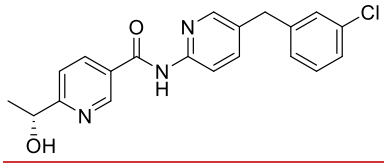
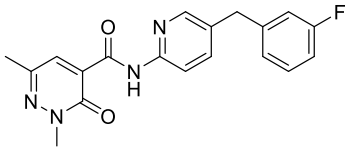
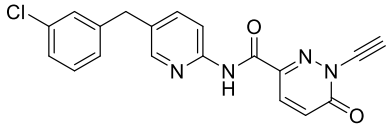
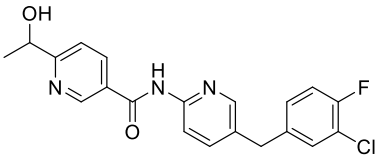
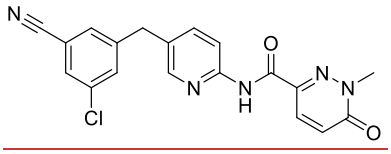
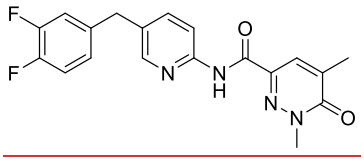
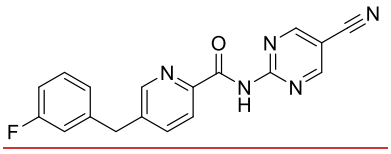
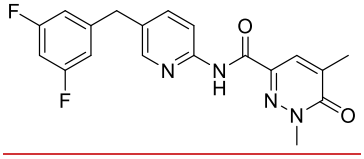
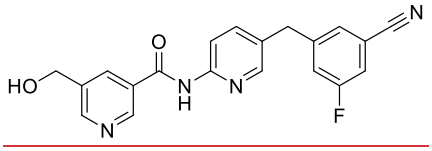
517		621	
518		622	
519		623	
520		624	
521			
522		626	
523		627	
524		628	

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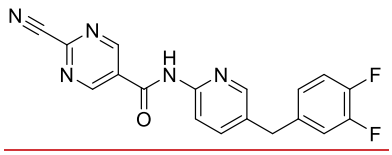
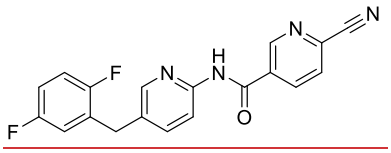
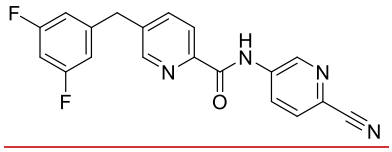
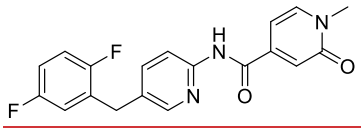
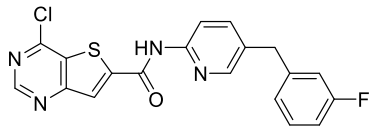
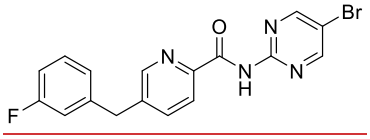
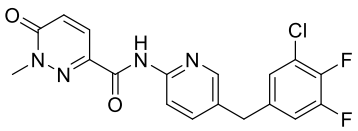
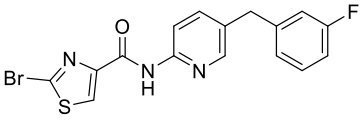
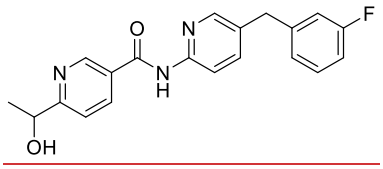
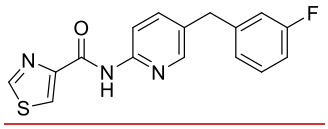
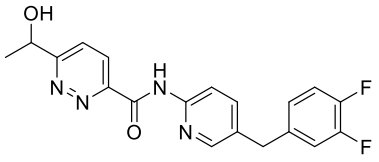
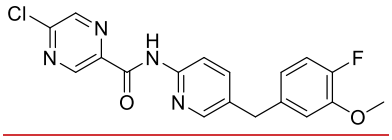
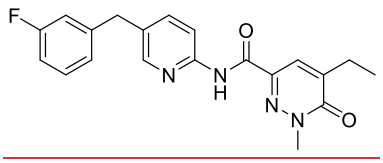
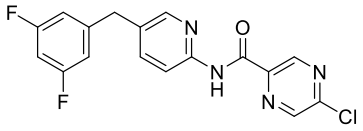
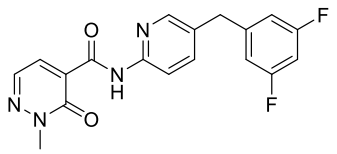
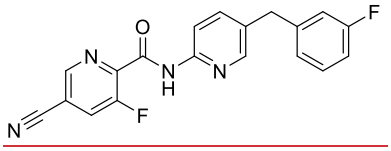
525		629	
526		630	
527		631	
528		632	
529		633	
530		634	
531		635	
532		636	

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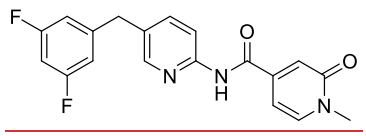
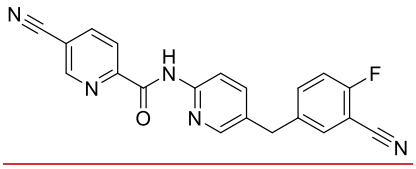
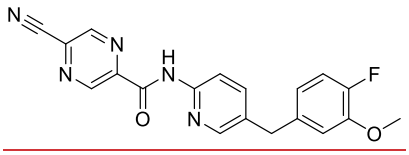
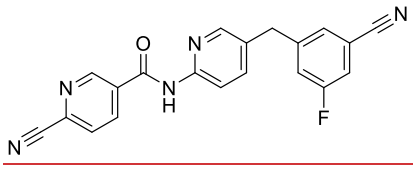
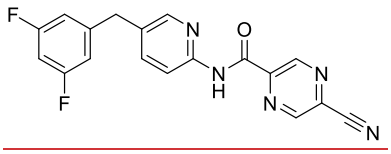
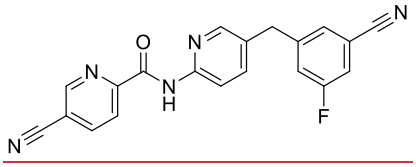
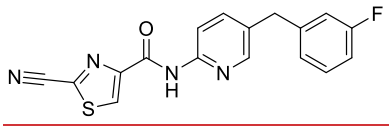
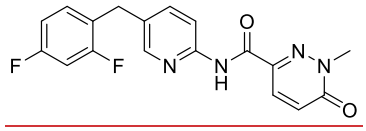
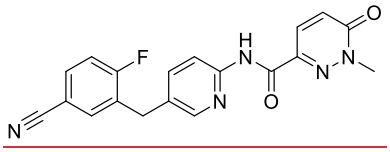
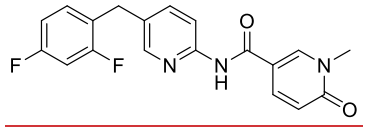
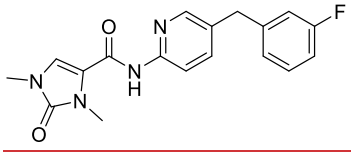
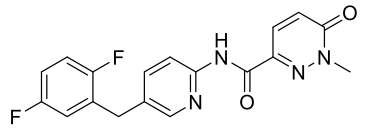
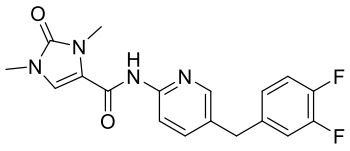
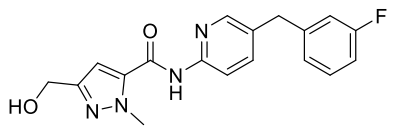
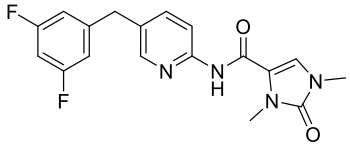
533			
534		638	
535		639	
536		640	
537		641	
538		642	
539		643	
540		644	

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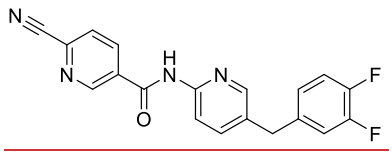
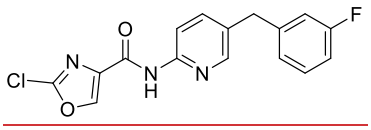
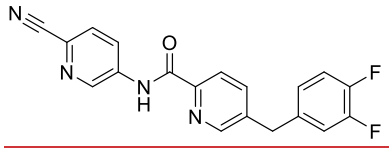
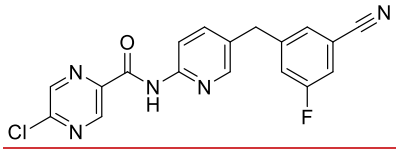
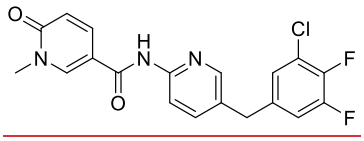
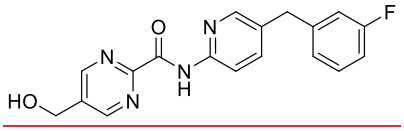
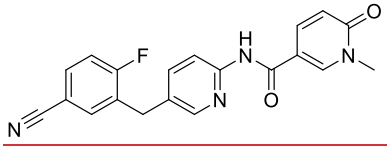
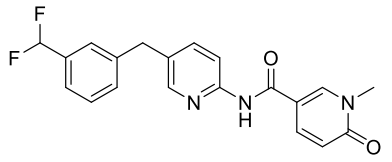
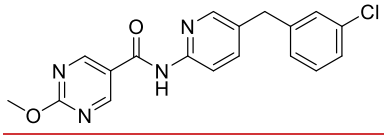
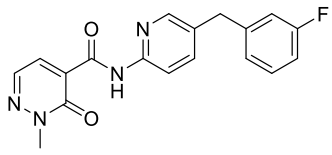
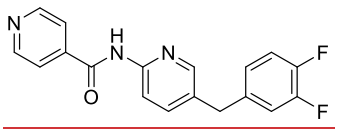
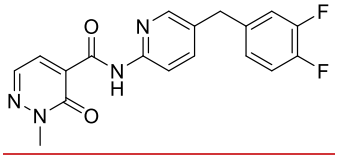
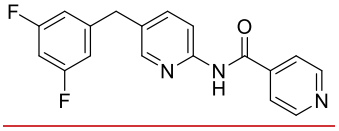
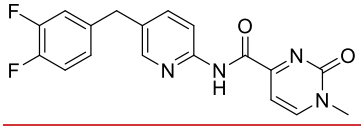
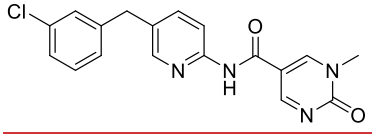
541		645	
542		646	
543			
544		648	
545		649	
546		650	
547		651	
548		652	

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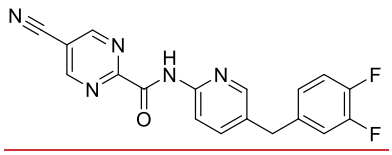
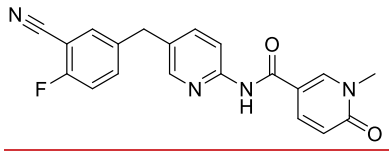
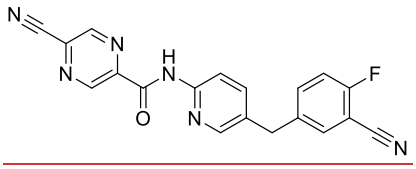
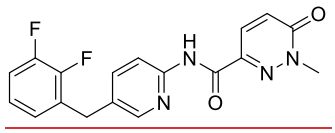
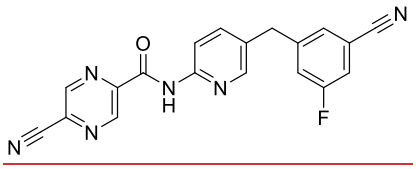
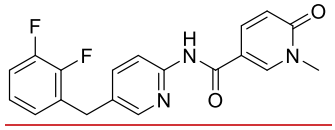
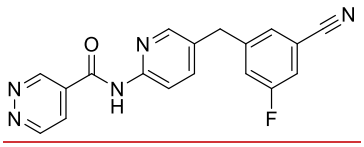
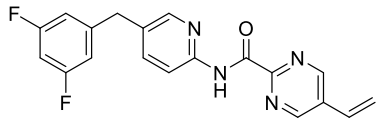
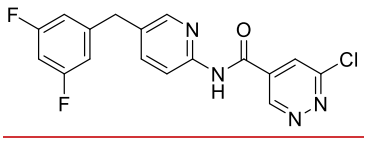
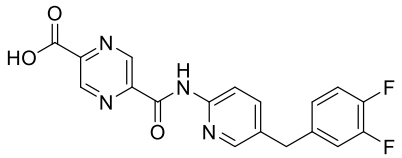
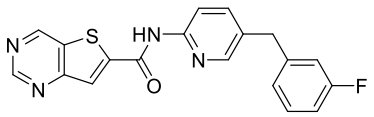
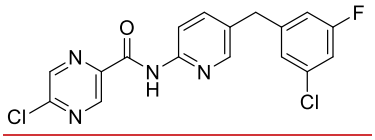
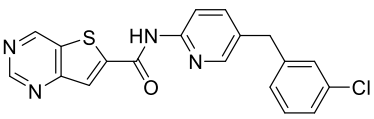
549			
550		654	
551		655	
552		656	
553		657	
554			
555		659	
556			

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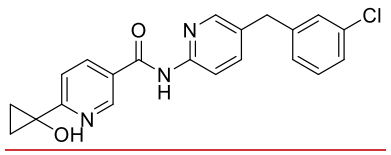
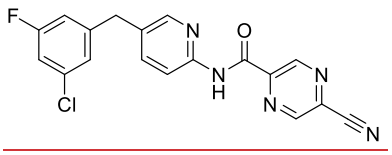
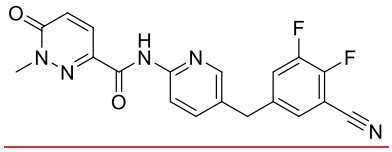
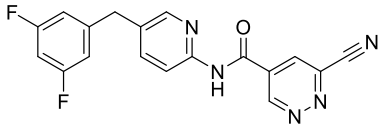
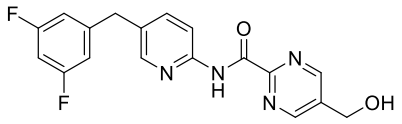
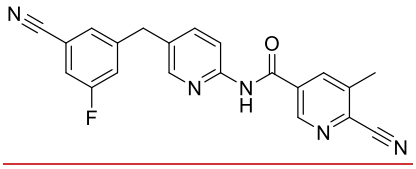
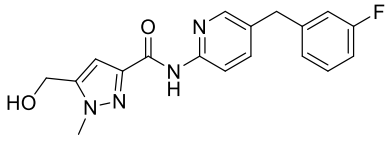
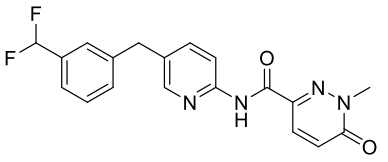
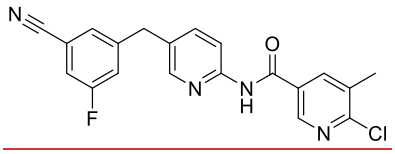
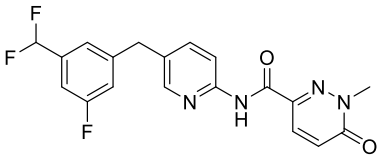
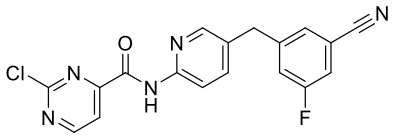
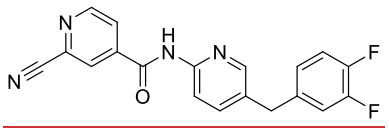
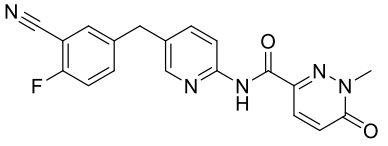
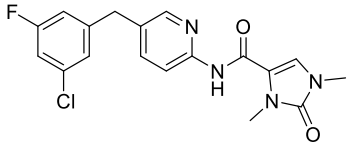
557		661	
558		662	
559		663	
560			
561		665	
562		666	
563			
564		668	

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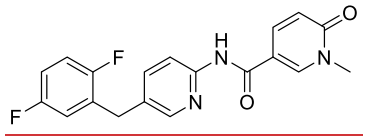
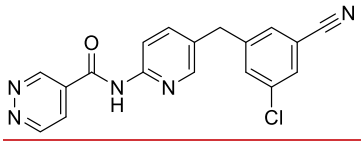
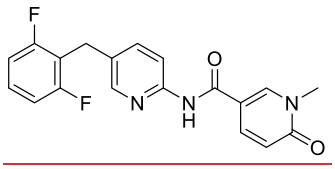
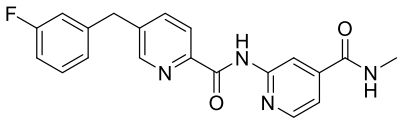
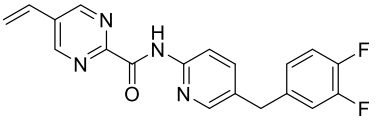
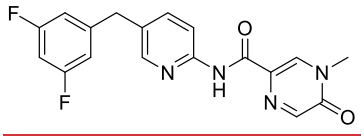
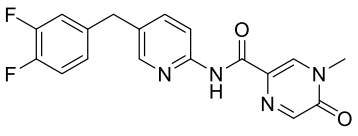
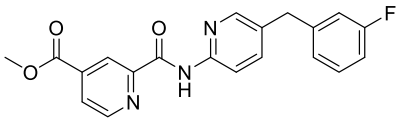
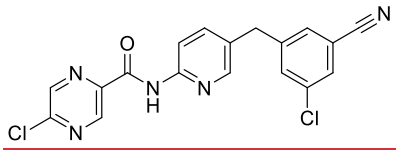
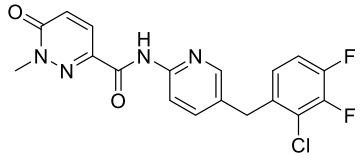
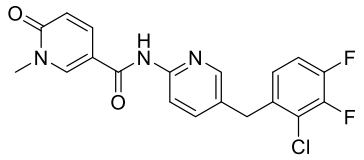
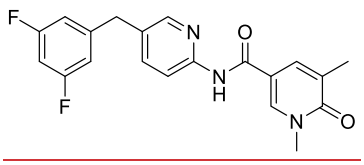
565		669	
566			
567			
568		672	
		673	
570		674	
571			
572		676	

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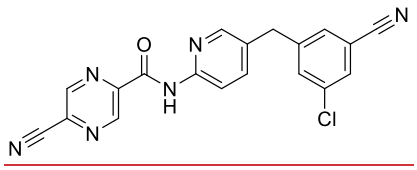
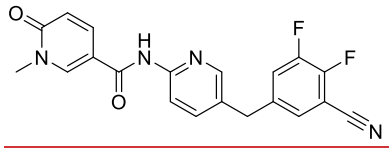
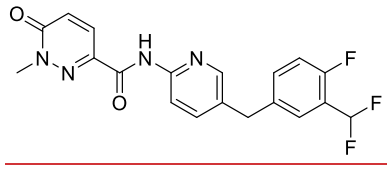
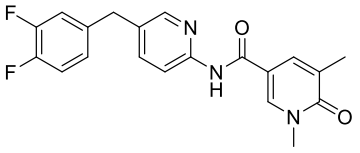
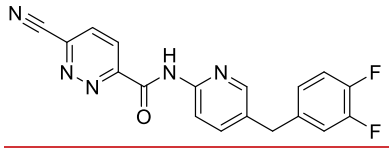
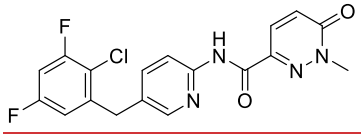
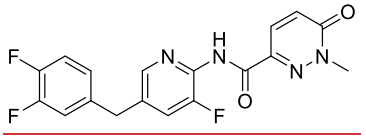
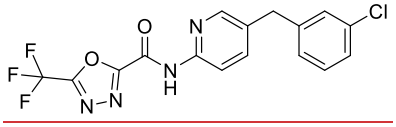
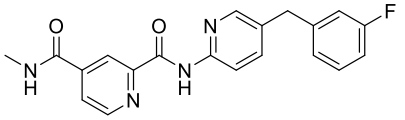
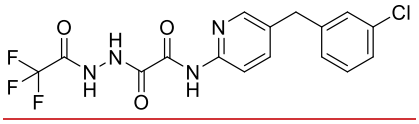
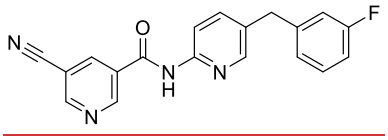
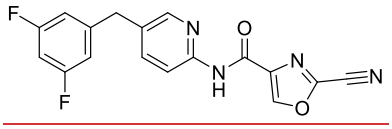
		677	
574			
575		679	
576		680	
577		681	
578		682	
579		683	

or pharmaceutically acceptable salt thereof.

~~16~~27. A pharmaceutical composition comprising a compound~~, or pharmaceutically acceptable salt thereof,~~ of claim ~~15~~26, and a pharmaceutically acceptable excipient.

28. Use of a compound of claim 26 in the manufacture of a medicament for the treatment of brain cancer in a subject in need thereof.

~~17. Use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for the treatment of a neurological disorder in a subject in need thereof.~~

~~18. Use of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting toxicity in a cell related to a protein.~~

~~19. The use of claim 18, wherein the toxicity is α-synuclein-related toxicity.~~

~~20. The use of claim 18, wherein the toxicity is ApoE4-related toxicity.~~

~~21. The use of any one of claims 18 to 20, wherein the cell is a mammalian neural cell.~~

~~22. Use of an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof.~~

~~23. The use of claim 22, wherein the SCD-associated disorder is a SCD5-associated disorder.~~

~~24. Use of an effective amount of a compound of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting SCD5.~~

~~25. Use of an effective amount of a compound of claim 15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for inhibiting SCD1.~~