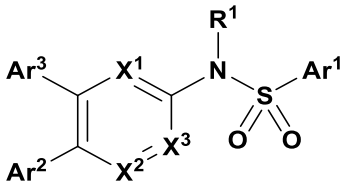
production of misfolded CFTR protein which, rather than traffic to the plasma membrane, is instead retained in the endoplasmic reticulum and targeted for degradation by the ubiquitin-proteasome system.

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 act as correctors and/or potentiators of CFTR. 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 an aspect of the present disclosure, there is provided a compound of Formula (I):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CH or N; wherein at least one of X^1, X^2 or X^3 is N;

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

Ar^1 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^2;

each R^2 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-NR^aR^b$ or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^2 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^3;

each R^3 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl substituted with 0-3 occurrences of R^5 or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^3 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^4;

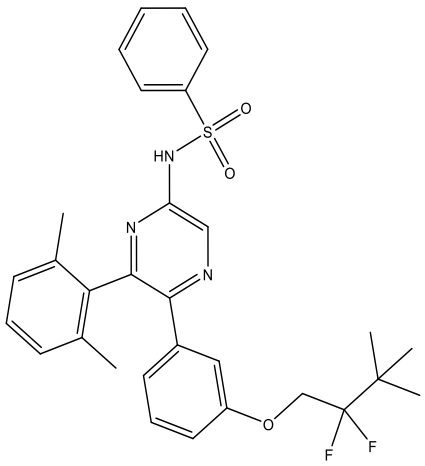
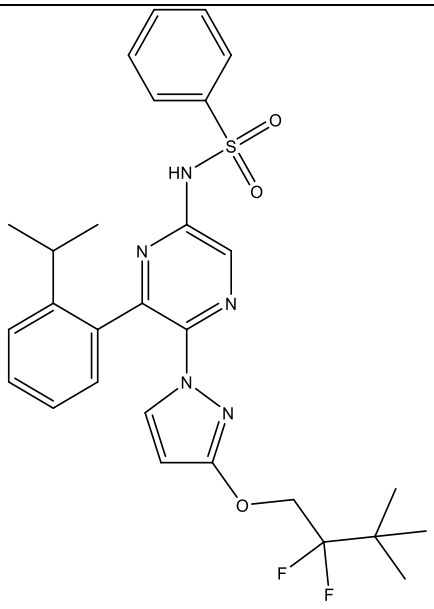
each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy;

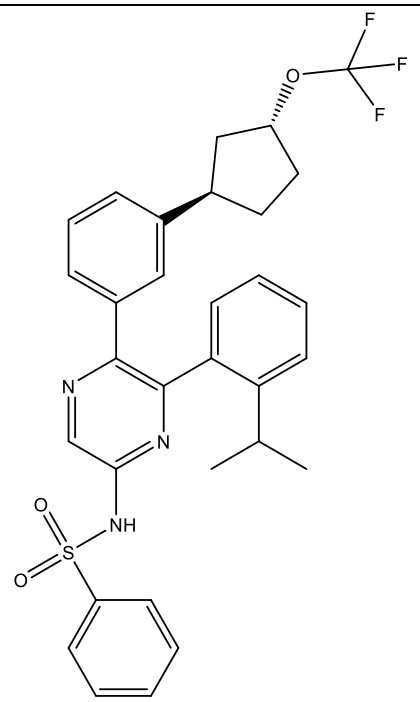
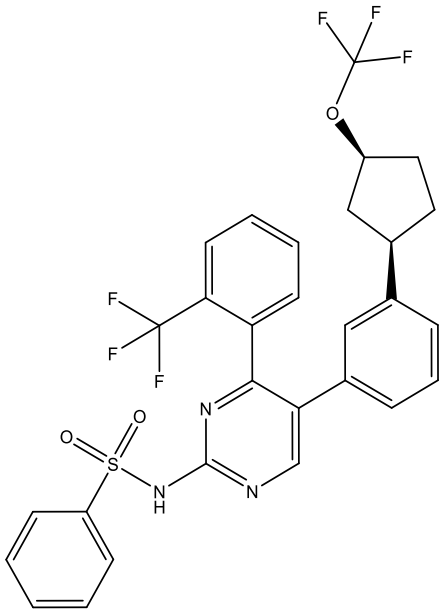
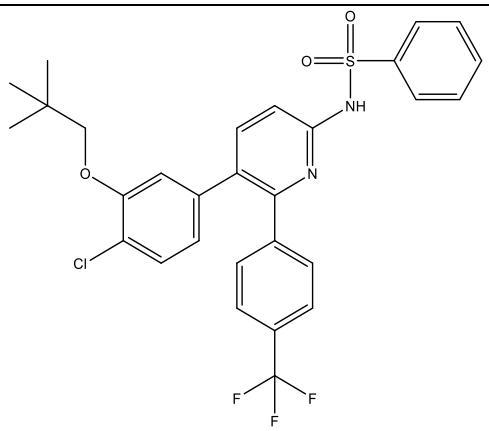
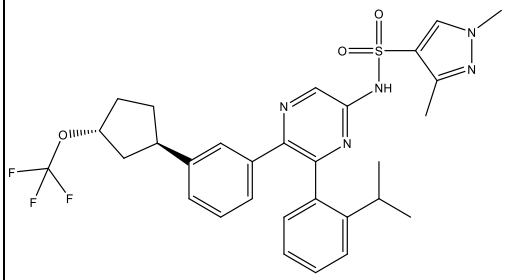
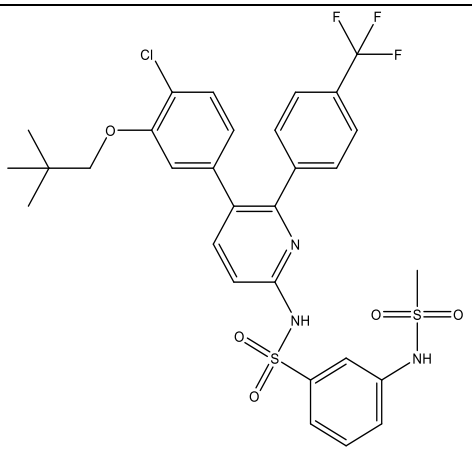
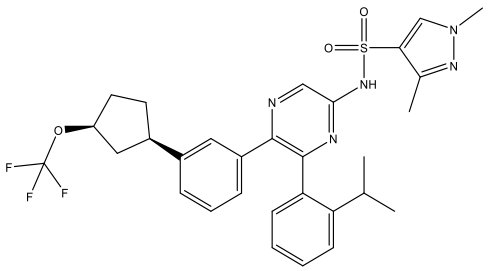
R^a is H or C_{1-4} alkyl;

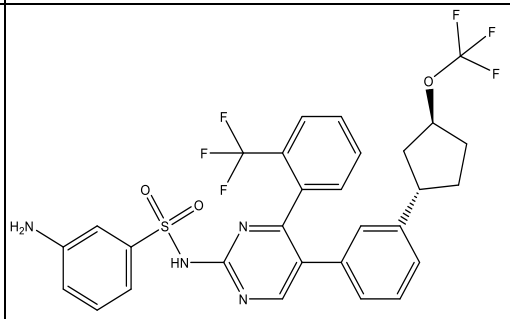
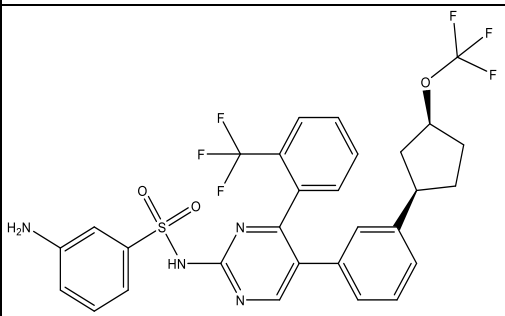
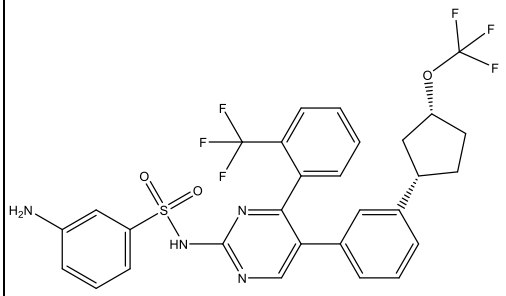
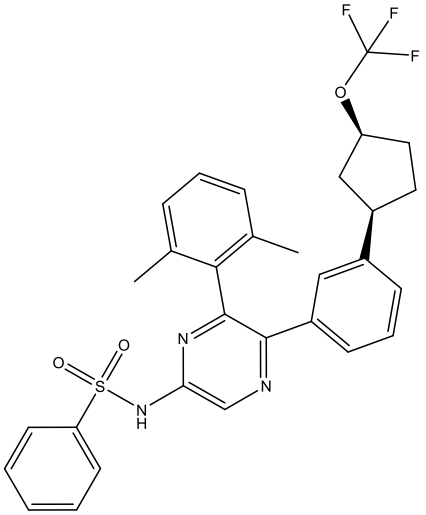
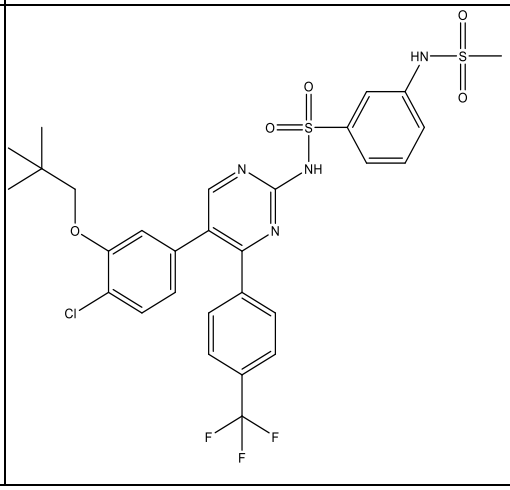
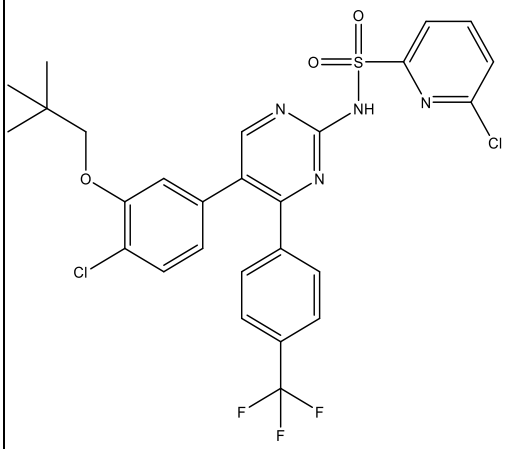
R^b is H, C_{1-4} alkyl, $-SO_2-C_{1-6}$ alkyl, C_{3-8} cycloalkyl or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5; and

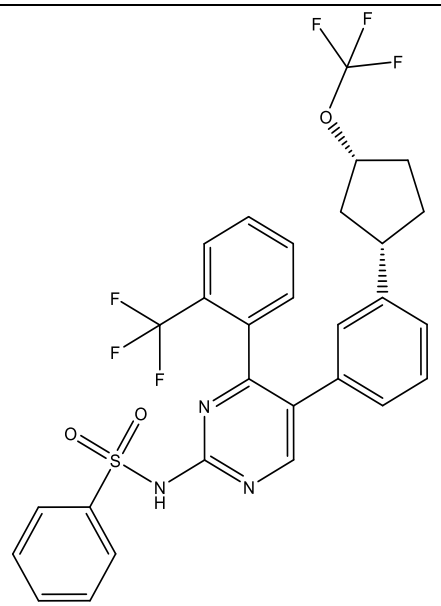
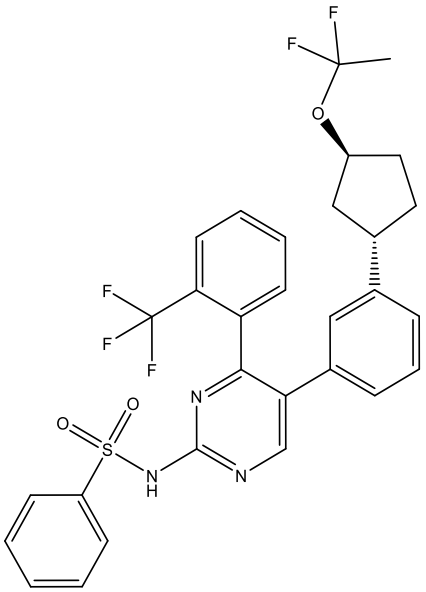
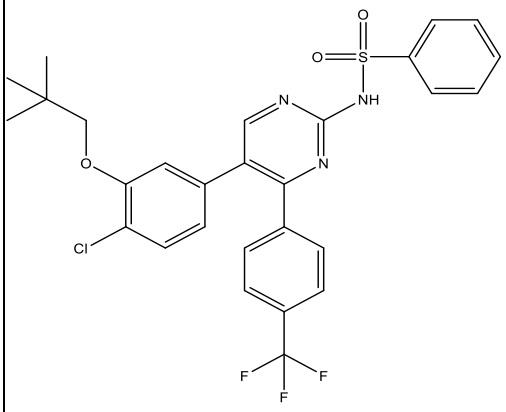
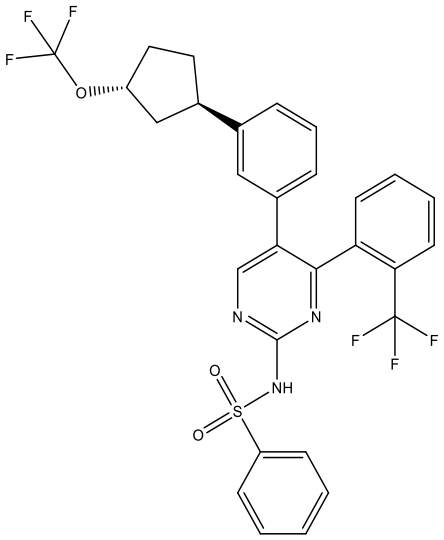
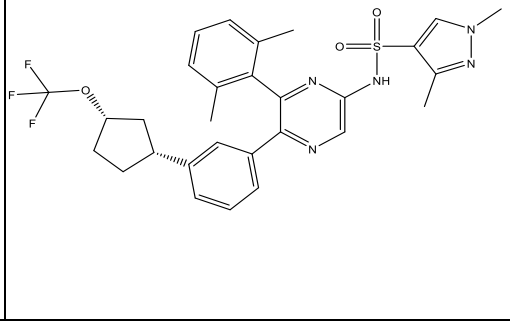
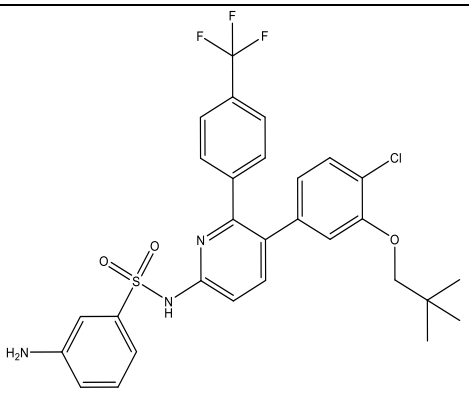
each R^5 is independently hydroxyl, CO_2H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy.

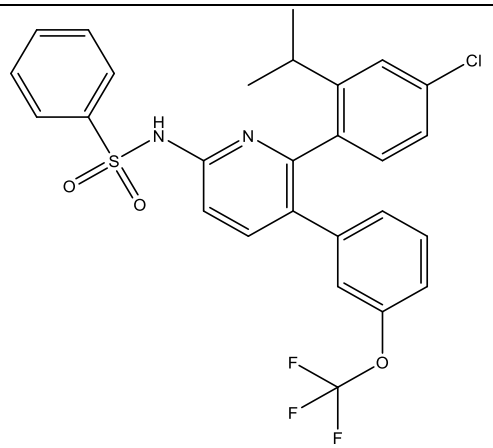
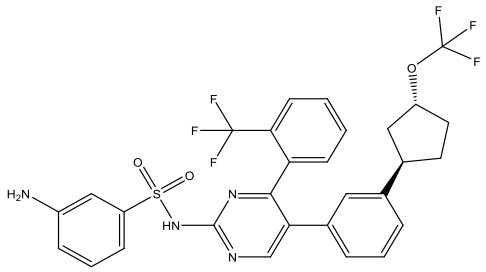
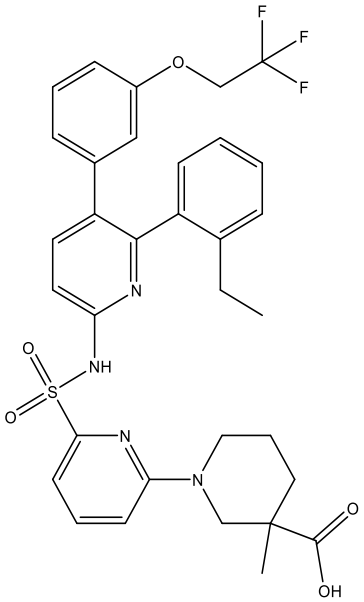
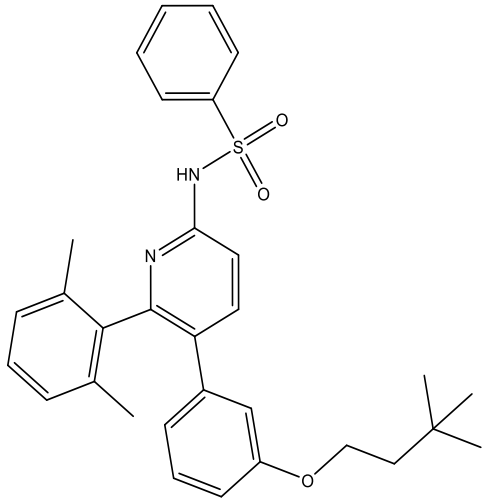
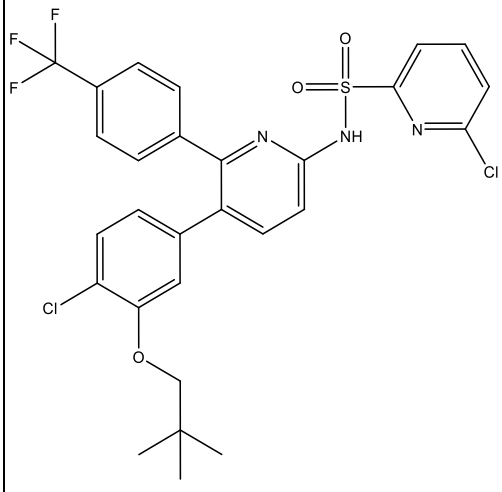
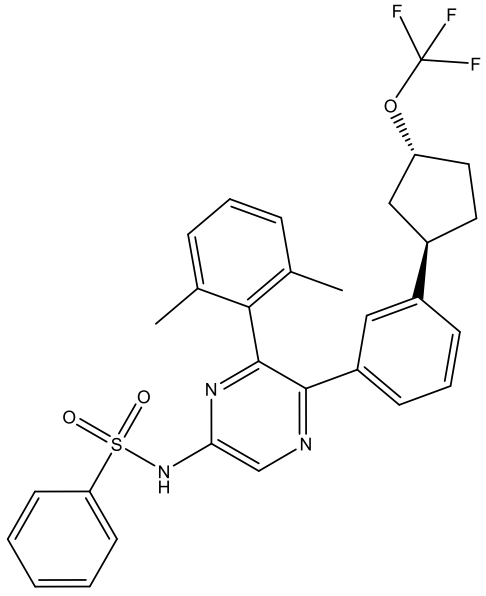
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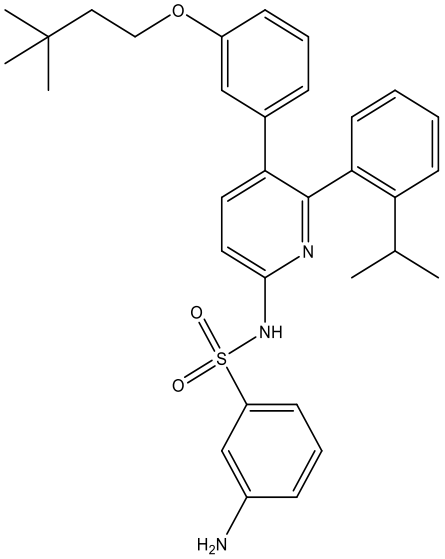
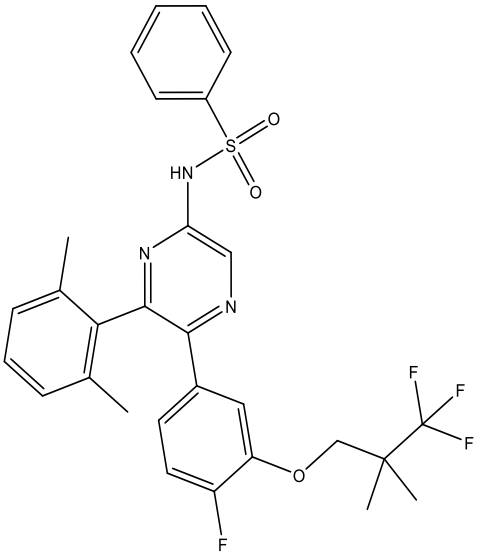
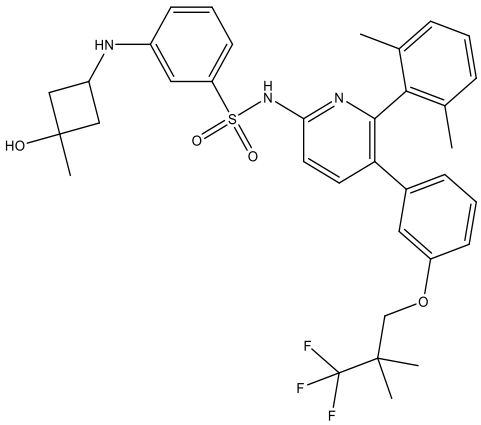
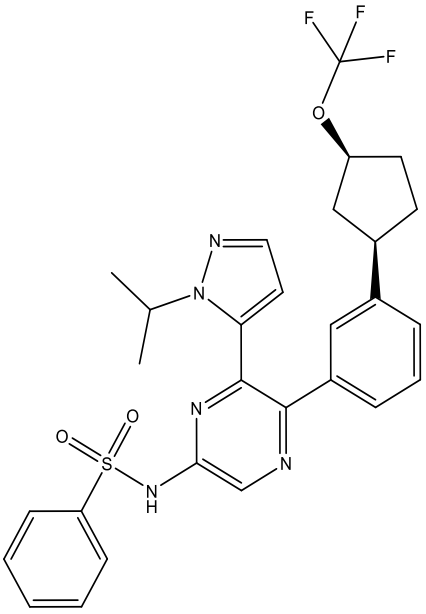
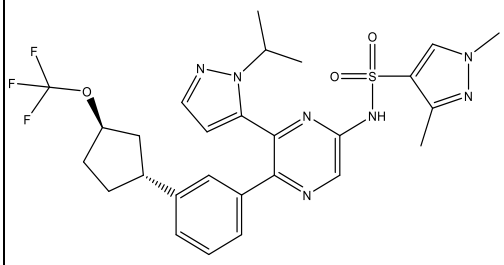
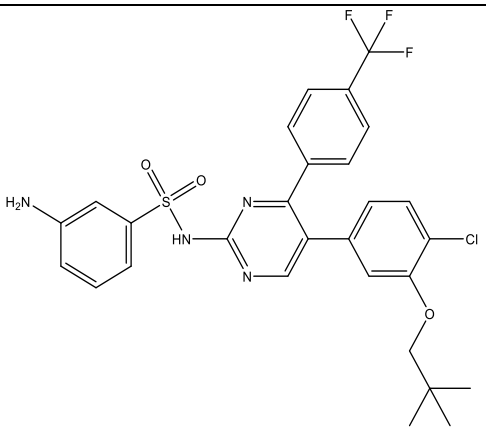
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2		**5**	

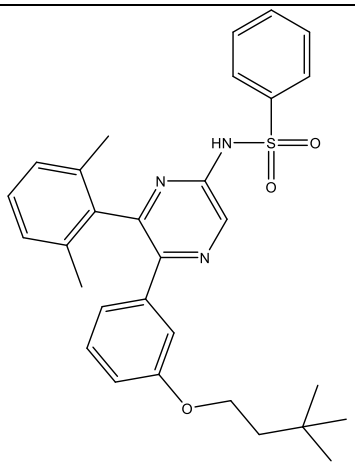
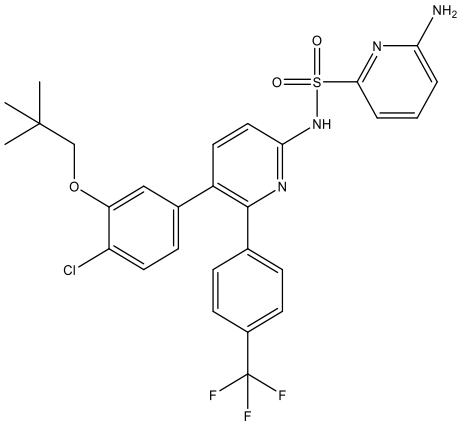
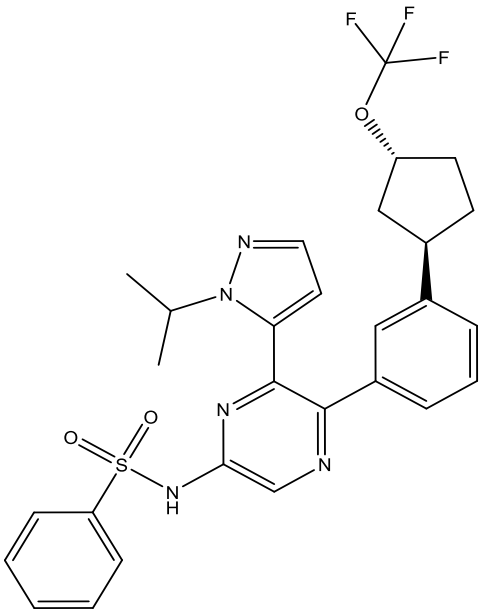
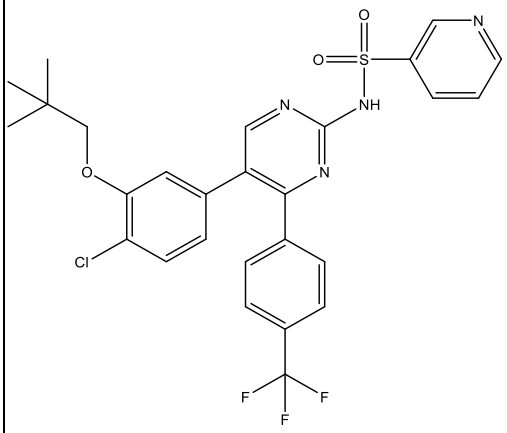
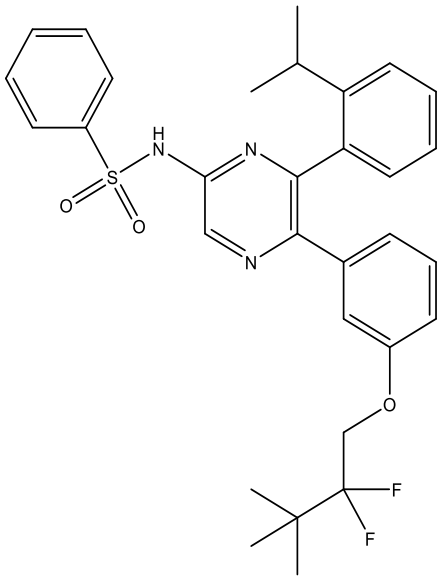
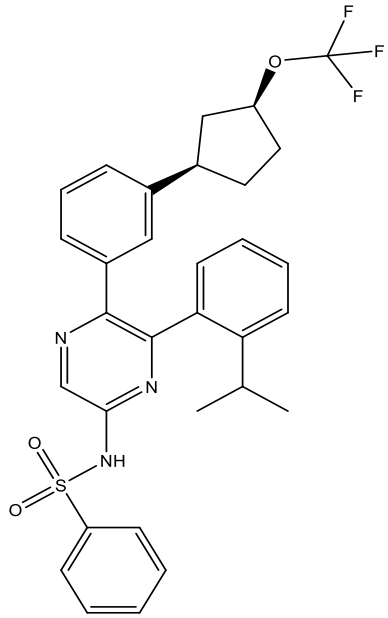
#	Compound	#	Compound
9b		**27b**	
14		**8b**	
18		**8a**	

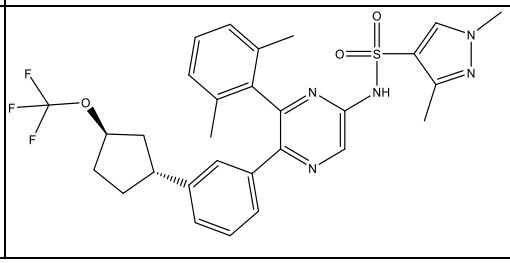
#	Compound	#	Compound
29b		**30a**	
29a		**6a**	
24		**26**	

#	Compound	#	Compound
28a		**27a**	
22		**28b**	
7a		**17**	

#	Compound	#	Compound
19		**30b**	
21		**15**	
12		**6b**	

#	Compound	#	Compound
16		**4**	
20		**10a**	
11		**23**	

#	Compound	#	Compound
3		**13**	
10b		**25**	
1		**9a**	

#	Compound	#	Compound
7b			

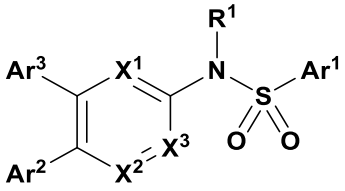
In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier or excipient.

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 deficient CFTR activity in a cell.

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

Disclosed herein are compounds of Formula (**I**):



(**I**)

wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CH or N; wherein at least one of X^1, X^2 or X^3 is N;

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

Ar^1 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^2;

each R^2 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-NR^aR^b$ or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^2 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^3;

each R^3 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl substituted with 0-3 occurrences of R^5 or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^3 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^4;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy;

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

R^b is H, C_{1-4} alkyl, $-SO_2-C_{1-6}$ alkyl, C_{3-8} cycloalkyl, or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

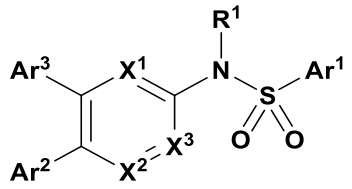
each R^5 is independently hydroxyl, CO_2H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy.

Disclosed herein are methods of treating deficient CFTR activity, thereby treating a disease or condition mediated by deficient CFTR activity. Such diseases and conditions include, but are not limited to, cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, pancreatic steatorrhea, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis, nasal polyposis, dry eye disease, protein C deficiency, abetalipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, congenital pneumonia, nontuberculous mycobacterial infection, constipation, pancreatic insufficiency, celiac disease, intestinal atresia, hereditary emphysema, and Sjogren's syndrome. In some examples, the disease is cystic fibrosis.

In certain examples, the present disclosure provides a pharmaceutical composition suitable for use in a subject in the treatment or prevention of disease and conditions associate with deficient CFTR activity, comprising an effective amount of any of the compounds described herein (e.g., a compound of the present disclosure, such as a compound of formula (I)), and one or more pharmaceutically acceptable excipients. In certain examples, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein.

CLAIMS

1. A compound of Formula (I):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CH or N; wherein at least one of X^1, X^2 or X^3 is N;

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

Ar^1 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^2;

each R^2 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-NR^aR^b$ or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^2 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^3;

each R^3 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl substituted with 0-3 occurrences of R^5 or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5;

Ar^3 is aryl or 5-6 membered heteroaryl substituted with 0-3 occurrences of R^4;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy;

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

R^b is H, C_{1-4} alkyl, $-SO_2-C_{1-6}$ alkyl, C_{3-8} cycloalkyl or 3-8 membered heterocyclyl substituted with 0-3 occurrences of R^5; and

each R^5 is independently hydroxyl, CO_2H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy.

2. The compound of claim 1, wherein X^1 is N and X^2 and X^3 are CH.

3. The compound of claim 1, wherein X1 and X2 are N and X3 is CH.

4. The compound of claim 1, wherein X1 and X3 are N and X2 is CH.

5. The compound of any preceding claim, wherein R1 is hydrogen.

6. The compound of any preceding claim, wherein Ar1 is aryl (e.g., phenyl) substituted with 0-3 occurrences of R2.

7. The compound of any preceding claim, wherein Ar1 is unsubstituted phenyl.

8. The compound of any one of claims 1-6, wherein Ar1 is phenyl substituted with 1 occurrence of R2.

9. The compound of claim 8, wherein R2 is –NRaRb.

10. The compound of claim 9, wherein Ra is hydrogen and Rb is hydrogen.

11. The compound of claim 9, wherein Ra is hydrogen and Rb is –SO2-C1-6 alkyl (e.g., -SO2-Me).

12. The compound of claim 9, wherein Ra is hydrogen and Rb is C3-8 cycloalkyl substituted with 0-3 occurrences of R5.

13. The compound of claim 12, wherein Ra is hydrogen and Rb is cyclobutyl substituted with 2 occurrences of R5.

14. The compound of claim 13, wherein one occurrence of R5 is hydroxyl and the other occurrence of R5 is C1-4 alkyl (e.g., methyl).

15. The compound of any preceding claim, wherein Ar1 is a 5-6 membered heteroaryl substituted with 0-3 occurrences of R2.

16. The compound of claim 15, wherein Ar1 is pyrazolyl (e.g. 4-pyrazolyl).

17. The compound of claim 16, wherein Ar1 is 4-pyrazolyl substituted with 2 occurrences of R2.

18. The compound of claim 17, wherein both R2 are C1-6 alkyl (e.g., methyl).

19. The compound of any one of claims 1-14, wherein Ar1 is a 6-membered heteroaryl substituted with 0-3 occurrences of R2.

20. The compound of claim 19, wherein Ar1 is pyridinyl (e.g. 2-pyridinyl or 3-pyridinyl).

21. The compound of claim 20, wherein Ar1 is 2-pyridinyl substituted with 0 or 1 occurrence of R2.

22. The compound of claim 21, wherein R2 is halo (e.g., chloro) or –NRaRb (e.g., -NH2).

23. The compound of claim 21, wherein R2 is 3-8 membered heterocyclyl substituted with 0-3 occurrences of R5.

24. The compound of claim 23, wherein R2 is piperidinyl (e.g., 1-piperidinyl).

25. The compound of claim 24, wherein R2 is 1-piperidinyl substituted with 2 occurrences of R5.

26. The compound of claim 25, wherein one occurrence of R5 is hydroxyl and the other occurrence of R5 is C1-4 alkyl (e.g., methyl).

27. The compound of any preceding claim, wherein Ar2 is aryl (e.g., phenyl) substituted with 0-3 occurrences of R3.

28. The compound of claim 27, wherein Ar2 is phenyl substituted with 0 or 1 occurrences of R3.

29. The compound of claim 28, wherein R3 is C1-6 alkoxy or C1-6 haloalkoxy.

30. The compound of claim 28, wherein R3 is selected from 2,2-dimethylpropoxy or 3,3-dimethylbutoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoro-3,3-dimethylbutoxy and 2,2-dimethyl-3,3,3-trifluoropropoxy.

31. The compound of claim 28, wherein R3 is C3-8 cycloalkyl substituted with 0-3 occurrences of R5.

32. The compound of claim 31, wherein R3 is cyclopentyl substituted with 1 occurrence of R5 and R5 is C1-4 haloalkoxy (e.g., trifluoromethoxy).

33. The compound of claim 27, wherein Ar2 is phenyl substituted with 2 occurrences of R3.

34. The compound of claim 33, wherein one occurrence of R3 is halo (e.g., fluoro or chloro) and the other occurrence of R3 is C1-6 alkoxy (e.g., 2,2-dimethylpropoxy).

35. The compound of claim 33, wherein one occurrence of R3 is halo (e.g., fluoro or chloro) and the other occurrence of R3 is C1-6 haloalkoxy (e.g., 2,2-dimethyl-3,3,3-trifluoropropoxy).

36. The compound of any one of claims 1-26, wherein Ar2 is 5-6 membered heteroaryl (e.g., 1-pyrazolyl) substituted with 0-3 occurrences of R3.

37. The compound of claim 36, wherein Ar2 is 1-pyrazolyl substituted with 1 occurrence of R3.

38. The compound of claim 37, wherein R3 is C1-6 haloalkoxy (e.g., 2,2-difluoro-2,2-dimethylbutoxy).

39. The compound of any preceding claim, wherein Ar3 is aryl (e.g., phenyl) substituted with 0-3 occurrences of R4.

40. The compound of claim 39, wherein Ar3 is phenyl substituted with 0 or 1 occurrences of R4.

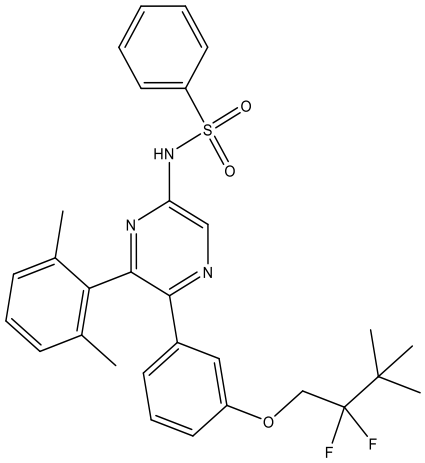
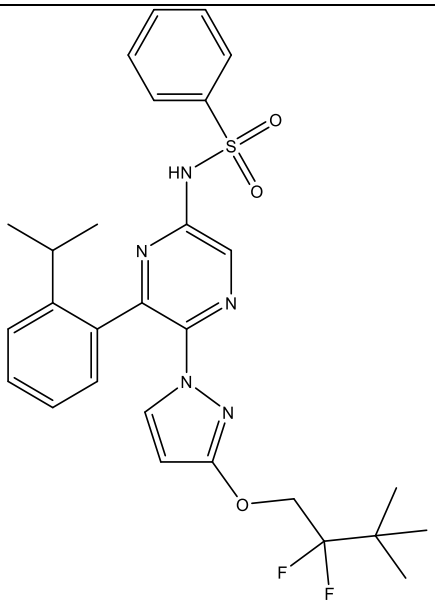
41. The compound of claim 40, wherein R4 is C1-6 alkyl (e.g., isopropyl or ethyl) or C1-6 haloalkyl (e.g., trifluoromethyl).

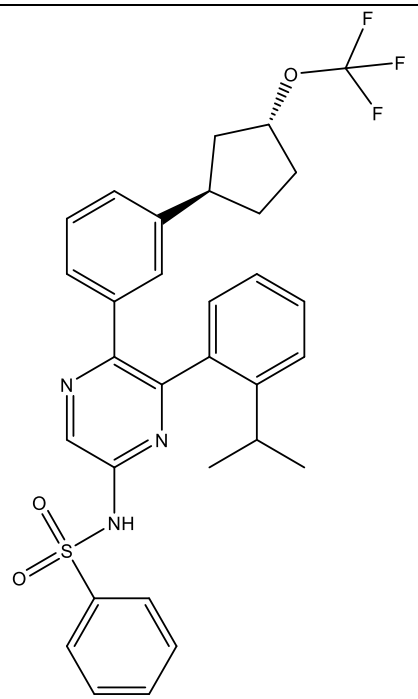
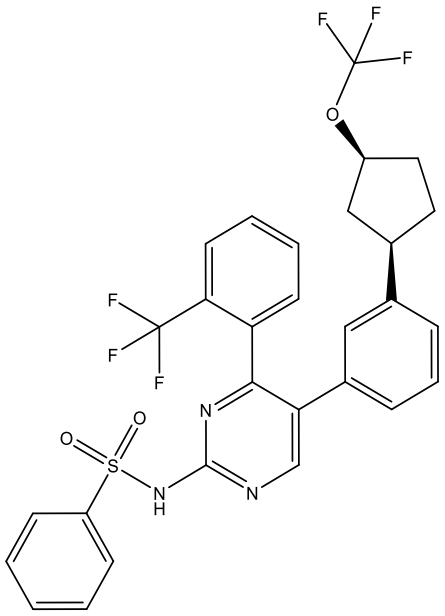
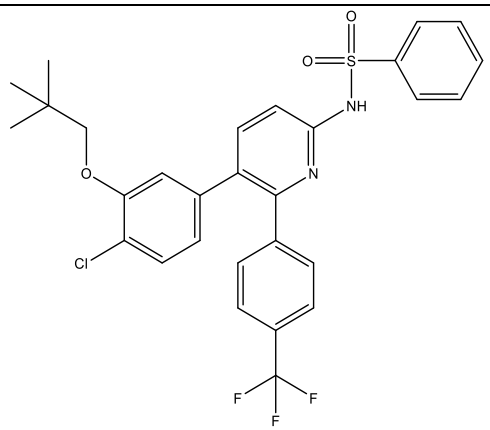
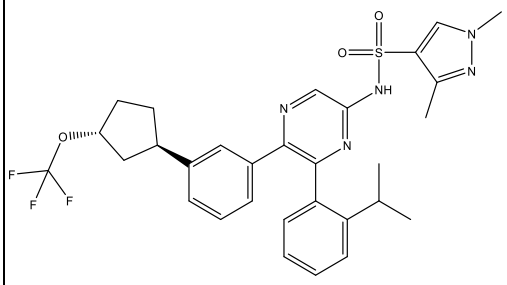
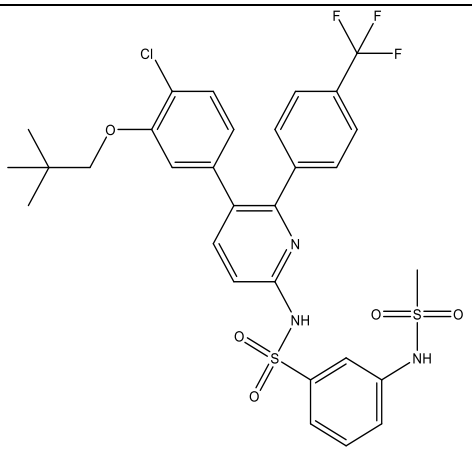
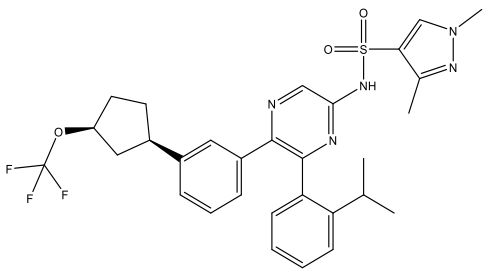
42. The compound of claim 39, wherein Ar3 is phenyl substituted with 2 occurrences of R4.

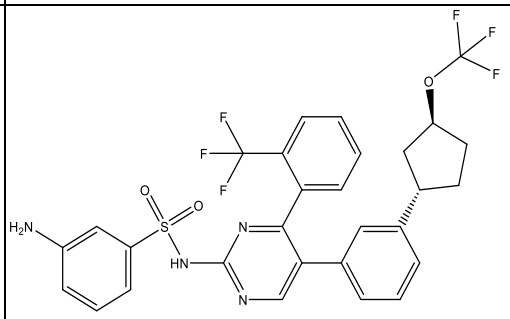
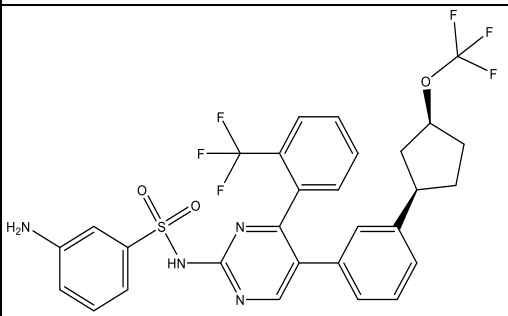
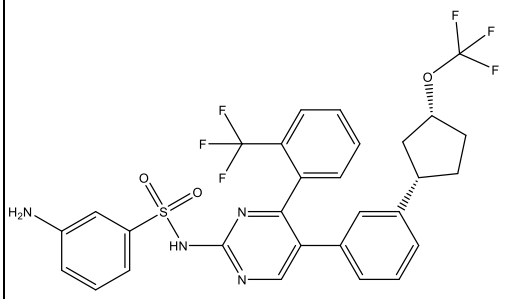
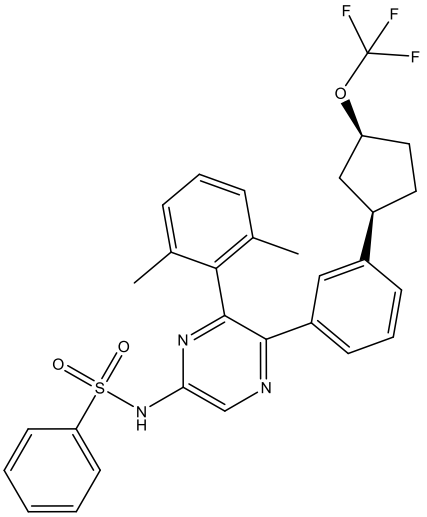
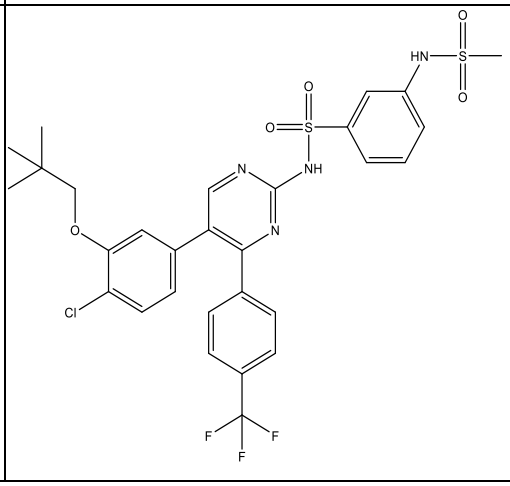
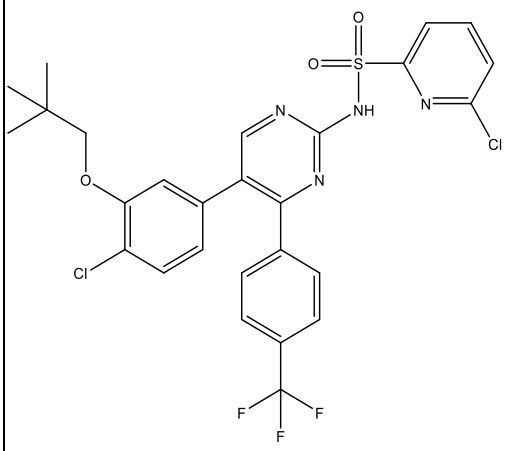
43. The compound of claim 42, wherein one occurrence of R4 is halo (e.g., fluoro or chloro) and the other occurrence of R4 is C1-6 alkyl (e.g., isopropyl).

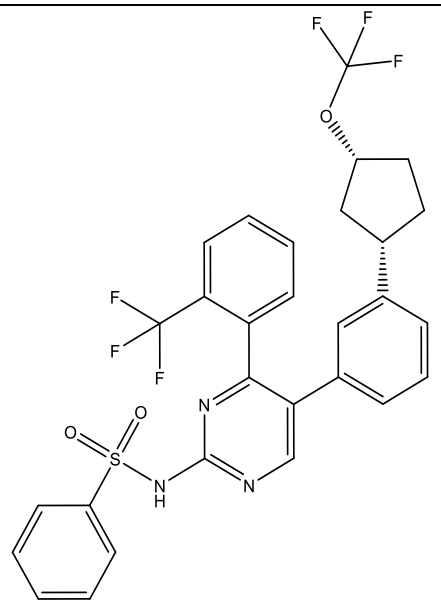
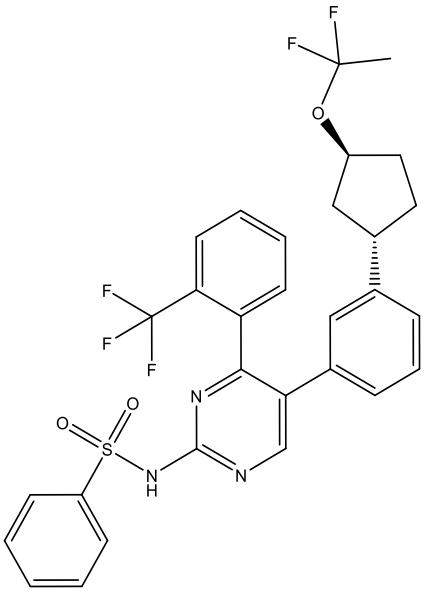
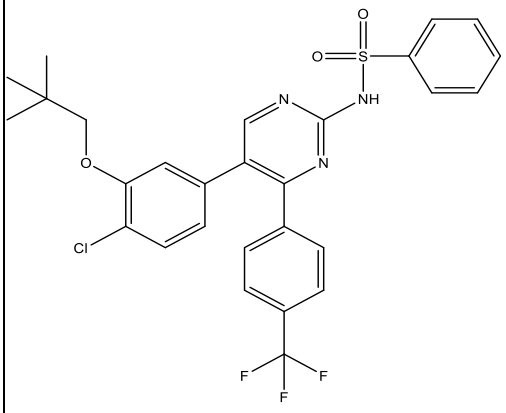
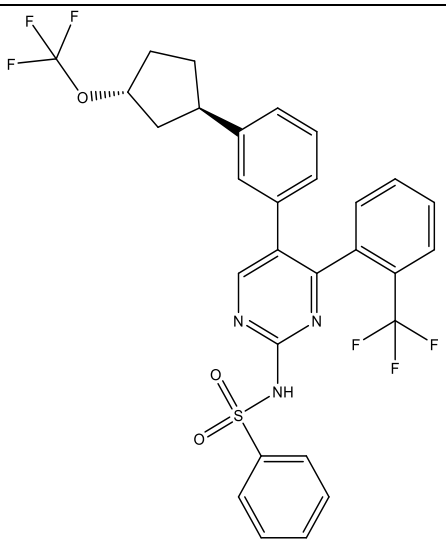
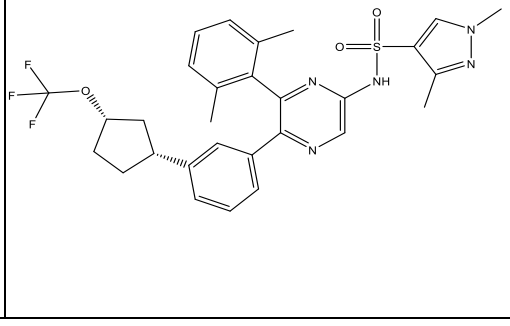
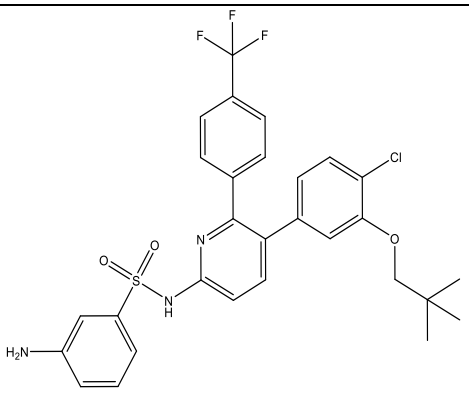
44. The compound of claim 42, wherein both occurrences of R4 are C1-6 alkyl (e.g., methyl).

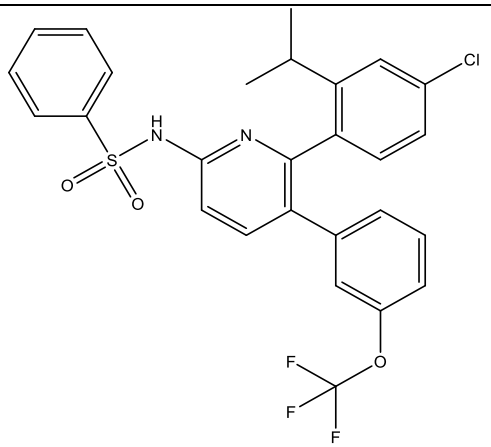
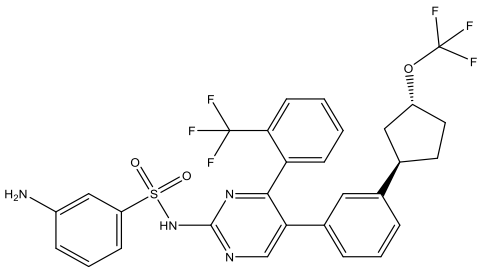
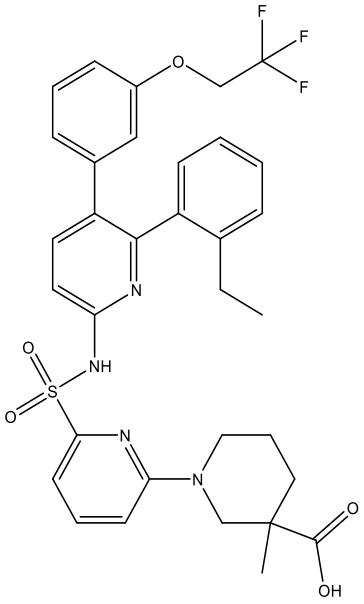
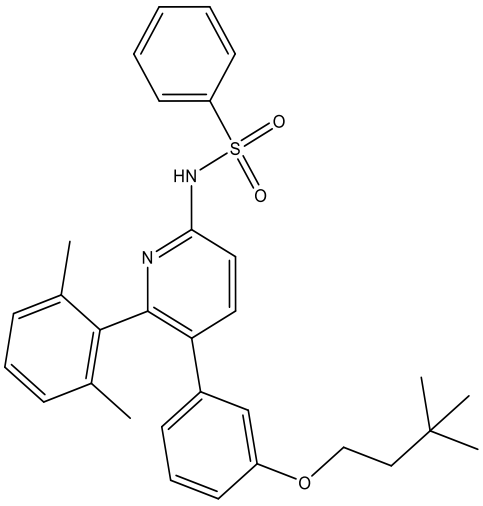
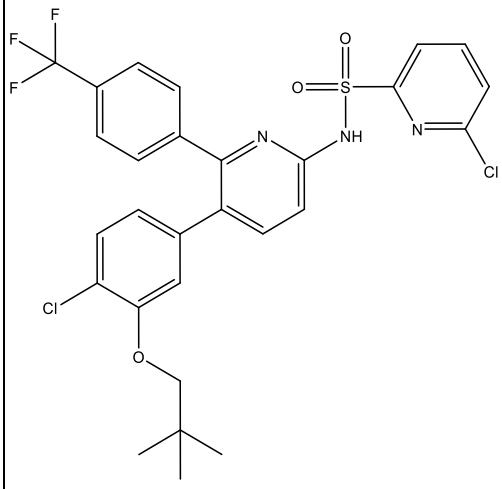
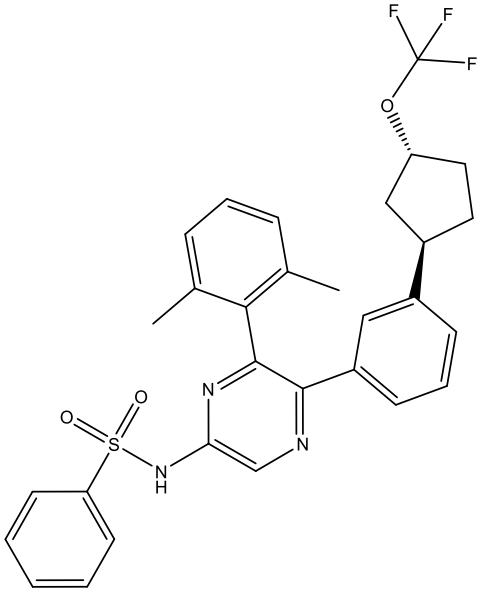
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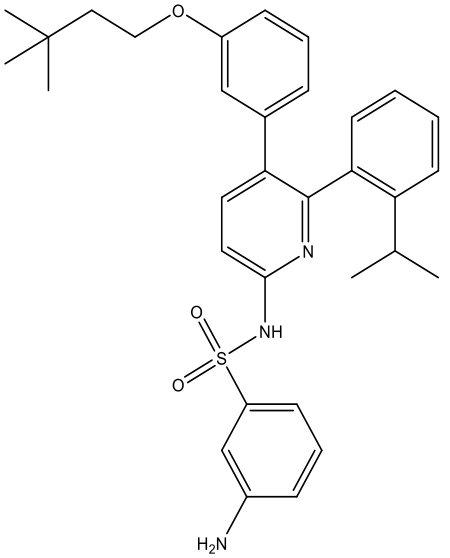
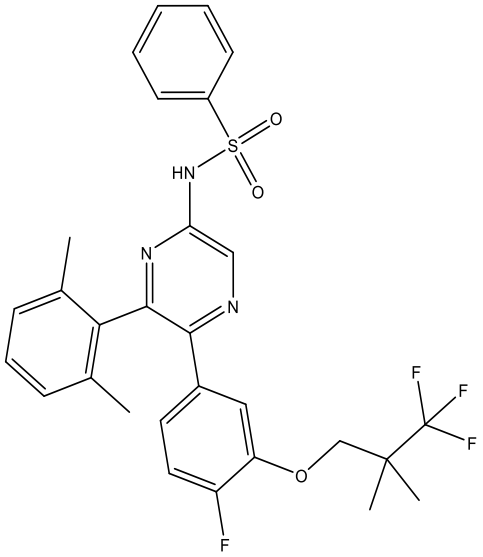
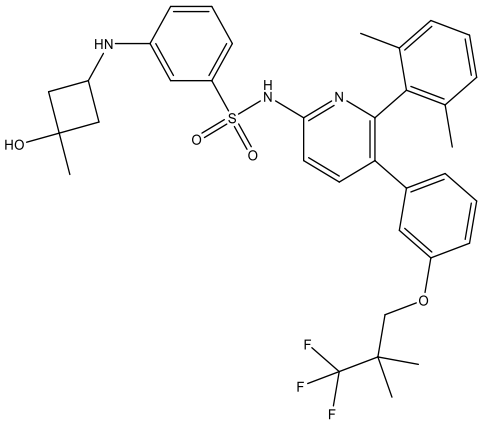
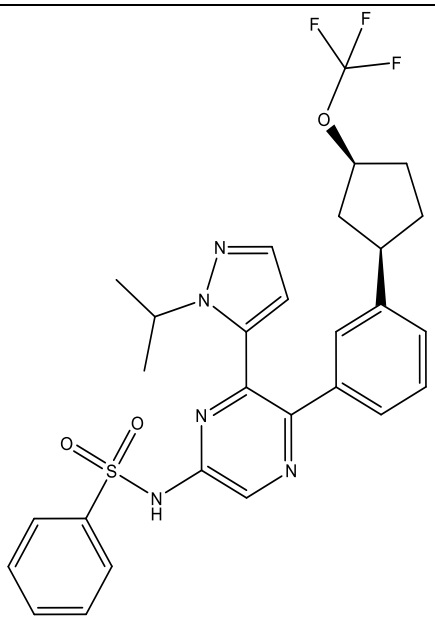
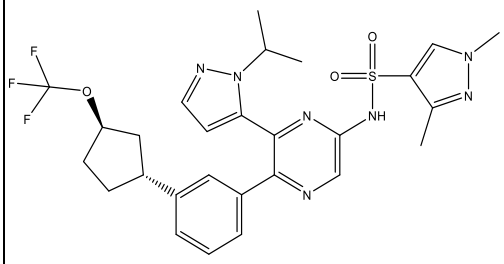
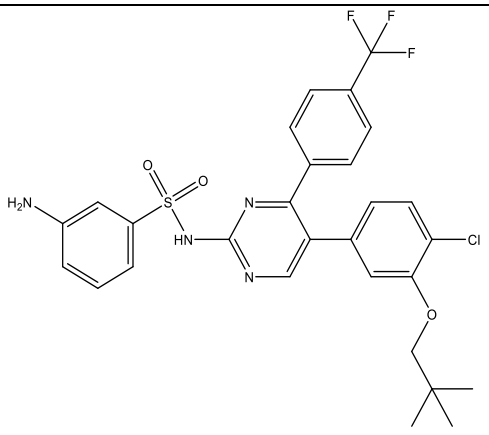
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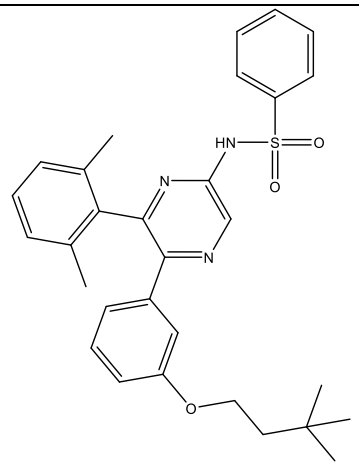
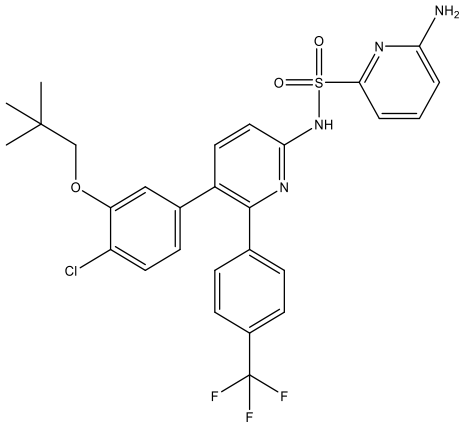
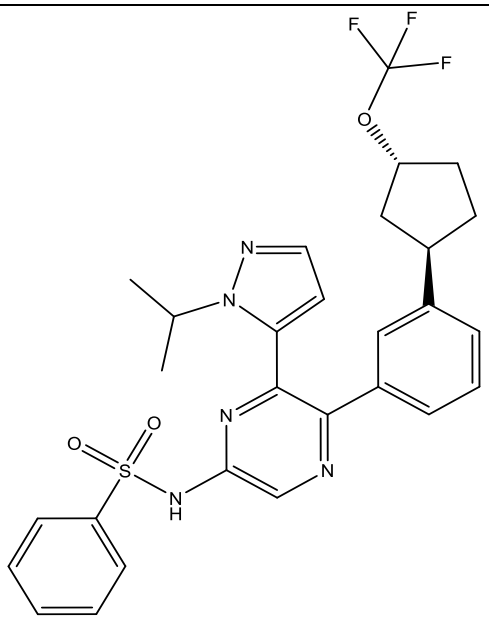
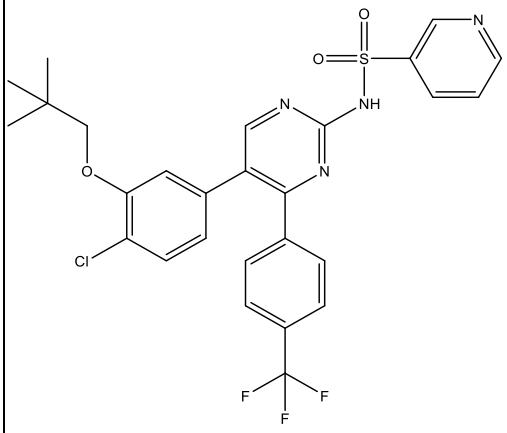
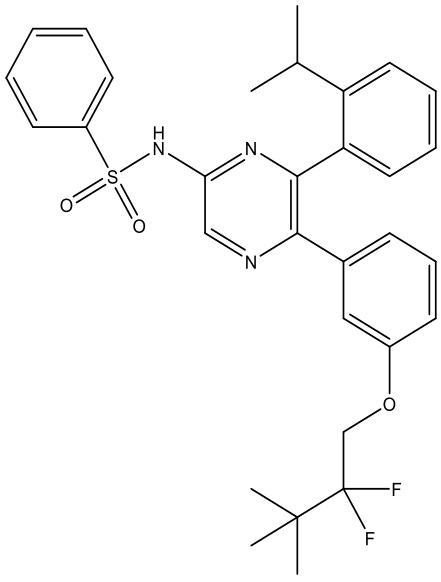
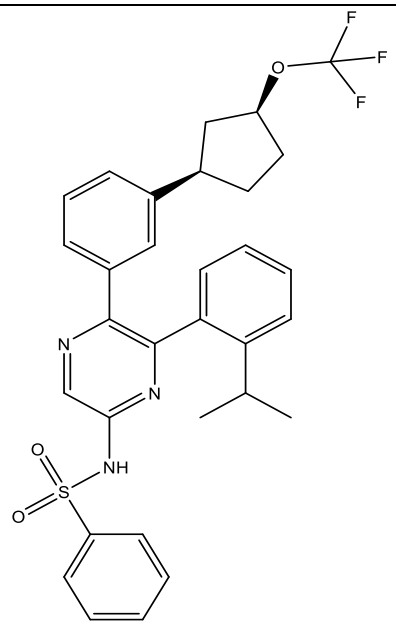
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9b		**27b**	
14		**8b**	
18		**8a**	

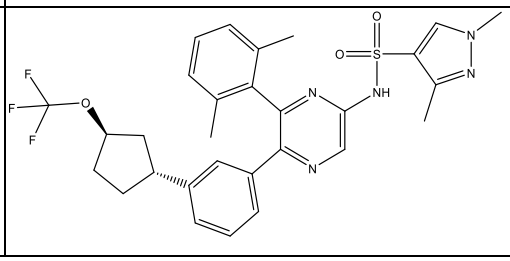
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29b		**30a**	
29a		**6a**	
24		**26**	

#	Compound	#	Compound
28a		**27a**	
22		**28b**	
7a		**17**	

#	Compound	#	Compound
19		**30b**	
21		**15**	
12		**6b**	

#	Compound	#	Compound
16		**4**	
20		**10a**	
11		**23**	

#	Compound	#	Compound
3		**13**	
10b		**25**	
1		**9a**	

#	Compound	#	Compound
7b			

46. The compound of any one of claims 1-45, wherein the compound is a CFTR corrector.

47. A pharmaceutical composition comprising a compound of any one of claims 1-46, and a pharmaceutically acceptable carrier or excipient.

48. The pharmaceutical composition of claim 47, further comprising one or more CFTR therapeutic agents.

49. Use of a compound according to any one of claims 1-46 in the manufacture of a medicament for treating deficient CFTR activity in a cell.

50. The use of claim 49, wherein the use treats a CFTR-mediated condition and/or disease.

51. The use of claim 50, wherein the disease or condition is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase

deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders, Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, myotonic dystrophy, spongiform encephalopathies, hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, Sjogren's disease, Osteoporosis, Osteopenia, bone healing and bone growth, bone repair, bone regeneration, reducing bone resorption, increasing bone deposition, Gorham's Syndrome, chloride channelopathies, myotonia congenita, Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus, PCD without situs inversus and ciliary aplasia.

52. The use of claim 50 or 51, wherein the disease or condition is selected from cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, abetalipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.

53. The use of any one of claims 50-52, wherein the disease or condition is cystic fibrosis.

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

55. The use of claim 54, wherein the subject is human.

56. The use according to claim 54 or 55, 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.

57. A compound according to any one of claims 1-46 for use in therapy.