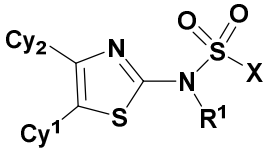
plasma membrane, is instead retained in the endoplasmic reticulum and targeted for degradation by the ubiquitin-proteasome system.

The loss of a functional CFTR channel at the plasma membrane disrupts ionic homeostasis and airway surface hydration leading to reduced lung function. Reduced periciliary liquid volume and increased mucus viscosity impede mucociliary clearance resulting in chronic infection and inflammation. In the lung, the loss of CFTR-function leads to numerous physiological effects downstream of altered anion conductance that result in the dysfunction of additional organs such as the pancreas, intestine and gall bladder.

Guided, in part, by studies of the mechanistic aspects of CFTR misfoldingand dysfunction, small molecule CFTR modulators have been identified, that can increase CFTR channel function. Despite the identification of compounds that modulate CFTR, there is no cure for this fatal disease and identification of new compounds and new methods of therapy are needed as well as new methods for treating or lessening the severity of cystic fibrosis and other CFTR mediated conditions and diseases in a patient.

SUMMARY

In one aspect of the present disclosure, there is provided a compound of Formula (**I**):



(**I**)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen;

X is phenyl, substituted with 0-3 occurrences of R^2;

Cy^1 is phenyl, substituted with 0-3 occurrences of R^3;

Cy^2 is phenyl, substituted with 1-3 occurrences of R^4;

each R^2 is independently halo, $-NH_2$, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 4-10 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-9} cycloalkyl, $-C(O)NH_2$, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, $-N(R^a)SO_2-R^5$, $-SO_2-R^5$, $-C(O)N(R^a)(R^5)$, $-S(O)-R^5$, $-N(R^a)S(O)(NH)-R^5$ or $-P(O)(R^5)_2$, wherein each C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^5;

each R^3 is independently halo, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{3-9} cycloalkyl, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{3-9}

cycloalkenyl, 5-6 membered heteroaryl, 4-10 membered heterocycloalkyl, -C(O)-R^7, -C(O)N(R^a)(R^7) or -N(R^a)(R^8), wherein each C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-8} alkoxy, 4-10 membered heterocycloalkyl, 5-6 membered aryl, 5-6 membered heteroaryl, cycloalkenyl, or C_{1-4} alkoxy-C_{3-9} cycloalkyl is further substituted with 0-3 occurrences of R^7;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, or N(R^a)$_2$ or 4-10 membered heterocycloalkyl;

each R^5 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-9} cycloalkyl, hydroxyl, -SO_2-R^6, -CO_2H, -NH_2, -CO_2-C_{1-4} alkyl or 4-10 membered heterocycloalkyl, wherein each C_{1-6} alkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^6;

each R^6 is independently hydroxyl, -NH_2, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, -CO_2H or -CO_2-(C_{1-4} alkyl);

each R^7 is independently halo, C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} haloalkyl, C_{1-5} haloalkoxy, C_{1-5} haloalkenyl, C_{3-7} cycloalkyl, hydroxyl, 5-6 membered aryl, aralkyl, aralkoxy, -C(O)-O-C_{1-4}alkyl, -C(O)N(R^a)(C_{1-4} alkyl), 5-6 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein each C_{3-7} cycloalkyl, 5-6 membered aryl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^8;

each R^8 is independently halo, C_{1-4} alkyl, C_{1-4} haloalkoxy, C(O)-C_{1-4} alkyl or C(O)N(R^a)(C_{1-4} alkyl);

each R^a is independently H or C_{1-6} alkyl; and

each R^b is C_{1-4} alkyl;

wherein

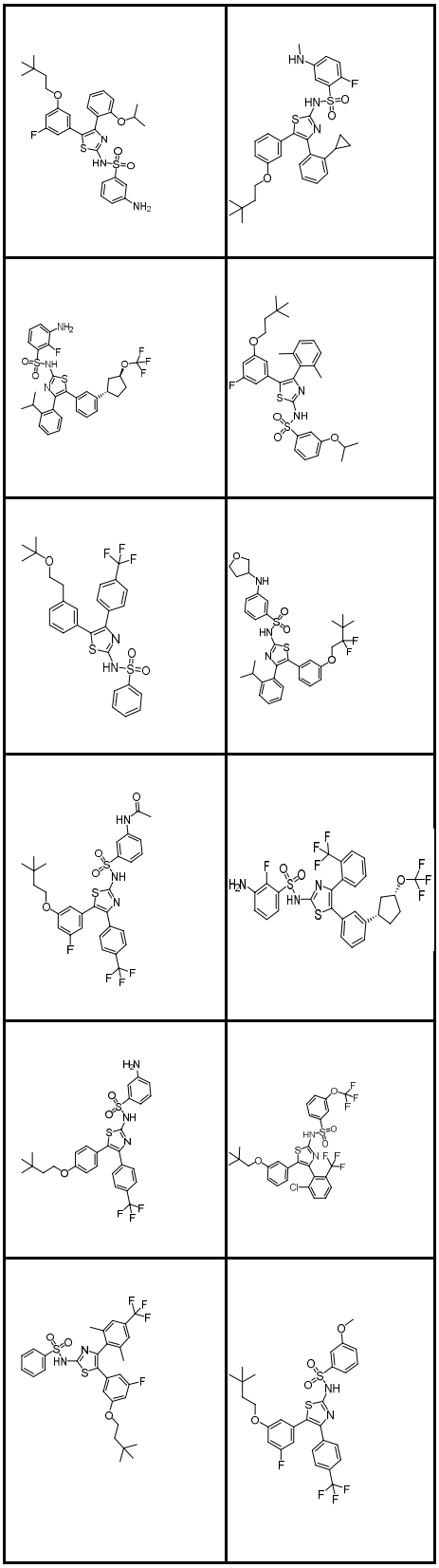
a) if Cy^1 has 3 occurrences of R^3, then each R^3 is not methoxy;

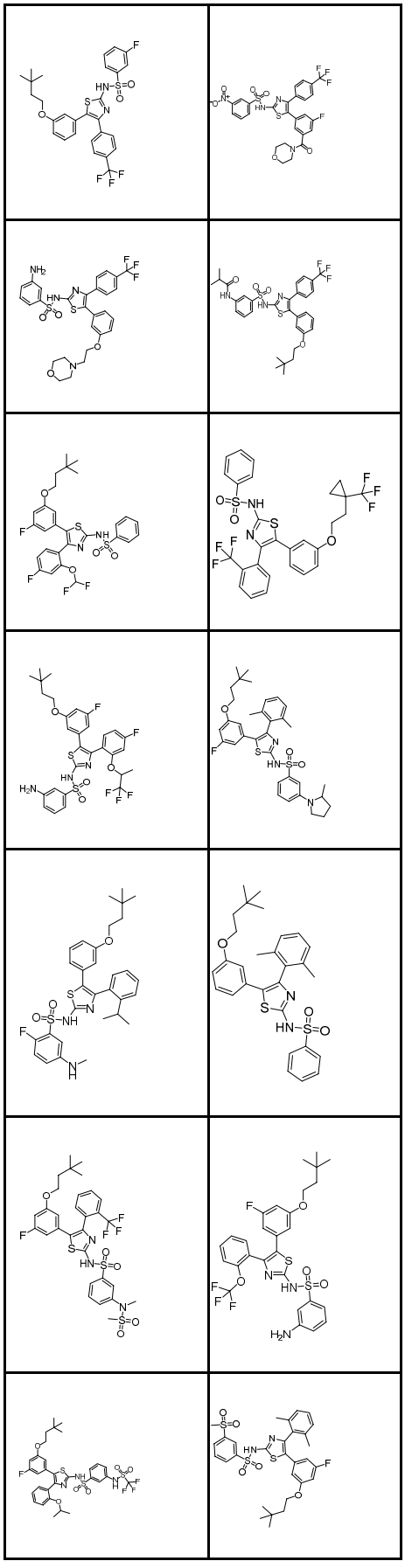
b) R^2 and R^4 are both methyl;

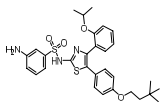
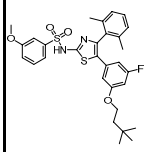
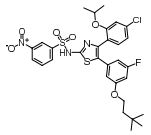
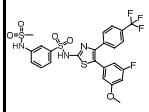
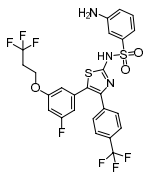
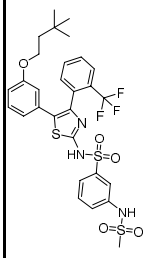
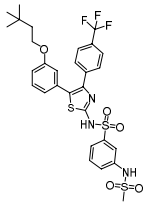
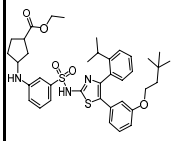
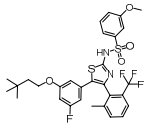
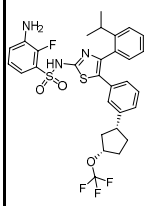
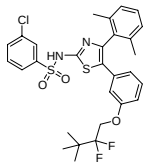
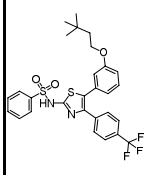
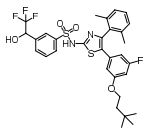
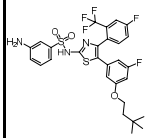
c) R^3 and R^4 are not both tert-butyl or both methoxy; and

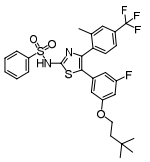
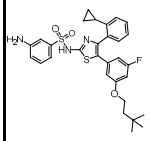
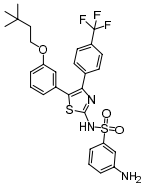
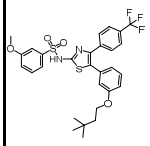
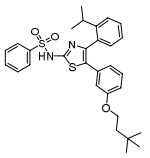
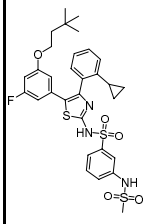
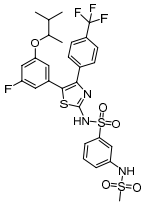
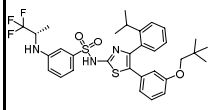
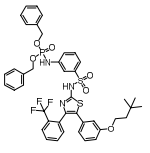
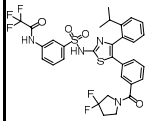
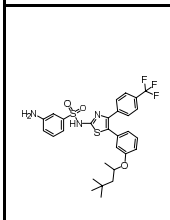
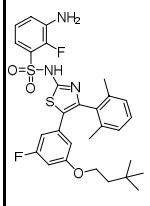
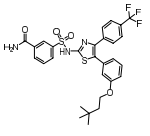
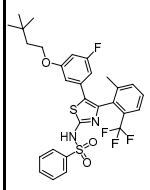
d) when Cy^1 and Cy^2 are both mono-substituted phenyl, R^3 is not Cl and R^4 is not OMe.

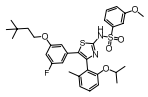
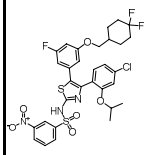
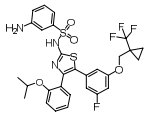
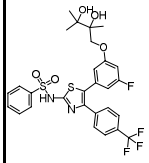
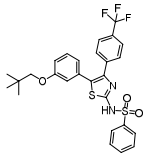
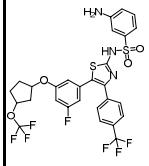
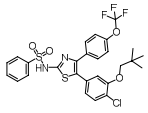
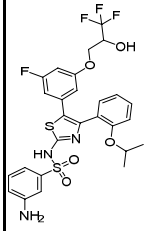
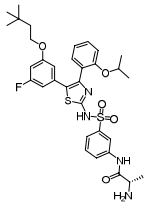
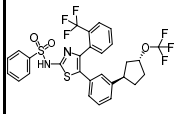
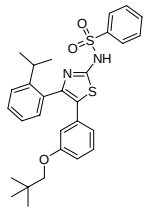
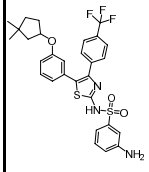
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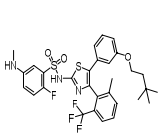
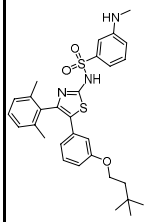
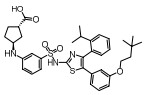
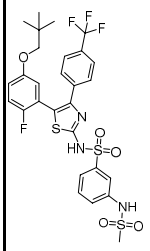
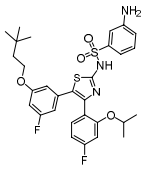
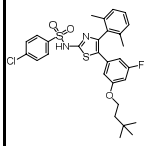
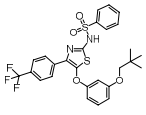
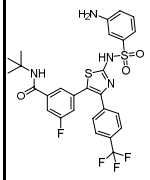
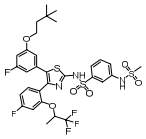
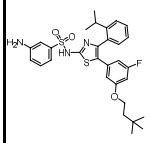
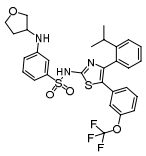
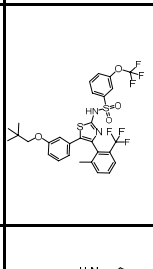
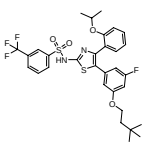
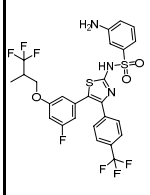


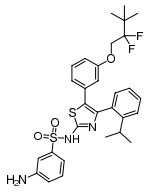
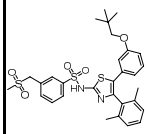
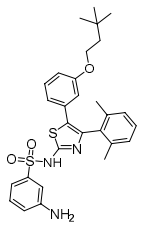
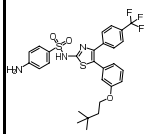
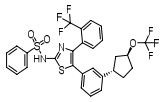
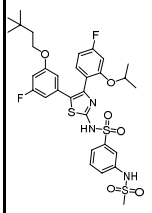
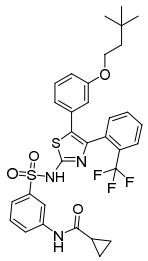
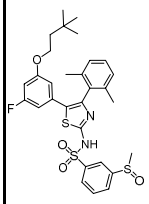
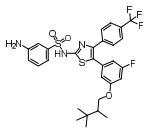
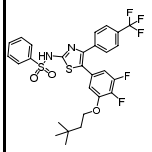
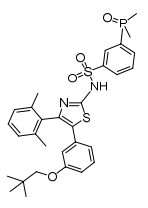
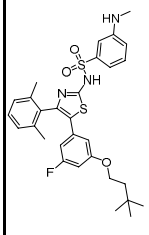


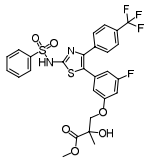
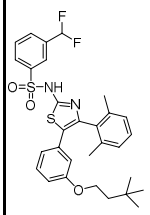
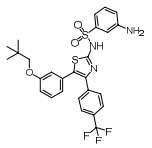
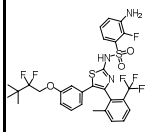
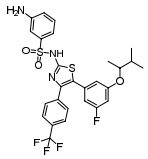
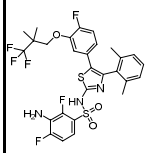
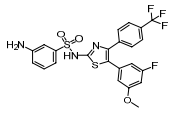
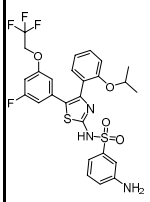
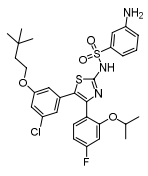
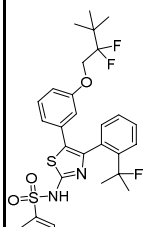
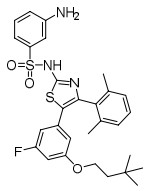
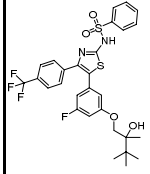
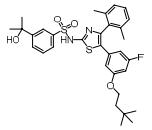
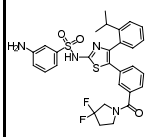
	
	
	
	
	
	
	

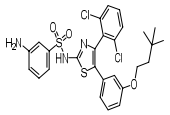
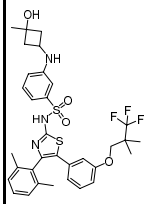
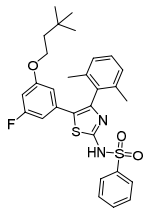
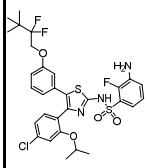
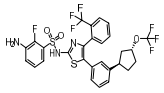
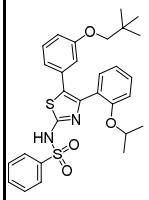
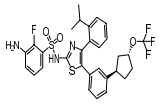
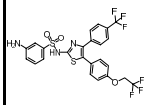
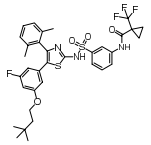
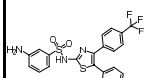
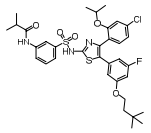
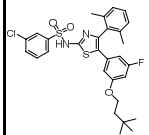
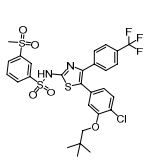
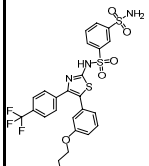
	
	
	
	
	
	
	

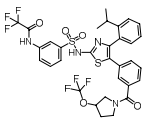
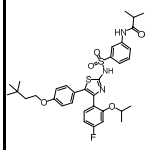
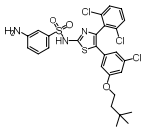
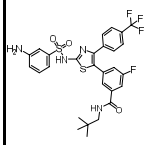
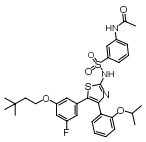
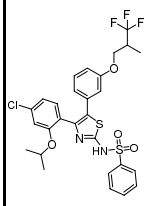
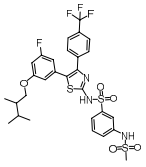
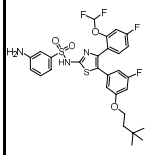
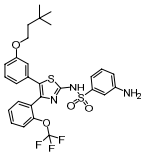
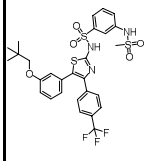
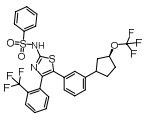
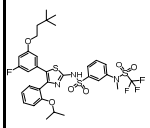
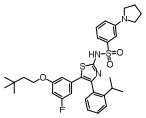
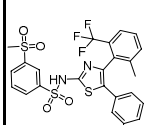
	
	
	
	
	
	

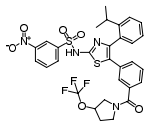
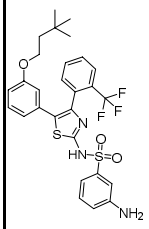
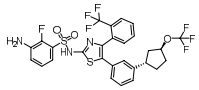
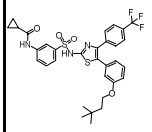
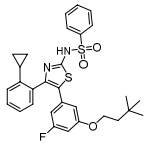
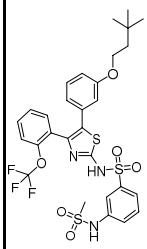
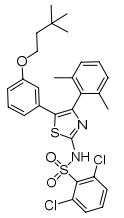
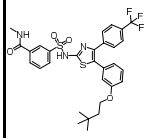
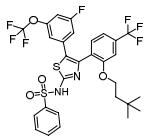
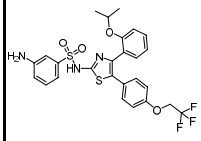
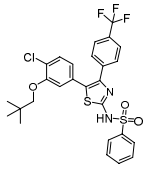
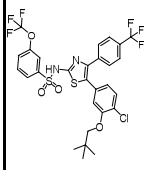
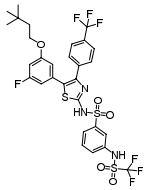
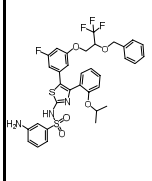
	
	
	
	
	
	
	

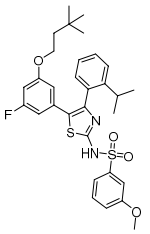
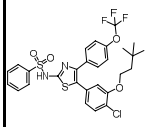
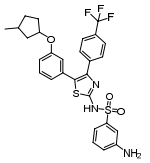
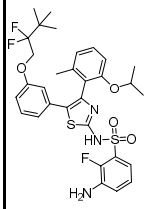
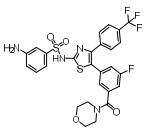
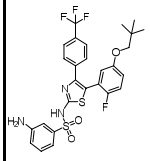
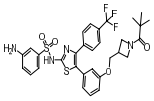
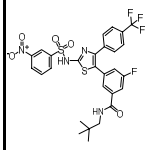
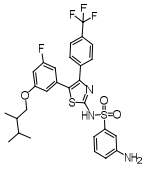
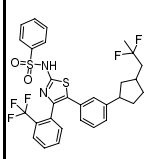
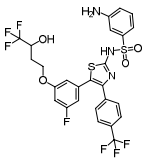
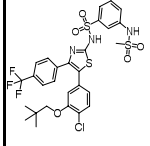
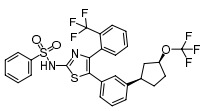
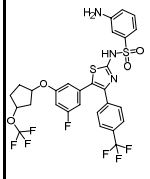
	
	
	
	
	
	

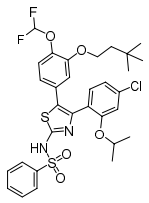
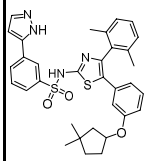
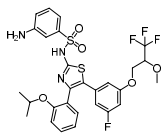
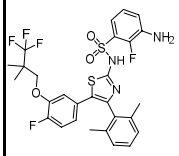
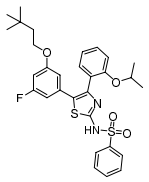
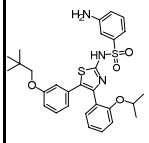
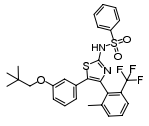
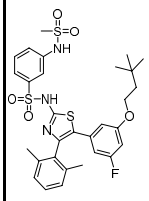
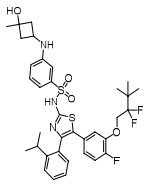
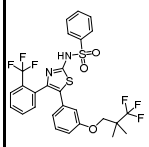
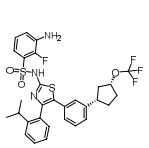
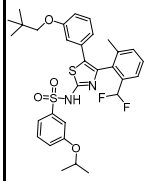
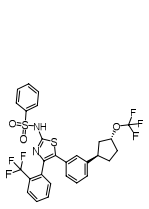
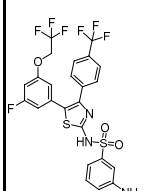
	
	
	
	
	
	
	

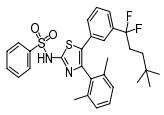
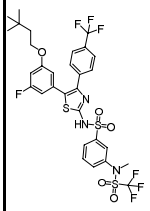
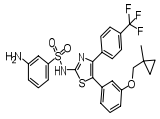
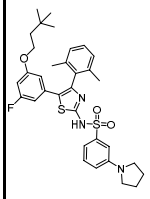
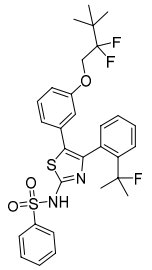
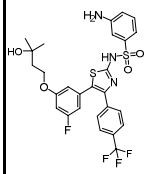
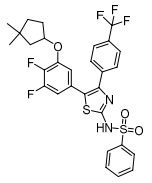
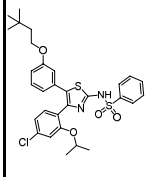
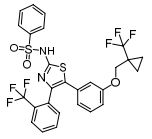
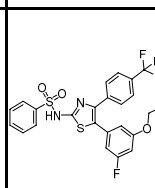
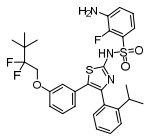
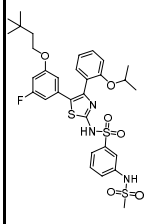
	
	
	
	
	
	
	

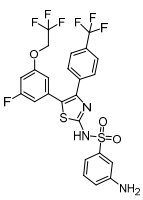
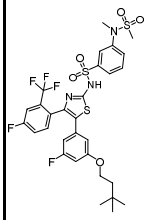
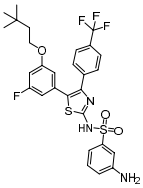
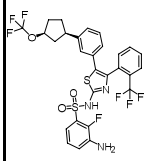
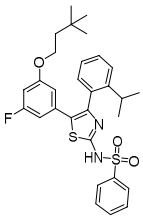
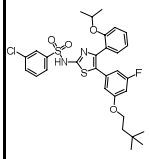
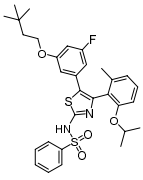
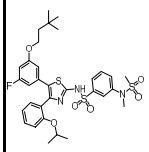
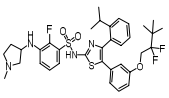
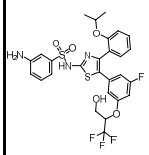
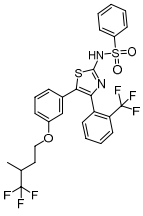
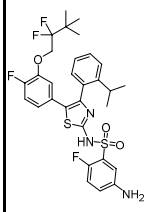
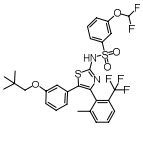
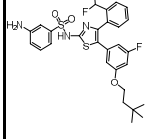
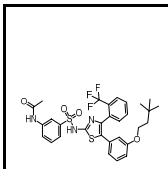
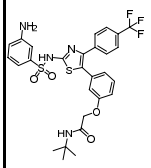
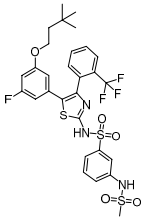
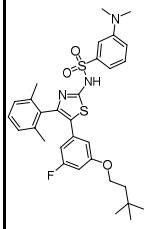
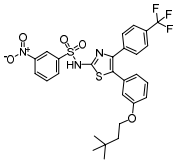
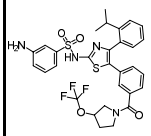
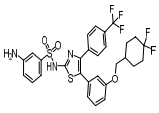
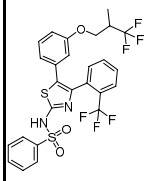
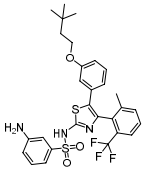
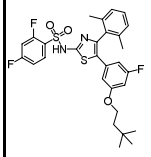
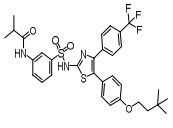
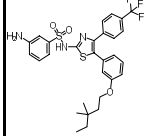
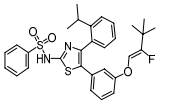
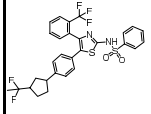
	
	
	
	
	
	
	

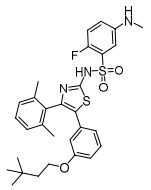
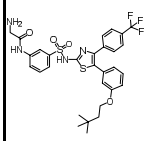
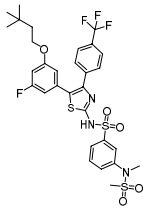
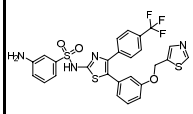
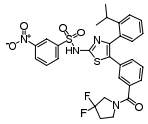
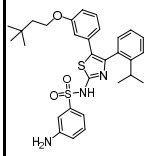
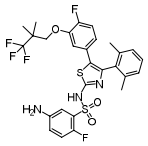
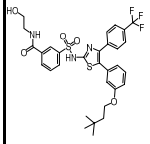
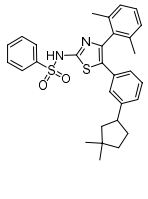
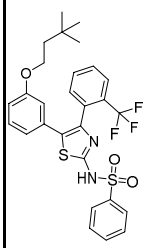
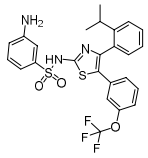
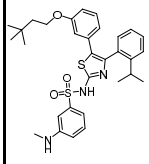
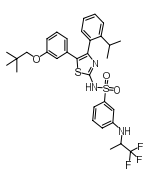
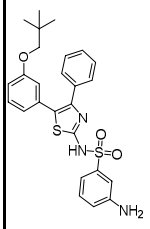
	
	
	
	
	
	
	

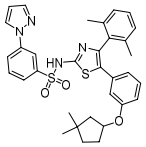
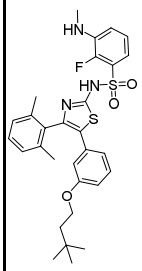
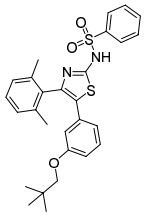
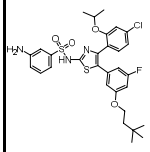
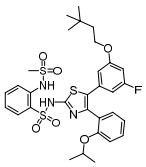
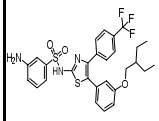
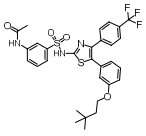
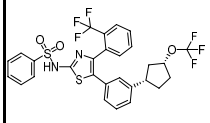
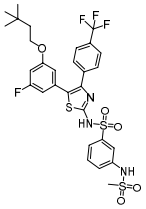
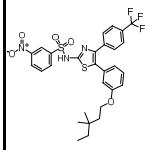
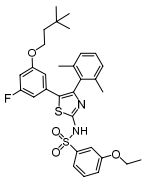
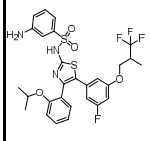
	
	
	
	
	
	
	

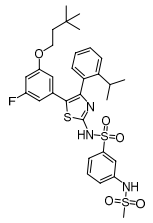
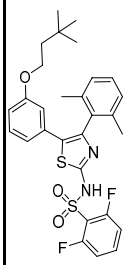
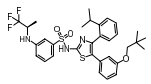
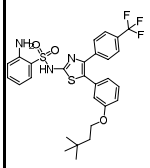
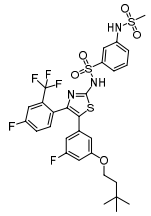
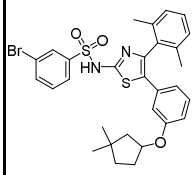
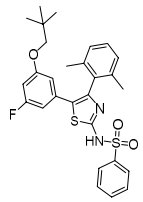
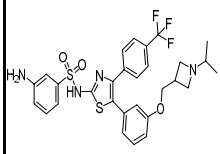
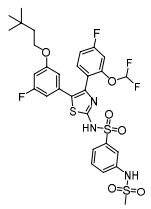
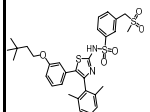
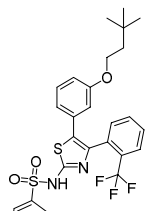
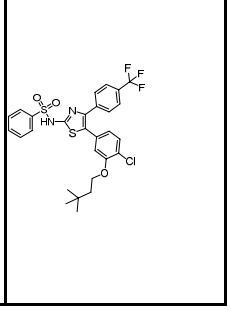
	
	
	
	
	
	
	

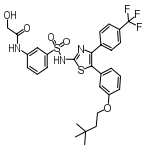
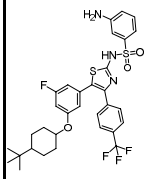
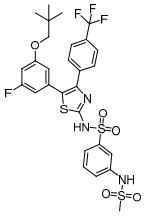
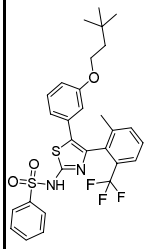
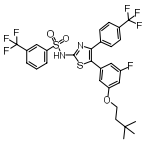
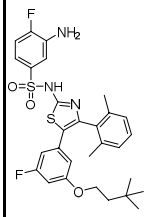
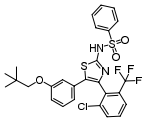
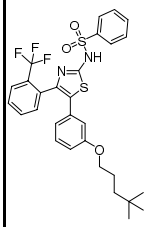
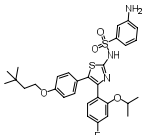
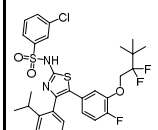
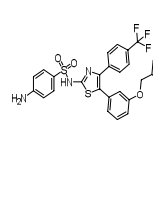
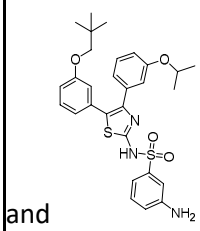
	
	
	
	
	
	

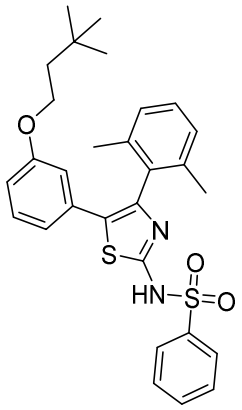
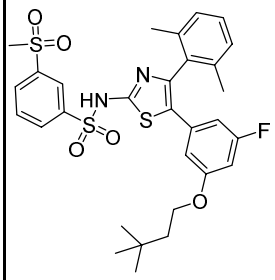
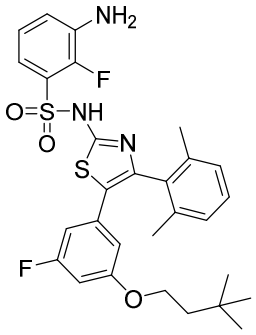
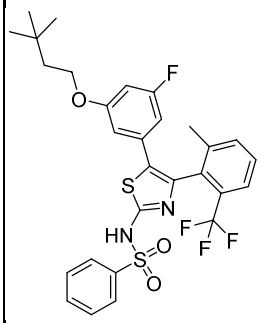
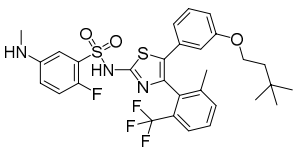
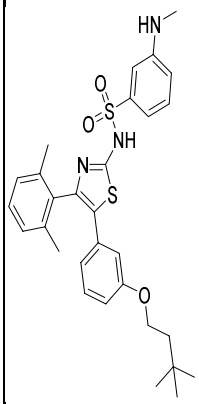
	
	
	
	
	
	

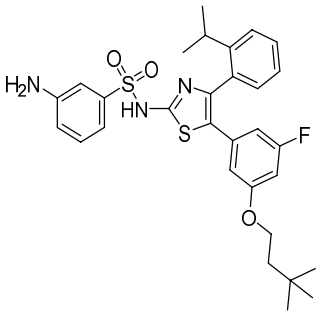
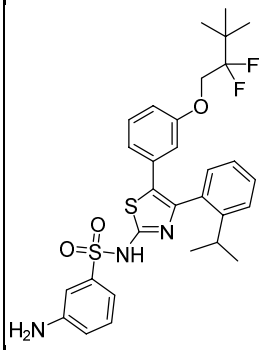
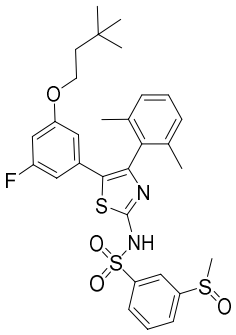
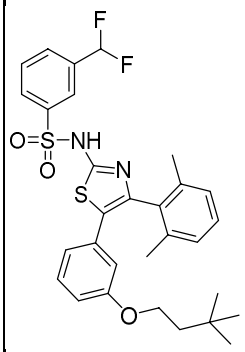
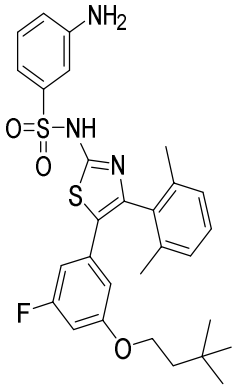
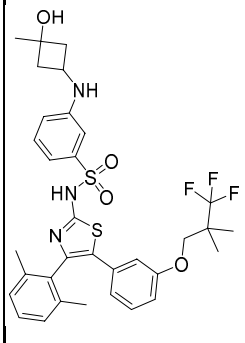
	
	
	
	
	
	

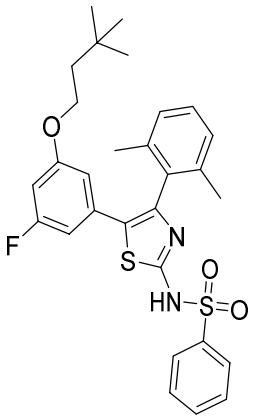
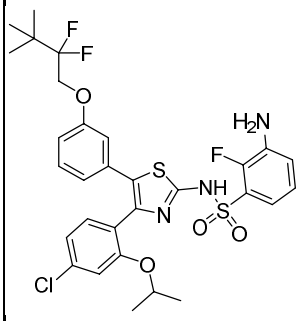
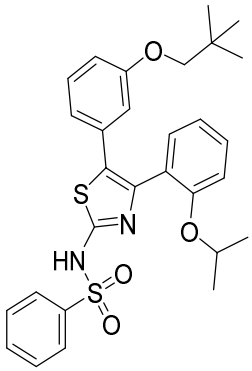
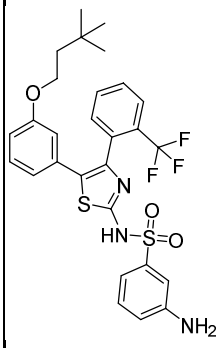
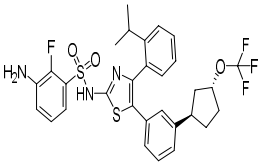
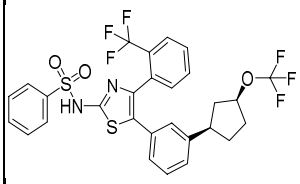
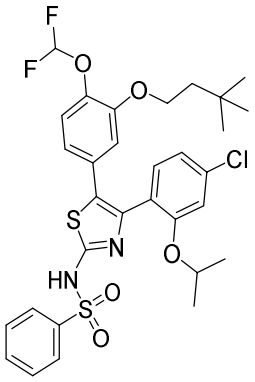
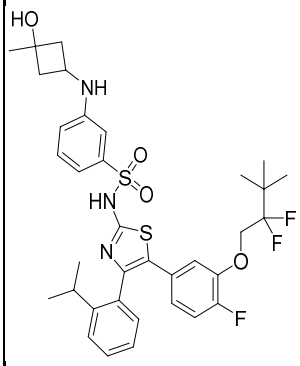
	
	
	
	
	
	
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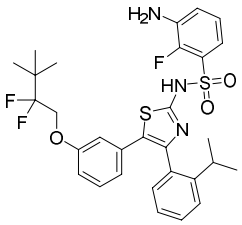
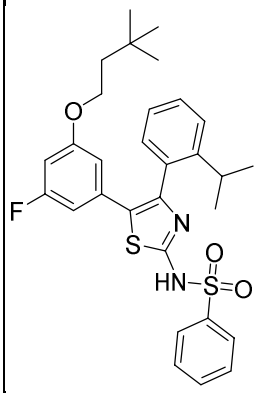
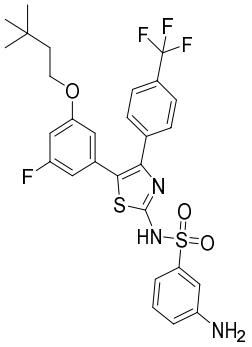
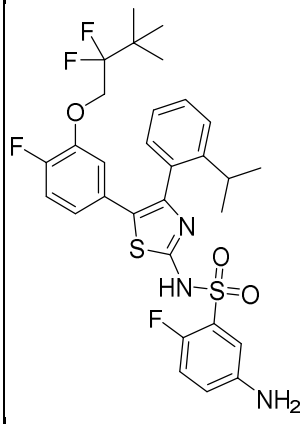
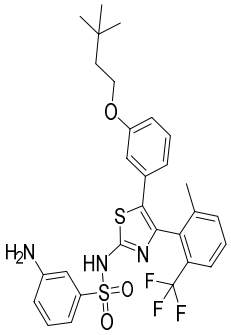
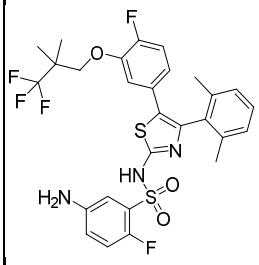
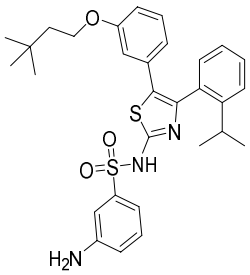
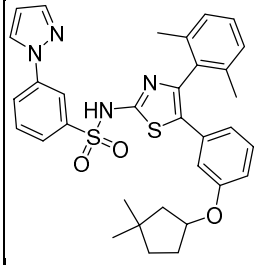
or a tautomer or pharmaceutically acceptable salt thereof.

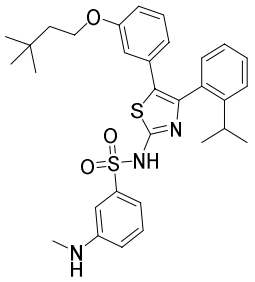
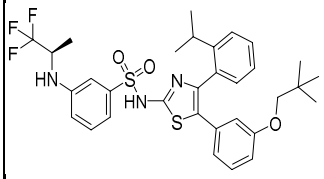
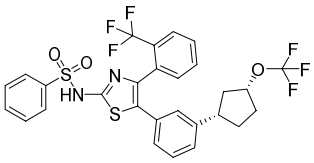
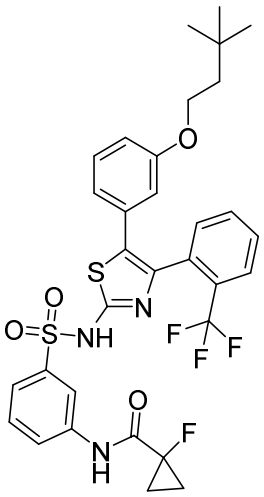
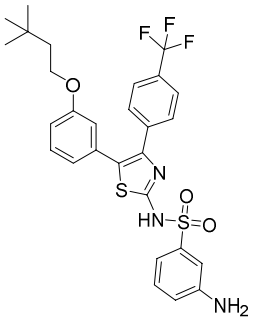
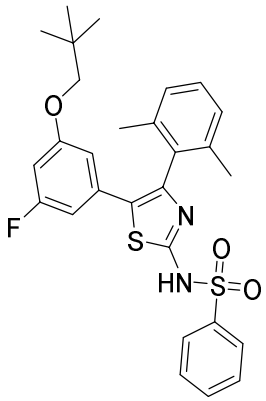
In a further aspect of the present disclosure, there is provided a compound selected from:

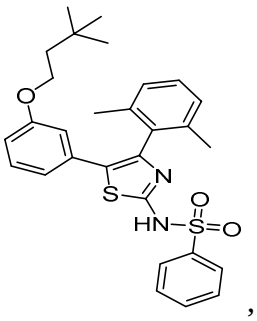
	
	
	
	

	
	
	 and

or a tautomer or pharmaceutically acceptable salt thereof.

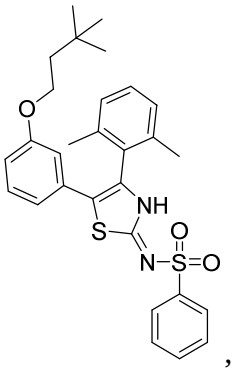
In another aspect of the present disclosure, there is provided a compound, wherein the compound is:



,

or a tautomer or pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound, wherein the compound is:



,

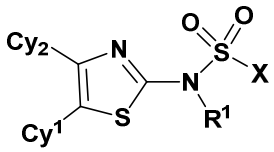
or pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier or excipient.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cystic fibrosis or a symptom thereof in a subject.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, for use in therapy.

In certain examples, the present application is directed to a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

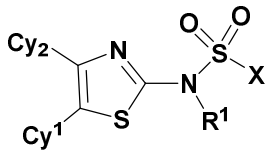
X is C_{1-6} alkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl, or 5-6 membered heteroaryl, each of which is substituted with 0-3 occurrences of R^2;

Cy^1 is C_{3-9} cycloalkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl or 5-6 membered heteroaryl, each of which is substituted with 0-3 occurrences of R^3;

Cy^2 is C_{3-9} cycloalkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl, or 5-6 membered heteroaryl, each of which is substituted with 1-3 occurrences of R^4;

CLAIMS

1. A compound of Formula (**I**):



(**I**)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen;

X is phenyl, substituted with 0-3 occurrences of R^2;

Cy^1 is phenyl, substituted with 0-3 occurrences of R^3;

Cy^2 is phenyl, substituted with 1-3 occurrences of R^4;

each R^2 is independently halo, $-NH_2$, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 4-10 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-9} cycloalkyl, $-C(O)NH_2$, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, $-N(R^a)SO_2-R^5$, $-SO_2-R^5$, $-C(O)N(R^a)(R^5)$, $-S(O)-R^5$, $-N(R^a)S(O)(NH)-R^5$ or $-P(O)(R^5)_2$,

wherein each C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^5;

each R^3 is independently halo, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{3-9} cycloalkyl, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{3-9} cycloalkenyl, 5-6 membered heteroaryl, 4-10 membered heterocycloalkyl, $-C(O)-R^7$, $-C(O)N(R^a)(R^7)$ or $-N(R^a)(R^8)$,

wherein each C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-8} alkoxy, 4-10 membered heterocycloalkyl, 5-6 membered aryl, 5-6 membered heteroaryl, cycloalkenyl, or C_{1-4} alkoxy-C_{3-9} cycloalkyl is further substituted with 0-3 occurrences of R^7;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, or $N(R^a)_2$ or 4-10 membered heterocycloalkyl;

each R^5 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-9} cycloalkyl, hydroxyl, $-SO_2-R^6$, $-CO_2H$, $-NH_2$, $-CO_2-C_{1-4}$ alkyl or 4-10 membered heterocycloalkyl,

wherein each C_{1-6} alkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^6;

each R^6 is independently hydroxyl, -NH_2, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, -CO_2H or -CO_2-(C_{1-4} alkyl);

each R^7 is independently halo, C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} haloalkyl, C_{1-5} haloalkoxy, C_{1-5} haloalkenyl, C_{3-7} cycloalkyl, hydroxyl, 5-6 membered aryl, aralkyl, aralkoxy, -C(O)-O-C_{1-4}alkyl, -C(O)N(R^a)(C_{1-4} alkyl), 5-6 membered heteroaryl or 4-10 membered heterocycloalkyl,

wherein each C_{3-7} cycloalkyl, 5-6 membered aryl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^8;

each R^8 is independently halo, C_{1-4} alkyl, C_{1-4} haloalkoxy, C(O)-C_{1-4} alkyl or C(O)N(R^a)(C_{1-4} alkyl);

each R^a is independently H or C_{1-6} alkyl; and

each R^b is C_{1-4} alkyl;

wherein

a) if Cy^1 has 3 occurrences of R^3, then each R^3 is not methoxy;

b) R^2 and R^4 are not both methyl;

c) R^3 and R^4 are not both tert-butyl or both methoxy; and

d) when Cy^1 and Cy^2 are both mono-substituted phenyl, R^3 is not Cl and R^4 is not OMe.

2. The compound of claim 1, wherein X is phenyl substituted with 0 occurrences of R^2.

3. The compound of claim 1, wherein X is phenyl substituted with 1 occurrence of R^2.

4. The compound of claim 3, wherein R^2 is 5-6 membered heteroaryl.

5. The compound of claim 3, wherein R^2 is -N(R^a)(R^5).

6. The compound of claim 5, wherein R^a is H or C_{1-6} alkyl, and R^5 is C_{1-6} alkyl

7. The compound of claim 5, wherein R^a is H and R^5 is selected from C_{1-6} haloalkyl, 4-10 membered heterocycloalkyl, and C_{3-9} cycloalkyl, wherein the 4-10 membered heterocyclyl or C_{3-9} cycloalkyl is substituted with 0 or 1 R^6.

8. The compound of claim 7, wherein R^6 is selected from -CO_2H, -$C(O)_2$-C_{1-4} alkyl, hydroxyl, and C_{1-4} alkyl.

9. The compound of claim 3, wherein R^2 is -N(R^a)C(O)-R^5.

10. The compound of claim 9, wherein R^a is H and R^5 is selected from C_{1-6} alkyl and C_{3-9} cycloalkyl, each substituted with 0-3 occurrences of R^6.

11. The compound of claim 10, wherein R^6 is selected from -NH_2, hydroxyl, halo, and C_{1-4} haloalkyl.

12. The compound of claim 3, wherein R^2 is 4-10 membered heterocycloalkyl substituted with 0-3 occurrences of R^5.

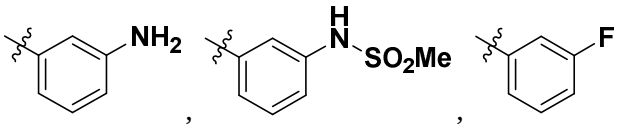
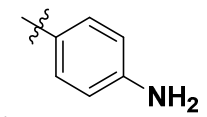
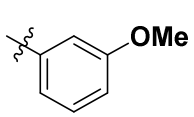
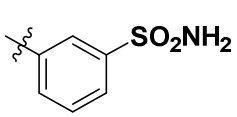
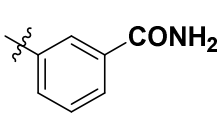
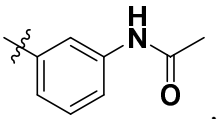
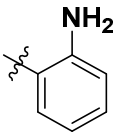
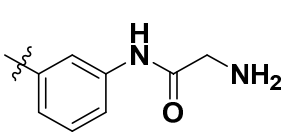
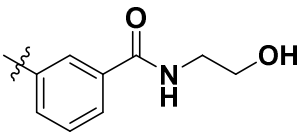
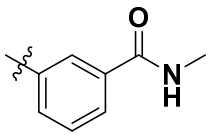
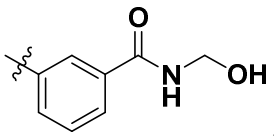
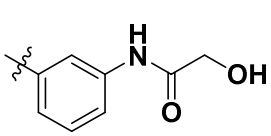
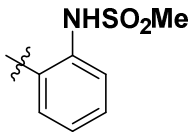
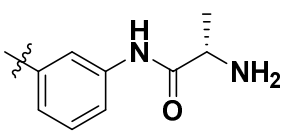
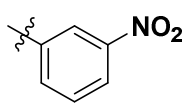
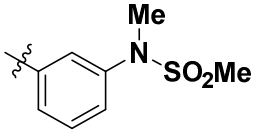
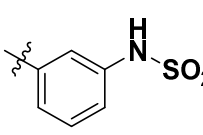
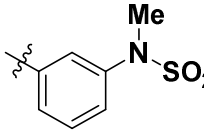
13. The compound of claim 12, wherein each R^5 is selected from C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

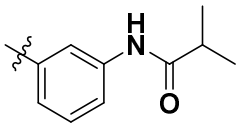
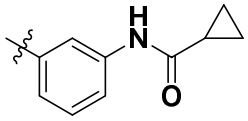
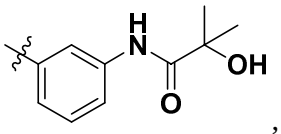
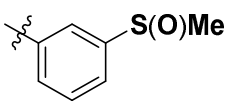
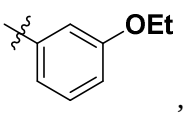
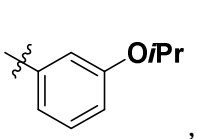
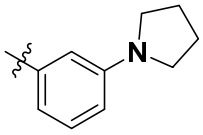
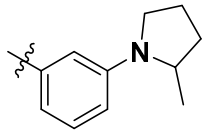
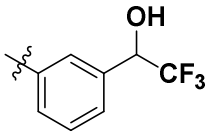
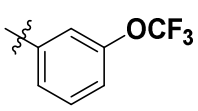
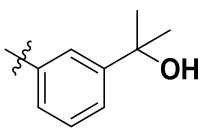
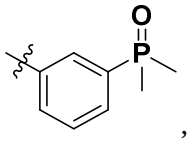
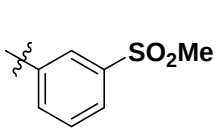
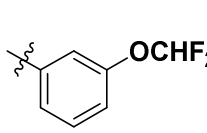
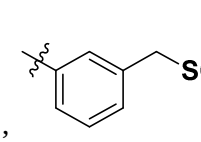
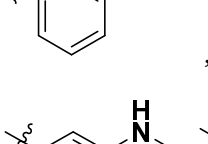
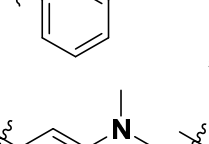
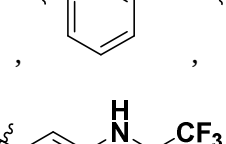
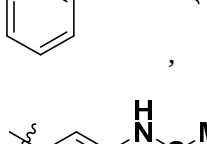
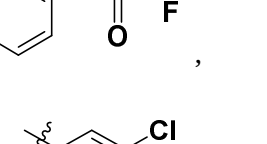
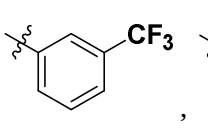
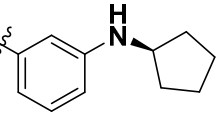
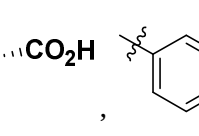
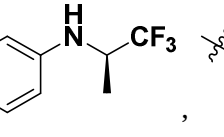
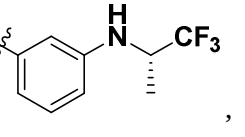
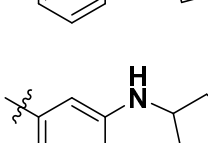
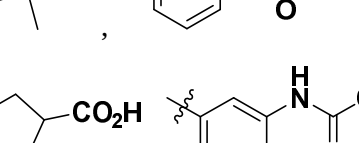
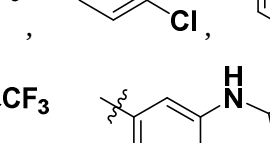
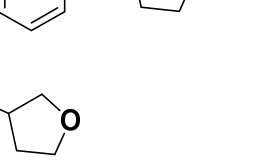
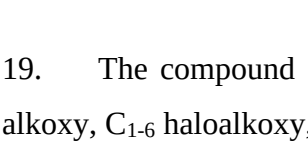
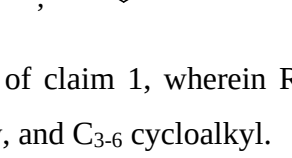
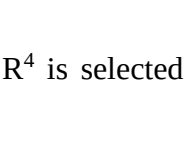
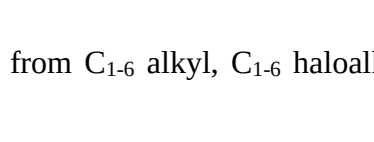
14. The compound of claim 3, wherein R^2 is -C(O)-N(R^a)(R^5).

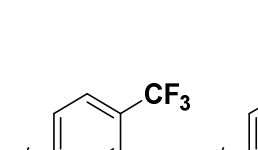
15. The compound of claim 14, wherein R^a is H and R^5 is C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

16. The compound of claim 3, wherein R^2 is -N(R^a)S(O)(NH)-R^5.

17. The compound of claim 16, wherein R^a is H and R^5 is C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

18. The compound of claim 3, wherein X is , , , , , , , , , , , , , , , , , , , 



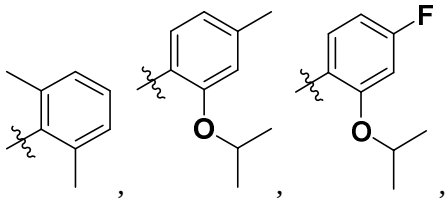
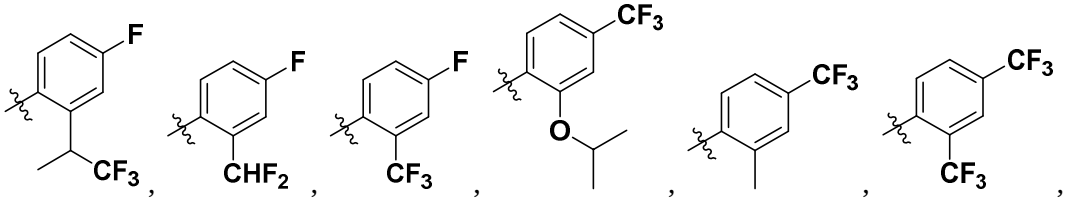
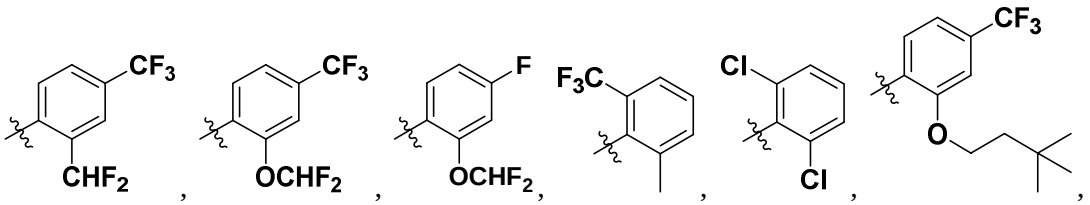
19. The compound of claim 1, wherein R^4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{3-6} cycloalkyl.

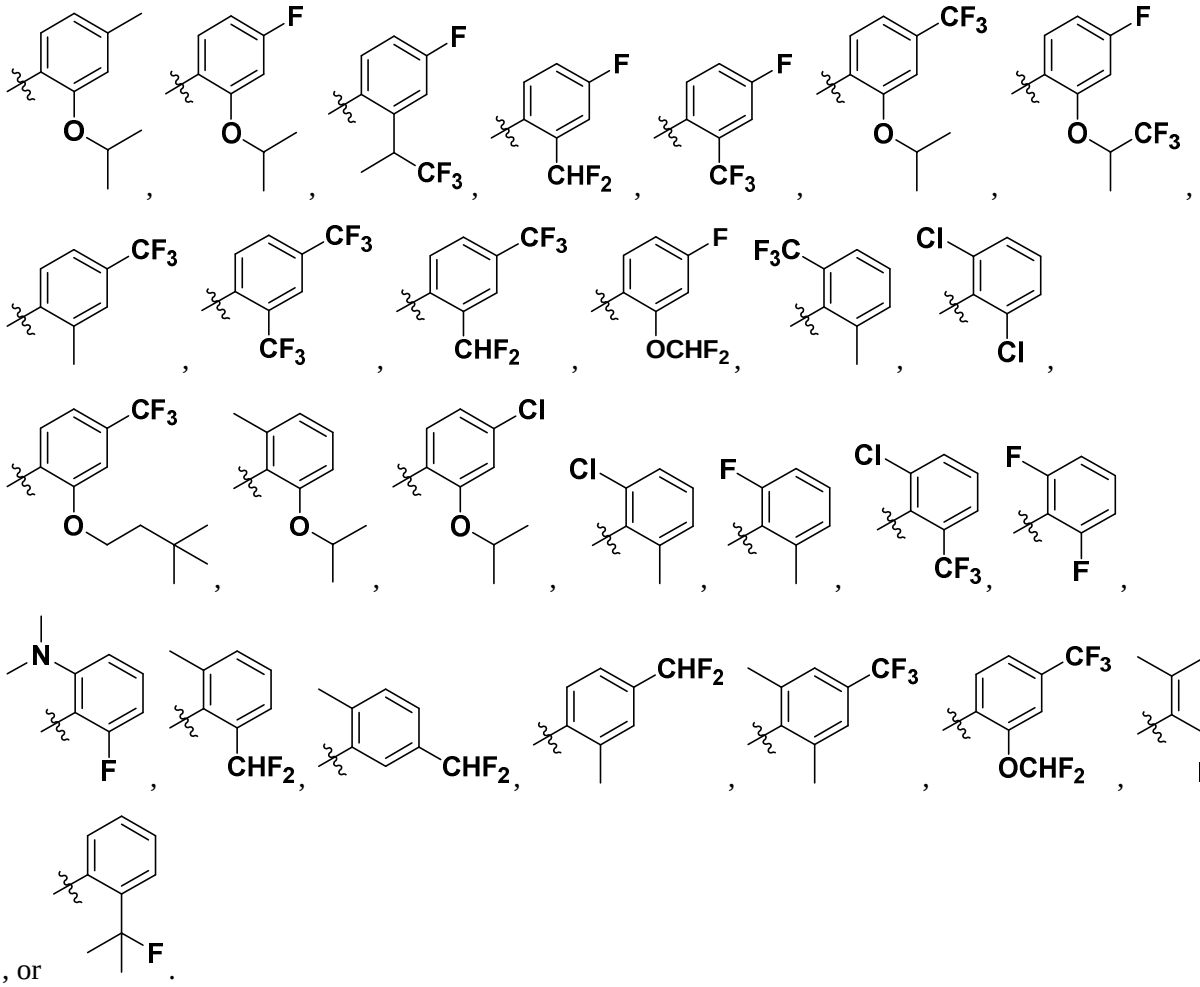
20. The compound of claim 19, wherein Cy^2 is

or .

21. The compound of claim 1, wherein Cy^2 is phenyl substituted with 2 or 3 occurrences of R^4.

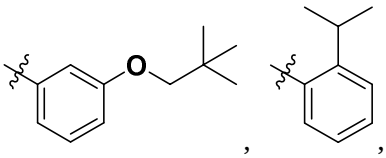
22. The compound of claim 21, wherein R^4 is selected from halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy and $-N(R^a)_2$.

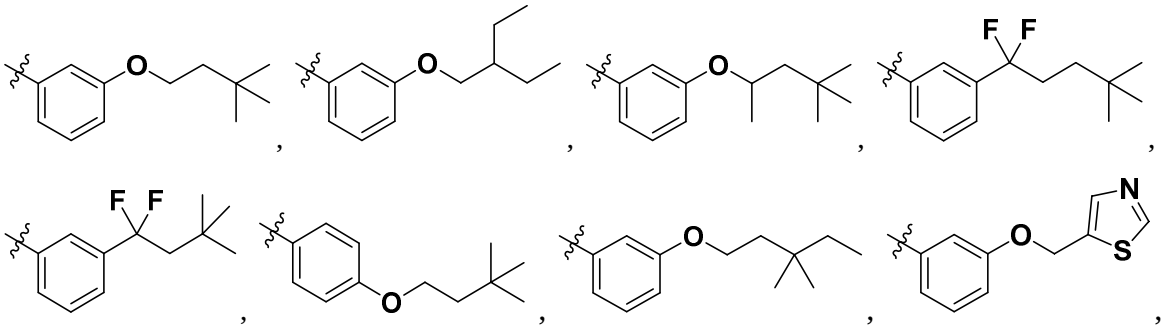
23. The compound of claim 22, wherein Cy^2 is , , ,

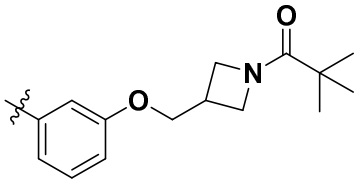
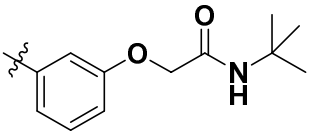
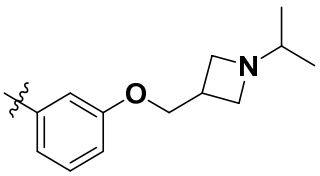
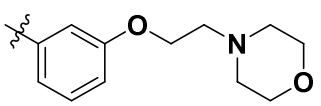
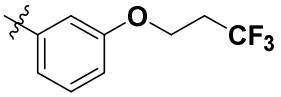
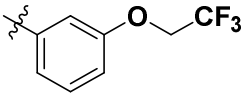
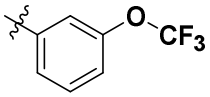
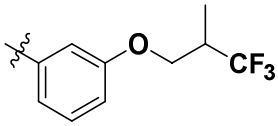
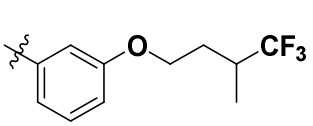
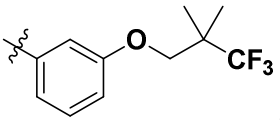
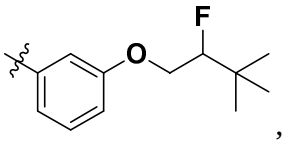
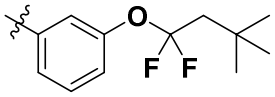
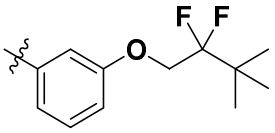
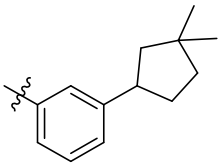
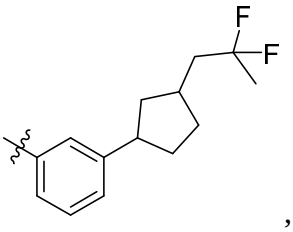
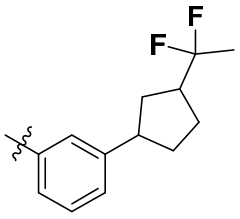
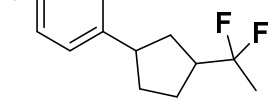
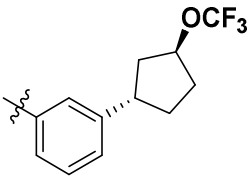
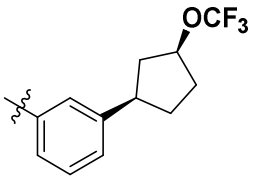
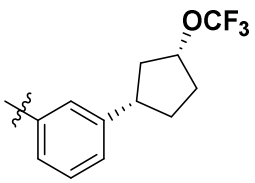
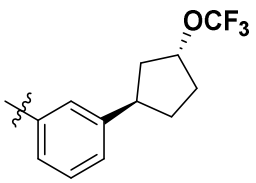
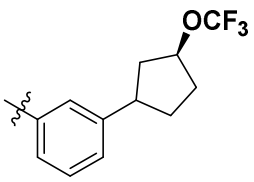
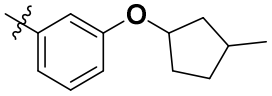
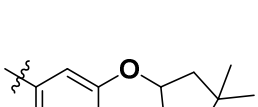
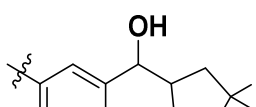
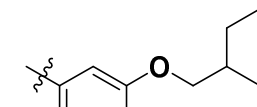


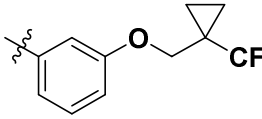
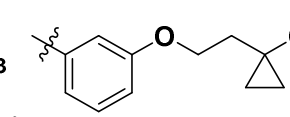
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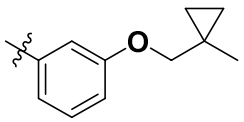
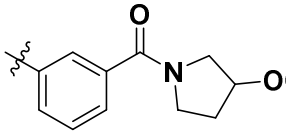
25. The compound of claim 1, wherein R^3 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy.

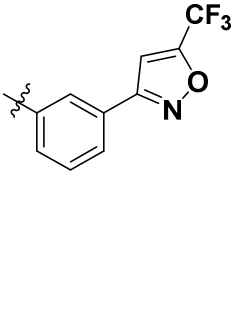
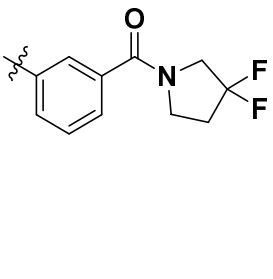
26. The compound of claim 1, wherein Cy^1 is ,




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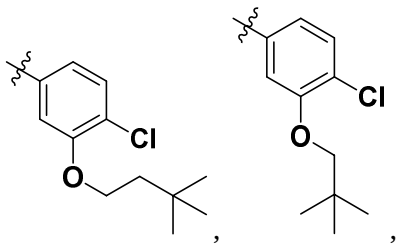
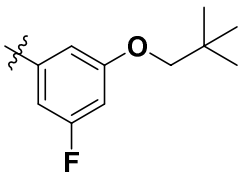
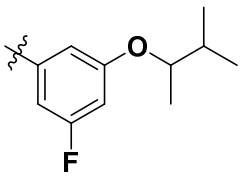
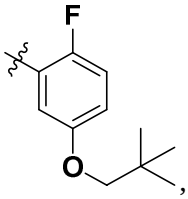
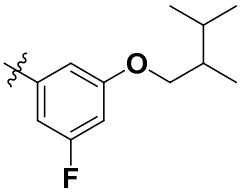
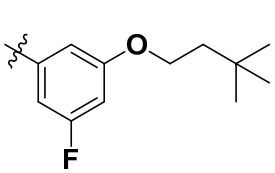
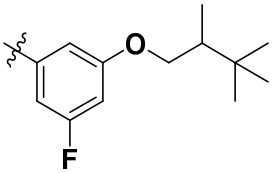
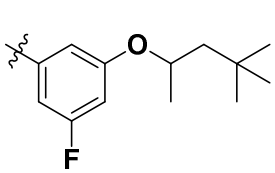
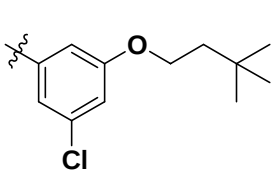
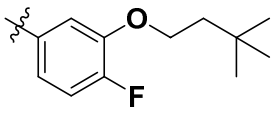
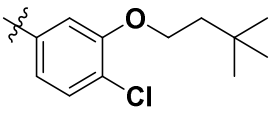
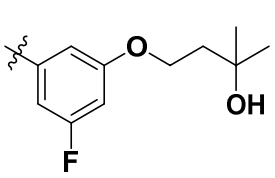
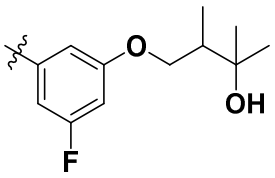
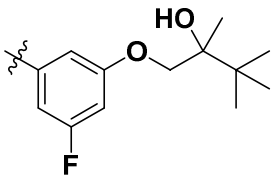
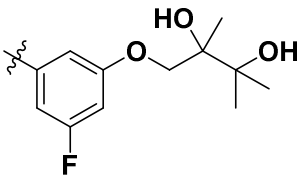
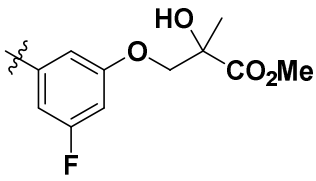
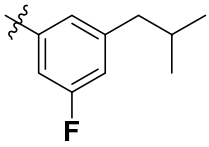
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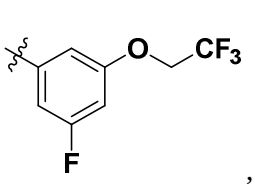
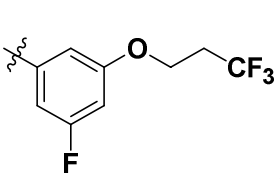
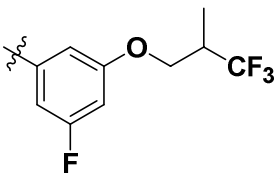
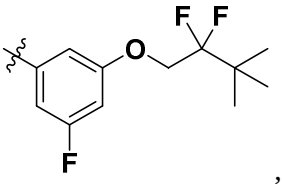
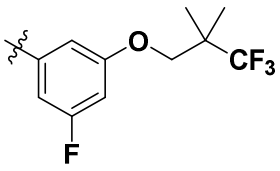
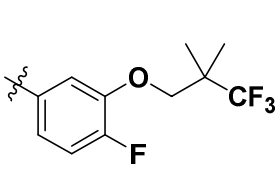
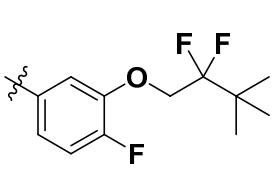
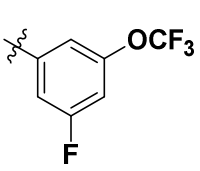
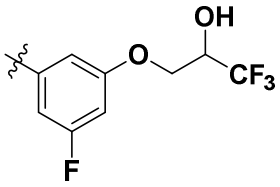
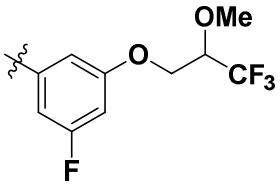
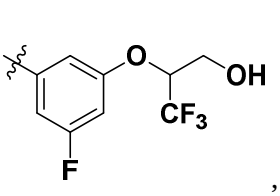
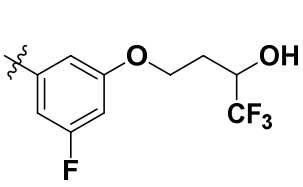
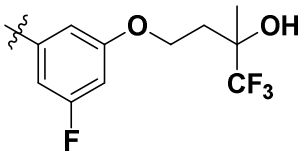
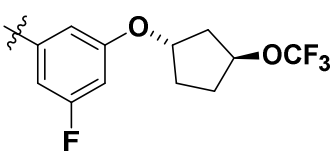
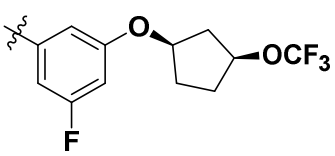
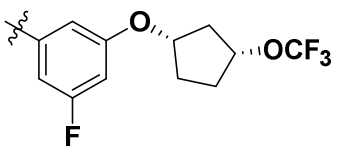
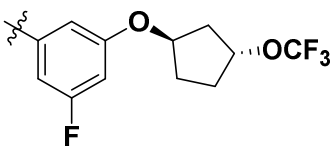
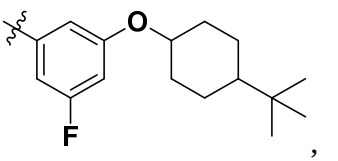
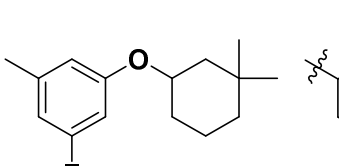
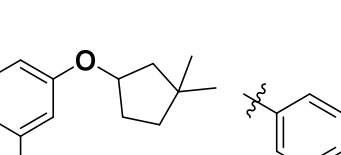
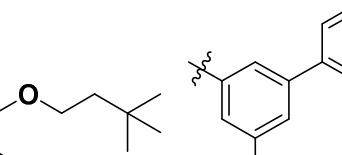
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27. The compound of claim 1, wherein Cy^1 is phenyl substituted with 2 occurrences of R^3.

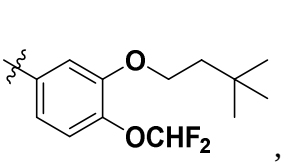
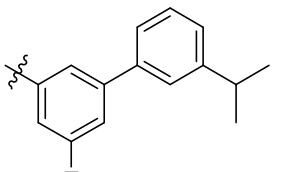
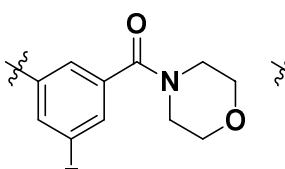
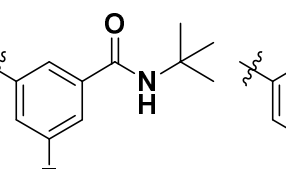
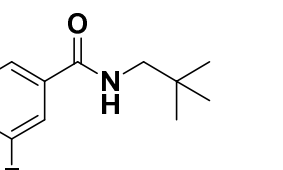
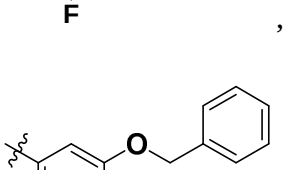
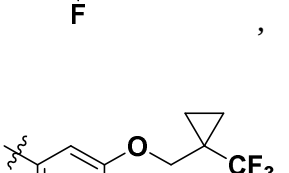
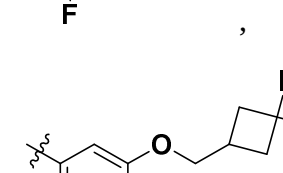
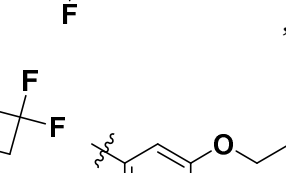
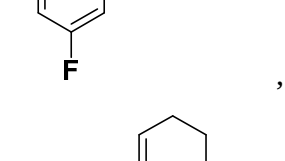
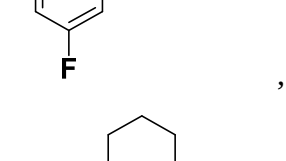
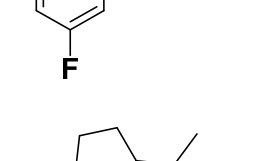
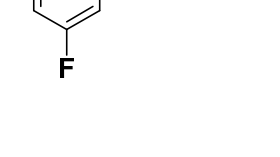
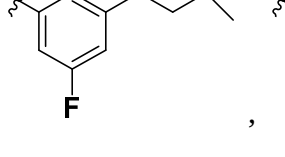
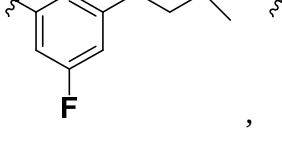
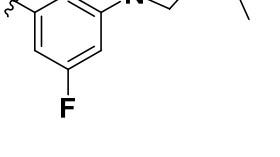
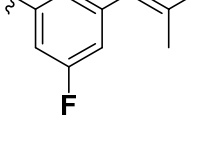
28. The compound of claim 27, wherein each R^3 is independently selected from halo, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-9} cycloalkyl, C_{1-8} alkoxy, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkenyl, C_{1-8} alkeny, aryl, 4-10 membered heterocycloalkyl, -C(O)R^7, and-C(O)N(R^a)(R^7).

29. The compound of claim 28, wherein R^3 is independently selected from C_{3-9} cycloalkyl, C_{1-8} alkoxy, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-4} alkoxy-C_{3-9} cycloalkyl , C_{3-9} cycloalkenyl, and 4-10 membered heterocycloalkyl, wherein the C_{3-9} cycloalkyl, C_{1-8} alkoxy, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkenyl, or heterocycloalkyl is further substituted with at least one R^7 selected from hydroxyl, -C(O)-O-C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, aralkoxy, C_{1-4} haloalkoxy, and 4-10 membered heterocycloalkyl.

30. The compound of claim 28 or 29, wherein Cy^1 is , , , , , , , , , , , , , , , , , .


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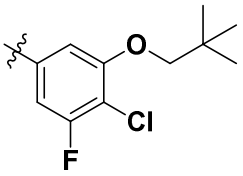
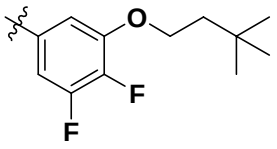
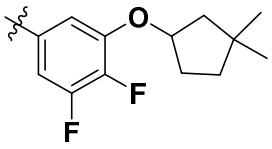
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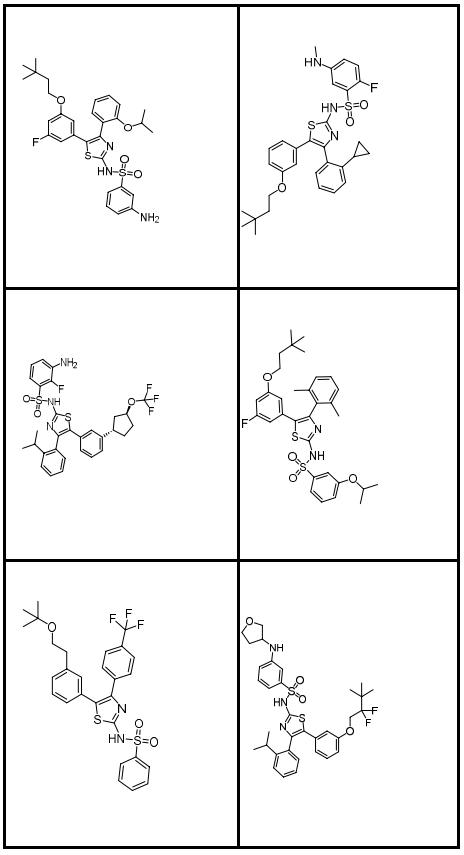
31. The compound of claim 1, wherein Cy^1 is phenyl substituted with 3 occurrences of R^3.

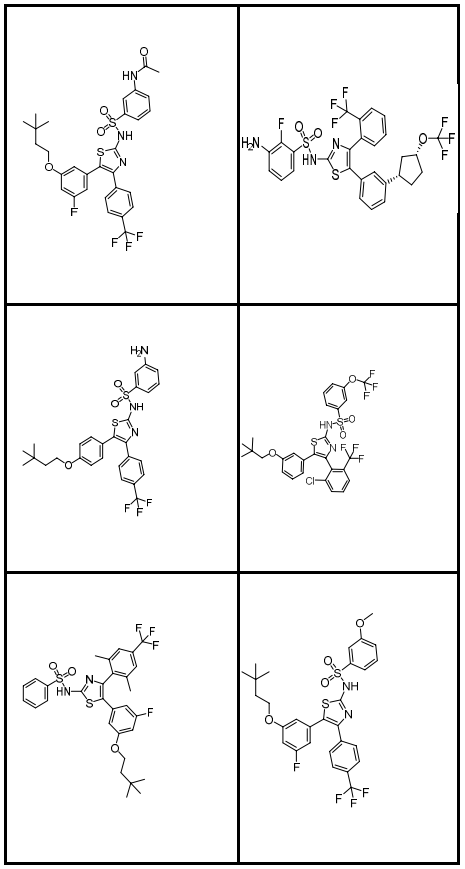
32. The compound of claim 31, wherein each R^3 is independently selected from halo, C_{1-8} alkoxy, and C_{3-9} cycloalkoxy.

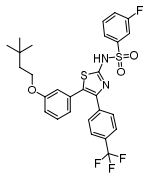
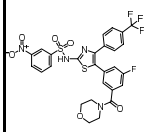
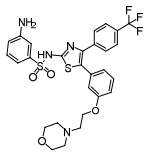
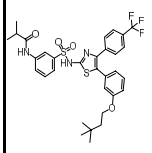
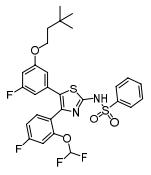
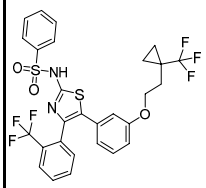
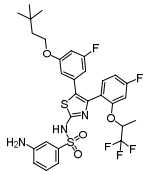
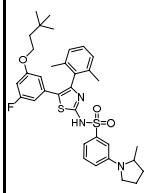
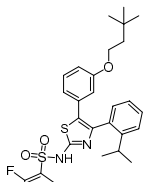
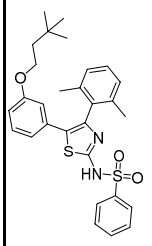
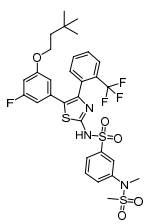
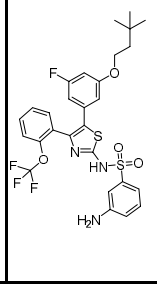
33. The compound of claim 32, wherein R^3 is independently selected from C_{1-8} alkoxy and C_{3-9} cycloalkoxy, wherein the C_{1-8} alkoxy or C_{3-9} cycloalkoxy is further substituted with at least one R^7 selected from C_{1-5} alkyl.

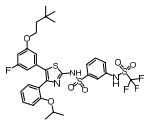
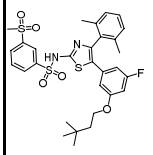
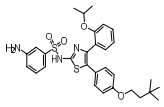
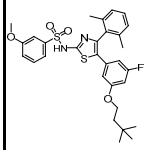
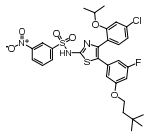
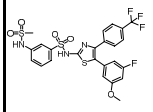
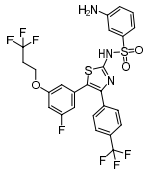
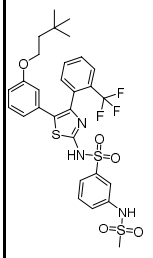
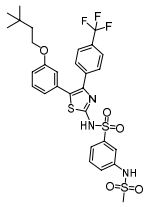
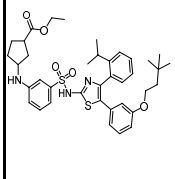
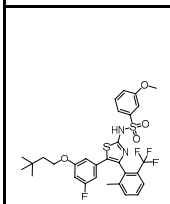
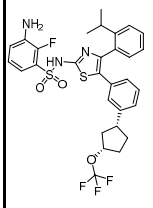
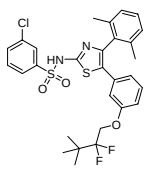
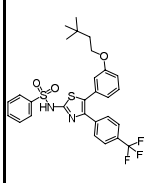
34. The compound of claim 32 or 33, wherein Cy^1 is ,  or .

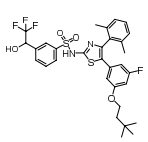
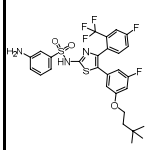
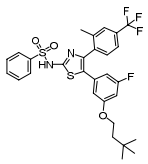
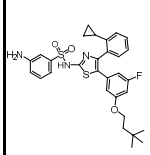
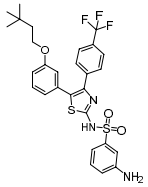
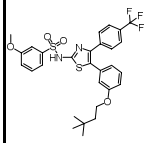
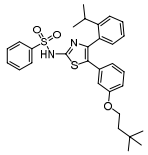
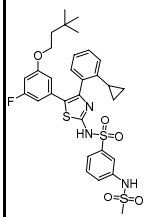
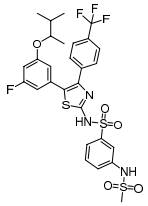
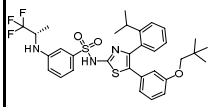
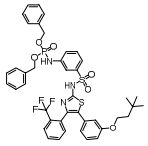
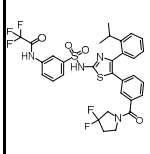
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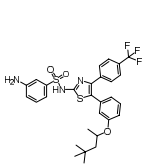
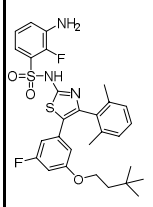
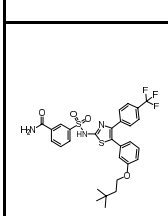
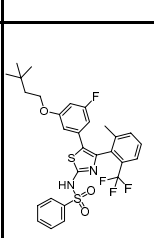
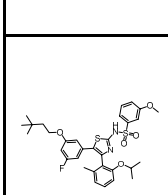
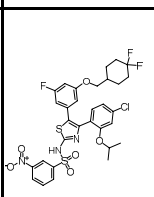
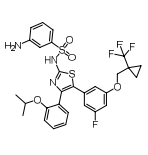
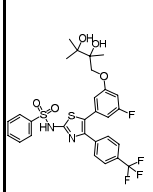
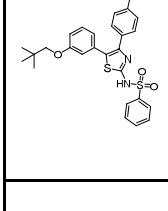
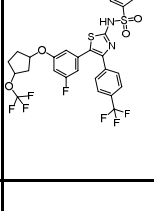
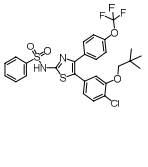
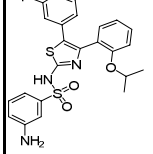


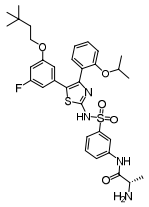
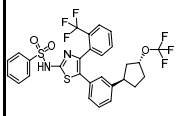
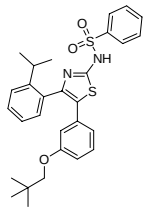
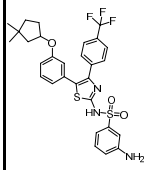
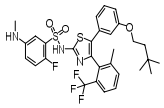
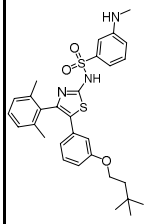
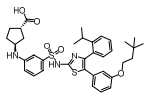
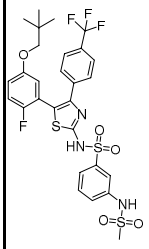
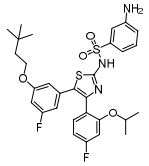
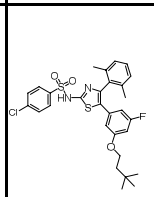
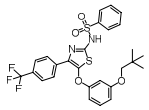
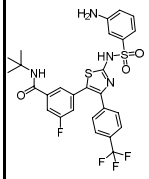


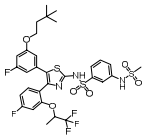
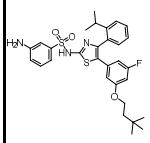
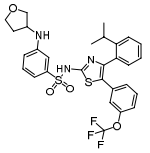
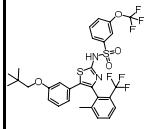
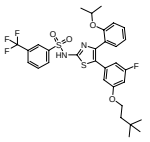
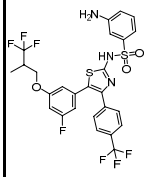
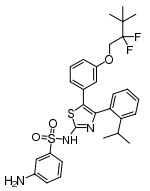
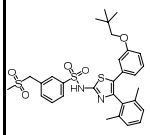
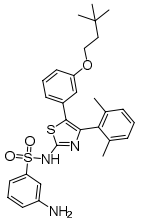
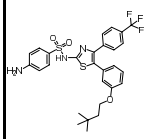
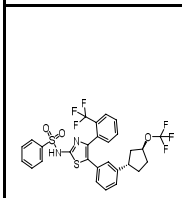
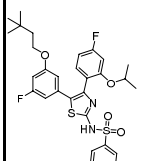
	
	
	
	
	
	

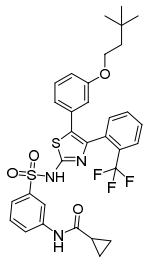
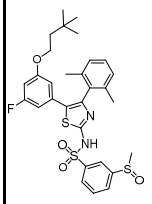
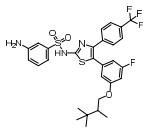
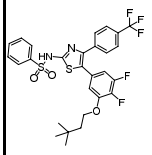
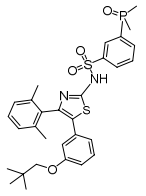
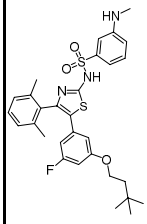
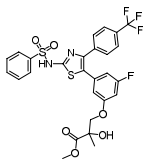
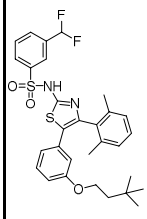
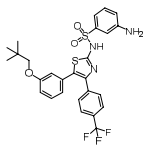
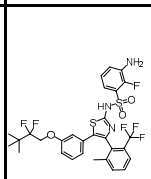
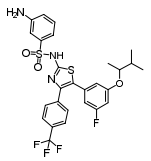
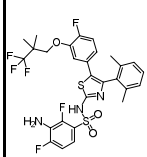
	
	
	
	
	
	
	

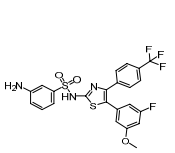
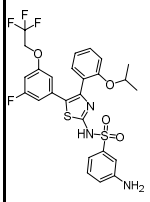
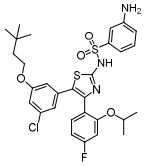
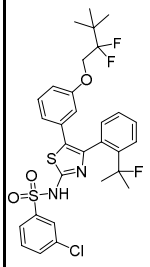
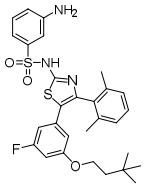
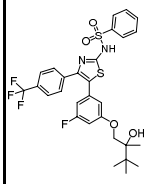
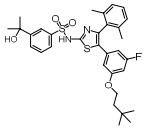
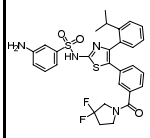
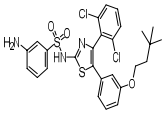
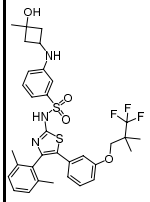
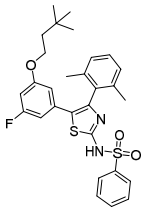
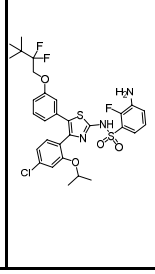
	
	
	
	
	
	

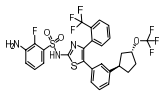
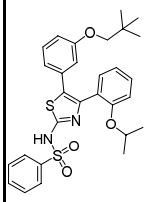
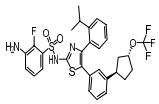
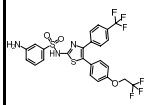
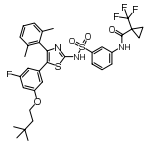
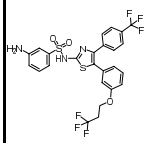
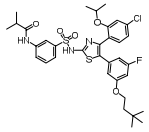
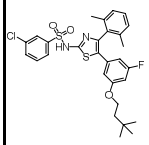
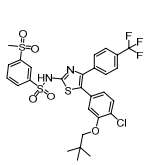
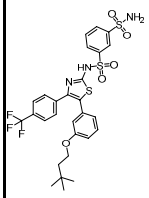
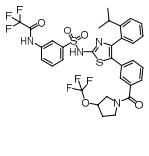
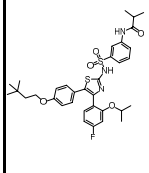
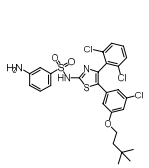
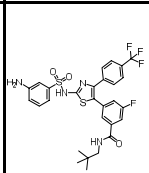
	
	
	
	
	
	

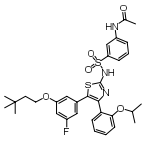
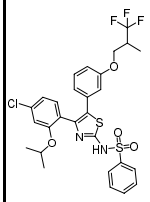
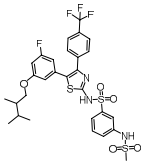
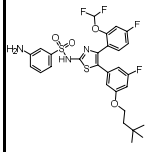
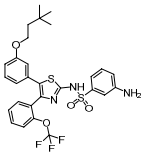
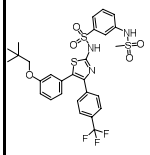
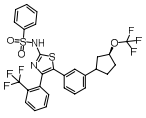
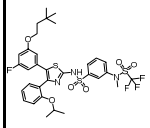
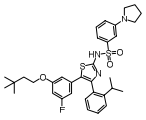
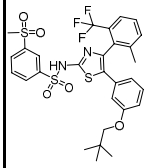
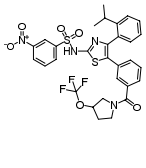
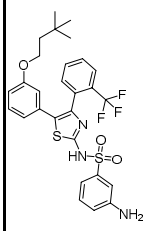
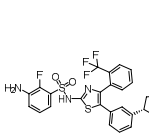
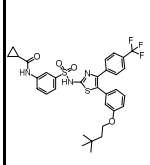
	
	
	
	
	
	

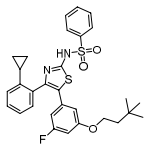
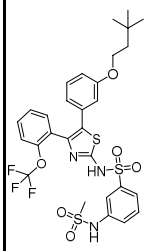
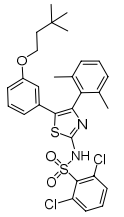
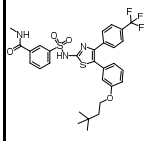
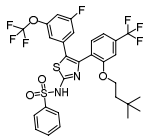
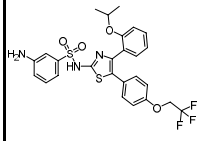
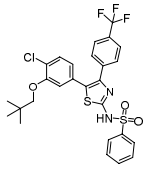
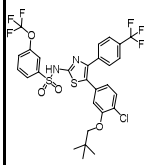
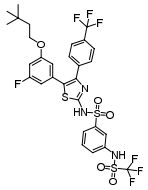
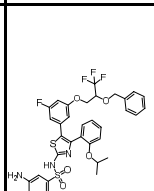
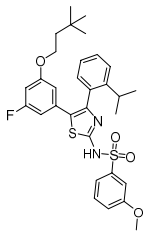
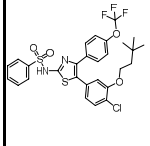
	
	
	
	
	
	

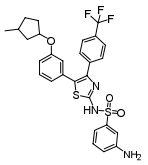
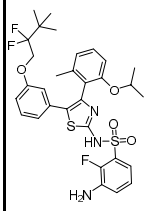
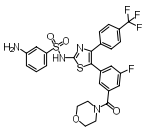
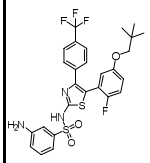
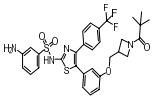
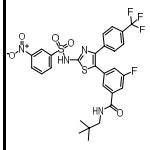
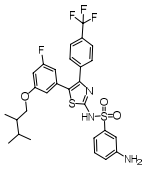
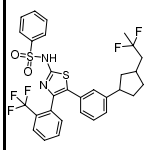
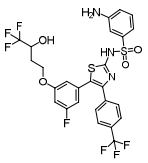
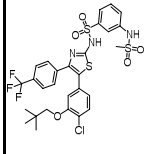
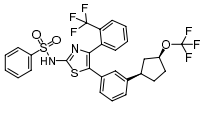
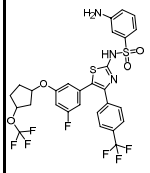
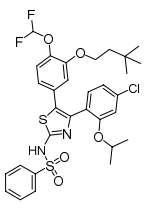
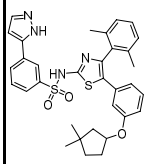
	
	
	
	
	
	

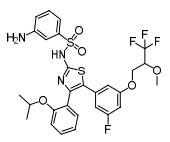
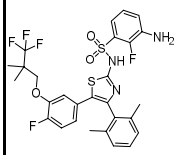
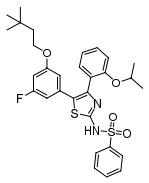
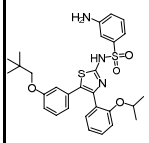
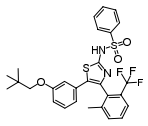
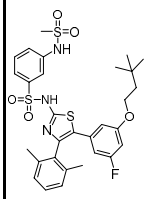
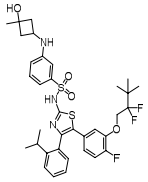
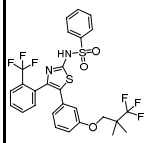
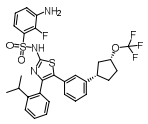
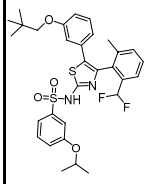
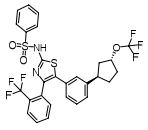
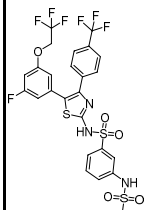
	
	
	
	
	
	

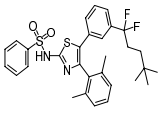
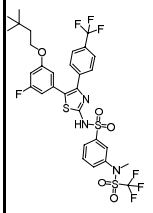
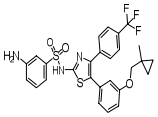
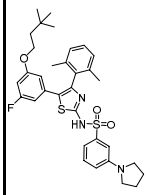
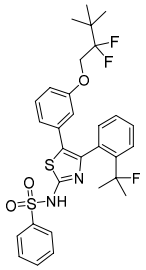
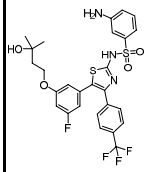
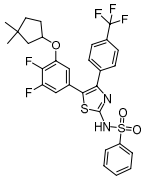
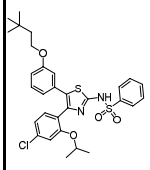
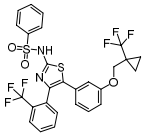
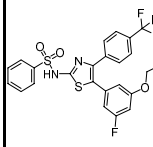
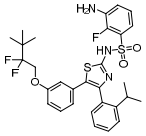
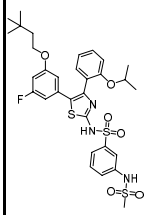
	
	
	
	
	
	
	

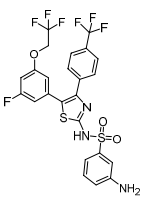
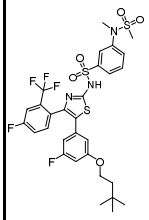
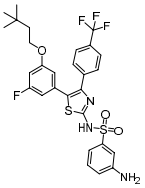
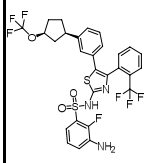
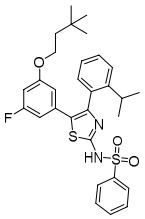
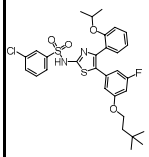
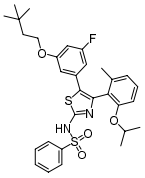
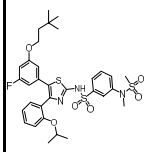
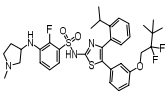
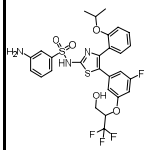
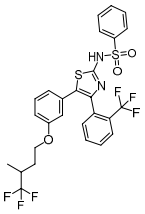
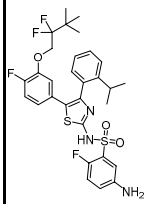
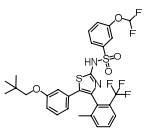
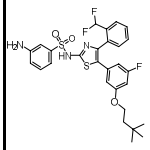
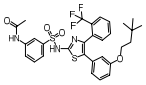
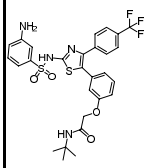
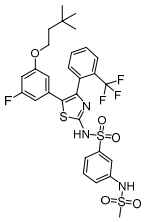
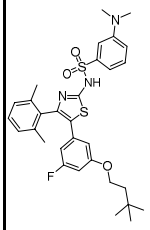
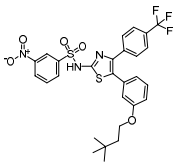
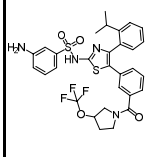
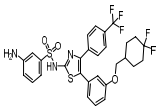
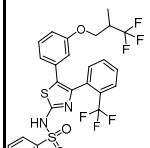
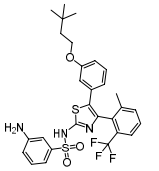
	
	
	
	
	
	
	

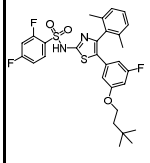
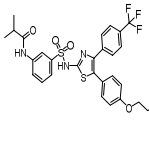
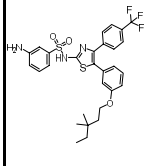
	
	
	
	
	
	

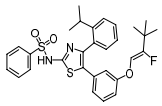
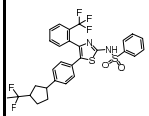
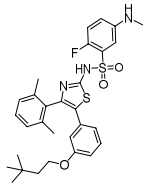
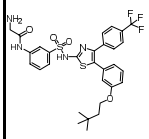
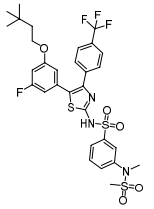
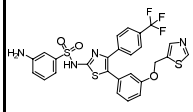
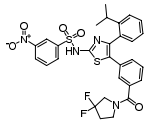
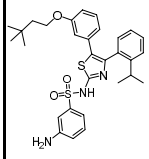
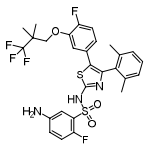
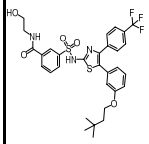
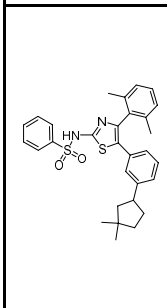
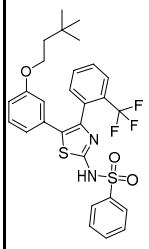
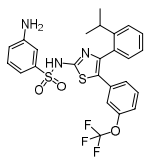
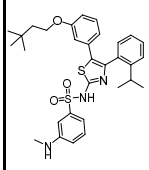
	
	
	
	
	
	
	

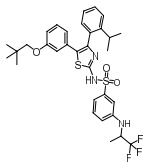
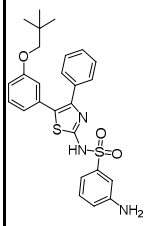
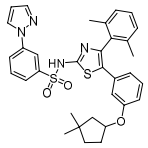
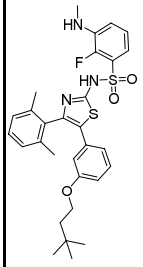
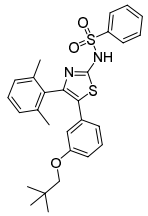
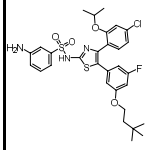
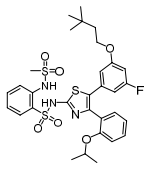
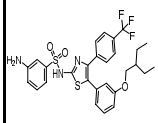
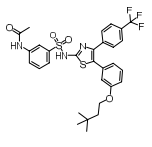
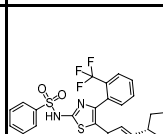
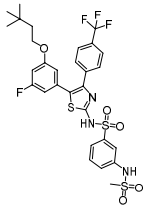
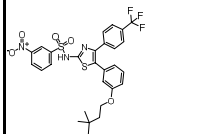
	
	
	
	
	
	

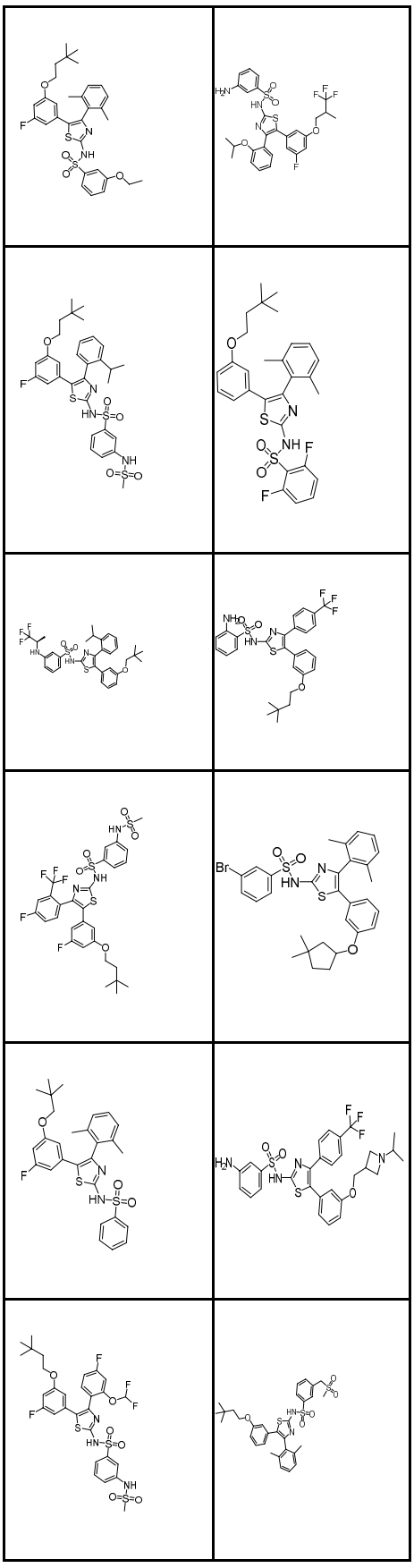
	
	
	
	
	
	

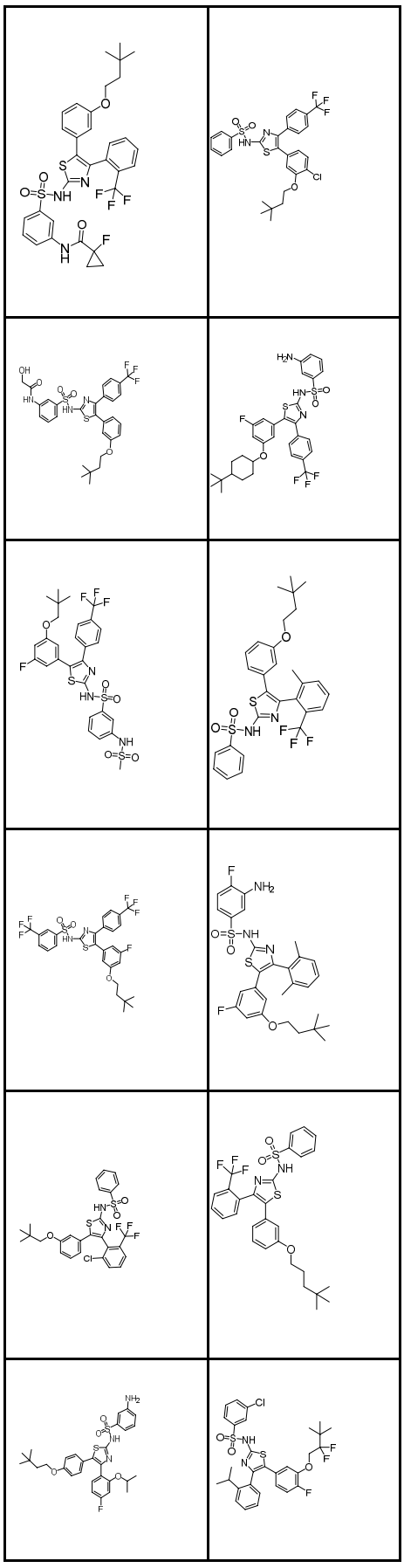
























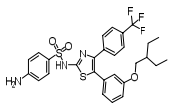
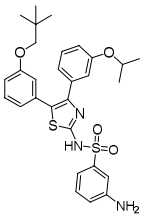




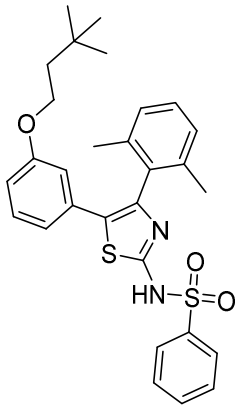
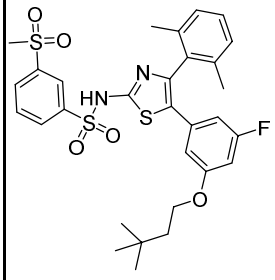
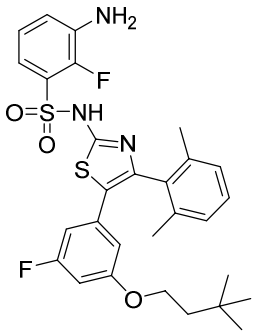
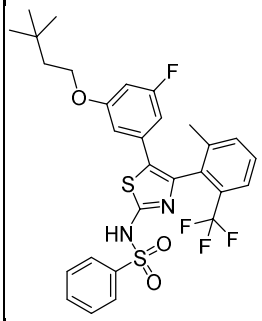


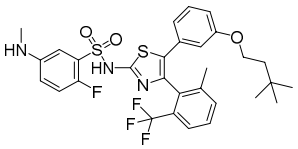
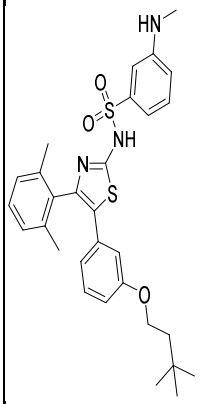
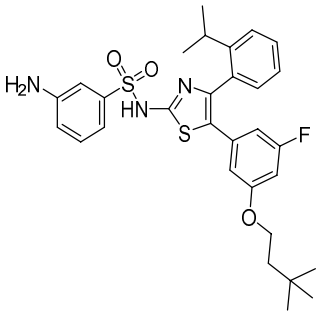
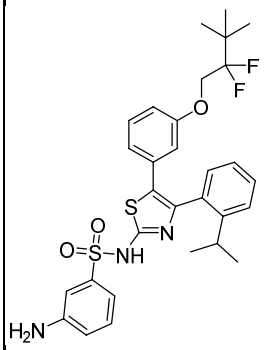
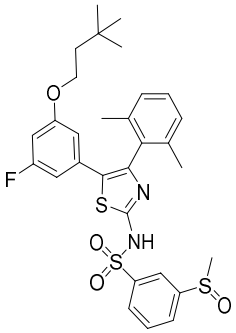
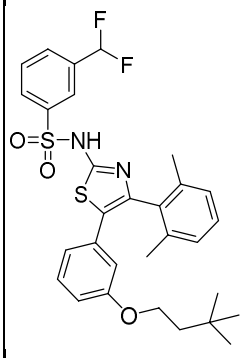


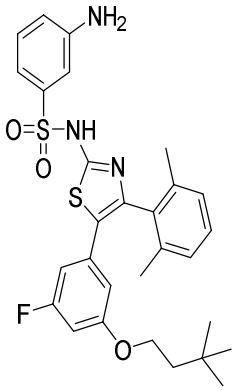
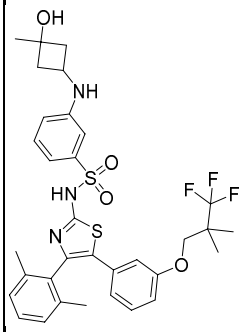
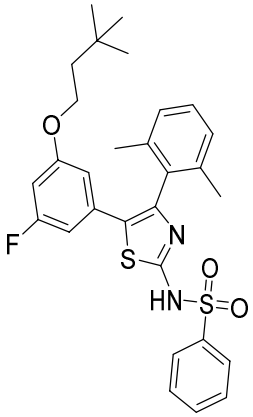
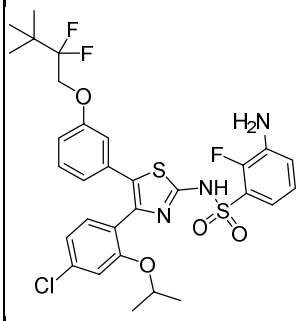
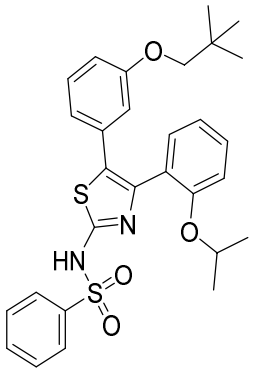
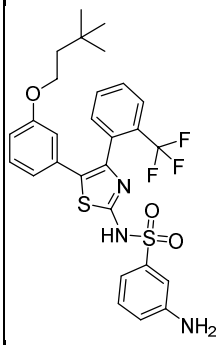
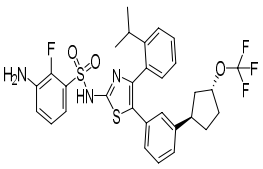
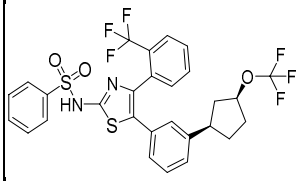
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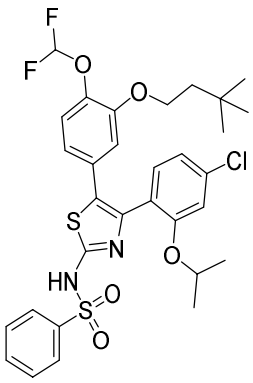
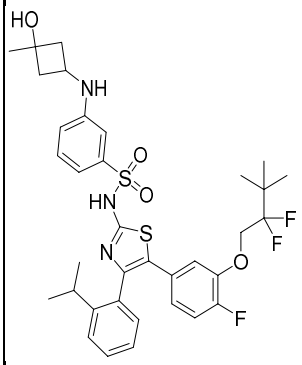
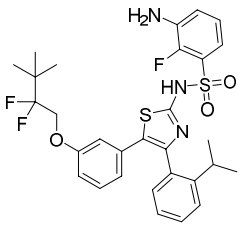
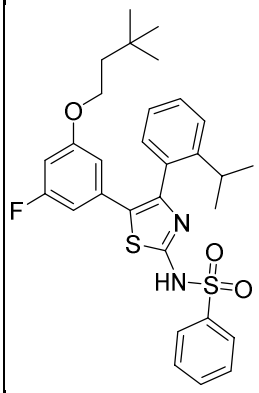
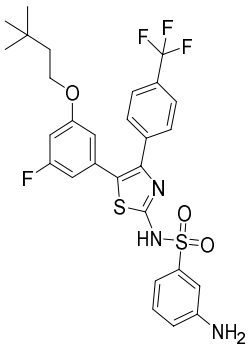
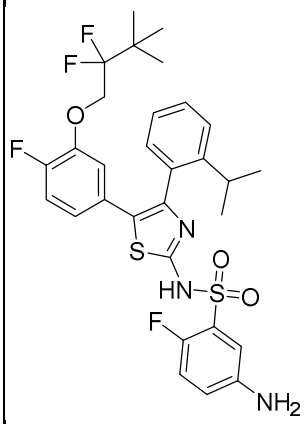
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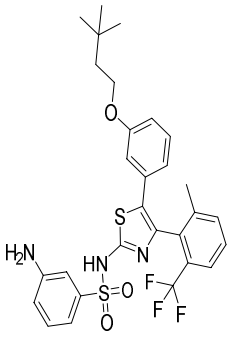
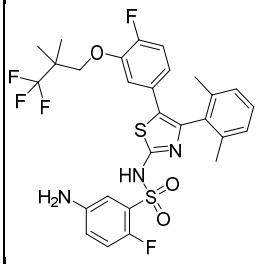
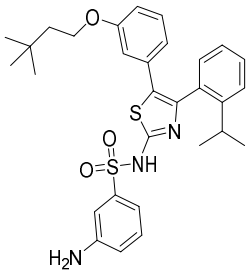
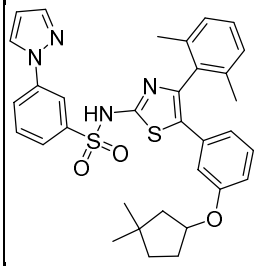
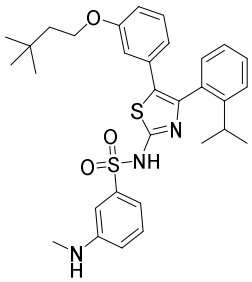
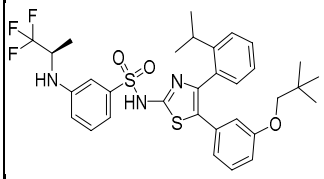
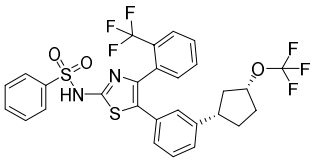
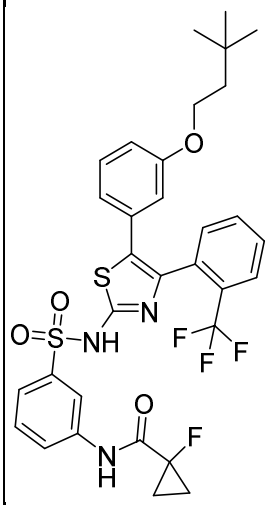
36. A compound selected from:

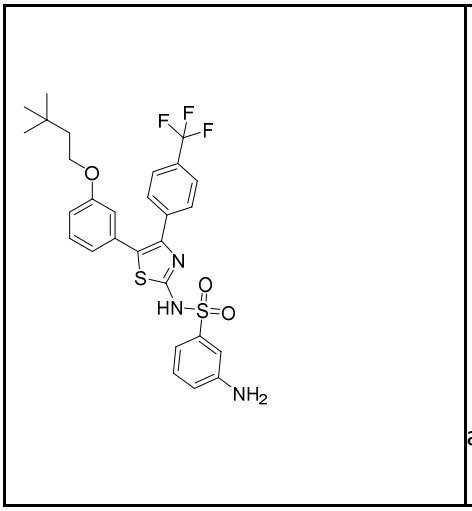
	
	

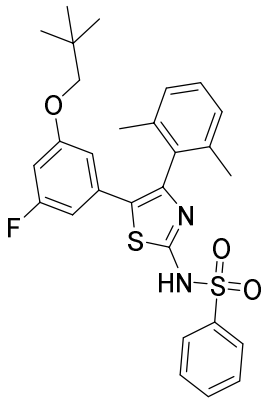
	
	
	
	

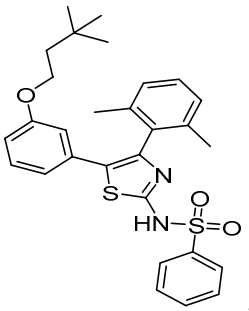


and



or a tautomer or pharmaceutically acceptable salt thereof.

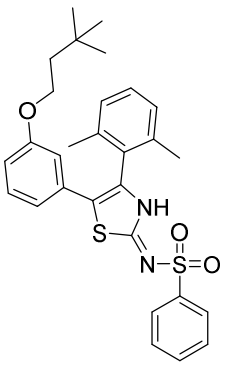
37. A compound, wherein the compound is:



,

or a tautomer or pharmaceutically acceptable salt thereof.

38. A compound, wherein the compound is:



,

or pharmaceutically acceptable salt thereof.

39. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier or excipient.

40. The pharmaceutical composition of claim 39, further comprising one or more CFTR therapeutic agents.

41. Use of a compound of claim 1 in the manufacture of a medicament for treating cystic fibrosis or a symptom thereof in a subject.

42. The use of claim 41, wherein the subject is human.

43. The use according to claim 41 or 42, wherein said subject is at risk of developing cystic fibrosis, and wherein the compound is to be administered prior to the onset of symptoms of cystic fibrosis in said subject.

44. A compound of any one of claims 1-38, for use in therapy.