

Compounds, Compositions, and Methods of Using Thereof

BACKGROUND

[001] Cystic fibrosis (CF), an autosomal recessive disorder, is caused by functional deficiency of the cAMP-activated plasma membrane chloride channel, cystic fibrosis transmembrane conductance regulator (CFTR), which can result in damage to the lung, pancreas and other organs. The gene encoding CFTR has been identified and sequenced (See Gregory, R. J. et al. (1990) Nature 347:382-386; Rich, D. P. et al. (1990) Nature 347:358-362; Riordan, J. R. et al. (1989) Science 245:1066-1073). CFTR, a member of the ATP binding cassette (ABC) superfamily is composed of two six membrane-spanning domains (MSD1 and MSD2), two nucleotide binding domains (NBD1 and NBD2), a regulatory region (R) and four cytosolic loops (CL1-4). Normally, CFTR protein is located primarily in the apical membrane of epithelial cells where it functions to conduct anions, including chloride, bicarbonate and thiocyanate into and out of the cell. CFTR may have a regulatory role over other electrolyte channels, including the epithelial sodium channel ENaC.

[002] In cystic fibrosis patients, the absence or dysfunction of CFTR leads to exocrine gland dysfunction and a multisystem disease, characterized by pancreatic insufficiency and malabsorption, as well as abnormal mucociliary clearance in the lung, mucostasis, chronic lung infection and inflammation, decreased lung function and ultimately respiratory failure.

[003] While more than 1,900 mutations have been identified in the CFTR gene, a detailed understanding of how each CFTR mutation may impact channel function is known for only a subset. (Derichs, European Respiratory Review, 22:127, 58-65 (2013)). The most frequent CFTR mutation is the in-frame deletion of phenylalanine at residue 508 ($\Delta F508$) in the first nucleotide binding domain (NBD1). Over 80% of cystic fibrosis patients have the deletion at residue 508 in at least one allele. The loss of this key phenylalanine renders the CFTR NBD1 domain conformationally unstable at physiological temperature and compromises the integrity of the interdomain interface between NBD1 and CFTR's second transmembrane domain (ICL4). The $\Delta F508$ mutation causes 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.

[004] 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

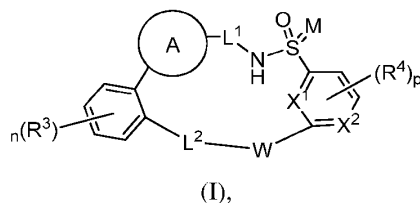
resulting in chronic infection and inflammation. In the lung, the loss of CFTR-function leads to numerous physiological effects downstream of altered anion conductance that result in the dysfunction of additional organs such as the pancreas, intestine and gall bladder.

[005] Guided, in part, by studies of the mechanistic aspects of CFTR misfolding and dysfunction, small molecule CFTR modulators have been identified, that can increase CFTR channel function.

[006] 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

[007] In one aspect, the present application is directed to a compound of Formula I:



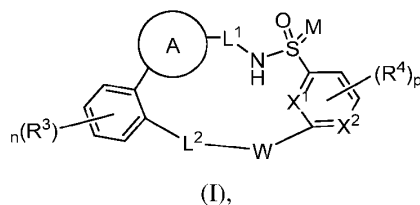
or a pharmaceutically acceptable salt thereof, wherein A, R³, R⁴, L¹, L², M, W, X¹, X², n and p are defined herein.

[008] Disclosed herein are combination therapies of compounds of Formula (I), and methods of using, methods of making, and pharmaceutical compositions thereof.

DETAILED DESCRIPTION

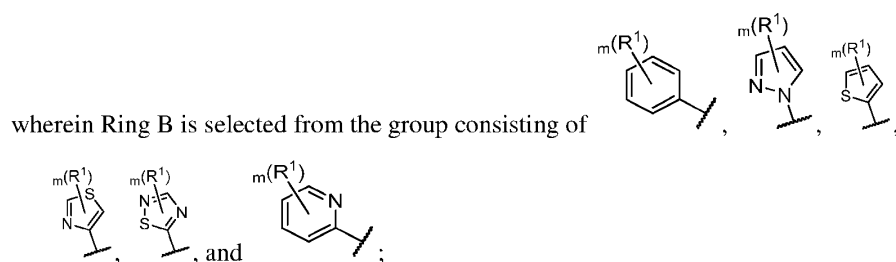
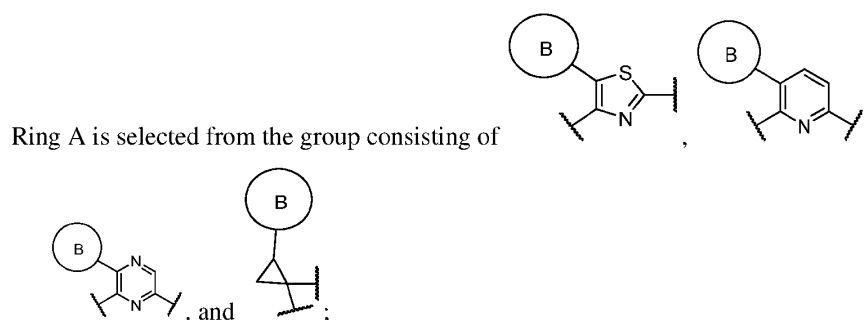
Compounds

[009] In certain aspects, the present application is directed to a compound of Formula I:



or a pharmaceutically acceptable salt thereof,

wherein



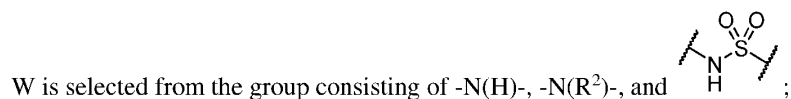
X^1 is $-C(H)=$, $-C(R^4)=$, or $-N=$;

X^2 is $-C(H)=$, $-C(R^4)=$, or $-N=$;

L^1 is a bond or $-C(=O)-$;

L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with $-O-$ or $-N(H)-$, and wherein L^2 is optionally substituted with 1-4 instances of halogen;

M is $=O$ or $=N(H)$;



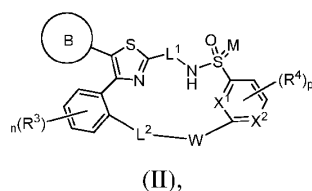
each R^1 is independently selected from the group consisting of H, halogen, optionally substituted C_{1-5} alkyl, and optionally substituted $-O-C_{1-8}$ alkyl, wherein $-O-C_{1-8}$ alkyl is optionally substituted with 1-3 instances of halogen;

R^2 is selected from the group consisting of optionally substituted C_{1-5} alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, wherein C_{1-5} alkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of optionally substituted halogen, C_{1-3} alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, and $-C(=O)OH$;

each R^3 is H, halogen, or optionally substituted C_{1-3} alkyl;

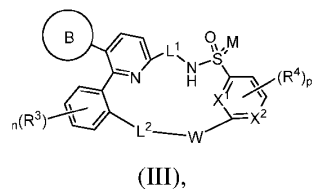
each R^4 is H, halogen, or optionally substituted C_{1-3} alkyl;
 m is selected from the group consisting of 1, 2, 3, 4, and 5;
 n is selected from the group consisting of 1, 2, 3, and 4; and
 p is 1 or 2.

[010] In some embodiments, the compound is a compound of Formula (II):



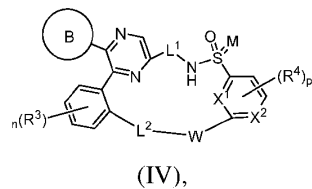
or a pharmaceutically acceptable salt thereof.

[011] In some embodiments, the compound is a compound of Formula (III):



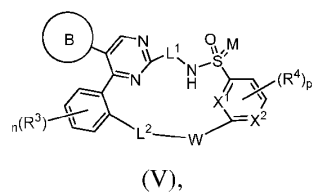
or a pharmaceutically acceptable salt thereof.

[012] In some embodiments, the compound is a compound of Formula (IV):



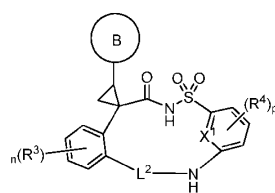
or a pharmaceutically acceptable salt thereof.

[013] In some embodiments, the compound is a compound of Formula (V):



or a pharmaceutically acceptable salt thereof.

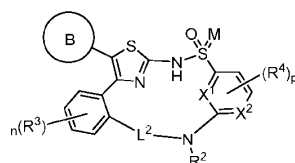
[014] In some embodiments, the compound is a compound of Formula (VI):



(VI),

or a pharmaceutically acceptable salt thereof.

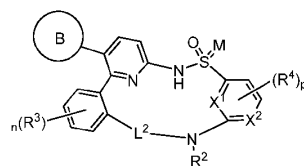
[015] In some embodiments, the compound is a compound of Formula (VII):



(VII),

or a pharmaceutically acceptable salt thereof.

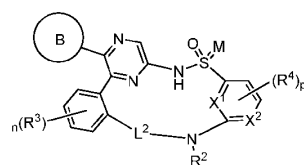
[016] In some embodiments, the compound is a compound of Formula (VIII):



(VIII),

or a pharmaceutically acceptable salt thereof.

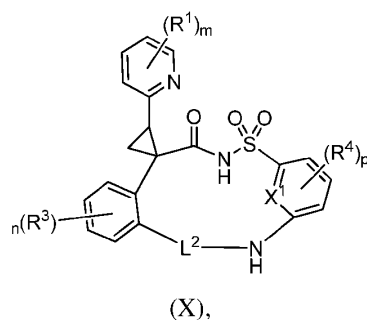
[017] In some embodiments, the compound is a compound of Formula (VIII):



(IX),

or a pharmaceutically acceptable salt thereof.

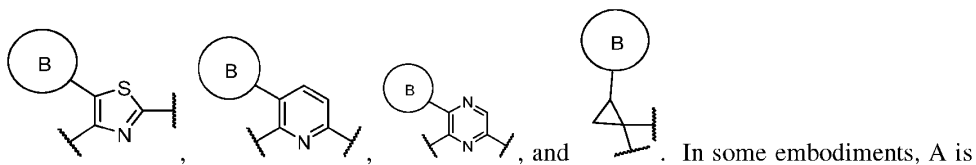
[018] In some embodiments, the compound is a compound of Formula (VII):



or a pharmaceutically acceptable salt thereof.

A

[019] In some embodiments, Ring A is selected from the group consisting of



selected from the group consisting of

In some

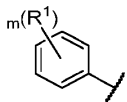
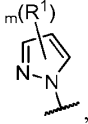
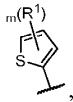
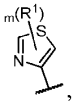
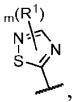
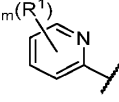
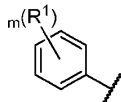
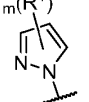
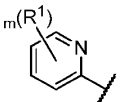
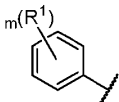
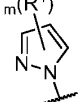
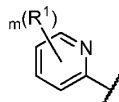
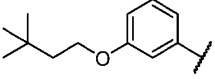
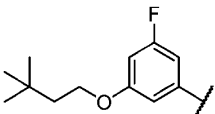
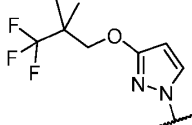
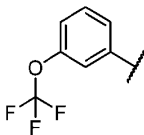
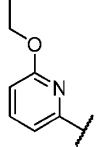
embodiments, A is

In some

embodiments, A is

In some embodiments, A is

B

[020] In some embodiments, Ring B is selected from the group consisting of , , , , , and . In some embodiments, B is selected from the group consisting of , , and . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is .

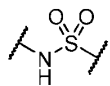
X¹ and X²

[021] In some embodiments, X¹ is -C(H)=, -C(R⁴)=, or -N=. In some embodiments, X¹ is -C(R⁴)=. In some embodiments, X¹ is -CH=. In some embodiments, X¹ is -CF=. In some embodiments, X¹ is -N=. In some embodiments, X² is -C(H)=, -C(R⁴)=, or -N=. In some embodiments, X² is -C(R⁴)=. In some embodiments, X² is -CH=. In some embodiments, X¹ is -CF=. In some embodiments, X² is -N=.

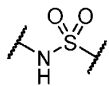
[022]

W

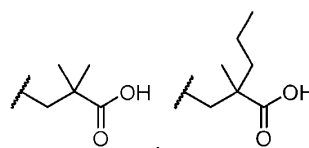
[023] In some embodiments, W is selected from the group consisting of -NH-, -NR²-, and



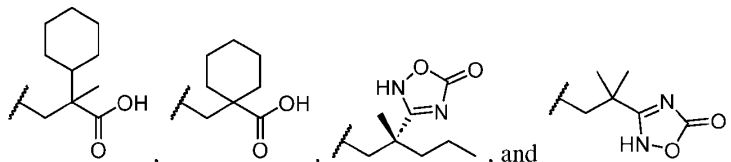
. In some embodiments, W is -NH. In some embodiments, W is -NR₂. In some



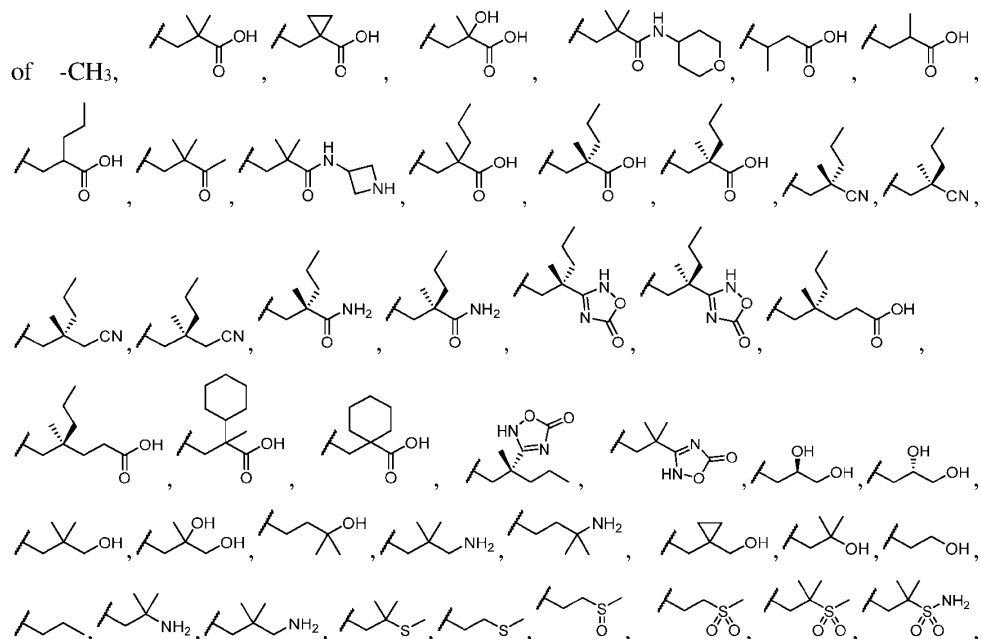
embodiments, W is NH . In some embodiments, W is $-\text{NR}^2$, wherein R^2 is optionally substituted C_{1-5} alkyl, wherein R^2 is optionally substituted with 1-3 instances of a substituent independently selected from the group consisting of C_{1-3} alkyl, 4-7 membered cycloalkyl, 4-7 membered heterocyclyl, and $-\text{C}(=\text{O})\text{OH}$. In some embodiments, W is $-\text{NR}^2$, and wherein R^2 is

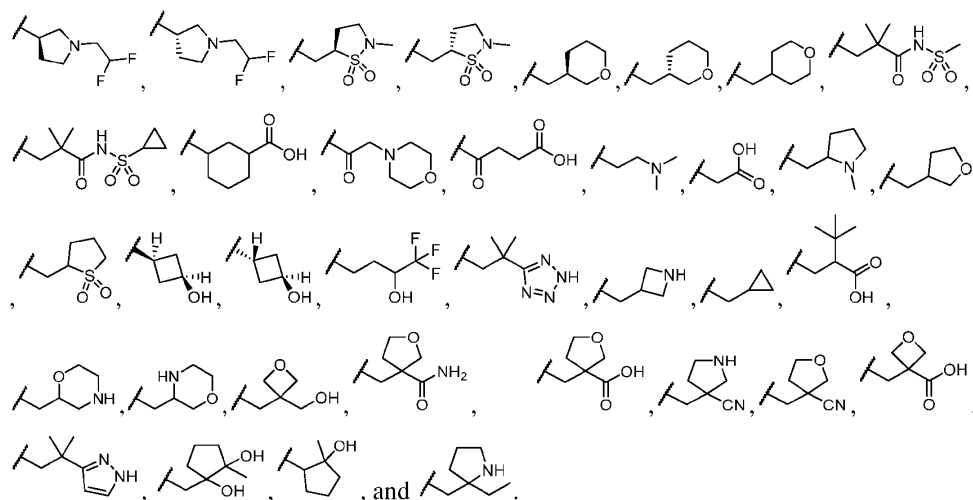


independently selected from the group consisting of H, -CH₃,



[024] In some embodiments, W is -NR², and wherein R² is selected from the group consisting





L¹

[025] In some embodiments, L¹ is a bond or -C(=O)-. In some embodiments, L¹ is a bond. In some embodiments, L¹ is -C(=O)-.

L²

[026] In some embodiments, L² is an optionally substituted C₄₋₈ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen. In some embodiments, L² is an optionally substituted C₅₋₈ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen. In some embodiments, L² is an optionally substituted C₆₋₈ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen. In some embodiments, L² is an optionally substituted C₇₋₈ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen. In some embodiments, L² is an optionally substituted C₅₋₆ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen. In some embodiments, L² is an optionally substituted C₅₋₇ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen.

In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen.

[027] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 2 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen.

[028] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and

wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1-4 instances of halogen.

[029] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 1 instance of halogen.

[030] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 1-

3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 2 instances of halogen.

[031] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-7} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 3 instances of halogen.

[032] In some embodiments, L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{6-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{7-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 4 instances of halogen. In some embodiments, L^2 is an optionally substituted C_{5-6} alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L^2 is optionally substituted with 4 instances of halogen. In some embodiments, L^2

is an optionally substituted C₅₋₇ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 4 instances of halogen.

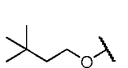
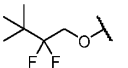
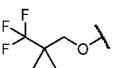
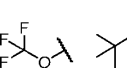
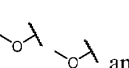
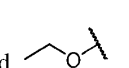
[033] In some embodiments, L² is an optionally substituted C₅₋₆alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 2 instances of halogen.

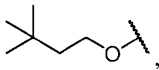
R¹

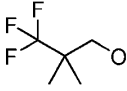
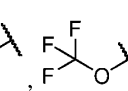
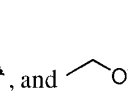
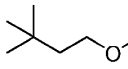
[034] In some embodiments, each R¹ is independently selected from the group consisting of H, halogen, optionally substituted C₁₋₈alkyl, and optionally substituted -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of halogen. In some embodiments, each R¹ is independently selected from the group consisting of H, halogen, and optionally substituted -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of halogen. In some embodiments, R¹ is H. In some embodiments, R¹ is halogen.

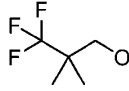
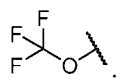
[035] In some embodiments, each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of halogen. In some embodiments, each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of fluoro. In some embodiments, each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of chloro. In some embodiments, each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of bromo. In some embodiments, each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of iodo.

[036] In some embodiments, each R¹ is independently selected from the group consisting of

-CH₃, , , , , , and . In some

embodiments, each R¹ is independently selected from the group consisting of ,

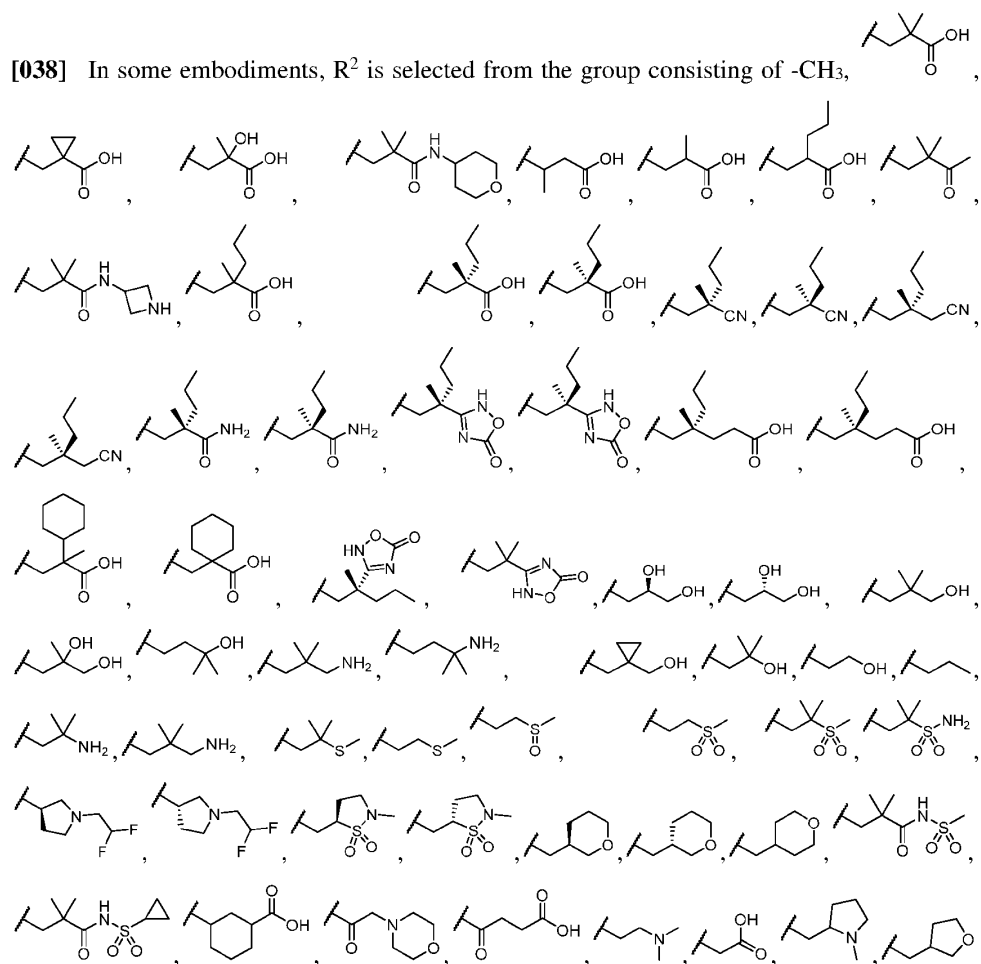
, , and . In some embodiments R¹ is . In some

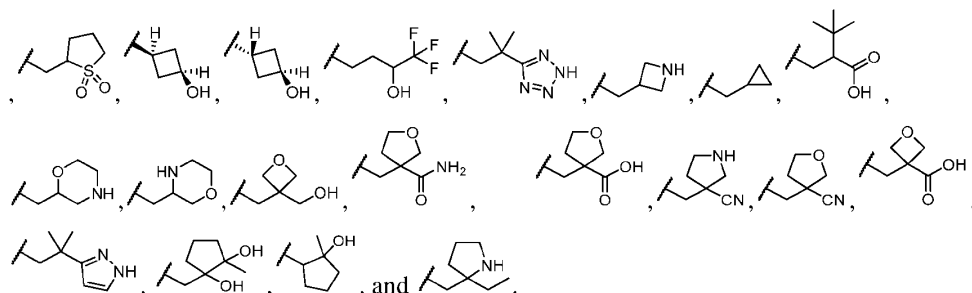
embodiments, R¹ is . In some embodiments, R¹ is . In some

embodiments, R¹ is .

R²

[037] In some embodiments, R² is hydrogen or optionally substituted C₁₋₅alkyl, wherein C₁₋₅alkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of optionally substituted C₁₋₃alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, and -C(=O)OH. In some embodiments, R² is hydrogen. In some embodiments, R² is optionally substituted C₁₋₅alkyl. In some embodiments, R² is optionally substituted C₂₋₅alkyl. In some embodiments, R² is optionally substituted C₃₋₅alkyl. In some embodiments, R² is optionally substituted C₄₋₅alkyl. In some embodiments, R² is optionally substituted C₁₋₄alkyl. In some embodiments, R² is optionally substituted C₂₋₄alkyl. In some embodiments, R² is optionally substituted C₃₋₄alkyl. In some embodiments, R² is -CH₃.



 R^3

[039] In some embodiments, each R^3 is H, halogen, or optionally substituted C_{1-3} alkyl. In some embodiments, R^3 is H. In some embodiments, R^3 is halogen. In some embodiments, R^3 is fluoro. In some embodiments, R^3 is chloro. In some embodiments, R^3 is bromo. In some embodiments, R^3 is iodo. In some embodiments, R^3 is optionally substituted C_{1-3} alkyl. In some embodiments, R^3 is optionally substituted C_{1-2} alkyl. In some embodiments, R^3 is optionally substituted C_{2-3} alkyl. In some embodiments, R^3 is $-CH_3$.

 R^4

[040] In some embodiments, each R^4 is H, halogen, or optionally substituted C_{1-3} alkyl. In some embodiments, R^4 is H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is fluoro. In some embodiments, R^4 is chloro. In some embodiments, R^4 is bromo. In some embodiments, R^4 is iodo. In some embodiments, R^4 is optionally substituted C_{1-3} alkyl. In some embodiments, R^4 is optionally substituted C_{1-2} alkyl. In some embodiments, R^4 is optionally substituted C_{2-3} alkyl.

 m

[041] In some embodiments, m is 0. In some embodiments, m is 1 or 2. In some embodiments, m is 1. In some embodiments, m is 2.

 n

[042] In some embodiments, n is 0. In some embodiments, n is 1 or 2. In some embodiments, n is 1. In some embodiments, n is 2.

p

[043] In some embodiments, *p* is 0. In some embodiments, *p* is 1 or 2. In some embodiments, *p* is 1. In some embodiments, *p* is 2.

[044] In another aspect, the compound of Formula (I) is selected from a compound of Table 1, or pharmaceutically acceptable thereof:

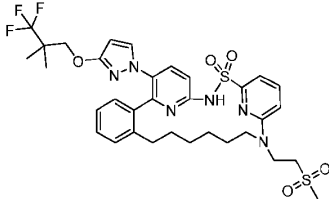
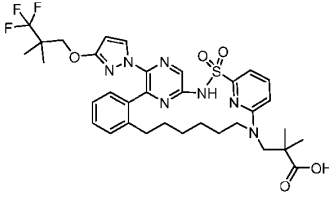
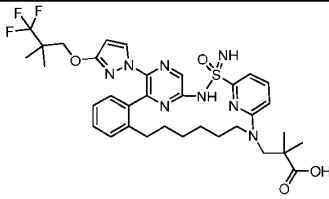
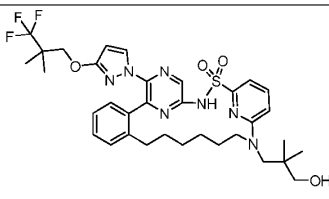
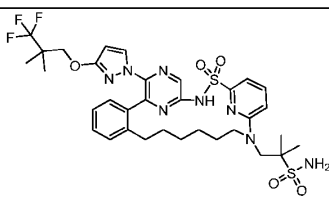
Table 1

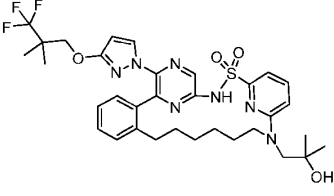
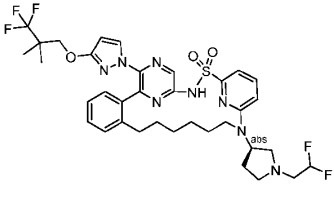
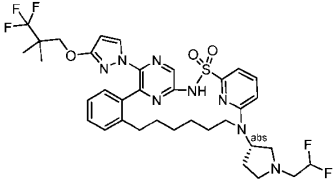
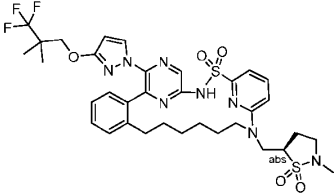
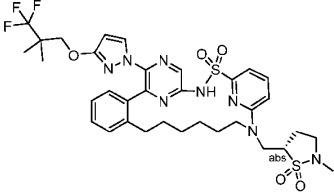
Compound No.	Structure	IUPAC name
1		6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
2		6-[3-(3,3-dimethylbutoxy)phenyl]-14-oxa-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
3		6-[3-(3,3-dimethylbutoxy)-5-fluoro-phenyl]-9,20-dimethyl-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(24),4(26),6,8(13),9,11,21(25),22-octaene 2,2-dioxide
4		3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid
5		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid

6		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
7(P1)		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
7(P2)		(2S)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
8		2-cyclohexyl-3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-methyl-propanoic acid
9		1-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]cyclohexanecarboxylic acid
10		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

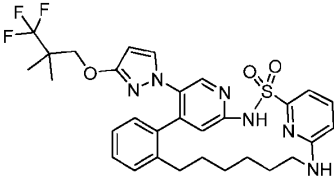
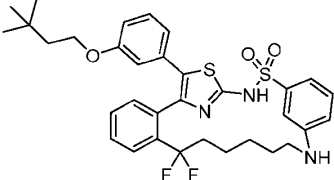
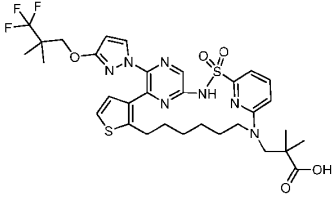
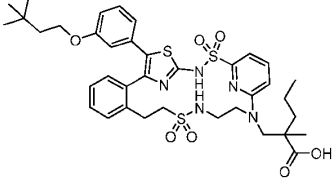
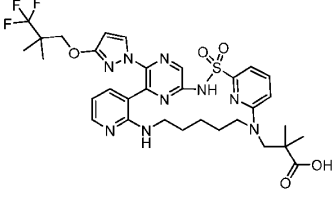
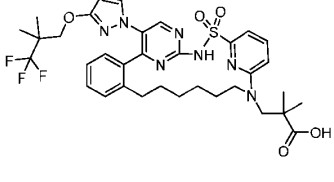
11		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ,6,5,19λ,6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
12		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ,6,5,19λ,6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
13		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
14		3-[2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-1,1-dimethylethyl]-2H-1,2,4-oxadiazol-5-one
15		3-[(1R)-1-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-1-methylbutyl]-2H-1,2,4-oxadiazol-5-one
16		2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-16-oxa-2λ,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid

17		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
18		(2'R,5R)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicos-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one
19		(2'S,5S)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicos-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one
20-P1		(2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
20-P2		(2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
21-P1		(2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
21-P2		(2S)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-

		1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
22		14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
23		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
24		3-[20-imino-20-oxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
25		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
26		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-2-sulfonamide

27		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene-14-yl]-2-methyl-propan-2-ol
28-P1		14-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
28-P2		14-[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
29-P1		14-[(5R)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
29-P2		14-[(5S)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

30		14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 20,20-dioxide
31		14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 20,20-dioxide
32-P1		14-[[[(3R)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 20,20-dioxide
32-P2		14-[[[(3S)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 20,20-dioxide
33		N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanamide
34		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid

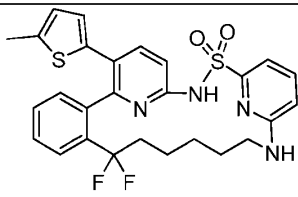
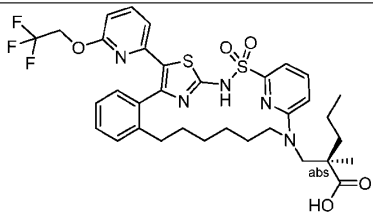
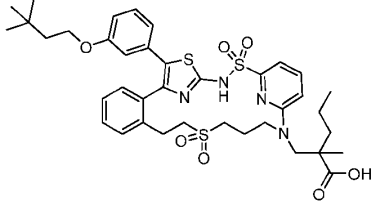
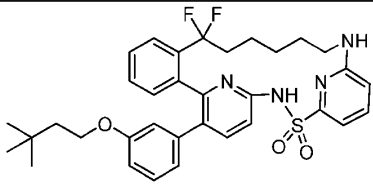
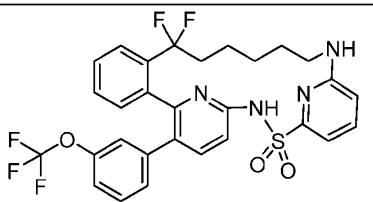
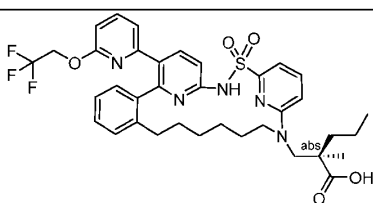
35		25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
36		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosan-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
37		3-[19,19-dioxo-24-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-5,19λ6-dithia-13,20,23,25,26-pentazatetracyclo[19.3.1.114,18.02,6]hexacosan-1(25),2(6),3,14(26),15,17,21,23-octaen-13-yl]-2,2-dimethylpropanoic acid
38		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,16,16-tetraoxo-2λ6,5,16λ6-trithia-3,17,20,25,26-pentazatetracyclo[19.3.1.14,7.08,13]hexacosan-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
39		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-6,8,14,21,24,26,27-heptazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(26),2(7),3,5,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethylpropanoic acid
40		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethylpropanoic acid

41		6-[3-(3,3-dimethylbutoxy)phenyl]-14,17-dioxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
42		6-[3-(3,3-dimethylbutoxy)phenyl]-17-oxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
43		6-[3-(3,3-dimethylbutoxy)-5-fluorophenyl]-9-methyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
44-P1		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid
44-P2		(2S)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid
45		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid

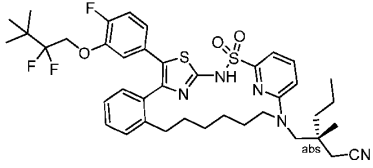
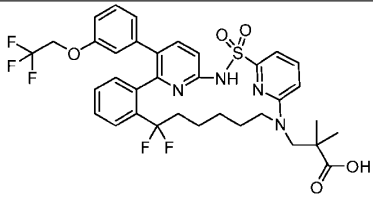
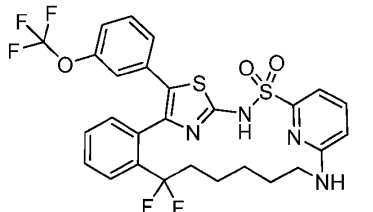
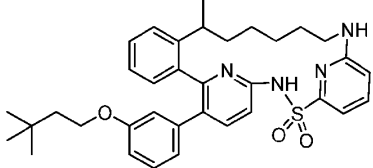
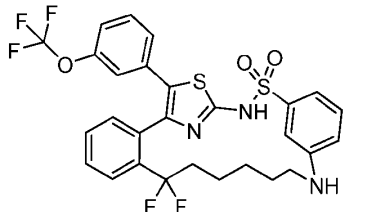
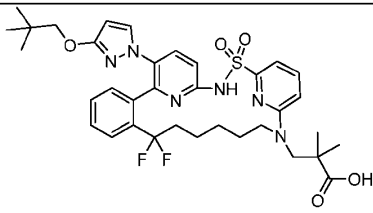
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46-P2		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanenitrile
47		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanamide
48		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanenitrile
49		(2R)-2-[[2,2-dioxo-6-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
50		3-[(1R)-1-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-1-methylbutyl]-2H-1,2,4-oxadiazol-5-one

51		3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]cyclohexanecarboxylic acid
52-P1		(2R)-2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]methyl]-2-methylpentanoic acid
52-P2		(2S)-2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]methyl]-2-methylpentanoic acid
53		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
54		14,14-difluoro-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
55		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

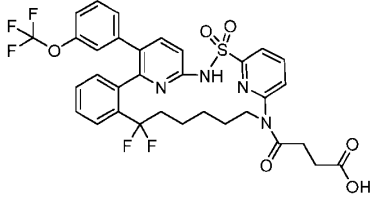
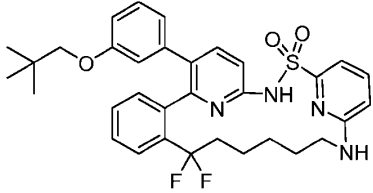
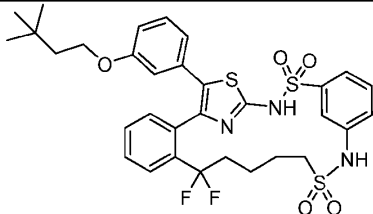
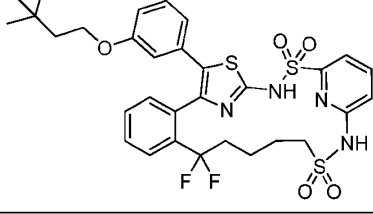
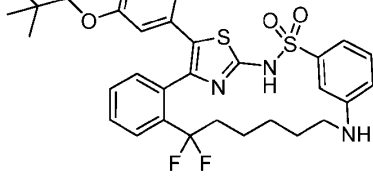
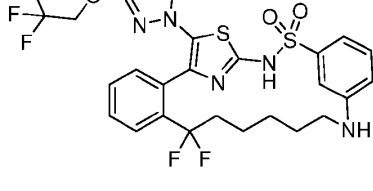
56		6-[3-(2,2-difluoro-3,3-dimethylbutoxy)phenyl]-25-fluoro-14-methyl-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
57		6-[3-(3,3-dimethylbutoxy)phenyl]-14-methyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
58-P1		(4S)-4-methyl-4-[[25-(5-methyl-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]heptanoic acid
58-P2		(4R)-4-methyl-4-[[25-(5-methyl-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]heptanoic acid
59-P1		(2R)-2-[[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
59-P2		(2S)-2-[[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid

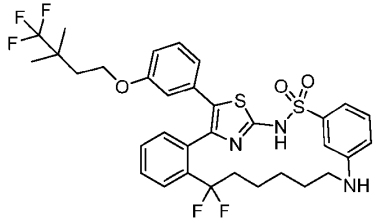
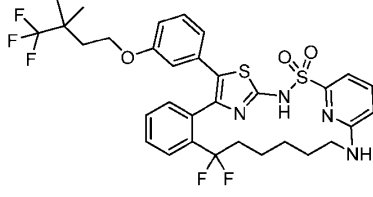
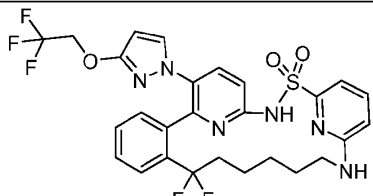
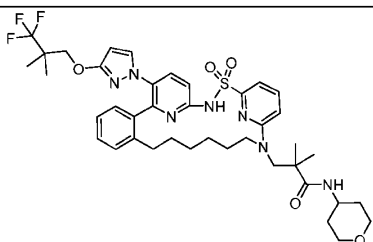
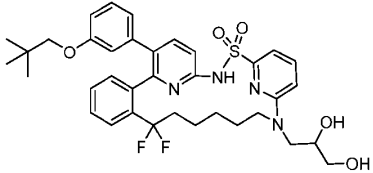
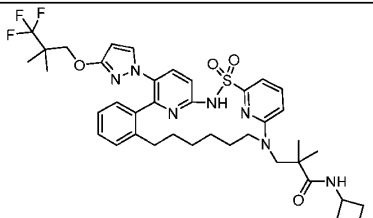
60		8,8-difluoro-25-(5-methyl-2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
61		(2R)-2-[[2,2-dioxo-6-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
62		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,16,16-tetraoxo-2λ6,5,16λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
63		25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
64		8,8-difluoro-25-[3-(trifluoromethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
65-P1		(2R)-2-[[20,20-dioxo-25-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid

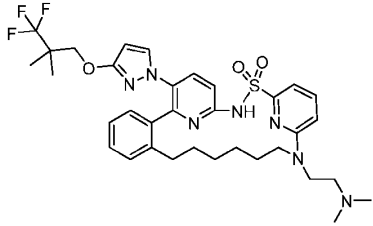
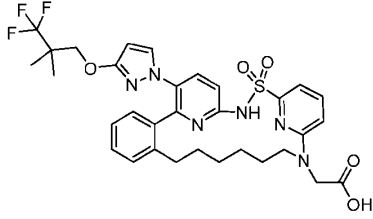
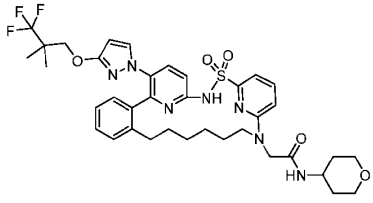
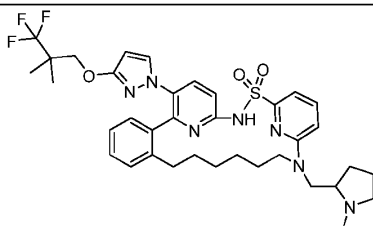
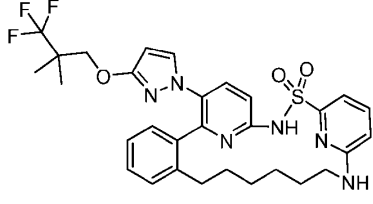
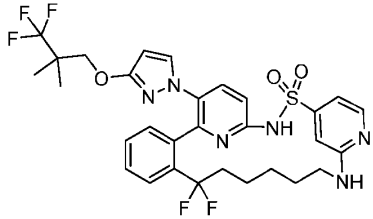
65-P2		(2S)-2-[[20,20-dioxo-25-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
66		3-[20,20-dioxo-25-[3-(trifluoromethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
67		3-[20,20-dioxo-25-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
68		3-[14,14-difluoro-2,2-dioxo-6-[3-(2,2,2-trifluoroethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid
69		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
70-P1		(3S)-3-[[6-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-3-methylhexanenitrile

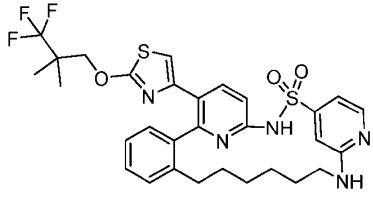
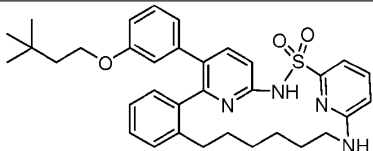
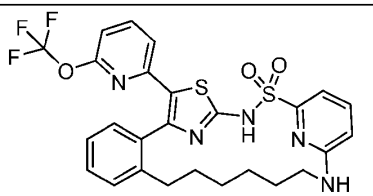
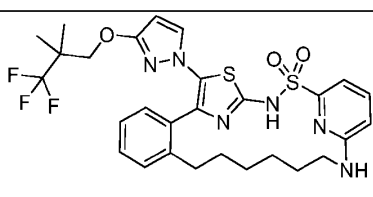
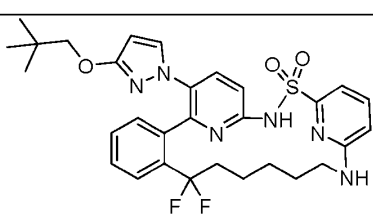
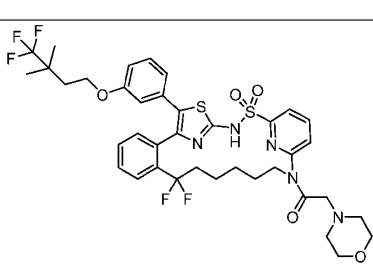
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71		3-[8,8-difluoro-20,20-dioxo-25-[3-(2,2,2-trifluoroethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
72		14,14-difluoro-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
73		25-[3-(3,3-dimethylbutoxy)phenyl]-8-methyl-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
74		14,14-difluoro-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
75		3-[25-[3-(2,2-dimethylpropoxy)pyrazol-1-yl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid

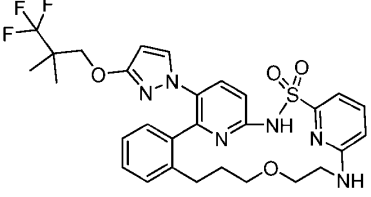
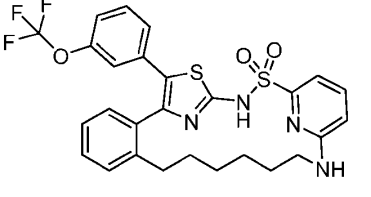
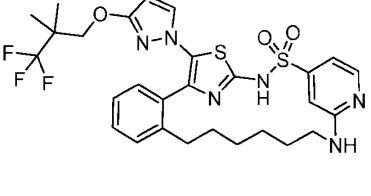
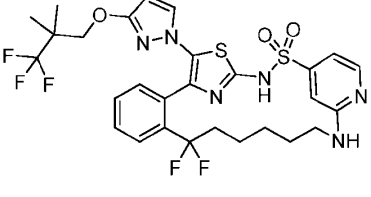
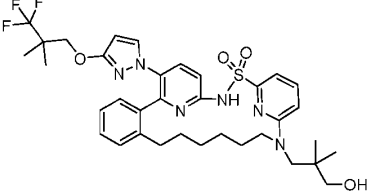
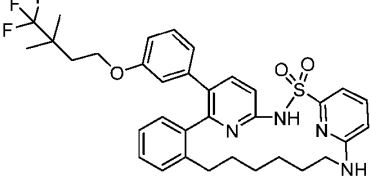
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77		8-methyl-25-[6-(trifluoromethoxy)-2-pyridyl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
78		14,14-difluoro-6-[6-(trifluoromethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
79		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanamide
80		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanenitrile
81		1-[6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2,2-dioxo-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-morpholinoethanone

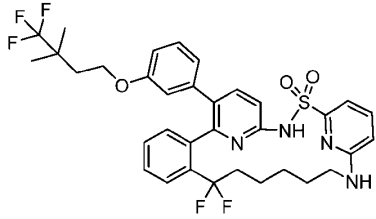
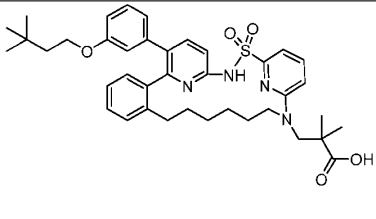
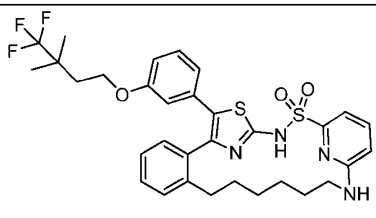
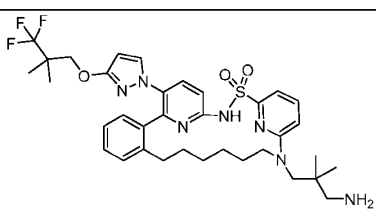
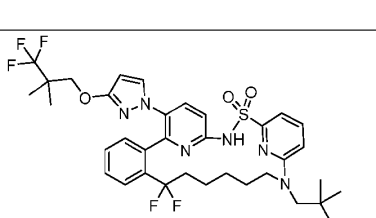
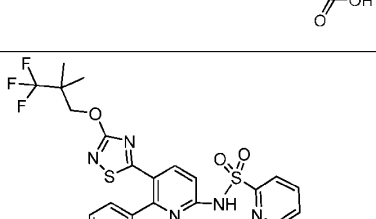
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83		25-[3-(2,2-dimethylpropoxy)phenyl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
84		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
85		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5,19λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
86		6-[3-(2,2-dimethylpropoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
87		14,14-difluoro-6-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

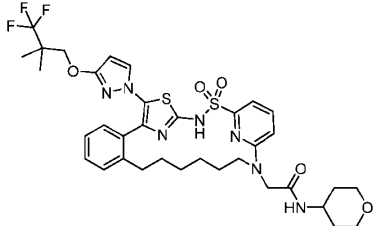
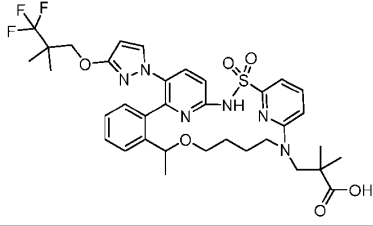
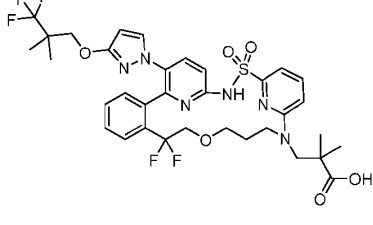
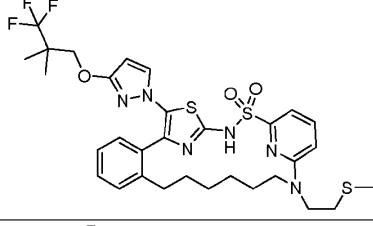
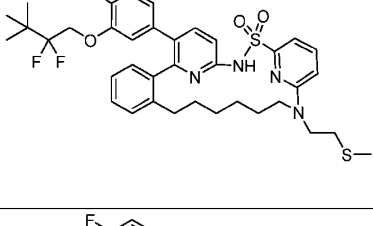
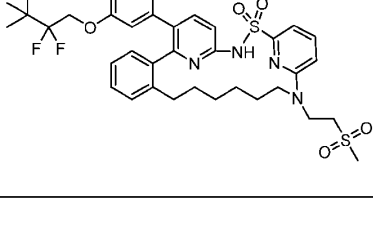
88		14,14-difluoro-6-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
89		14,14-difluoro-6-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
90		8,8-difluoro-25-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
91		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-N-tetrahydropyran-4-yl-propanamide
92		3-[25-[3-(2,2-dimethylpropoxy)phenyl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
93		N-(azetidin-3-yl)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide

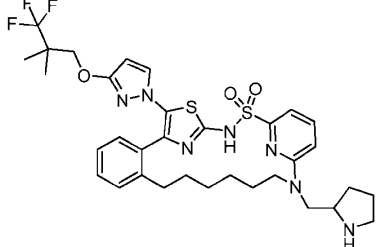
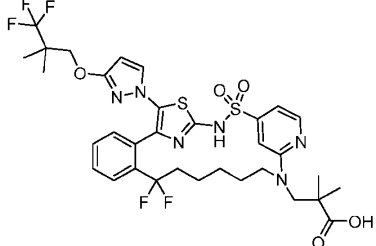
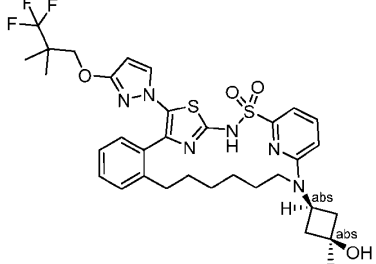
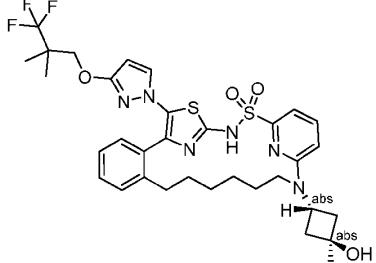
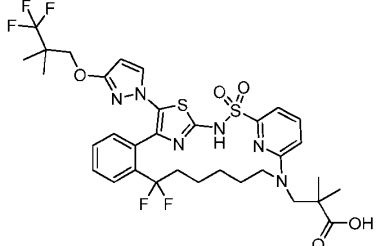
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95		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]acetic acid
96		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-N-tetrahydropyran-4-yl-acetamide
97		14-[(1-methylpyrrolidin-2-yl)methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
98		25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
99		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

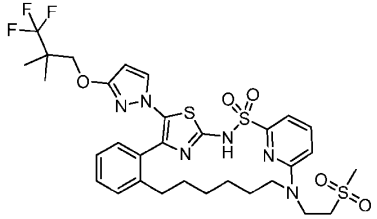
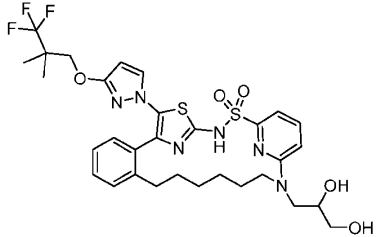
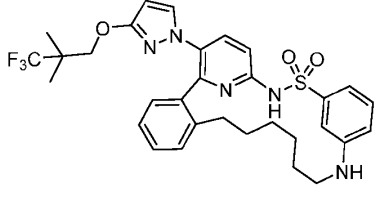
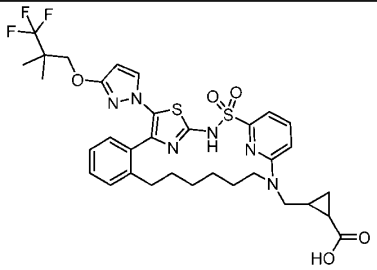
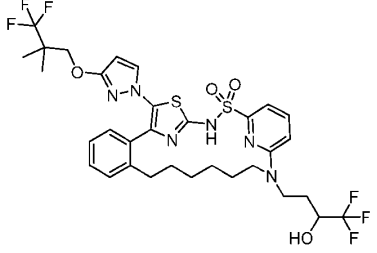
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101		25-[3-(3,3-dimethylbutoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
102		6-[6-(trifluoromethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
103		6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
104		25-[3-(2,2-dimethylpropoxy)pyrazol-1-yl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
105		1-[14,14-difluoro-2,2-dioxo-6-[3-(4,4,4-trifluoro-3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]-2-morpholino-ethanone

106		25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-11-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
107		6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
108		6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
109		14,14-difluoro-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
110		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol
111		25-[3-(4,4,4-trifluoro-3,3-dimethylbutoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

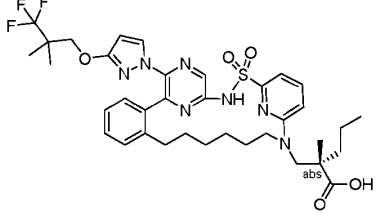
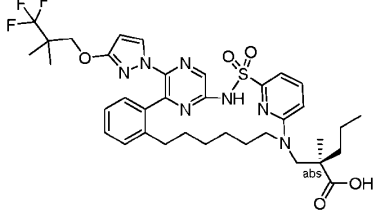
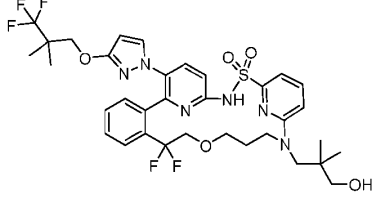
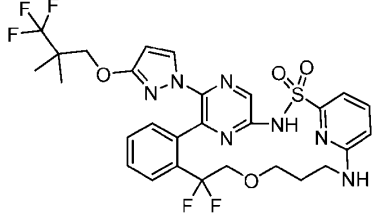
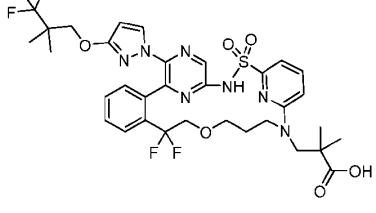
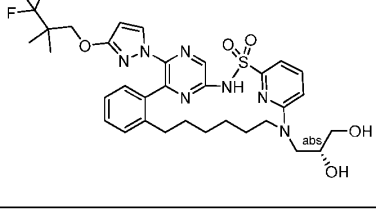
112		8,8-difluoro-25-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
113		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene-14-yl]-2,2-dimethyl-propanoic acid
114		6-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
115		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene-14-yl]-2,2-dimethyl-propan-1-amine
116		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene-14-yl]-2,2-dimethyl-propanoic acid
117		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1,2,4-thiadiazol-5-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene-14-yl]-2,2-dimethyl-propanoic acid

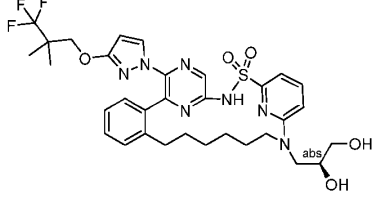
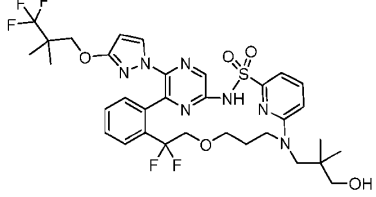
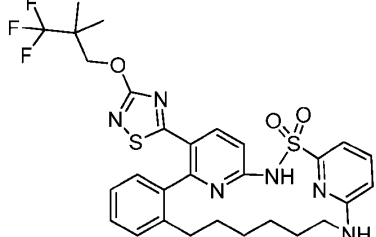
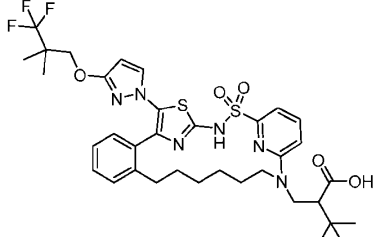
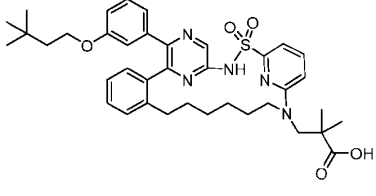
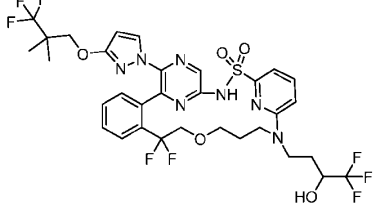
118		2-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-N-tetrahydropyran-4-yl-acetamide
119		2,2-dimethyl-3-[8-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-9-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propanoic acid
120		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
121		20-(2-methylsulfanylethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
122		25-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-14-(2-methylsulfanylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
123		25-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-14-(2-methylsulfanylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

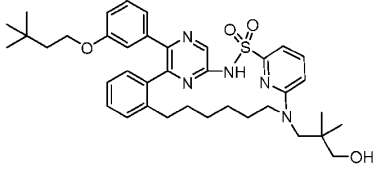
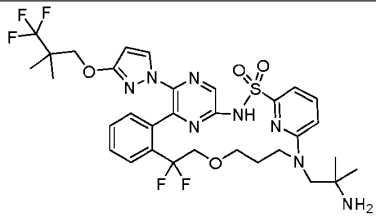
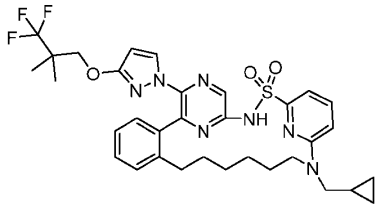
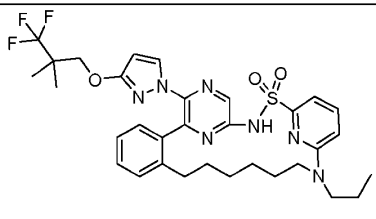
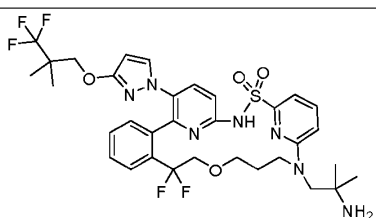
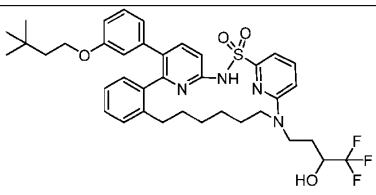
124		20-(pyrrolidin-2-ylmethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
125		3-[14,14-difluoro-2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid
126-P1		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1-methyl-cyclobutanol
126-P2		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1-methyl-cyclobutanol
127		3-[14,14-difluoro-2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid

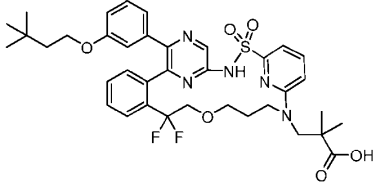
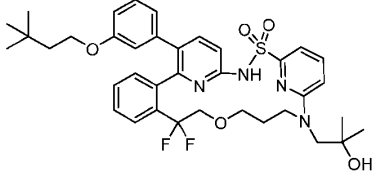
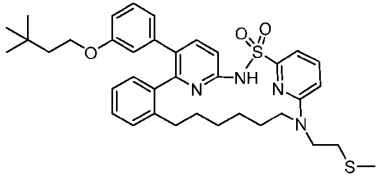
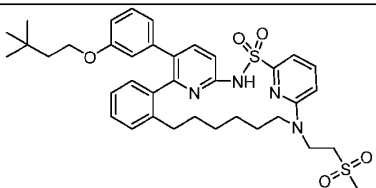
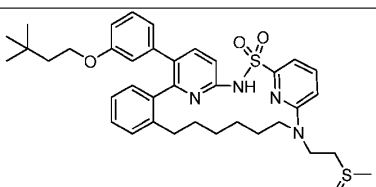
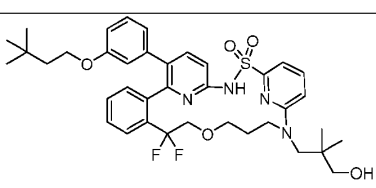
128		20-(2-methylsulfonyl-ethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
129		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]propane-1,2-diol
130		25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26-triazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
131		2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]cyclopropanecarboxylic acid
132		4-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1,1,1-trifluoro-butan-2-ol

133		20-[2-methyl-2-(2H-tetrazol-5-yl)propyl]-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
134		2-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]ethanol
135		20-(azetidin-3-ylmethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
136		1-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-methyl-propan-2-ol
137		20-[(1,1-dioxothiolan-2-yl)methyl]-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

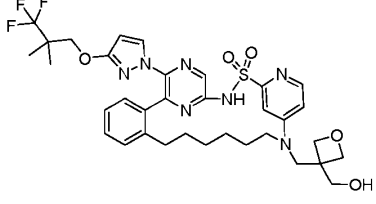
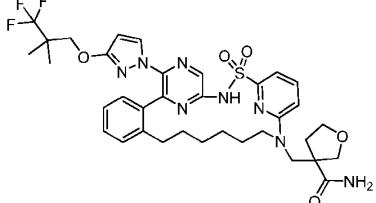
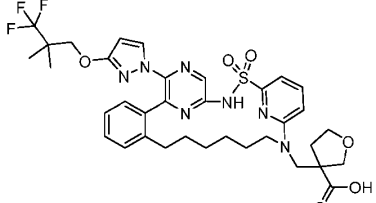
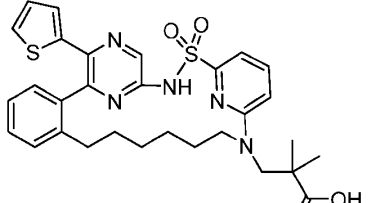
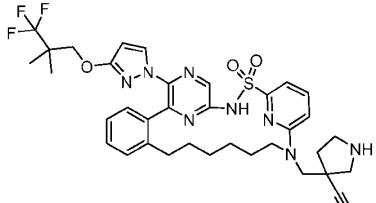
138-P1		(2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid
138-P2		(2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid
139		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
140		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
141		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
142-P1		(2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol

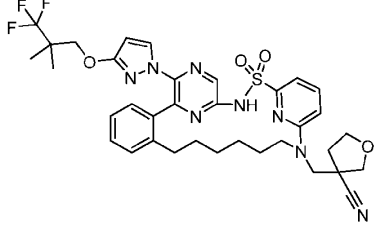
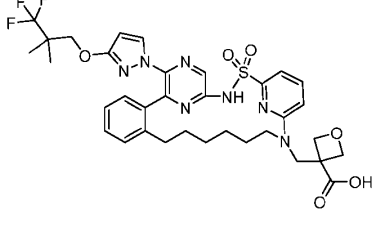
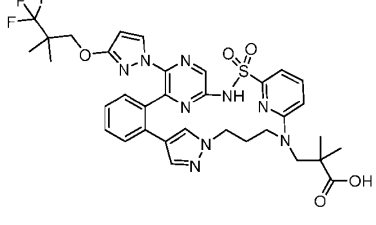
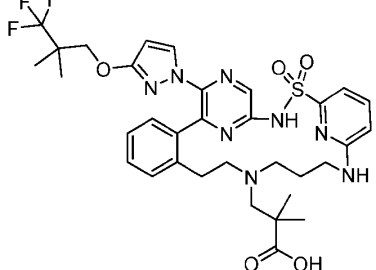
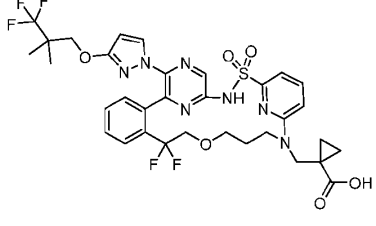
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143		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol
144		25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,2,4-thiadiazol-5-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
145		2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-3,3-dimethylbutanoic acid
146		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
147		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluorobutan-2-ol

148		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
149		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-amine
150		14-(cyclopropylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
151		14-propyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
152		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-amine
153		4-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol

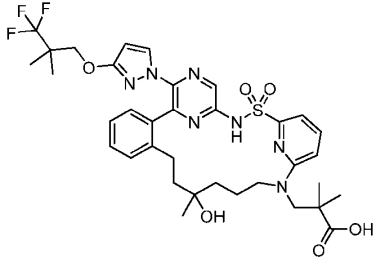
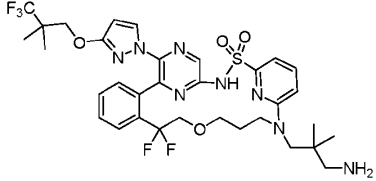
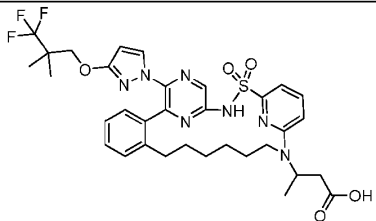
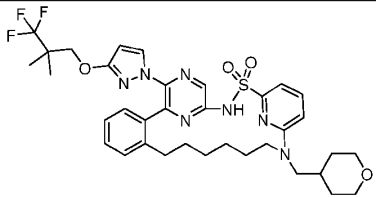
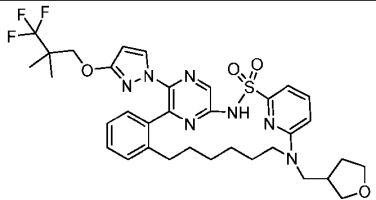
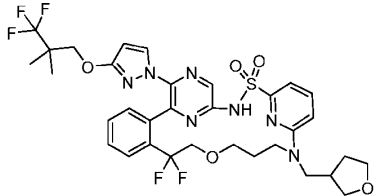
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155		1-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-ol
156		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonyl-ethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
157		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonyl-ethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
158		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonyl-ethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
159		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

160		4-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol
161		14-(morpholin-2-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
162		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonyl-ethyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
163		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol
164		1-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropanecarboxylic acid
165		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-N-methylsulfonyl-propanamide

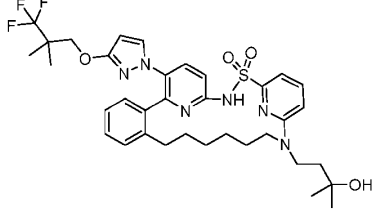
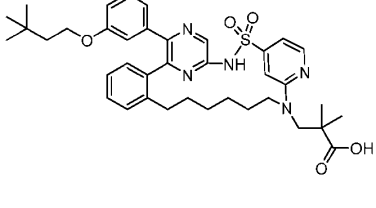
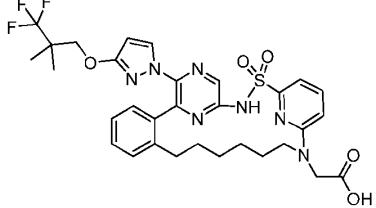
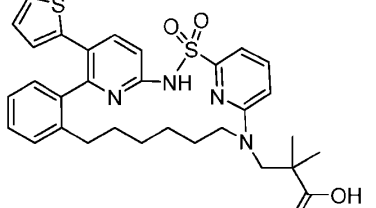
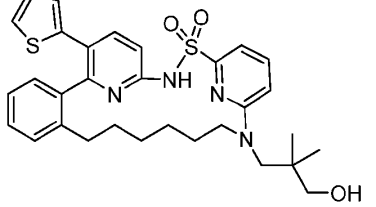
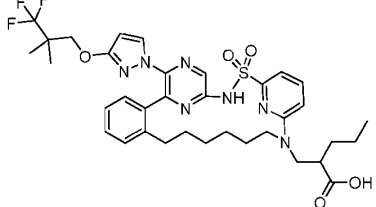
166		[3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,18,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]oxetan-3-yl]methanol
167		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carboxamide
168		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carboxylic acid
169		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
170		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]pyrrolidine-3-carbonitrile

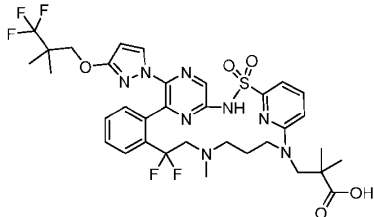
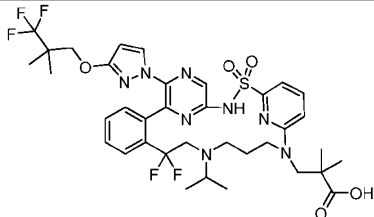
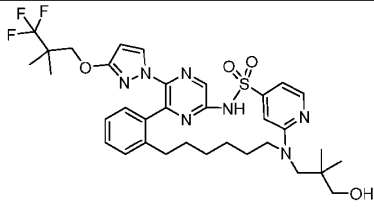
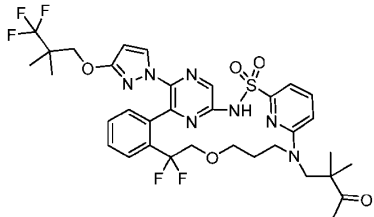
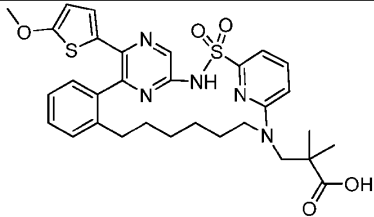
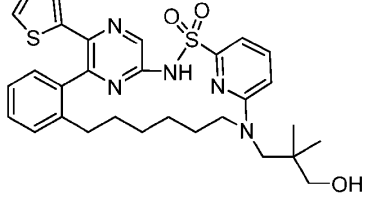
171		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carbonitrile
172		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]oxetane-3-carboxylic acid
173		3-[21,21-dioxo-26-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-21λ6-thia-10,11,15,22,25,27,28-heptazapentacyclo[21.3.1.18,11.116,20.02,7]nonacosa-1(26),2,4,6,8(29),9,16,18,20(28),23(27),24-undecaen-15-yl]-2,2-dimethyl-propanoic acid
174		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-10-yl]-2,2-dimethyl-propanoic acid
175		1-[[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropanecarboxylic acid

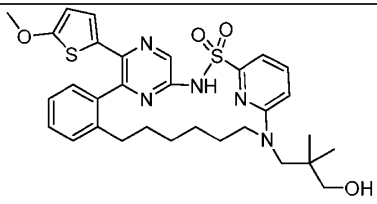
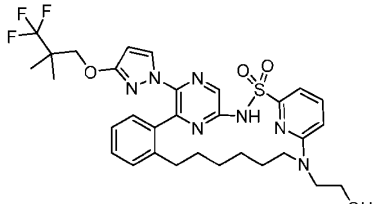
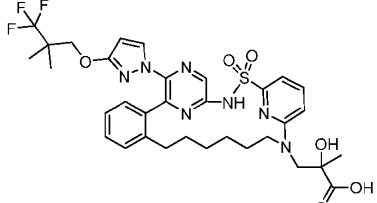
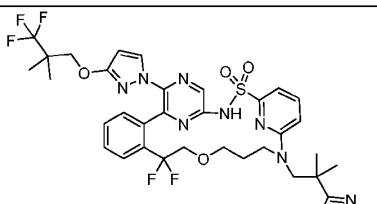
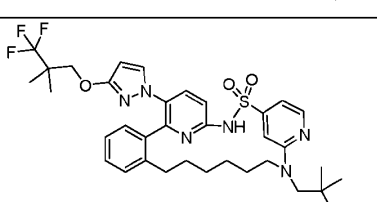
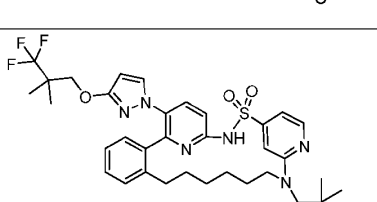
176		[1-[[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropyl]methanol
177		14-(morpholin-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
178		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
179		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
180		8,8-difluoro-14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
181		8,8-difluoro-14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

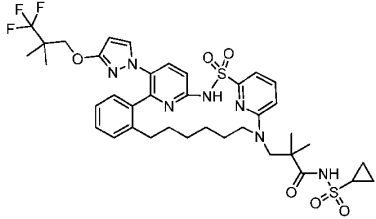
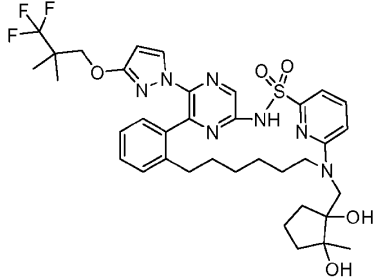
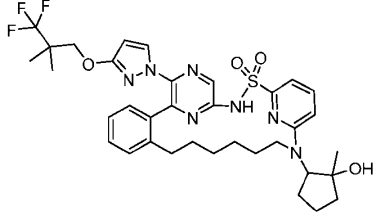
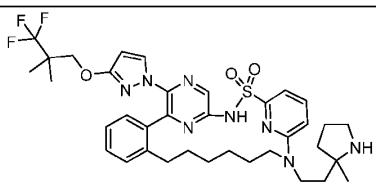
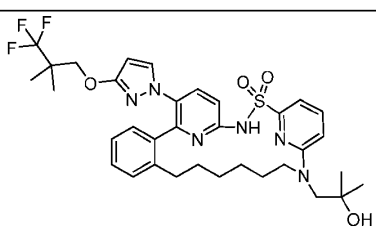
182		3-[10-hydroxy-10-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
183		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-amine
184		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]butanoic acid
185		14-(tetrahydropyran-4-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
186		14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
187		8,8-difluoro-14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

188		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-1,2-diol
189		8,8-difluoro-14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
190		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propanoic acid
191		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-butan-2-ol
192		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-butanoic acid
193		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-butan-2-amine

194		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2-methyl-butan-2-ol
195		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethylpropanoic acid
196		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]acetic acid
197		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
198		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol
199		2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]methyl]pentanoic acid

200		3-[8,8-difluoro-10-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
201		3-[8,8-difluoro-10-isopropyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
202		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
203		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-3,3-dimethyl-butan-2-one
204		3-[25-(5-methoxy-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
205		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

206		3-[25-(5-methoxy-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
207		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]ethanol
208		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-hydroxy-2-methyl-propanoic acid
209		8,8-difluoro-14-[2-methyl-2-(1H-pyrazol-3-yl)propyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
210		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
211		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

212		N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide
213		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]methyl]-2-methyl-cyclopentane-1,2-diol
214		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-1-methyl-cyclopentanol
215		14-[2-(2-methylpyrrolidin-2-yl)ethyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
216		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2-methyl-propan-2-ol

Definitions

[045] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art of the present disclosure. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[046] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

[047] The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbyl-C(O)-, preferably alkyl-C(O)-.

[048] The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbyl-C(O)NH-.

[049] The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbyl-C(O)O-, preferably alkyl-C(O)O-.

[050] The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

[051] The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

[052] The term "alkenyl", as used herein, refers to a straight chained or branched aliphatic group containing at least one double bond. Typically, an alkenyl group has from 2 to about 20 carbon atoms, preferably from 2 to about 10, more preferably from 2-6 or 2-4, unless otherwise defined. The term "alkenyl" is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents

replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

[053] An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, more preferably from 1-6 or 1-4, unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C₁-C₆ straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

[054] Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

[055] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of

unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[056] The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms "C_{2-y}alkenyl" and "C_{2-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[057] The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

[058] The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkyl-S-.

[059] The term "haloalkyl", as used herein, refers to an alkyl group in which at least one hydrogen has been replaced with a halogen, such as fluoro, chloro, bromo, or iodo. Exemplary haloalkyl groups include trifluoromethyl, difluoromethyl, fluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl.

[060] The term "alkynyl", as used herein, refers to a straight chained or branched aliphatic group containing at least one triple bond. Typically, an alkenyl group has from 2 to about 20 carbon atoms, preferably from 2 to about 10, more preferably from 2-6 or 2-4, unless otherwise defined. The term "alkynyl" is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents

replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

[061] The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

[062] The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably, the ring is a 6- to 10-membered ring, such as a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

[063] The terms “carbocycle”, and “carbocyclic”, as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond.

[064] The term “carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-

indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

[065] A “cycloalkyl” group is a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 9 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings.

[066] A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds. The cycloalkenyl ring may have 3 to 10 carbon atoms, such as 4 to 9 carbon atoms. As such, cycloalkenyl groups can be monocyclic or multicyclic. Individual rings of such multicyclic cycloalkenyl groups can have different connectivities, e.g., fused, bridged, spiro, etc. in addition to covalent bond substitution. Exemplary cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentyl, cyclohexenyl, cycloheptenyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl and 1,5-cyclooctadienyl.

[067] Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornanyl, bicyclo[3.2.1]octanyl, octahydro-pentalenyl, spiro[4.5]decanyl, cyclopropyl, and adamantyl.

[068] The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

[069] The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2\text{-R}^{10}$, wherein R^{10} represents a hydrocarbyl group.

[070] The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

[071] The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^{10}$ wherein R^{10} represents a hydrocarbyl group.

[072] The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle.

Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

[073] The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

[074] The terms “hetaralkyl” and “heteroalkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

[075] The term “heteroalkyl”, as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

[076] The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 3- to 10-membered rings, more preferably 5- to 9-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

[077] Individual rings of such multicyclic heteroaryl groups can have different connectivities, e.g., fused, etc. in addition to covalent bond substitution. Exemplary heteroaryl groups include furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1,2]pyrindinyl, benzo[b]thiophenyl, 5,6,7,8-tetrahydroquinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indoliziny, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxaliny, quinazolinyl and benzoxazinyl, etc. In general, the heteroaryl group typically is attached to the main structure via a carbon atom.

[078] The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

[079] The terms “heterocyclyl”, “heterocycle”, and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom,

preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heterocyclyl” and “heterocyclic” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

[080] Individual rings of such multicyclic heterocycloalkyl groups can have different connectivities, e.g., fused, bridged, spiro, etc. in addition to covalent bond substitution. Exemplary heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranal, thiopyranal, azindinyl, azetidinal, oxiranal, methylenedioxy, chromenyl, barbituryl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, piperizin-2-onyl, piperizin-3-onyl, chromanyl, 2-pyrrolinyl, 3-pyrrolinyl, imidazolidinyl, 2-imidazolidinyl, 1,4-dioxanyl, 8-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[4.1.0]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azaspiro[4.4]nonanyl, 7-oxa-1-aza-spiro[4.4]nonanyl, 7-azabicyclo[2.2.2]heptanyl, octahydro-1H-indolyl, etc. In general, the heterocycloalkyl group typically is attached to the main structure via a carbon atom or a nitrogen atom.

[081] The term “heterocyclylalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

[082] The term “hydrocarbyl”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

[083] The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

[084] As described herein, compounds of the disclosure may contain “optionally substituted” moieties. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[085] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-$

$(\text{CH}_2)_{0-4}\text{S}(\text{O})_2\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{OS}(\text{O})_2\text{R}^\circ$; $-\text{S}(\text{O})_2\text{NR}^\circ_2$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{R}^\circ$; $-\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{NH})\text{NR}^\circ_2$; $-\text{P}(\text{O})_2\text{R}^\circ$; $-\text{P}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})(\text{OR}^\circ)_2$; SiR°_3 ; $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{O}-\text{N}(\text{R}^\circ)_2$; or $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{C}(\text{O})\text{O}-\text{N}(\text{R}^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, $-\text{CH}_2$ -(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[086] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(\text{CH}_2)_{0-2}\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-(\text{CH}_2)_{0-2}\text{OH}$, $-(\text{CH}_2)_{0-2}\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{CH}(\text{OR}^\bullet)_2$; $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{N}_3$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{R}^\bullet$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$, $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$, $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$ wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=\text{O}$ and $=\text{S}$.

[087] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=\text{O}$, $=\text{S}$, $=\text{NNR}^{*2}$, $=\text{NNHC}(\text{O})\text{R}^*$, $=\text{NNHC}(\text{O})\text{OR}^*$, $=\text{NNHS}(\text{O})_2\text{R}^*$, $=\text{NR}^*$, $=\text{NOR}^*$, $-\text{O}(\text{C}(\text{R}^{*2}))_{2-3}\text{O}-$, or $-\text{S}(\text{C}(\text{R}^{*2}))_{2-3}\text{S}-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-\text{O}(\text{C}(\text{R}^{*2}))_{2-3}\text{O}-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[088] Suitable substituents on the aliphatic group of R^* include halogen, $-R^*$, $-(haloR^*)$, $-OH$, $-OR^*$, $-O(haloR^*)$, $-CN$, $-C(O)OH$, $-C(O)OR^*$, $-NH_2$, $-NHR^*$, $-NR^{*2}$, or $-NO_2$, wherein each R^* is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[089] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^\dagger$, $-NR^{\dagger2}$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^{\dagger2}$, $-C(S)NR^{\dagger2}$, $-C(NH)NR^{\dagger2}$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[090] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^*$, $-(haloR^*)$, $-OH$, $-OR^*$, $-O(haloR^*)$, $-CN$, $-C(O)OH$, $-C(O)OR^*$, $-NH_2$, $-NHR^*$, $-NR^{*2}$, or $-NO_2$, wherein each R^* is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[091] The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

[092] The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

[093] The term “protecting group” refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups*

in *Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("Fmoc"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

[094] The present disclosure also includes various isomers and mixtures thereof. Certain of the compounds of the present disclosure may exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "R" and "S" represent the configuration of substituents around one or more chiral carbon atoms. When a chiral center is not defined as R or S, either a pure enantiomer or a mixture of both configurations is present.

[095] "Racemate" or "racemic mixture" means a compound of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. In certain embodiments, compounds of the present disclosure may be racemic.

[096] In certain embodiments, compounds of the present disclosure may be enriched in one enantiomer. For example, a compound of the present disclosure may have greater than about 30% ee, about 40% ee, about 50% ee, about 60% ee, about 70% ee, about 80% ee, about 90% ee, or even about 95% or greater ee. In certain embodiments, compounds of the present disclosure may have more than one stereocenter. In certain such embodiments, compounds of the present disclosure may be enriched in one or more diastereomer. For example, a compound of the present disclosure may have greater than about 30% de, about 40% de, about 50% de, about 60% de, about 70% de, about 80% de, about 90% de, or even about 95% or greater de.

[097] In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of Formula I). An enantiomerically enriched mixture may comprise, for example, at least about 60 mol percent of one enantiomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than about 10%, or less than about 5%, or less than about 4%, or less than about 3%, or less than about 2%, or less than about 1% as compared to the amount of the other enantiomer, e.g., in the composition or compound mixture. For example, if a composition or compound mixture contains about 98 grams of a first enantiomer and about 2 grams of a second enantiomer, it would be said to contain about 98 mol percent of the first enantiomer and only about 2% of the second enantiomer.

[098] In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of Formula I). A diastereomerically enriched mixture may comprise, for example, at least about 60 mol percent of one diastereomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent.

[099] The compounds of the present disclosure may be prepared as individual isomers by either isomer specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

[100] When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer that is present divided by the combined weight of the enantiomer that is present and the weight of its optical isomer.

[101] In the pictorial representation of the compounds given through this application, a thickened tapered line () indicates a substituent which is above the plane of the ring to which the asymmetric carbon belongs and a dotted line () indicates a substituent which is below the plane of the ring to which the asymmetric carbon belongs.

[102] As used herein a compound of the present disclosure can be in the form of one of the possible rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

[103] The term "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys. Preferred subjects are humans.

[104] As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

[105] The term "treating" means to decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease. Treatment includes treating a symptom of a disease, disorder or condition. Without being bound by any theory, in some embodiments, treating includes augmenting deficient CFTR activity.

[106] A "therapeutically effective amount", as used herein refers to an amount that is sufficient to achieve a desired therapeutic effect. For example, a therapeutically effective amount can refer to an amount that is sufficient to improve at least one sign or symptom of cystic fibrosis.

[107] A “response” to a method of treatment can include a decrease in or amelioration of negative symptoms, a decrease in the progression of a disease or symptoms thereof, an increase in beneficial symptoms or clinical outcomes, a lessening of side effects, stabilization of disease, partial or complete remedy of disease, among others.

[108] As used herein, “CFTR” means cystic fibrosis transmembrane conductance regulator. Loss of function mutations of CFTR are a cause of cystic fibrosis and lead to exocrine gland dysfunction and abnormal mucociliary clearance. Mutations in the CFTR gene or protein may result in reduced activity of CFTR. The most common mutation is a specific mutation of the deletion of three nucleotides of the codon for phenylalanine at position 508 (about 70% of cystic fibrosis patients) referred to as “ $\Delta F508$ ”. The $\Delta F508$ mutation decreases the stability of the CFTR NBD1 domain and limits CFTR interdomain assembly. A patient can be $\Delta F508$ homozygous or $\Delta F508$ heterozygous ($\Delta F508/\Delta F508$). In particular mutations, the result is a gating mutation leading to a low probability of the ion channel in the open position. Such mutations include but are not limited to G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.

[109] As used herein, the term “CFTR modulator” refers to a compound that increases the activity of CFTR. In certain aspects, a CFTR modulator is a CFTR corrector or a CFTR potentiator or a dual-acting compound having activities of a corrector and a potentiator. These dual acting agents are useful when the mutations result in absence or reduced amount of synthesized CFTR protein.

[110] As used herein, the term “CFTR corrector” refers to a compound that increases the amount of functional CFTR protein to the cell surface and thus enhances ion transport. The CFTR correctors partially “rescue” misfolding of CFTR, thereby permitting its maturation and functional expression on the cell surface and may modify the folding environment and compounds that interact directly to modify folding and conformational maturation during synthesis. Examples of correctors include, but are not limited to, VX-809, VX-661, VX-152, VX-440, VX-983, and GLPG2222.

[111] As used herein, the term “CFTR potentiator” refers to a compound that increases the ion channel activity of CFTR protein located at the cell surface, resulting in enhanced ion transport. CFTR potentiators repair the defective channel functions caused by mutations. Examples of potentiators include, but are not limited to, ivacaftor (VX770), deuterated ivacaftor (CPT 656), genistein and GLPG1837.

[112] As used herein, the term “CFTR pharmacological chaperone” (PC) refers to compounds that stabilize the CFTR protein in its native state by binding directly to the protein.

[113] As used herein, the term “CFTR proteostasis regulator” (PR) refers to compounds that enhance the protein folding efficiency within the cell. PRs can alter the activity of transcriptional, folding and/or membrane trafficking machinery, as well as impeding the degradation of partially folded, but functional, conformers at the endoplasmic reticulum (ER) or plasma membrane.

[114] As used herein, “CFTR disease or condition” refers to a disease or condition associated with deficient CFTR activity, for example, cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, smoking-related lung diseases, such as chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A.beta.-lipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.

Alternative Embodiments

[115] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be ^2H (D or deuterium) or ^3H (T or tritium); carbon may be, for example, ^{13}C or ^{14}C ; oxygen may be, for example, ^{18}O ; nitrogen may be, for example, ^{15}N , and the like. In other embodiments, a particular isotope (*e.g.*, ^3H , ^{13}C , ^{14}C , ^{18}O , or ^{15}N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

Methods of Use

[116] Disclosed herein are methods of treating deficient CFTR activity in a cell, comprising contacting the cell with a compound of formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, contacting the cell occurs in a subject in need thereof, thereby treating a disease or disorder mediated by deficient CFTR activity.

[117] Also, disclosed herein are methods of treating a disease or a disorder mediated by deficient CFTR activity comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is a mammal,

preferably a human. In some embodiments, the disease is associated with the regulation of fluid volumes across epithelial membranes, particularly an obstructive airway disease such as CF or COPD.

[118] Such diseases and conditions include, but are not limited to, 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, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, 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, myeloperoxidase 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, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolusian, 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.

[119] Such diseases and conditions include, but are not limited to, 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 rhinosinusitis, congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection,

pancreatic steatorrhea, intestinal atresia, dry eye disease, protein C deficiency, Abetalipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome. In some embodiments, the disease is cystic fibrosis.

[120] Provided herein are methods of treating cystic fibrosis, comprising administering to a subject in need thereof, a compound as disclosed herein or a pharmaceutically acceptable salt thereof. Also provided herein are methods of lessening the severity of cystic fibrosis, comprising administering to a subject in need thereof, a compound as disclosed herein or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is a human. In some embodiments, the subject is at risk of developing cystic fibrosis, and administration is carried out prior to the onset of symptoms of cystic fibrosis in the subject.

[121] Provided herein are compounds as disclosed herein for use in treating a disease or condition mediated by deficient CFTR activity. Also provided herein are uses of a compound as disclosed herein for the manufacture of a medicament for treating a disease or condition mediated by deficient CFTR activity.

[122] The compounds and methods described herein can be used to treat subjects who have deficient CFTR activity and harbor CFTR mutations like $\Delta F508$. The $\Delta F508$ mutation impedes normal CFTR folding, stability, trafficking, and function by decreasing the stability of CFTR's NBD1 domain, the competency of CFTR domain-domain assembly, or both. Due their impact on the ICL4 interface, a CFTR corrector with an ICL4-directed mechanism can be effective in subjects harboring the following mutations: $\Delta F508$ -CFTR (>70% of all CF patients harbor at least one copy) and mutations that cause ICL4 interface instability for example: G85E, H139R, H1054D, L1065P, L1077P, R1066C and other CFTR mutations where ICL4 interface stability is compromised.

[123] Provided herein are kits for use in measuring the activity of CFTR or a fragment thereof in a biological sample in vitro or in vivo. The kit can contain: (i) a compound as disclosed herein, or a pharmaceutical composition comprising the disclosed compound, and (ii) instructions for: a) contacting the compound or composition with the biological sample; and b) measuring activity of said CFTR or a fragment thereof. In some embodiments, the biological sample is biopsied material obtained from a mammal or extracts thereof; blood, saliva, urine, feces, semen, tears, other body fluids, or extracts thereof. In some embodiments, the mammal is a human.

Combination Treatments

[124] As used herein, the term "combination therapy" means administering to a subject (e.g., human) two or more CFTR modulators, or a CFTR modulator and an agent such as antibiotics, ENaC inhibitors, GSNO (S-nitrosothiol s-nitrosoglutathione) reductase inhibitors, and a CRISPR Cas correction therapy or system (as described in US 2007/0022507 and the like).

[125] In certain embodiments, the method of treating or preventing a disease or condition mediated by deficient CFTR activity comprises administering a compound as disclosed herein conjointly with one or more other therapeutic agent(s). In some embodiments, one other therapeutic agent is administered. In other embodiments, at least two other therapeutic agents are administered.

[126] Additional therapeutic agents include, for example, ENaC inhibitors, mucolytic agents, bronchodilators, antibiotics, anti-infective agents, anti-inflammatory agents, ion channel modulating agents, therapeutic agents used in gene therapy, agents that reduce airway surface liquid and/or reduce airway surface PH, CFTR correctors, and CFTR potentiators, or other agents that modulate CFTR activity.

[127] In some embodiments, at least one additional therapeutic agent is selected from one or more CFTR modulators, one or more CFTR correctors and one or more CFTR potentiators.

[128] Non-limiting examples of CFTR modulators, correctors and potentiators include VX-770 (Ivacaftor), VX-809 (Lumacaftor, 3-(6-(1-(2,2,5 difluorobenzo[d][1, 3]dioxo1-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl) benzoic acid, VX-661 (Tezacaftor, 1-(2,2-difluoro-1, 3-benzodioxo1-5-yl)-N-[1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(2-hydroxy-1, 1-dimethylethyl)- 1H-indol-5-yl]- cyclopropanecarboxamide), VX-983, VX-152, VX-440, VX-445, VX-659, VX-371, VX-121, Orkambi, compounds described in US20190248809A1, Ataluren (PTC 124) (3-[5-(2-fluorophenyl)-1, 2,4-oxadiazol-3-yl]benzoic acid), PTI-130 (Proteostasis), PTI-801, PTI-808, PTI-428, N91115.74 (cavosonstat), QBW251 (Novartis) compounds described in WO2011113894, compounds N30 Pharmaceuticals (e.g., WO 2014/186704), deuterated ivacaftor (e.g., CTP-656 or VX-561), GLPG2222, GLPG3221, GLPG2451, GLPG3067, GLPG2851, GLPG2737, GLPG1837 (N-(3-carbamoyl-5,5,7,7-tetramethyl-5,7-dihydro-4H-thieno[2,3-c]pyran-2-yl)-1H-pyrazole-5-carboxamide), GLPG2665 (Galapagos), ABBV-191 (Abbvie), ABBV-974, FDL 169 (Flatley Discovery lab), FDL 176, FDL438, FDL304, FD2052160, FD1881042, FD2027304, FD2035659, FD2033129, FD1860293, CFFT-Pot01, CFFT-Pot-02, P-1037, glycerol, phenylbutyrate, and the like. Non-limiting examples of anti-inflammatory agents are N6022 (3-(5-(4-(1H-imidazol-1-yl)10 phenyl)-1-(4-carbamoyl-2-methylphenyl)-H-pyrrol-2-yl)

propanoic acid), Ibuprofen, Lenabasum (anabasum), Acebilustat (CTX-4430), LAU-7b, POL6014, docosahexaenoic acid, alpha-1 anti-trypsin, sildenafil. Additional therapeutic agents also include, but are not limited to a mucolytic agent, a modifier of mucus rheology (such as hypertonic saline, mannitol, and oligosaccharide based therapy), a bronchodilator, an anti-infective (such as tazobactam, piperacillin, rifampin, meropenem, ceftazidime, aztreonam, tobramycin, fosfomycin, azithromycin, vancomycin, gallium and colistin), an anti-infective agent, an anti-inflammatory agent, a CFTR modulator other than a compound of the present disclosure, and a nutritional agent. Additional therapeutic agents can include treatments for comorbid conditions of cystic fibrosis, such as exocrine pancreatic insufficiency which can be treated with Pancrelipase or Liprotamase.

[129] Examples of CFTR potentiators include, but are not limited to, Ivacaftor (VX-770), CTP-656, NVS-QBW251, PTI-808, ABBV-3067, ABBV-974, ABBV-191, FDL176, FD1860293, GLPG2451, GLPG1837, and N-(3-carbamoyl-5,5,7,7-tetramethyl-5,7-dihydro-4H-thieno[2,3-c]pyran-2-yl)-1H-pyrazole-5-carboxamide. Examples of potentiators are also disclosed in publications: WO2005120497, WO2008147952, WO2009076593, WO2010048573, WO2006002421, WO2008147952, WO2011072241, WO2011113894, WO2013038373, WO2013038378, WO2013038381, WO2013038386, WO2013038390, WO2014180562, WO2015018823, and U.S. patent application Ser. Nos. 14/271,080, 14/451,619 and 15/164,317.

[130] Non-limiting examples of correctors include Lumacaftor (VX-809), 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane carboxamide (VX-661), VX-983, GLPG2222, GLPG2665, GLPG2737, GLPG3221, GLPG2851, VX-152, VX-440, VX-121, VX-445, VX-659, PTI-801, FDL169, FDL304, FD2052160, and FD2035659. Examples of correctors are also disclosed in US20160095858A1, US20190248809A1, and U.S. application Ser. Nos. 14/925,649 and 14/926,727.

[131] In certain embodiments, the additional therapeutic agent is a CFTR amplifier. CFTR amplifiers enhance the effect of known CFTR modulators, such as potentiators and correctors. Examples of CFTR amplifier include PTI130 and PTI-428. Examples of amplifiers are also disclosed in publications: WO2015138909 and WO2015138934.

[132] In certain embodiments, the additional therapeutic agent is an agent that reduces the activity of the epithelial sodium channel blocker (ENaC) either directly by blocking the channel or indirectly by modulation of proteases that lead to an increase in ENaC activity (e.g., serine proteases, channel-activating proteases). Exemplary of such agents include camostat (a trypsin-

like protease inhibitor), QAU145, 552-02, ETD001, GS-9411, INO-4995, Aerolytic, amiloride, AZD5634, and VX-371. Additional agents that reduce the activity of the epithelial sodium channel blocker (ENaC) can be found, for example, in PCT Publication No. WO2009074575 and WO2013043720; and U.S. Pat. No. 8,999,976.

[133] In one embodiment, the ENaC inhibitor is VX-371. In one embodiment, the ENaC inhibitor is SPX-101 (S18).

[134] In certain embodiments, the additional therapeutic agent is an agent that modulates the activity of the non-CFTR Cl⁻ channel TMEM16A. Non-limiting examples of such agents include TMEM16A activators, denufosal, Melittin, Cinnamaldehyde, 3,4,5-Trimethoxy-N-(2-methoxyethyl)-N-(4-phenyl-2-thiazolyl)benzamide, INO-4995, CLCA1, ETX001, ETD002 and phosphatidylinositol diC8-PIP2, and TMEM16A inhibitors, 10bm, Arctigenin, dehydroandrographolide, Ani9, Niclosamide, and benzbromarone.

[135] In certain embodiments, the combination of a compound of Formula (I), with a second therapeutic agent may have a synergistic effect in the treatment of cancer and other diseases or disorders mediated by adenosine. In other embodiments, the combination may have an additive effect.

[136] In some embodiments, an additional therapeutic agent is a compound disclosed in WO2023/034946 or WO 2023/034992, both of which are incorporated by reference in their entirety.

Pharmaceutical Compositions

[137] The compositions and methods of the present disclosure may be utilized to treat a subject in need thereof. In certain embodiments, the subject is a mammal such as a human, or a non-human mammal. When administered to subject, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the present disclosure and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs.

The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

[138] A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the present disclosure. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the present disclosure. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

[139] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[140] The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters,

such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[141] A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

[142] The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[143] Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the present disclosure, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present disclosure with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[144] Formulations of the present disclosure suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present disclosure as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

[145] To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[146] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[147] The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[148] Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[149] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[150] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metal hydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[151] Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers

comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[152] Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

[153] Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

[154] Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[155] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

[156] The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[157] Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[158] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present disclosure to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[159] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this disclosure. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by

reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

[160] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[161] Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[162] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the present disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[163] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

[164] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having

poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[165] Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

[166] For use in the methods of this disclosure, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[167] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow-release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

[168] Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[169] The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors well known in the medical arts.

[170] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect

and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective amount” is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the subject's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the present disclosure. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

[171] In general, a suitable daily dose of an active compound used in the compositions and methods of the present disclosure will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

[172] If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present disclosure, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

[173] In certain embodiments, the dosing follows a 3+3 design. The traditional 3+3 design requires no modeling of the dose–toxicity curve beyond the classical assumption for cytotoxic drugs that toxicity increases with dose. This rule-based design proceeds with cohorts of three patients; the first cohort is treated at a starting dose that is considered to be safe based on extrapolation from animal toxicological data, and the subsequent cohorts are treated at increasing dose levels that have been fixed in advance. In some embodiments, the three doses of a compound of formula (I) range from about 100 mg to about 1000 mg orally, such as about 200 mg to about 800 mg, such as about 400 mg to about 700 mg, such as about 100 mg to about 400 mg, such as about 500 mg to about 1000 mg, and further such as about 500 mg to about 600 mg. Dosing can be three times a day when taken with without food, or twice a day when taken with food. In certain embodiments, the three doses of a compound of formula (I) range from about 400 mg to about 800 mg, such as about 400 mg to about 700 mg, such as about 500 mg to about 800 mg, and further such as about 500 mg to about 600 mg twice a day. In certain preferred embodiments, a dose of greater than about 600 mg is dosed twice a day.

[174] If none of the three patients in a cohort experiences a dose-limiting toxicity, another three patients will be treated at the next higher dose level. However, if one of the first three patients experiences a dose-limiting toxicity, three more patients will be treated at the same dose level. The dose escalation continues until at least two patients among a cohort of three to six patients experience dose-limiting toxicities (i.e., $\geq$ about 33% of patients with a dose-limiting toxicity at that dose level). The recommended dose for phase II trials is conventionally defined as the dose level just below this toxic dose level.

[175] In certain embodiments, the dosing schedule can be about 40 mg/m² to about 100 mg/m², such as about 50 mg/m² to about 80 mg/m², and further such as about 70 mg/m² to about 90 mg/m² by IV for 3 weeks of a 4-week cycle.

[176] In certain embodiments, compounds of the present disclosure may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (*e.g.*, the two compounds are simultaneously effective in the subject, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one h, 12 h, 24 h, 36 h, 48 h, 72 h, or a week of one another. Thus, a subject who receives such treatment can benefit from a combined effect of different therapeutic compounds.

[177] In certain embodiments, conjoint administration of compounds of the present disclosure with one or more additional therapeutic agent(s) (*e.g.*, one or more additional chemotherapeutic agent(s)) provides improved efficacy relative to each individual administration of the compound of the present disclosure (*e.g.*, compound of formula I or Ia) or the one or more additional therapeutic agent(s). In certain such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects of individual administration of the compound of the present disclosure and the one or more additional therapeutic agent(s).

[178] This present disclosure includes the use of pharmaceutically acceptable salts of compounds of the present disclosure in the compositions and methods of the present disclosure. A salt of a compound of this present disclosure is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the

compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[179] A “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this present disclosure. A “pharmaceutically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[180] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[181] In certain embodiments, contemplated salts of the present disclosure include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the present disclosure include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the present disclosure include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

[182] The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[183] Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[184] Although specific embodiments of the present disclosure will now be described with reference to the preparations and schemes, it should be understood that such embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

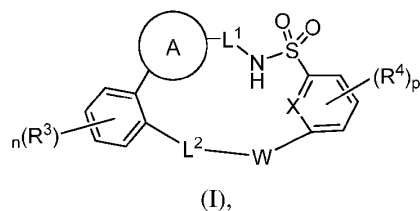
[185] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which this disclosure belongs. Although other compounds or methods can be used in practice or testing, certain preferred methods are now described in the context of the following preparations and schemes.

[186] A number of synthetic protocols were used to produce the compounds described herein. These synthetic protocols (see schemes below) have common intersections and can be used alternatively for synthesis of the compounds described herein.

Enumerated Embodiments

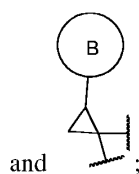
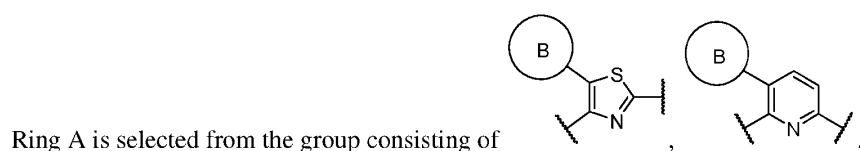
[187] The present disclosure includes the following enumerated embodiments:

1. A compound of Formula (I):

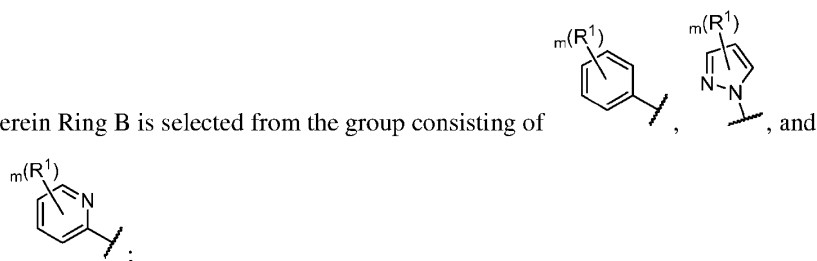


or a pharmaceutically acceptable salt thereof,

wherein



wherein Ring B is selected from the group consisting of



X is $-\text{C}(\text{R}^1)=$ or $-\text{N}=$;

L^1 is a bond or $-\text{C}(=\text{O})-$;

L^2 is an optionally substituted C_{4-8} alkylene chain, wherein 1-3 methylene units are optionally replaced with $-\text{O}-$ or $-\text{N}(\text{H})-$, and wherein L^2 is optionally substituted with 1-4 instances of halogen;

W is selected from the group consisting of $-\text{NH}$, $-\text{NR}^2$, and

each R^1 is independently selected from the group consisting of H, halogen, and

optionally substituted $-\text{O}-\text{C}_{1-8}\text{alkyl}$, wherein $-\text{O}-\text{C}_{1-8}\text{alkyl}$ is optionally substituted

with 1-3 instances of halogen;

R^2 is hydrogen or optionally substituted C_{1-5} alkyl, wherein C_{1-5} alkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of optionally substituted C_{1-3} alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, and $-C(=O)OH$;

each R^3 is H, halogen, or optionally substituted C_{1-3} alkyl;

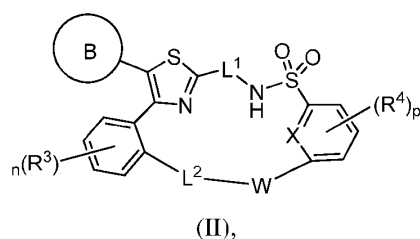
each R^4 is H, halogen, or optionally substituted C_{1-3} alkyl;

m is selected from the group consisting of 0, 1, 2, 3, 4, and 5;

n is selected from the group consisting of 0, 1, 2, 3, and 4; and

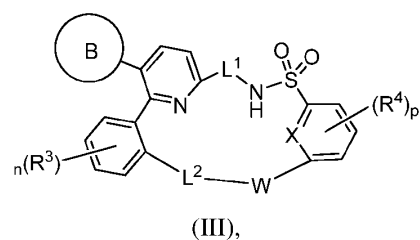
p is selected from the group consisting of 0, 1, 2, and 3.

2. The compound of embodiment 1, wherein the compound is a compound of Formula (II):



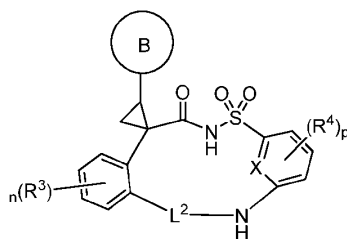
or a pharmaceutically acceptable salt thereof.

3. The compound of embodiment 1, wherein the compound is a compound of Formula (III):



or a pharmaceutically acceptable salt thereof.

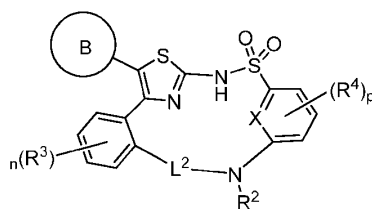
4. The compound of embodiment 1, wherein the compound is a compound of Formula (IV):



(IV),

or a pharmaceutically acceptable salt thereof.

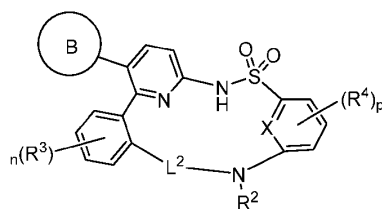
5. The compound of embodiment 1, wherein the compound is a compound of Formula (V):



(V),

or a pharmaceutically acceptable salt thereof.

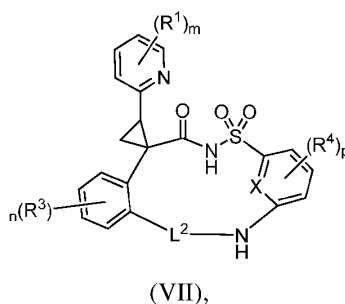
6. The compound of embodiment 1, wherein the compound is a compound of Formula (VI):



(VI),

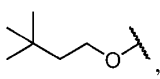
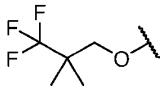
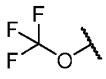
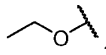
or a pharmaceutically acceptable salt thereof.

7. The compound of embodiment 1, wherein the compound is a compound of Formula (VII):



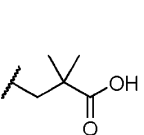
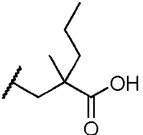
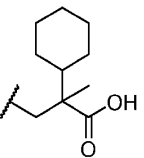
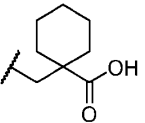
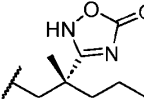
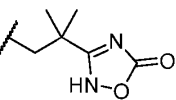
or a pharmaceutically acceptable salt thereof.

8. The compound of any one of embodiments 1-7, wherein X is -N=.
9. The compound of any one of embodiments 1-7, wherein X is -C(R¹)=.
10. The compound of embodiment 9, wherein X is -CH=.
11. The compound of embodiment 9, wherein X is -CF=.
12. The compound of any one of embodiments 1-11, wherein L¹ is a bond.
13. The compound of any one of embodiments 1-11, wherein L¹ is -C(=O)-.
14. The compound of any one of embodiments 1-13, wherein L² is an optionally substituted C₅₋₆alkylene chain, wherein 1 methylene unit is optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 2 instances of halogen.
15. The compound of any one of embodiments 1-13, wherein each R¹ is independently -O-C₁₋₈alkyl, wherein -O-C₁₋₈alkyl is optionally substituted with 1-3 instances of halogen.
16. The compound of embodiment 15, wherein the halogen is fluoro.
17. The compound of any one of embodiments 1-13, wherein each R¹ is independently

selected from the group consisting of , , , and .

18. The compound of any one of embodiments 1-17, wherein W is -NR², wherein R² is optionally substituted C₁₋₅alkyl, wherein R² is optionally substituted with 1-3 instances of a substituent independently selected from the group consisting of C₁₋₃alkyl, 4-7 membered cycloalkyl, 4-7 membered heterocyclyl, and -C(=O)OH.

19. The compound of any one of embodiments 1-17, wherein W is -NR², and wherein R²

is selected from the group consisting of -CH₃, , , , , , and .

20. The compound of embodiment 19, wherein R² is -CH₃.

21. The compound of any one of embodiments 1-20, wherein at least one R³ is -CH₃.

22. The compound of any one of embodiments 1-20, wherein at least one R³ is halogen.

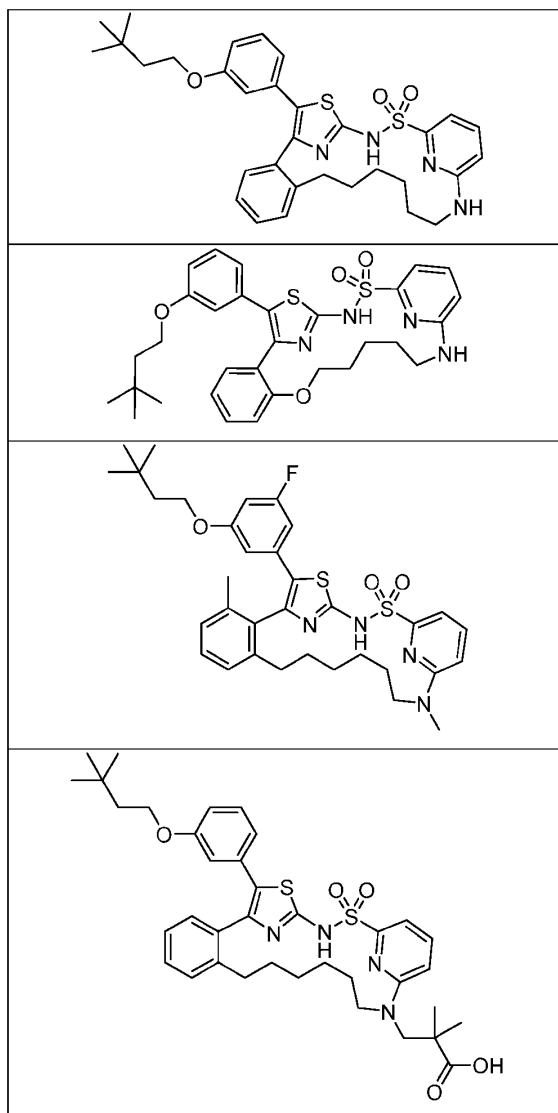
23. The compound of any one of embodiments 1-20, wherein at least one R⁴ is halogen.

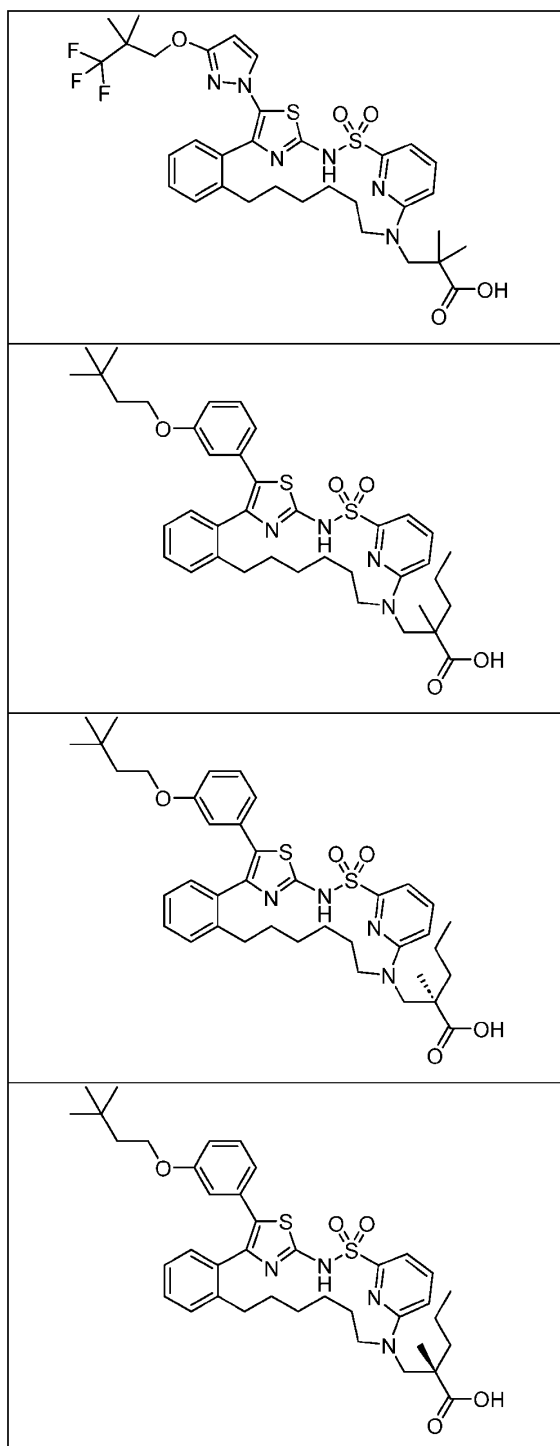
24. The compound of any one of embodiments 1-20, wherein m is 1 or 2.

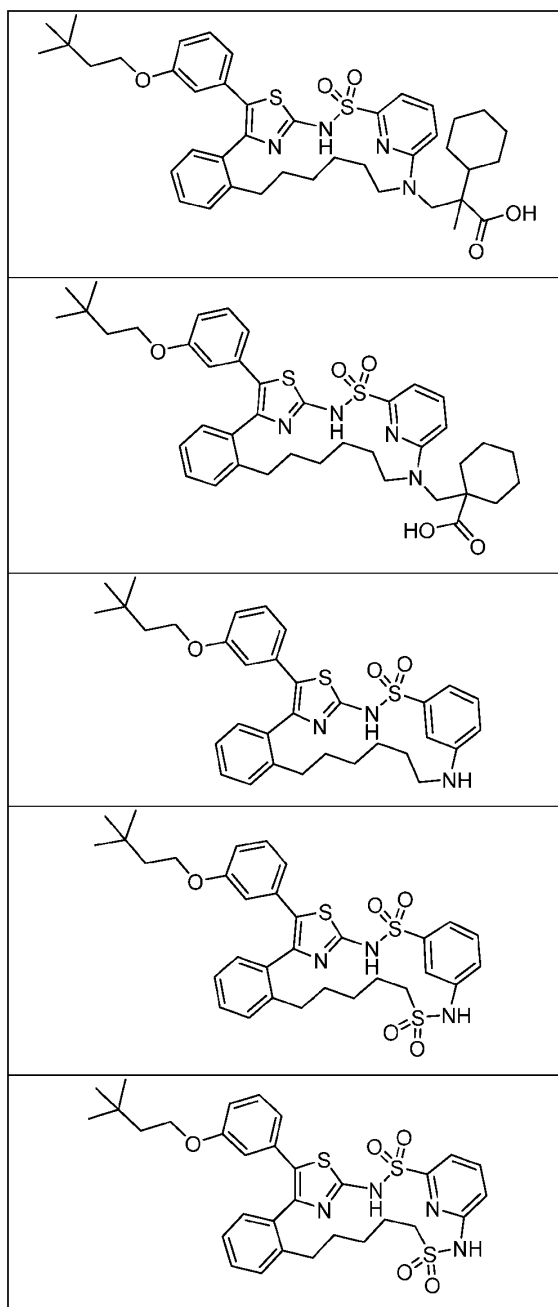
25. The compound of any one of embodiments 1-20, wherein n is 1 or 2.

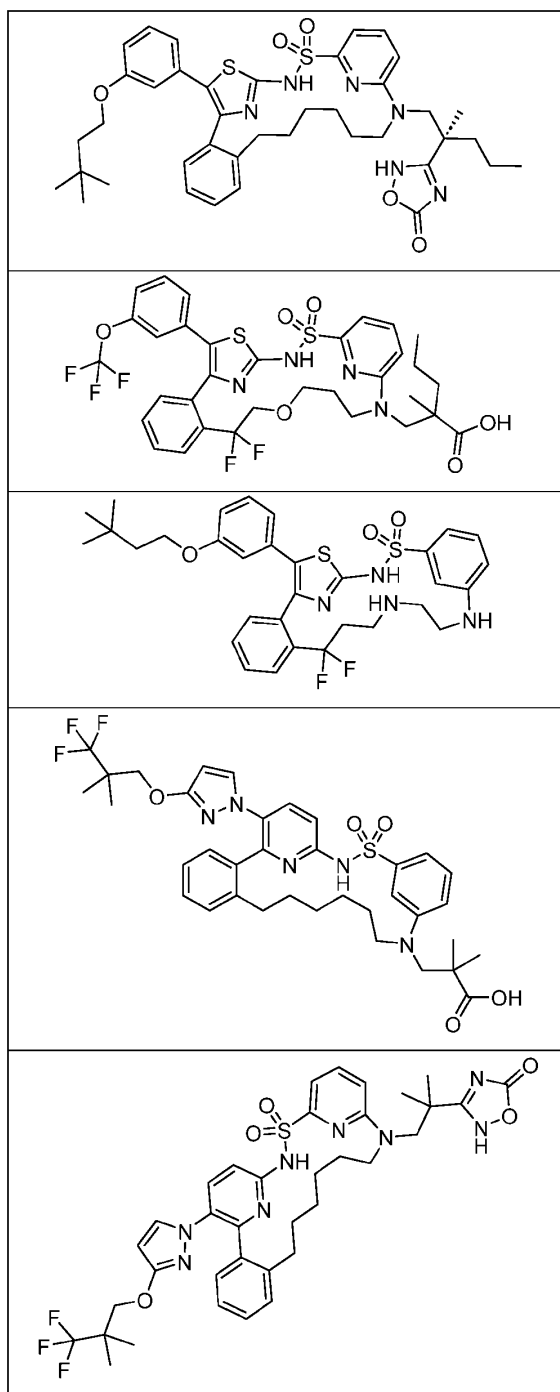
26. The compound of any one of embodiments 1-20, wherein p is 1 or 2.

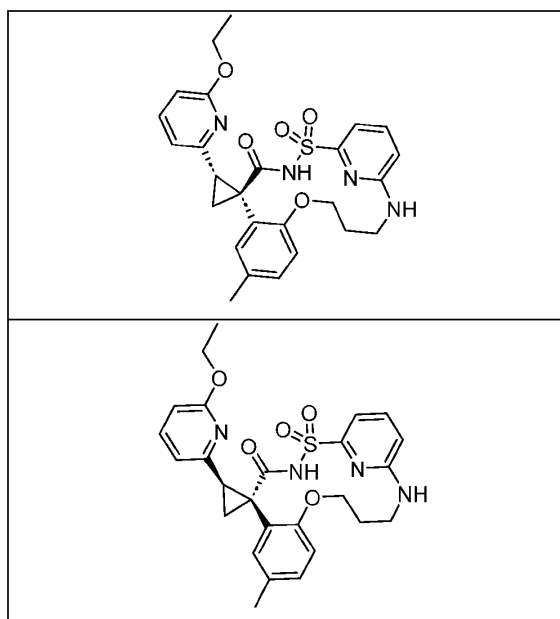
27. A compound selected from:





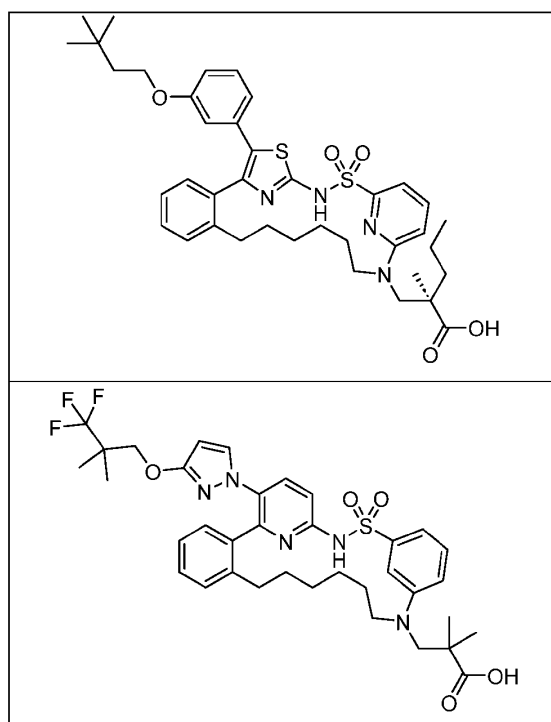


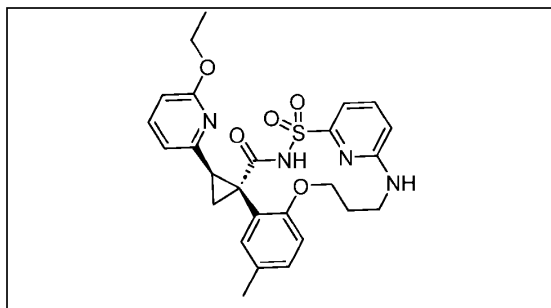




or a pharmaceutically acceptable salt thereof.

28. The compound of embodiment 27, wherein the compound is selected from:





or a pharmaceutically acceptable salt thereof.

29. The compound of any one of embodiments 1-28, wherein the compound is a CFTR corrector.
30. A pharmaceutical composition comprising a compound of any one of the preceding embodiments, and one or more pharmaceutically acceptable carriers or excipients.
31. The pharmaceutical composition of embodiment 30, further comprising one or more CFTR therapeutic agents.
32. A method of treating deficient CFTR activity in a cell, comprising contacting the cell with a compound of any one of embodiments 1-29, or the pharmaceutical composition of embodiment 30 or 31.
33. The method of embodiment 32, wherein contacting the cell occurs in a subject in need thereof, thereby treating a CFTR-mediated condition and/or disease.
34. The method of embodiment 33, 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, 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, myeloperoxidase 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, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolusian, 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.

35. The method of embodiment 33 or 34, 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, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.

36. The method of any one of embodiments 33-35, wherein the disease or condition is cystic fibrosis.

37. A method of treating cystic fibrosis in a subject, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-29, or the pharmaceutical composition of embodiment 30 or 31.
38. The method of embodiment 37, wherein the subject is human.
39. The method according to embodiment 37 or 38, wherein said subject is at risk of developing cystic fibrosis, and wherein said administering step is carried out prior to the onset of symptoms of cystic fibrosis in said subject.

Analytical Methods

[188] The ^1H NMR spectra were recorded at Bruker AC 400 MHz or Varian Mercury 400 spectrometer with an ASW 5 mm probe, and usually recorded at ambient temperature in a deuterated solvent, such as D_2O , $\text{CH}_3\text{OH}-d_4$, $\text{DMSO}-d_6$ or CDCl_3 unless otherwise noted. Chemical shifts values (δ) are indicated in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard and coupling constants (J) in hertz (Hz).

[189] High Pressure Liquid Chromatography-Mass Spectrometry (LCMS) experiments to determine the retention time and associated MS. The LCMS was performed using one of the following methods:

LCMS (Method 1): Column: **Sunfire** C18, 3.5 μm 4.6 $\times$ 50 mm.

Mobile Phase: A: water (0.01%TFA). B: ACN (0.01%TFA).

Gradient: 5%-95% B in 1.5 min. Flow Rate: 2.0 ml/min.

Oven Temperature: 50 $^\circ\text{C}$. Mass Range: 110-1000 UV: 214 nm; 254 nm.

LCMS (Method 2): Column: **Poroshell** 120 EC-C18 (3.0 $\times$ 30 mm, 2.7 μm).

Mobile phase: A: H_2O (0.01%TFA). B: ACN (0.01%TFA).

Elution program: Gradient from 5% B increase to 95% B within 1.0 min, 95% B for 0.8 min.

Temperature: 50 $^\circ\text{C}$. Detection: UV (214 nm, 254 nm) and MS (ESI, Pos mode, 110 to 1500 amu).

LCMS (Method 3): **Column: HALO** C18 (4.6 $\times$ 30 mm, 3.7 μm).

Mobile phase: A: H₂O (0.01%TFA). B: ACN (0.01%TFA).

Elution program: Gradient from 5 to 95% of B in 1.5 min at 1.8 ml/min.

Temperature: 50 °C. Detection: UV (214 nm; 254 nm) and MS (ESI, Pos mode, 103 to 1000 amu).

LCMS (Method 4): Column: **Xbridge** C18(2) (4.6 x 50 mm, 3.5 µm).

Mobile phase: A: H₂O (10 mmol NH₄HCO₃). B: ACN.

Elution program: Gradient from 5 to 90% of B in 1.4 min at 1.8 ml/min.

Temperature: 50 °C. Detection: UV (214 nm, 254 nm) and MS (ESI, Pos mode, 105 to 900 amu).

LCMS (Method 5): Column: **Xbridge** C18 (4.6 x 50 mm, 3.5 µm).

Mobile phase: A: H₂O (10 mmol NH₄HCO₃). B: ACN.

Elution program: Gradient from 10 to 95% of B in 1.5 min at 1.8 ml/min.

Temperature: 50 °C. Detection: UV (214 nm, 254 nm) and MS (ESI, NEG mode, 70 to 900 amu).

LCMS (Method 6): Column Agilent Infinity Lab Poroshell 120EC-C18 4.6 x 50mm 4 micron

Mobile Phase: A: Water (0.01% TFA) B:ACN(0.01% TFA)

Gradient: 10% increase to 95%B within 1.5 min,95%B for 1.5 min; Flow Rate: 1.8 ml/min

Column Temperature:50 °C Detection: UV (214, 254 nm) and MS (ESI, Pos mode,110 to 1500 amu)

LCMS (Method 7): Column: Kinetex EVO C18 100A, 4.6 * 50 mm, 2.6 µm.

Mobile Phase: A: water (0.01% TFA) B: ACN(0.01% TFA).

Gradient: 5%B increase to 95%B within 1.3 min, 95%B for 1.7 min. Flow Rate: 1.8 ml/min.

Column Temperature: 50 °C Detection: UV (214, 254 nm) and MS (ESI, Pos mode, 110 to 1500 amu).

LCMS (Method 8): Mobile Phase: A: Water (10 mM NH₄HCO₃) B: ACN.

Gradient: 5%B increase to 95% B within 1.3 min,95%B for 1.7 min. Flow Rate: 1.8 ml/min.

Column: Xtimate C18, 3.5um, 4.6*50mm

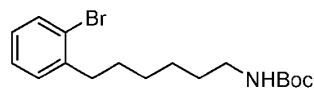
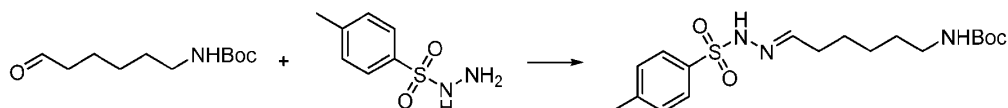
Column Temperature: 40 °C. Detection: UV (214, 254 nm) and MS (ESI, Pos mode, 110 to 1000 amu).

EXAMPLES

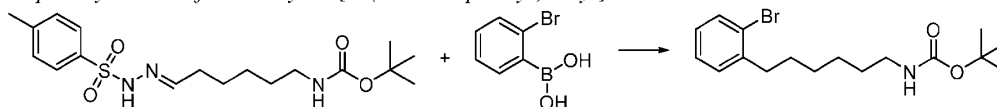
Abbreviations

ACN	acetonitrile
AUC	area under the curve
Boc	tert-butyloxycarbonyl
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
DAST	diethylaminosulfur trifluoride
DEA	diethyl amine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane/methylene chloride
DIAD	diisopropyl azodicarboxylate
DIEA	N,N-Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
DTT	dithiothreitol
EA	ethyl acetate
ESI	electron spray ionization
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
HPLC	high performance liquid chromatography
LC	liquid chromatography
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
MOM-Br	bromo(methoxy)methane
MS	mass spectrometry
MSD	membrane-spanning domain
NBD	nucleotide binding domain

NIS	<i>N</i> -iodosuccinimide
PCC	pyridinium chlorochromate
Pd/C	Palladium on carbon
PE	petroleum ether
RT	LC retention time (min).
rt	room temperature
SFC	supercritical fluid chromatography
S-BINAP	(S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
TBS	<i>tert</i> -Butyldimethylsilyl
TFA	trifluoroacetic acid
TEA	triethylamine
TIPS	triisopropylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS-CF ₃	Trimethyl(trifluoromethyl)silane
Ts	tosyl
VT	transepithelial voltage

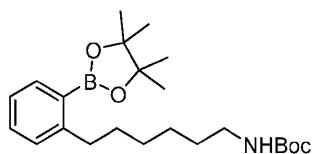
Synthesis of the IntermediatesIntermediate 1:*tert-Butyl (6-(2-bromophenyl)hexyl)carbamate**Step 1. Synthesis of tert-butyl N-[(6E)-6-(p-tolylsulfonylhydrazono)hexyl]carbamate*

[190] To a solution of tert-butyl N-(6-oxohexyl)carbamate (5.10 g, 23.7 mmol) in methanol (60 mL) was added p-toluenesulfonylhydrazide (4.41 g, 23.7 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated and purified by flash column chromatography on silica gel (eluting with PE : EA = 1:1) to give tert-butyl N-[(6E)-6-(p-tolylsulfonylhydrazono)hexyl]carbamate (6.00 g, 15.6 mmol, 66.0 % yield) as a white solid. LCMS (Method 4): LC retention time = 1.94 min. MS (ESI) m/z 284.1 $[M+H-tBuOCO]^+$.

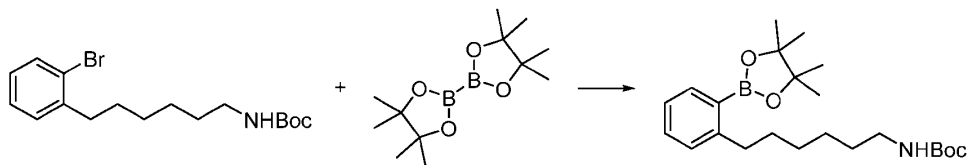
Step 2. Synthesis of tert-butyl N-[6-(2-bromophenyl)hexyl]carbamate

[191] To a solution of tert-butyl N-[(6E)-6-(p-tolylsulfonylhydrazono)hexyl]carbamate (6.00 g, 15.6 mmol) and (2-bromophenyl)boronic acid (4.71 g, 23.5 mmol) in 1,4-dioxane (30 mL) was added potassium carbonate (4.32 g, 31.3 mmol). The reaction mixture was stirred at 120 °C for 16 h, then cooled to rt. The mixture was diluted with water (20 mL) and extracted with EA (50 mL $\times$ 3). The organic extracts were combined and washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 10:1) to give tert-butyl N-[6-(2-bromophenyl)hexyl]carbamate (1.70 g, 4.77 mmol, 30.5 % yield) as a yellow oil. LCMS (Method 4): LC retention time = 2.43 min. MS (ESI) m/z 300, 302 $[M+H-tBu]^+$.

Intermediate 1A:*tert-Butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate*



Step 1. Synthesis of tert-butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate

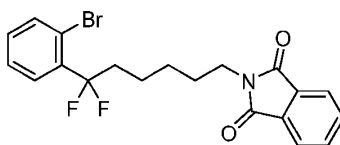


[192] To a solution of tert-butyl N-[6-(2-bromophenyl)hexyl]carbamate (6000 mg, 16.8 mmol) in 1,4-dioxane (100 mL) were added bis(pinacolato)diboron (6414 mg, 25.3 mmol), potassium acetate (4958 mg, 50.5 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (370 mg, 0.505 mmol) under N₂. The mixture was stirred at 100 °C for 4 h under N₂. The mixture was concentrated to afford a residue which was purified by column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 10:1) to give tert-butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate (6000 mg, 14.7 mmol, 87.5 % yield) as a colorless oil.

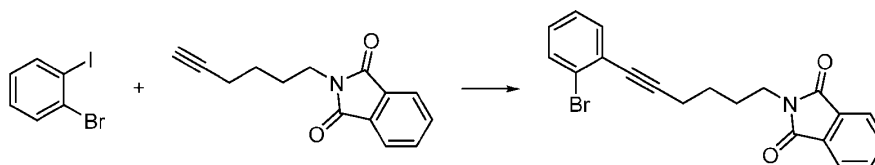
LCMS (Method 2): LC retention time = 2.22 min. MS (ESI) m/z 304.3 [M+H- tBuOCO]⁺.

Intermediate 2:

2-[6-(2-Bromophenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione



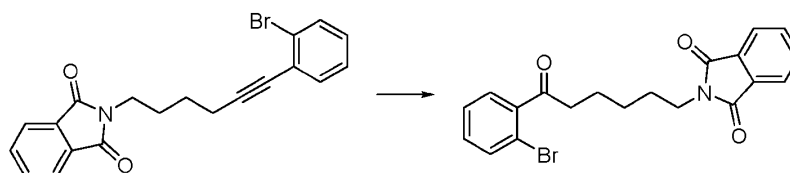
Step 1. Synthesis of 2-[6-(2-bromophenyl)hex-5-ynyl]isoindoline-1,3-dione



[193] To a solution of 2-hex-5-ynylisoindoline-1,3-dione (15000 mg, 66.0 mmol) in THF (300 mL) were added 1-bromo-2-iodobenzene (10 mL, 79.2 mmol), bis(triphenylphosphine) palladium (II) chloride (1500 mg, 2.14 mmol), copper (I) iodide (1500 mg, 7.88 mmol), and triethylamine (45 mL, 323 mmol). The mixture was stirred at rt for 4 h. The solids were filtered off. The filtrate was concentrated to give a residue which was purified by column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 3:1) to obtain 2-[6-(2-bromophenyl)hex-5-ynyl]isoindoline-1,3-dione (20000 mg, 51.8 mmol, 78.5 % yield) as an off-white solid.

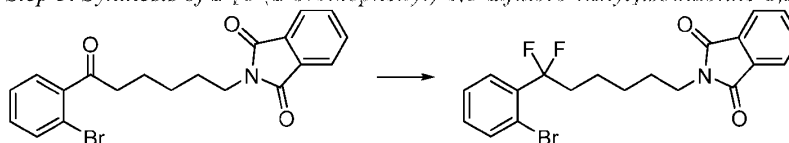
LCMS (Method 1): LC retention time = 2.68 min. MS (ESI) m/z 382.0, 384 $[M+H]^+$.

Step 2. Synthesis of 2-[6-(2-bromophenyl)-6-oxo-hexyl]isoindoline-1,3-dione



[194] A solution of 2-[6-(2-bromophenyl)hex-5-ynyl]isoindoline-1,3-dione (30000 mg, 78.5 mmol) in sulfuric acid (116 mL, 2169 mmol) was stirred at room temperature for 15 min to give a suspension. The mixture was poured into ice water (1.5 L) and the pH adjusted to 8 with solid Na_2CO_3 . The aqueous mixture was extracted with EA (500 mL $\times$ 3). The combined organic extracts were concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with PE : EA = 3:1) to give 2-[6-(2-bromophenyl)-6-oxo-hexyl]isoindoline-1,3-dione (15000 mg, 35.6 mmol, 45.4 % yield) as a light yellow solid. LCMS (Method 1): LC retention time = 2.53 min. MS (ESI) m/z 400.1, 402 $[M+H]^+$.

Step 3. Synthesis of 2-[6-(2-bromophenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione



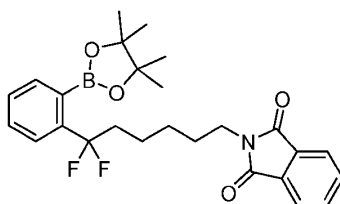
[195] To a solution of 2-[6-(2-bromophenyl)-6-oxo-hexyl]isoindoline-1,3-dione (20.00 g, 50.0 mmol) in chloroform (60 mL) was added diethylamino-sulfur trifluoride (60 mL, 454 mmol). The mixture was stirred at 70 °C for 16 h. The mixture was poured into ice water (500 mL) and the pH adjusted to 8 with solid Na_2CO_3 . The aqueous mixture was extracted with EA (300 mL $\times$ 2). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4 , and filtered. The solvent was evaporated under reduced pressure. The residue was

purified by flash column chromatography on silica gel (eluting with PE : EA = 5:1) to give 2-[6-(2-bromophenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione (10.00 g, 23.7 mmol, 47.4 % yield) as a brown solid.

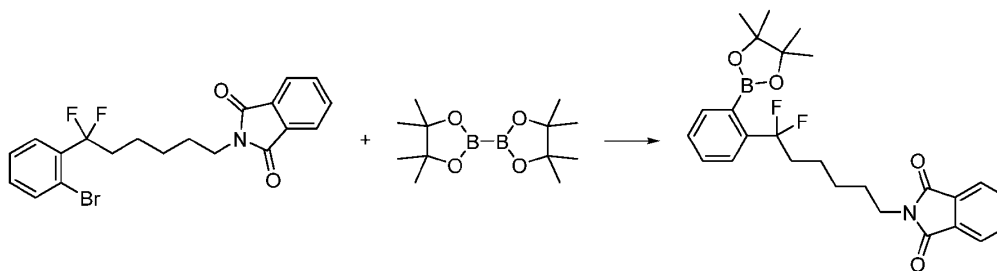
LCMS (Method 4): LC retention time = 1.86 min. MS (ESI) m/z 439.1, 441 $[M+NH_4]^+$.

Intermediate 2A:

2-[6,6-Difluoro-6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]isoindoline-1,3-dione



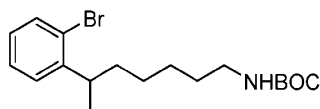
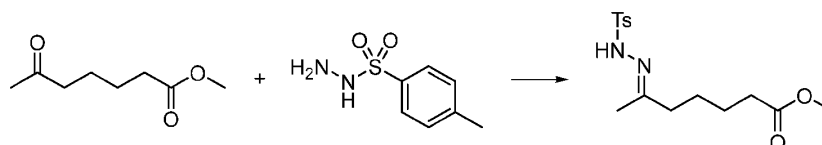
Step 1. Synthesis of 2-[6,6-difluoro-6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]isoindoline-1,3-dione



[196] To a solution of 2-[6-(2-bromophenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione (**Intermediate 2**, 500 mg, 1.18 mmol) in 1,4-dioxane (10 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) dichloromethane complex (**CAS#:** **72287-26-4**, 87 mg, 0.118 mmol), bis(pinacolato)diboron (301 mg, 1.18 mmol) and potassium acetate (232 mg, 2.37 mmol). The mixture was stirred at 90 °C for 12 h under N₂. The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with 10% EtOAc in petroleum ether, to give 2-[6,6-difluoro-6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]isoindoline-1,3-dione (250 mg, 0.533 mmol, 45.0 % yield) as a colorless oil.

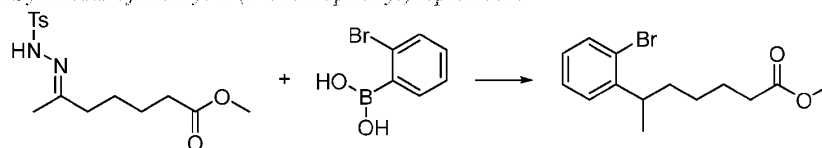
LCMS (Method 4): LC retention time = 2.13 min. MS (ESI) m/z 487.0 $[M+H_2O]^+$.

Intermediate 3:

tert-Butyl (6-(2-bromophenyl)heptyl)carbamate*Step 1. Synthesis of methyl (6E)-6-(p-tolylsulfonylhydrazono)heptanoate*

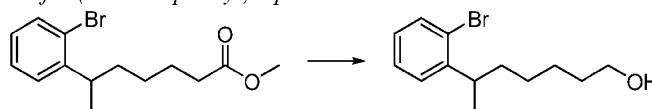
[197] To a solution of methyl 6-oxoheptanoate (5.00 g, 31.6 mmol) in 1,4-dioxane (60 mL) was added p-toluenesulfonylhydrazide (5.89 g, 31.6 mmol). The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was concentrated and purified by flash column chromatography on silica gel (eluting with PE : EA = 1:1) to give methyl (6E)-6-(p-tolylsulfonylhydrazono)heptanoate (9.30 g, 28.5 mmol, 90.2 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.84 min. MS (ESI) m/z 327.1 [M+H]⁺.

Step 2. Synthesis of methyl 6-(2-bromophenyl)heptanoate

[198] To a solution of methyl (6E)-6-(p-tolylsulfonylhydrazono)heptanoate (5.00 g, 15.3 mmol) and (2-bromophenyl)boronic acid (6.15 g, 30.6 mmol) in 1,4-dioxane (30 mL) was added potassium carbonate (8.47 g, 61.3 mmol). The mixture was stirred at 120 °C for 16 h. Then the reaction was diluted with water (20 mL) and extracted with EA (50 mL × 3). The separated organic phases were combined and washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 10:1) to afford methyl 6-(2-bromophenyl)heptanoate (1.60 g, 5.35 mmol, 34.9 % yield) as a yellow oil.

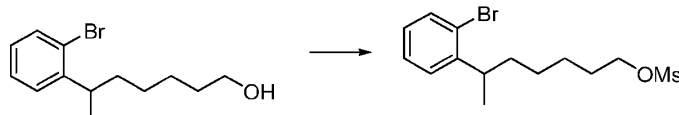
LCMS (Method 4): LC retention time = 2.37 min. MS (ESI) m/z 316.1, 318.1 [M+H₂O]⁺.

Step 3. Synthesis of 6-(2-bromophenyl)heptan-1-ol

[199] To a suspension of lithium aluminum hydride (0.11 g, 3.01 mmol) in THF (10 mL) was added methyl 6-(2-bromophenyl)heptanoate (600 mg, 2.01 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by slowly adding 15% aqueous NaOH (0.11 mL). Anhydrous Na₂SO₄ was added to the mixture and stirring was continued for several minutes. The solid was removed by filtration through a Celite pad. The filtrate was concentrated under vacuum to give 6-(2-bromophenyl)heptan-1-ol (520 mg, 1.92 mmol, 95.6 % yield) as a colorless oil. This sample was used directly in the next step without further purification.

LCMS (Method 4): LC retention time = 2.13 min. MS (ESI) m/z 288.1, 290.1 [M+H₂O]⁺.

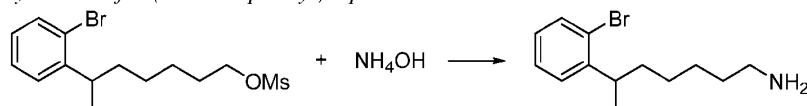
Step 4. Synthesis of 6-(2-bromophenyl)heptyl methanesulfonate



[200] To a solution of 6-(2-bromophenyl)heptan-1-ol (520 mg, 1.92 mmol) and triethylamine (0.80 mL, 5.75 mmol) in DCM (5 mL) was added methane sulfonyl chloride (0.18 mL, 2.30 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min, diluted with water (20 mL), and extracted with DCM (20 mL × 3). The organic phases were combined, washed with brine, and dried over Na₂SO₄. The organics were concentrated under vacuum to give 6-(2-bromophenyl)heptyl methanesulfonate (680 mg, 1.95 mmol, 101.5 % yield) as a colorless oil which was used directly in the next step without purification.

LCMS (Method 4): LC retention time = 2.23 min. MS (ESI) m/z 364.1, 366.1 [M+H₂O]⁺.

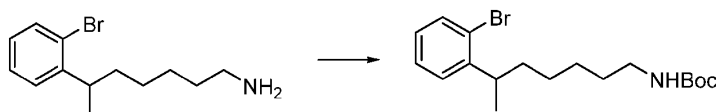
Step 5. Synthesis of 6-(2-bromophenyl)heptan-1-amine



[201] To a solution of 6-(2-bromophenyl)heptyl methane sulfonate (680 mg, 1.95 mmol) in 1,4-dioxane (2 mL) was added ammonium hydroxide (68 mg, 1.95 mmol). The reaction mixture was stirred at 80 °C for 3 h. Then the mixture was concentrated under vacuum to give 6-(2-bromophenyl)heptan-1-amine (500 mg, 1.85 mmol, 95.1 % yield) as a yellow oil which was used directly in the next step without purification.

LCMS (Method 4): LC retention time = 1.97 min. MS (ESI) m/z 270.1, 272.1 [M+H]⁺.

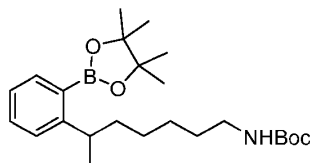
Step 6. Synthesis of tert-butyl N-[6-(2-bromophenyl)heptyl]carbamate



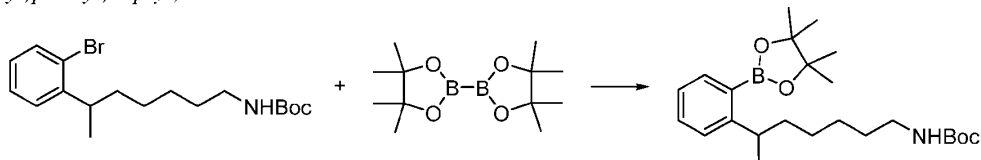
[202] To a solution of 6-(2-bromophenyl)heptan-1-amine (500 mg, 1.85 mmol) and triethylamine (0.77 mL, 5.55 mmol) in DCM (10 mL) was added dropwise di-tert-butyl dicarbonate (0.86 mL, 3.70 mmol). The reaction mixture was stirred at rt for 30 min, concentrated under reduced pressure, and purified by reversed-phase chromatography (C18, eluting with 0.1% NH_4HCO_3 in water, 10-100% ACN) to give tert-butyl N-[6-(2-bromophenyl)heptyl]carbamate (400 mg, 1.08 mmol, 58.4 % yield) as a colorless oil. LCMS (Method 4): LC retention time = 2.50 min. MS (ESI) m/z 314.1, 316.1 $[\text{M}+\text{H}-\text{tBu}]^+$.

Intermediate 3A:

tert-Butyl (6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)heptyl)carbamate



Step 1. Synthesis of tert-butyl (6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)heptyl)carbamate

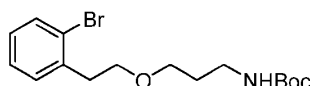


[203] **Intermediate 3A** was synthesized by following the procedures used for the synthesis of **Intermediate 2A**, except starting from **Intermediate 3**.

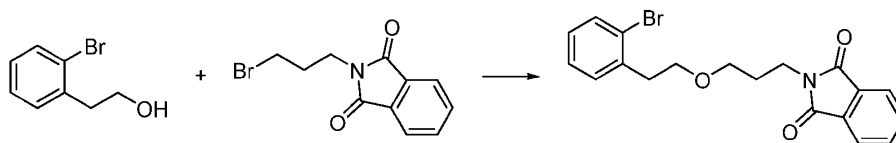
LCMS (Method 4): LC retention time = 2.66 min. MS (ESI) m/z 288.1 $[\text{M}+\text{H}-100]^+$.

Intermediate 4:

tert-Butyl (3-(2-bromophenoxy)propyl)carbamate



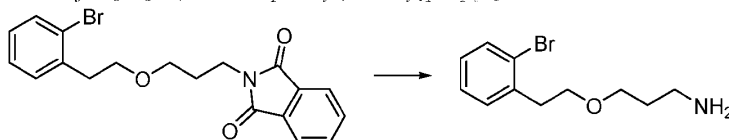
Step 1. Synthesis of 2-[3-[2-(2-bromophenyl)ethoxy]propyl]isoindoline-1,3-dione



[204] To a solution of 2-(2-bromophenyl)ethanol (5000 mg, 24.9 mmol) in DMF (20 mL) was added 2-(3-bromopropyl)isoindoline-1,3-dione (8001 mg, 29.8 mmol) and potassium tert-butoxide (8371 mg, 74.6 mmol). The reaction was stirred at rt for 16 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with water (50 mL), and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield 2-[3-[2-(2-bromophenyl)ethoxy]propyl]isoindoline-1,3-dione (1930 mg, 4.97 mmol, 20.0 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.20 min. MS (ESI) m/z 388.0, 390.0 $[M+H]^+$.

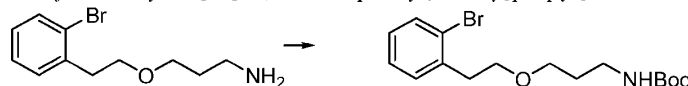
Step 2. Synthesis of 2-[3-[2-(2-bromophenyl)ethoxy]propyl]isoindoline-1,3-dione



[205] To a solution of 2-[3-[2-(2-bromophenyl)ethoxy]propyl]isoindoline-1,3-dione (1930 mg, 4.97 mmol) in methanol (10 mL) was added hydrazine hydrate (1 mL). The reaction was stirred at 60 °C for 3 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic extracts were washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column eluting with 30% ethyl acetate in petroleum ether) to yield 3-[2-(2-bromophenyl)ethoxy]propan-1-amine (1200 mg, 4.65 mmol, 93.5 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.47 min. MS (ESI) m/z 258.1, 260.1 $[M+H]^+$.

Step 3. Synthesis of tert-butyl N-[3-[2-(2-bromophenyl)ethoxy]propyl]carbamate

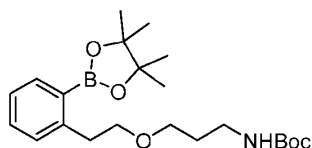


[206] To a solution of 3-[2-(2-bromophenyl)ethoxy]propan-1-amine (1200 mg, 4.65 mmol) in DCM (10 mL) was added di-tert-butyl dicarbonate (1.3 mL, 5.58 mmol) and N,N-diisopropylethylamine (2.4 mL, 13.9 mmol). The reaction was stirred at 25 °C for 3 h quenched with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers

were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column, eluting with 30% ethyl acetate in petroleum ether) to yield *tert*-butyl *N*-[3-[2-(2-bromophenyl)ethoxy]propyl]carbamate (1310 mg, 3.66 mmol, 78.7 % yield) as a yellow solid. LCMS (Method 1): LC retention time = 2.04 min. MS (ESI) m/z 257.1, 259.1 [M+H-BOC]⁺.

Intermediate 4A:

tert-Butyl *N*-[3-[2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethoxy]propyl]carbamate

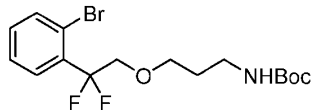


Intermediate 4A was synthesized by following procedures similar to those used in the synthesis of **Intermediate 2A**, except starting from **Intermediate 4**.

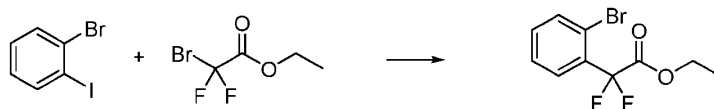
LCMS (Method 1): LC retention time = 2.10 min. MS (ESI) m/z 306.3 [M+H-BOC]⁺.

Intermediate 5:

tert-Butyl *N*-[3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl]carbamate

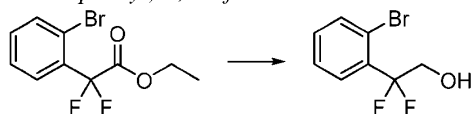


Step 1. Synthesis of ethyl 2-(2-bromophenyl)-2,2-difluoro-acetate



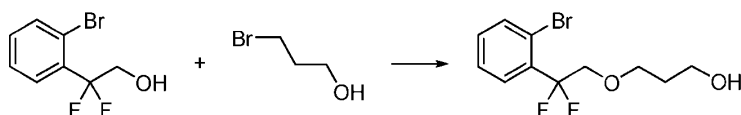
[207] To a solution of 1-bromo-2-iodobenzene (30 mL, 230 mmol) in DMSO (300 mL) was added copper (37.96 g, 597 mmol) and ethyl bromodifluoroacetate (33 mL, 253 mmol). The reaction was stirred at 50 °C for 16 h under N₂. The reaction mixture was poured into water (3000 mL) and extracted with ethyl acetate (300 mL × 3). The combined organic extracts were washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 4% EtOAc in petroleum ether to give ethyl 2-(2-bromophenyl)-2,2-difluoro-acetate (31.00 g, 111 mmol, 48.4 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 2.44 min. MS (ESI) m/z 279, 281 [M+H]⁺.

Step 2. Synthesis of 2-(2-bromophenyl)-2,2-difluoro-ethanol

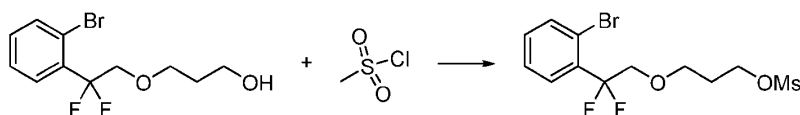
[208] To a solution of ethyl 2-(2-bromophenyl)-2,2-difluoroacetate (31.00 g, 111 mmol) in methanol (100 mL) was added sodium borohydride (5.04 g, 133 mmol) in five portions at 0 °C. The mixture was stirred at 0 °C for 30 min followed by the addition of 2N aqueous HCl (100 mL) at 0 °C. and the resulting mixture was extracted with EA (100 mL × 3), the organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 5:1) to give 2-(2-bromophenyl)-2,2-difluoro-ethanol (23.00 g, 97.0 mmol, 87.4 % yield) as a colorless oil.

LCMS (Method 3): LC retention time = 2.01 min. MS (ESI) *m/z* not observed.

Step 3. Synthesis of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-ol

[209] To a solution of 2-(2-bromophenyl)-2,2-difluoro-ethanol (5000 mg, 21.1 mmol), tetrabutylammonium bromide (680 mg, 2.11 mmol) and 3-bromo-1-propanol (2.2 mL, 25.3 mmol) in 1,4-dioxane (17 mL) was added sodium hydroxide (11.2M, 4.3 mL, 48.2 mmol). The reaction mixture was stirred at rt for 16 h. The reaction was quenched with water (30 mL), the aqueous mixture was extracted with EA (30 mL × 3). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 0-50% EA in PE) to give 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-ol (3000 mg, 10.1 mmol, 47.7 % yield) as a yellow oil.

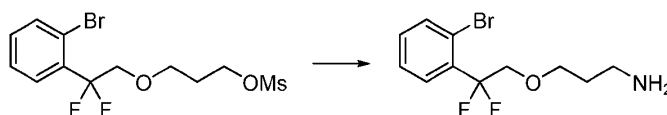
LCMS (Method 1): LC retention time = 1.83 min. MS (ESI) *m/z* 317.0, 319 [M+Na]⁺.

Step 4. Synthesis of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl methanesulfonate

[210] To a solution of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-ol (3000 mg, 10.2 mmol) and triethylamine (3.5 mL, 25.4 mmol) in DCM (30 mL) was added methanesulfonyl chloride (1.0 mL, 13.2 mmol) dropwise. The mixture was stirred at rt for 1 h, followed by the addition of water (30 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 3). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated to give 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl methanesulfonate (3000 mg, 7.23 mmol, 71.2 % yield) as a yellow oil which was used in next step without purification.

LCMS (Method 1): LC retention time = 1.87 min. MS (ESI) m/z 373.0, 375.0 [M+H]⁺.

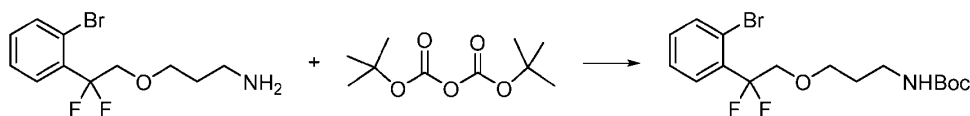
Step 5. Synthesis of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-amine



[211] To a solution of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl methanesulfonate (3000 mg, 8.04 mmol) in 1,4-dioxane (15 mL) was added ammonium hydroxide (15 mL, 385 mmol). The mixture was stirred at 80 °C for 16 h, cooled to rt, followed by the addition of water (30 mL). The resulting mixture was extracted with EA (30 mL $\times$ 3). The combined organic extracts were washed with brine (30 mL) dried over Na₂SO₄, and concentrated to afford 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-amine (2800 mg, 3.81 mmol, 47.4 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.36 min. MS (ESI) m/z 294.0, 296.0 [M+H]⁺.

Step 6. Synthesis of tert-butyl N-[3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl]carbamate



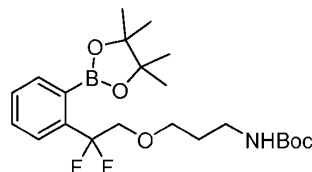
[212] To a solution of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-amine (13.00 g, 44.2 mmol) and triethylamine (18 mL, 133 mmol) in DCM (50 mL) was added di-tert-butyl dicarbonate (15 mL, 66.3 mmol) dropwise. The reaction mixture was stirred at rt for 30 min. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluting with PE : EA = 5 : 1) to give tert-butyl N-[3-[2-(2-

bromophenyl)-2,2-difluoro-ethoxy]propyl]carbamate (17.00 g, 43.1 mmol, 97.6 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 2.14 min. MS (ESI) m/z 294.0, 296.0 [M+H-Boc]⁺.

Intermediate 5A:

tert-Butyl (3-(2,2-difluoro-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethoxy)propyl)carbamate

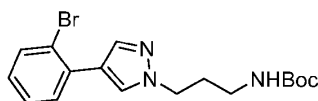


[213] **Intermediate 5A** was synthesized by following procedures similar to those used to prepare **Intermediate 2A**, except using **Intermediate 5** as a starting material.

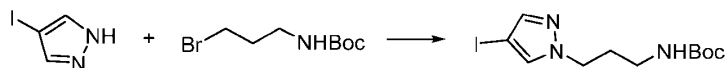
LCMS (Method 4): LC retention time = 2.66 min. MS (ESI) m/z no MS signal was observed.

Intermediate 6:

tert-Butyl (3-(4-(2-bromophenyl)-1H-pyrazol-1-yl)propyl)carbamate



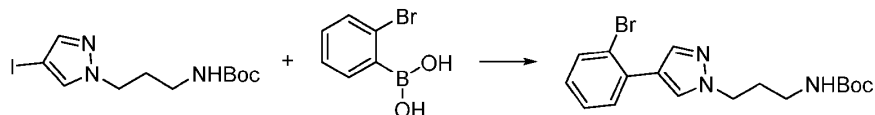
Step 1. Synthesis of tert-butyl N-[3-(4-iodopyrazol-1-yl)propyl]carbamate



[214] To a solution of 4-iodo-1H-pyrazole (5000 mg, 25.8 mmol) in DMF (50 mL) was added sodium hydride (1237 mg, 51.6 mmol) at 0 °C under N₂. The mixture was stirred at rt for 1 h, cooled to 0 °C under N₂, and *tert*-butyl N-(3-bromopropyl)carbamate (12275 mg, 51.6 mmol) was added dropwise at 0 °C over 10 min. The mixture was stirred at rt for 3 h. The reaction was quenched with saturated aqueous NH₄Cl solution (50 mL) at 0 °C, and the resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined extracts were concentrated and the crude residue was purified by flash column chromatography on silica gel (eluting with EtOAc in PE: 0-100% for 30 min) to afford *tert*-butyl N-[3-(4-iodopyrazol-1-yl)propyl]carbamate (8000 mg, 22.8 mmol, 88.4 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 1.77 min. MS (ESI) m/z 352.0 [M+H]⁺.

Step 2. tert-butyl N-[3-[4-(2-bromophenyl)pyrazol-1-yl]propyl]carbamate

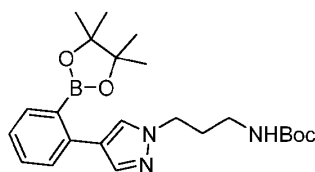


[215] To a solution of tert-butyl N-[3-(4-iodopyrazol-1-yl)propyl]carbamate (5000 mg, 14.2 mmol) in 1,4-dioxane (50 mL) and water (10 mL) were added (2-bromophenyl)boronic acid (719 mg, 28.5 mmol), potassium carbonate (5903 mg, 42.7 mmol), and tetrakis(triphenylphosphine)palladium (0) (3290 mg, 2.85 mmol). The mixture was stirred at 85 °C overnight under N₂. After cooling to room temperature, the reaction mixture was filtered, and the solids washed with EA (30 mL). The combined filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with EtOAc in PE, 0-50% for 50 min) to obtain tert-butyl N-[3-[4-(2-bromophenyl)pyrazol-1-yl]propyl]carbamate (2000 mg, 5.26 mmol, 36.9 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 1.58 min. MS (ESI) *m/z* 380.0, 382.0 [M+H]⁺.

Intermediate 6A:

tert-Butyl N-[3-[4-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-1-yl]propyl]carbamate

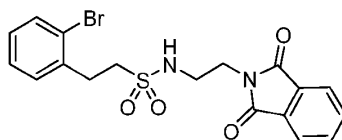


[216] **Intermediate 6A** was synthesized by following procedures similar to those employed in the synthesis of **Intermediate 2A**, except using **Intermediate 6** as a starting material.

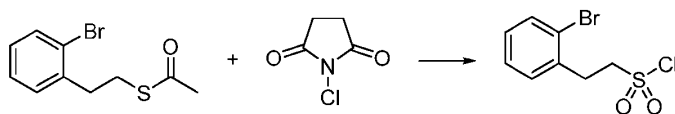
LCMS (Method 4): LC retention time = 1.99min. MS (ESI) *m/z* 428.0 [M+H]⁺.

Intermediate 7:

2-(2-Bromophenyl)-N-(2-(1,3-dioxoisindolin-2-yl)ethyl)ethane-1-sulfonamide

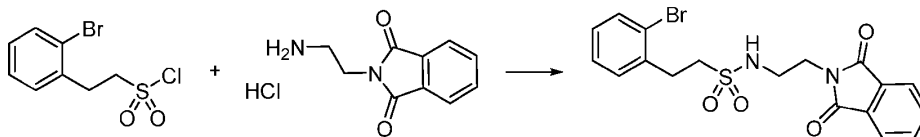


Step 1. Synthesis of 2-(2-bromophenyl)ethanesulfonyl chloride



[217] To a solution of *S*-[2-(2-bromophenyl)ethyl]ethanethioate (10.00 g, 38.6 mmol) in MeCN (50 mL) and 2N HCl (10 mL) was added N-chlorosuccinimide (20.61 g, 154 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h, concentrated, and purified by flash column chromatography on silica gel (eluting with PE : EA = 20:1) to give 2-(2-bromophenyl)ethanesulfonyl chloride (10.00 g, 35.3 mmol, 91.4 % yield) as a white solid. LCMS (Method 3): LC retention time = 2.02 min. No MS signal was observed.

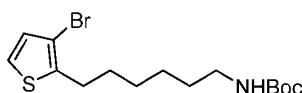
Step 2. Synthesis of 2-(2-bromophenyl)-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide



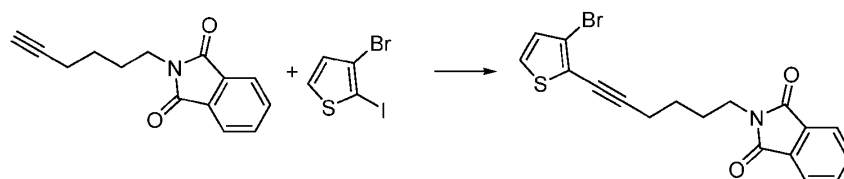
[218] To a solution of 2-(2-aminoethyl)isoindoline-1,3-dione hydrochloride (6.00 g, 26.4 mmol) and triethylamine (7.4 mL, 52.9 mmol) in DCM (50 mL) was added 2-(2-bromophenyl)ethanesulfonyl chloride (5.00 g, 17.6 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, diluted with water (30 mL) and extracted with DCM (30 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 1:1) to give 2-(2-bromophenyl)-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide (5.30 g, 12.1 mmol, 68.7 % yield) as a white solid. LCMS (Method 3): LC retention time = 1.90 min. MS (ESI) *m/z* 437.1, 439.1 [M+H]⁺.

Intermediate 8:

tert-Butyl *N*-[6-(3-bromo-2-thienyl)hexyl]carbamate



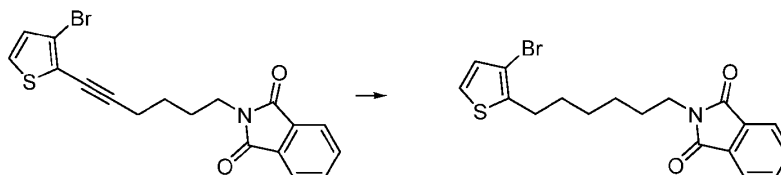
Step 1. Synthesis of 2-[6-(3-bromo-2-thienyl)hex-5-ynyl]isoindoline-1,3-dione



[219] To a solution of 2-hex-5-ynylisoindoline-1,3-dione (30 mg, 0.132 mmol) and 3-bromo-2-iodothiophene (76 mg, 0.264 mmol) in THF (2 mL) was added bis(triphenylphosphine)palladium (II) chloride (9.3 mg, 0.0132 mmol), copper (I) iodide (2.5 mg, 0.0132 mmol), and triethylamine (0.046 mL, 0.330 mmol). The mixture was stirred at rt for 4 h and poured into water (5 mL). The resulting suspension was extracted with EA (15 mL $\times$ 3). The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was first purified by reverse-phase flash chromatography (C18, 0.1%TFA in water, 10-100% MeCN), followed by another reverse-phase flash chromatography run (C18, 0.1% NH₄HCO₃ in water, 10-100% MeCN) to give 2-[6-(3-bromo-2-thienyl)hex-5-ynyl]isoindoline-1,3-dione (2.0 mg, 0.00515 mmol, 3.9 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.03 min. MS (ESI) m/z 388 and 390 [M+H]⁺.

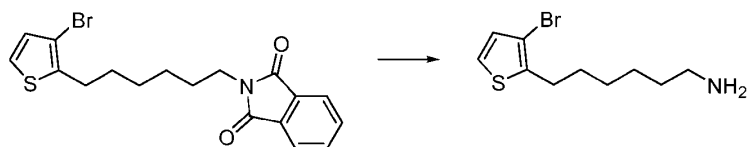
Step 2. Synthesis of 2-[6-(3-bromo-2-thienyl)hexyl]isoindoline-1,3-dione



[220] A mixture of 2-[6-(3-bromo-2-thienyl)hex-5-ynyl]isoindoline-1,3-dione (350 mg, 0.901 mmol), p-toluenesulfonylhydrazide (2518 mg, 13.5 mmol) and sodium acetate (1109 mg, 13.5 mmol) in 1,2-dimethoxyethane and water (5:1, v/v) was stirred at 90 °C for 16 h. To this mixture was added water (10 mL). The aqueous solution was extracted with EA (15 mL $\times$ 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 5:1) to give 2-[6-(3-bromo-2-thienyl)hexyl]isoindoline-1,3-dione (170 mg, 0.433 mmol, 48.1 % yield) as a colorless oil.

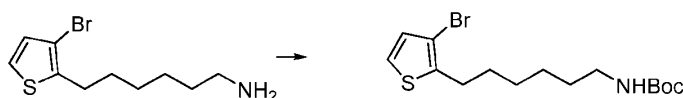
LCMS (Method 1): LC retention time = 2.19 min. No MS (ESI) signal was observed.

Step 3. Synthesis of 6-(3-bromo-2-thienyl)hexan-1-amine



[221] 6-(3-bromo-2-thienyl)hexan-1-amine was synthesized (in 72.4% yield) by following essentially the same procedure as in Step 3 of the synthesis of **Intermediate 4**. LCMS (Method 1): LC retention time = 1.51 min. MS (ESI) m/z 262 and 264 $[M+H]^+$.

Step 4. Synthesis of tert-butyl N-[6-(3-bromo-2-thienyl)hexyl]carbamate

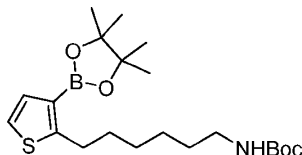


tert-Butyl N-[6-(3-bromo-2-thienyl)hexyl]carbamate was synthesized (in 52.8% yield) by following essentially the same procedure as in Step 2 of the synthesis of **Intermediate 4**.

LCMS (Method 1): LC retention time = 1.59 min. MS (ESI) m/z 306 and 308 $[M+H-tBu]^+$.

Intermediate 8A:

tert-Butyl N-[6-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]hexyl]carbamate

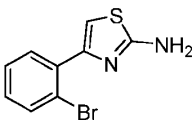


[222] **Intermediate 8A** was synthesized in 29.5% yield by following essentially the same procedure as in the synthesis of **Intermediate 2A**, except using **Intermediate 8** as a starting material.

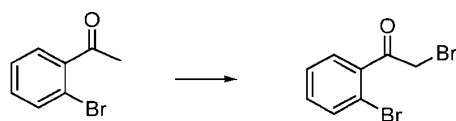
LCMS (Method 1): LC retention time = 2.49 min. MS (ESI) m/z 354.2 $[M+H-tBu]^+$.

Intermediate A-1:

4-(2-Bromophenyl)thiazol-2-amine



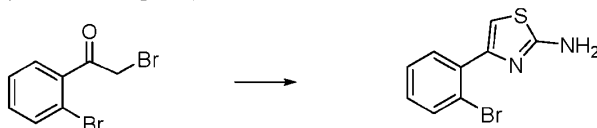
Step 1. Synthesis of 2-bromo-1-(2-bromophenyl)ethanone



[223] To a solution of 1-(2-bromophenyl)ethanone (1.00 eq, 150.00 g, 754 mmol) in acetonitrile (1500 mL) was added pyridine hydrobromide perbromide (1.00 eq, 241.02 g, 754 mmol). The mixture was stirred at room temperature for 4 h. The reaction was quenched with water. The aqueous solution was extracted with EA. The organic phase was washed sequentially with saturated aqueous NaHCO_3 , aqueous $\text{Na}_2\text{S}_2\text{O}_3$, brine, and then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to yield the title compound (200.00 g, 720 mmol, 95.5 % yield) as a brown oil.

LCMS (Method 1): LC retention time = 1.93 min. MS (ESI) m/z 277, 279 $[\text{M}+\text{H}]^+$.

Step 2. Synthesis of 4-(2-bromophenyl)thiazol-2-amine

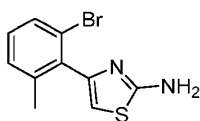


[224] To a solution of 2-bromo-1-(2-bromophenyl)ethanone (1.00 eq, 100 mg, 0.360 mmol) in ethanol (1 mL) was added thiourea (1.00 eq, 27 mg, 0.360 mmol). The reaction was heated at reflux for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with EA (10 mL $\times$ 3). The combined EA extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by silica gel column chromatography (0-60% EA in heptane) to yield the title compound as a pale-yellow solid.

LCMS (Method 2): LC retention time = 1.02 min. MS (ESI) m/z 255, 257 $[\text{M}+\text{H}]^+$.

Intermediate A-1a:

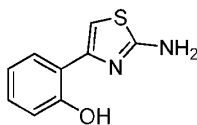
4-(2-Bromo-6-methyl-phenyl)thiazol-2-amine



[225] **Intermediate A-1a** was prepared in essentially the same manner as **Intermediate A-1** starting from 1-(2-bromo-6-methylphenyl)ethan-1-one.

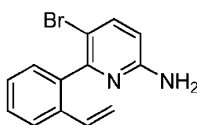
LCMS (Method 3): LC retention time = 1.57 min. MS (ESI) m/z 269, 271 $[\text{M}+\text{H}]^+$.

Intermediate A-2:

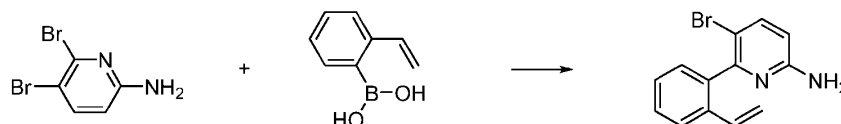
2-(2-Aminothiazol-4-yl)phenol

[226] **Intermediate A-2** was prepared in essentially the same manner as **Intermediate A-1** starting from 1-(2-hydroxyphenyl)ethan-1-one.

LCMS (Method 1): LC retention time = 1.74 min. MS (ESI) m/z 193.0 [M+H]⁺.

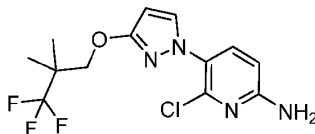
Intermediate A-3:*5-Bromo-6-(2-vinylphenyl)pyridin-2-amine*

Step 1. Synthesis of 5-bromo-6-(2-vinylphenyl)pyridin-2-amine

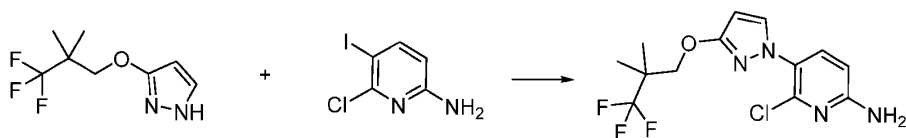


[227] To a solution of (2-vinylphenyl)boronic acid (1.00 eq, 5874 mg, 39.7 mmol) in 1,4-dioxane (100 mL) and water (10 mL) were added 5,6-dibromopyridin-2-amine (1.00 eq, 10000 mg, 39.7 mmol), potassium carbonate (3.95 eq, 21667 mg, 157 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.0218 eq, 1000 mg, 0.865 mmol) under N₂. The reaction was stirred at 90 °C for 12 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether : ethyl acetate = 3 : 1) to obtain the title compound (5.50 g, 19.0 mmol, 47.8 % yield) as a light-yellow solid.

LCMS (Method 4): LC retention time = 1.78 min. MS (ESI) m/z 275.0, 277.0 [M+H]⁺.

Intermediate A-4:*6-Chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine*

Step 1. Synthesis of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine

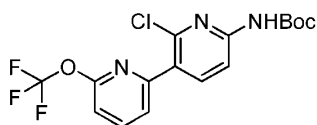


[228] To a solution of 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (1.00 eq, 208 mg, 0.999 mmol) in DMF (5 mL) were added 6-chloro-5-iodo-pyridin-2-amine (1.50 eq, 381 mg, 1.50 mmol), copper (I) iodide (0.500 eq, 95 mg, 0.500 mmol), N,N'-dimethylethane-1,2-diamine (0.500 eq, 44 mg, 0.500 mmol), and potassium acetate (3.00 eq, 294 mg, 3.00 mmol). The mixture was stirred at 100 °C for 8 hours under N₂. The reaction mixture was poured into water (30 mL) while stirring. The aqueous solution was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography, eluting with 35% ethyl acetate in petroleum ether to give the title compound (50 mg, 0.149 mmol, 15.0 % yield) as a yellow solid.

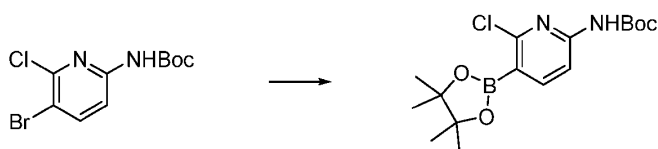
LCMS (Method 1): LC retention time = 1.89 min. MS (ESI) m/z 335.0 [M+H]⁺.

Intermediate A-5:

tert-Butyl N-[6-chloro-5-[6-(trifluoromethoxy)-2-pyridyl]-2-pyridyl]carbamate



Step 1. Synthesis of *tert*-butyl N-[6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]carbamate

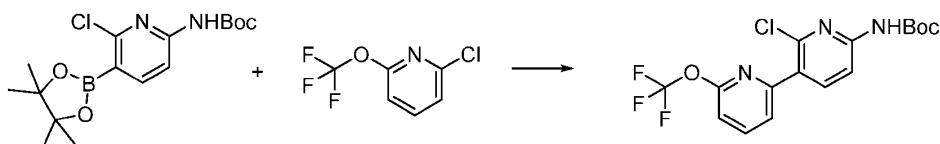


[229] To a solution of *tert*-butyl N-(5-bromo-6-chloro-2-pyridyl)carbamate (1.00 eq, 15.00 g, 48.8 mmol) in 1,4-dioxane (150 mL) were added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.10 eq, 3.57 g, 4.88 mmol), bis(pinacolato)diboron (1.30 eq, 16.10 g, 63.4 mmol), and potassium acetate (2.50 eq, 11.97 g, 122 mmol) at rt. Then the mixture was stirred at 100 °C for 3 h under Ar. The reaction mixture was diluted with water (100 mL), the resulting aqueous solution was extracted with EA (100 mL × 3). The organic extracts were washed with brine (100 mL), dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by flash

chromatography (330 g silica gel column, eluting with 0-5% ethyl acetate in petroleum) to give the title compound (17.00 g, 47.9 mmol, 98.3 % yield)

LCMS (Method 2): LC retention time = 2.23 min. MS (ESI) m/z 355.0 $[M+H]^+$.

Step 2. Synthesis of tert-butyl N-[6-chloro-5-[6-(trifluoromethoxy)-2-pyridyl]-2-pyridyl]carbamate

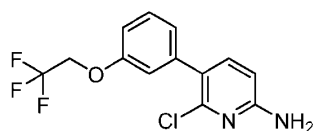


[230] To a solution of tert-butyl N-[6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]carbamate (1.00 eq, 300 mg, 0.846 mmol) in 1,4-dioxane (6 mL) and water (0.6 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.100 eq, 62 mg, 0.0846 mmol), 2-chloro-6-(trifluoromethoxy)pyridine (1.20 eq, 201 mg, 1.02 mmol), and potassium carbonate (2.50 eq, 292 mg, 2.11 mmol) at rt. The reaction was stirred at 100 °C for 2 h under Ar. The mixture was diluted with water (10 mL). The resulting aqueous solution was extracted with EA (10 mL $\times$ 3). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash chromatography (25 g silica gel column, eluting with 0-10% ethyl acetate in petroleum) to give the title compound (80 mg, 0.205 mmol, 24.3 % yield).

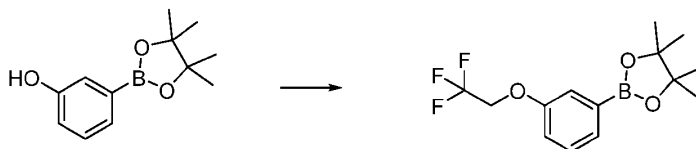
LCMS (Method 2): LC retention time = 2.20 min. MS (ESI) m/z 334.0 $[M+H-tBu]^+$.

Intermediate A-6:

6-Chloro-5-(3-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-amine



Step 1. Synthesis of 4,4,5,5-tetramethyl-2-[3-(2,2,2-trifluoroethoxy)phenyl]-1,3,2-dioxaborolane

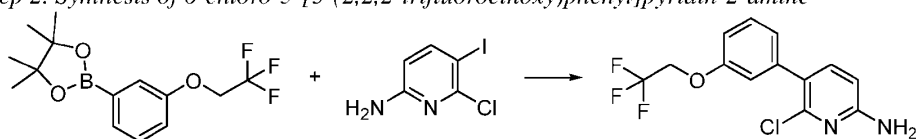


[231] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1000 mg, 4.54 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2109 mg, 9.09 mmol) in THF (5

mL) was added sodium (545 mg, 0.136 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with water (50 mL x 2) and brine (50 mL x 2), dried over anhydrous sodium sulphate, filtered, and concentrated. The residue was purified by flash chromatography (25 g silica gel column, eluting with 0-5% ethyl acetate in petroleum ether) to give 4,4,5,5-tetramethyl-2-[3-(2,2,2-trifluoroethoxy)phenyl]-1,3,2-dioxaborolane (910 mg, 3.01 mmol, 66.3 % yield).

LCMS (Method 4): LC retention time = 2.01 min. MS (ESI) m/z 303.3 [M+H]⁺.

Step 2. Synthesis of 6-chloro-5-[3-(2,2,2-trifluoroethoxy)phenyl]pyridin-2-amine

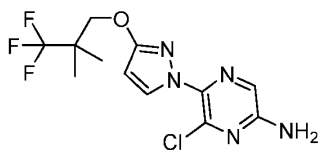


[232] To a solution of 6-chloro-5-iodo-pyridin-2-amine (1.00 g, 3.93 mmol) in 1,4-dioxane (15 mL) and water (1.5 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (144 mg, 0.196 mmol), 4,4,5,5-tetramethyl-2-[3-(2,2,2-trifluoroethoxy)phenyl]-1,3,2-dioxaborolane (1187 mg, 3.93 mmol) and potassium carbonate (1086 mg, 7.86 mmol). The reaction mixture was stirred at 80 °C for 3 h under N₂, then poured into water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 25% EtOAc in petroleum ether to give 6-chloro-5-[3-(2,2,2-trifluoroethoxy)phenyl]pyridin-2-amine (800 mg, 2.64 mmol, 67.3 % yield) as a white solid.

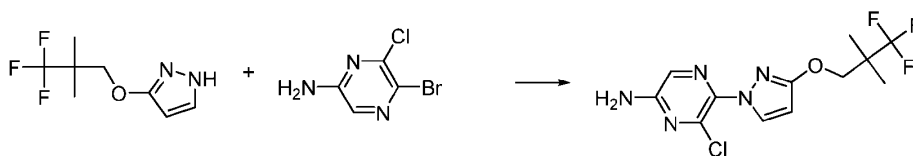
LCMS (Method 4): LC retention time = 1.79 min. MS (ESI) m/z 303.0 [M+H]⁺.

Intermediate A-7:

6-Chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine



Step 1. Synthesis of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine

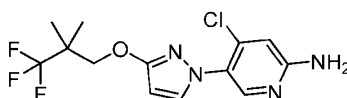


[233] To a solution of 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (5000 mg, 24.0 mmol) in DMF (50 mL) were added 5-bromo-6-chloro-pyrazin-2-amine (7509 mg, 36.0 mmol), potassium carbonate (9958 mg, 72.1 mmol), copper(I) iodide (915 mg, 4.80 mmol), and N,N'-dimethylethane-1,2-diamine (847 mg, 9.61 mmol). The mixture was stirred at 80 °C for 2 days and quenched with water (30 mL). The aqueous solution was extracted with EA (30 mL × 3), washed with brine (30 mL), dried over Na₂SO₄, then concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-50% EA in PE) to give 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (3000 mg, 8.85 mmol, 36.8 % yield) as a yellow solid.

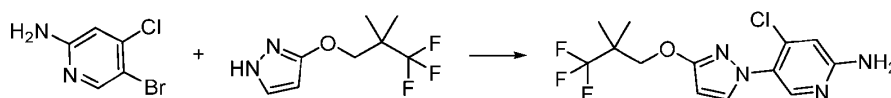
LCMS (Method 4): LC retention time = 1.80 min. MS (ESI) *m/z* 336.1 [M+H]⁺.

Intermediate A-8:

4-Chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine



Step 1. Synthesis of 4-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine



[234] To a solution of 5-bromo-4-chloro-pyridin-2-amine (1000 mg, 4.82 mmol) in DMF (10 mL) were added 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (2007 mg, 9.64 mmol), copper (I) iodide (184 mg, 0.964 mmol), potassium carbonate (1999 mg, 14.5 mmol), and N,N'-dimethylethane-1,2-diamine (4249 mg, 48.2 mmol). The mixture was stirred at 100 °C overnight under Ar. After cooling to room temperature, the reaction mixture was filtered and the solids were washed with EA (50 mL). The combined filtrates were concentrated under vacuum. The crude product was purified by prep-HPLC (NH₄HCO₃) and freeze-dried to

obtain 4-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (800 mg, 2.39 mmol, 49.6 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.85 min. MS (ESI) m/z 335.0 $[M+H]^+$.

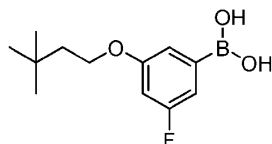
Intermediate A-9 to Intermediate A-12:

[235] The following intermediates were synthesized similarly by following the synthetic protocols for synthesis of **Intermediate A-6** and **Intermediate A-7**.

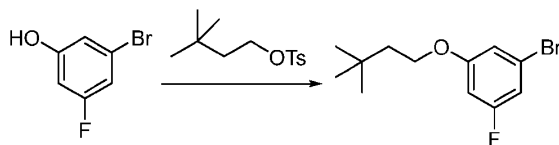
Intermediate	Structure	Name	Analytical
A-9		6-Chloro-5-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)phenyl]pyrazin-2-amine	LCMS (Method 1): LC retention time = 2.12 min. MS (ESI) m/z 306 $[M+H]^+$
A-10		6-Chloro-5-[3-(2,2-difluoro-3,3-dimethylbutoxy)phenyl]pyrazin-2-amine	LCMS (Method 1): LC retention time = 2.17 min. MS (ESI) m/z 342.1 $[M+H]^+$
A-11		6-Chloro-5-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)phenyl]pyridin-2-amine	LCMS (Method 2): Rt 2.12 min. MS (ESI) m/z 305.1 $[M+H]^+$
A-12		2'-Chloro-6-(trifluoromethoxy)-[2,3'-bipyridin]-6'-amine	LCMS (Method 1): LC retention time = 1.91 min. MS (ESI) m/z 290.0 $[M+H]^+$

Intermediate B-1:

(3-(3,3-Dimethylbutoxy)-5-fluorophenyl)boronic acid



Step 1. Synthesis of 1-bromo-3-(3,3-dimethylbutoxy)-5-fluorobenzene

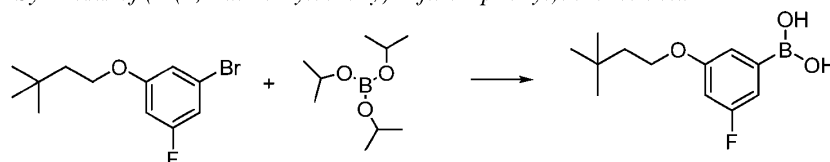


[236] To a solution of 3-bromo-5-fluorophenol (4.80 g, 25.1 mmol) in NMP (22 mL) was added Cs_2CO_3 (16.4 g, 50.3 mmol) and 3,3-dimethylbutyl 4-methylbenzenesulfonate (7.73 g, 30.2 mmol). The mixture was stirred at 138 °C overnight. The volatiles were removed under

reduced pressure. The residue was purified by silica gel column chromatography (eluting with PE) to afford the title compound (6.554 g, 93.5%) as a colorless oil.

LCMS (Method 1): LC retention time = 2.18 min. Molecular ion not observed.

Step 2. Synthesis of (3-(3,3-dimethylbutoxy)-5-fluorophenyl)boronic acid

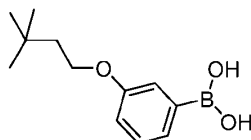


[237] To a cooled (-78 °C) and stirred solution of 1-bromo-3-(3,3-dimethylbutoxy)-5-fluorobenzene (6.55 g, 23.8 mmol) in anhydrous THF (65 mL) was added dropwise n-BuLi (2.5M in hexane, 26.2 mmol). The reaction mixture was stirred for 30 min. Triisopropyl borate (6.72 g, 35.7 mmol) was added dropwise while keeping the temperature of the reaction at -78 °C. The reaction was allowed to warm to rt and stirred at rt for 2 h. To the reaction mixture was added water and 2N aqueous HCl (50 mL) and stirring continued for 2 h. After reaction completion, ethyl acetate (60 mL) and water (40 mL) were added. The resulting two liquid phases were separated, and the organic phase was dried over MgSO₄, and concentrated to afford the title compound (5.3 g).

LCMS (Method 1): LC retention time = 2.12 min. MS (ESI) m/z 241 [M+H]⁺.

Intermediate B-2:

[3-(3,3-Dimethylbutoxy)phenyl]boronic acid

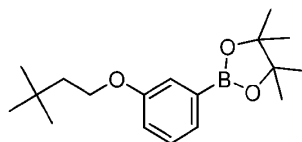


[238] **Intermediate B-2** was prepared in essentially the same manner as **Intermediate B-1** starting from 3-bromophenol.

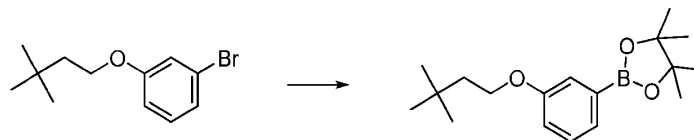
LCMS: LC retention time = 1.99 min. MS (ESI) m/z 223 [M+H]⁺.

Intermediate B-2a:

2-[3-(3,3-Dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. Synthesis of 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



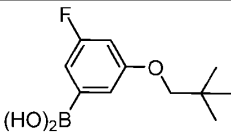
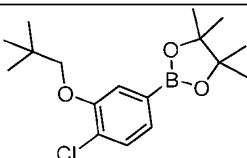
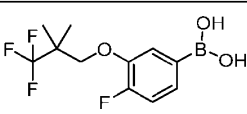
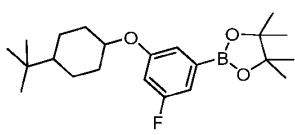
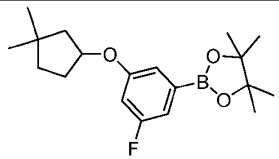
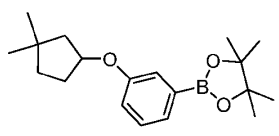
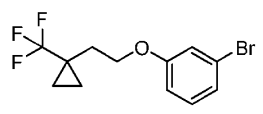
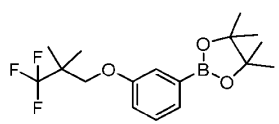
[239] To a solution of 1-bromo-3-(3,3-dimethylbutoxy)benzene (prepared similarly to **Intermediate B-1**, Step 1) (1.00 eq, 960 mg, 3.73 mmol) in 1,4-dioxane (10 mL) were added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.0198 eq, 54 mg, 0.0738 mmol), bis(pinacolato)diboron (1.19 eq, 1.13 g, 4.45 mmol), and potassium acetate (3.00 eq, 1.10 g, 11.2 mmol). The reaction was stirred at 100 °C for 12 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and quenched with water (100 mL). The aqueous solution was extracted with ethyl acetate (100 mL × 3). The combined organic extracts were washed with water (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column @ 50 mL/min, eluting with petroleum ether) to give the title compound (750 mg, 2.47 mmol, 66.0 % yield).

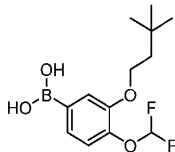
LCMS (Method 1): LC retention time = 2.25 min. MS (ESI) m/z 305.2 $[M+H]^+$.

Intermediate B-3 to Intermediate B-13:

[240] The following intermediates (**Intermediate B-3** to **Intermediate B-13**) were prepared similarly by following the procedures detailed in preparation of **Intermediate B-1** and **Intermediate B-2a**:

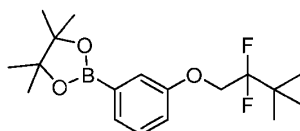
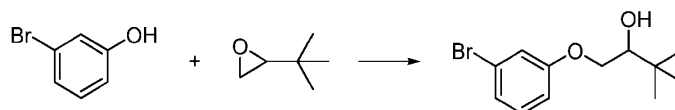
Intermediate ID	Structure	Name
Intermediate B-3		2-(2-Fluoro-5-(neopentyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Intermediate B-4		4,4,5,5-Tetramethyl-2-(3-(neopentyloxy)phenyl)-1,3,2-dioxaborolane
Intermediate B-5		2-(3-Fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Intermediate B-6		(3-Fluoro-5-(neopentyloxy)phenyl)boronic acid
Intermediate B-7		2-(4-Chloro-3-(neopentyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Intermediate B-8		(4-Fluoro-3-(3,3,3-trifluoro-2,2-dimethylpropoxy)phenyl)boronic acid
Intermediate B-9		2-(3-((4-(tert-Butyl)cyclohexyl)oxy)-5-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Intermediate B-10a		2-[3-(3,3-Dimethylcyclopentoxy)-5-fluorophenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Intermediate B-10b		2-(3-((3,3-Dimethylcyclopentyl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
Intermediate B-11		1-Bromo-3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)benzene
Intermediate B-12		4,4,5,5-Tetramethyl-2-(3-(3,3,3-trifluoro-2,2-dimethylpropoxy)phenyl)-1,3,2-dioxaborolane

Intermediate B-13		2-(4-(Difluoromethoxy)-3-(3,3-dimethylbutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
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Intermediate B-14:

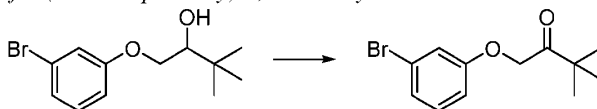
2-(3-(2,2-Difluoro-3,3-dimethylbutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

*Step 1. Synthesis of 1-(3-bromophenoxy)-3,3-dimethylbutan-2-ol*

[241] To a solution of 3-bromophenol (1.9 g, 11.0 mmol) in DMF (20 mL) were added 2-(*tert*-butyl)oxirane (1.65 g, 16.5 mmol) and cesium carbonate (7.16 g, 22.0 mmol) at room temperature. The resulting mixture was stirred at 80 °C overnight. The mixture was cooled to room temperature, diluted with water (150 mL), and extracted with ethyl acetate (40 mL × 3). The organic extracts were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with 9 % ethyl acetate in petroleum ether) to give the title compound (2.46 g, 82.0% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.24 min. MS (ESI) m/z 273, 275.0 $[M+H]^+$.

^1H NMR (400 MHz, chloroform- d) δ 7.17-7.06 (m, 3 H), 6.87-6.84 (m, 1 H), 4.10-4.07 (m, 1 H), 3.85 (t, J = 9.2 Hz, 1 H) 3.69-3.66 (m, 1 H), 2.36 (d, J = 3.2 Hz, 1 H), 1.01 (s, 9 H) ppm.

Step 2. Synthesis of 1-(3-bromophenoxy)-3,3-dimethylbutan-2-one

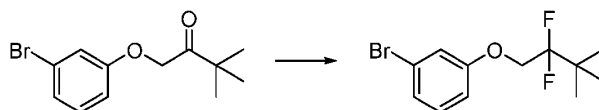
[242] To a solution of 1-(3-bromophenoxy)-3,3-dimethylbutan-2-ol (2.46 g, 9.01 mmol) in dichloromethane (30 mL) was added (1,1-diacetoxy-3-oxo-1 λ 5,2-benziodoxol-1-yl) acetate (5.73 g, 13.5 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was

purified by silica gel chromatography (eluting with 10% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (2.18 g, 89% yield).

LCMS: LC retention time = 2.18 min. MS (ESI) m/z 271, 273 $[M+H]^+$.

^1H NMR (400 MHz, chloroform- d) δ 7.16-7.10 (m, 2 H), 7.02 (s, 1 H), 6.81 (d, J = 7.2 Hz, 1 H), 4.85 (s, 2 H), 1.25 (s, 9 H) ppm.

Step 3. Synthesis of 1-bromo-3-(2,2-difluoro-3,3-dimethylbutoxy)benzene

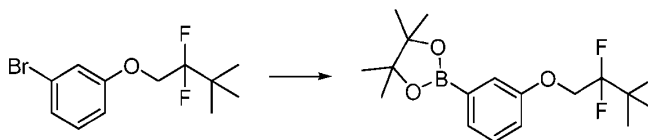


[243] To a solution of 1-(3-bromophenoxy)-3,3-dimethylbutan-2-one (2.18 g, 8.04 mmol) in anhydrous dichloromethane (20 mL) was added N-ethyl-N-(trifluoro-lambda4-sulfanyl)ethanamine (5.18 g, 32.2 mmol) dropwise at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 65 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution. After CO₂ evolution ceased, the solution was extracted with dichloromethane (30 mL $\times$ 3). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with petroleum ether) to give the title compound (1.56 g, 66.1 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.35 min. MS (ESI) signal not observed.

^1H NMR (400 MHz, chloroform- d) δ 7.18-7.10 (m, 3 H), 6.88 (m, 1 H), 4.23 (t, J = 13.2 Hz, 2 H), 1.14 (s, 9 H) ppm.

Step 4. Synthesis of 2-(3-(2,2-difluoro-3,3-dimethylbutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



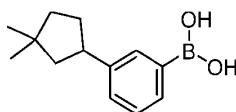
[244] To a solution of 1-bromo-3-(2,2-difluoro-3,3-dimethylbutoxy)benzene (1.56 g, 5.32 mmol) in anhydrous 1,4-dioxane (20.0 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.03 g, 7.99 mmol), potassium acetate (1.56 g, 15.96 mmol), and [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium (II) (389 mg, 0.532 mmol). The reaction was stirred at 90 °C overnight under an argon atmosphere. The solids were filtered off. The filtrate was diluted with water (120 mL) and extracted with ethyl acetate (50 mL $\times$ 3).

The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with 3% ethyl acetate in petroleum ether) to give the title compound (1.343 g, 74% yield) as a colorless oil.

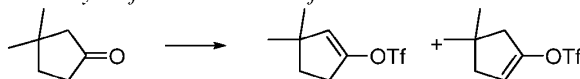
LCMS (Method 1): LC retention time = 2.42 min. MS (ESI) m/z 341.1 $[M+H]^+$.

Intermediate B-15:

(3-(3,3-Dimethylcyclopentyl)phenyl)boronic acid



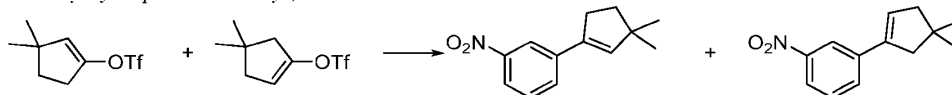
Step 1. Synthesis of 3,3-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate and 4,4-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate



[245] To a cooled (0 °C) solution of diisopropylamine (5.2 g, 51.4 mmol) in anhydrous THF (40 mL) was added n-BuLi (2.5M in hexane, 18.8 mL, 47.1 mmol) under Ar. The solution was stirred at 0 °C for 15 min, and then cooled to -78 °C. To the above reaction solution was added a solution of 3,3-dimethylcyclopentanone (7.37 g, 40 mmol) in anhydrous THF (40 mL). The mixture was stirred at -78 °C for 2 h. A solution of bis(trifluoromethanesulfonyl)aniline (16.80 g, 47.1 mmol) in anhydrous THF (80 mL) was added, and the mixture was warmed to 0 °C and stirred overnight. The mixture was poured into saturated aqueous NH₄Cl and extracted with Et₂O. The combined organic extracts were washed with water, brine, dried, and concentrated to give the title compound (8.00 g, 76.6%) as a colorless oil.

¹H NMR (400 MHz, chloroform-*d*) δ 5.56-5.49 (m, 1H), 2.66-2.62 (m, 1H), 2.42-2.40 (m, 1H), 2.23-2.21 (m, 1H), 1.85 (t, J = 8.1 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H) ppm.

Step 2. Synthesis of 1-(3,3-dimethylcyclopent-1-en-1-yl)-3-nitrobenzene and 1-(4,4-dimethylcyclopent-1-en-1-yl)-3-nitrobenzene

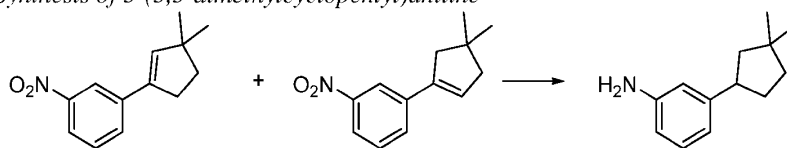


[246] To a solution of 3,3-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate in toluene/EtOH/water (60 mL/30 mL/15 mL) were added 4,4-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (2.00 g, 8.18 mmol), (3-nitrophenyl)boronic acid (1.71 g, 10.2 mmol), tetrakis (triphenylphosphine) palladium (236 mg, 0.205 mmol), and sodium carbonate

(2.60 g, 24.6 mmol). The mixture was stirred at 90 °C for 16 h and concentrated. The residue was suspended in water (50 mL) and extracted with ethyl acetate (50 mL × 2). The organic extracts were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with PE) to obtain the title compound (1.3 g, 73.1%) as a yellow oil.

¹HNMR (400 MHz, chloroform-*d*) δ 8.23-8.20 (m, 1H), 8.06-8.03 (m, 1H), 7.72-7.69 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 6.24-6.14 (m, 1H), 2.80-2.76 (m, 1H), 2.57-2.55 (m, 1H), 2.40-2.39 (m, 1H), 1.89 (t, *J* = 7.2 Hz, 1H), 1.19 (s, 3H), 1.16 (s, 3H) ppm.

Step 3. Synthesis of 3-(3,3-dimethylcyclopentyl)aniline

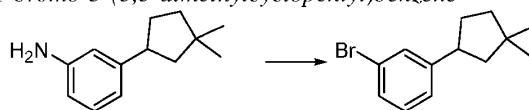


[247] To a solution of 1-(3,3-dimethylcyclopent-1-en-1-yl)-3-nitrobenzene and 1-(4,4-dimethylcyclopent-1-en-1-yl)-3-nitrobenzene (1.30 g, 6.00 mmol) in MeOH (50 mL) was added 10 wt % Pd/C (130 mg) under an Ar atmosphere at room temperature. The flask was flushed with hydrogen and the mixture stirred under a hydrogen atmosphere for 16 h. The reaction mixture was filtered, and the filtrate was concentrated to obtain the title compound (700 mg, 62.0 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.95 min. MS (ESI) *m/z* 190.0 [M+H]⁺.

¹HNMR (400 MHz, chloroform-*d*) δ 7.09 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.59 (s, 1H), 6.52-6.49 (m, 1H), 3.59 (br, 2H), 3.14-3.09 (m, 1H), 2.10-2.06 (m, 1H), 1.85-1.47 (m, 5H), 1.16 (s, 3H), 1.14 (s, 3H) ppm.

Step 4. Synthesis of 1-bromo-3-(3,3-dimethylcyclopentyl)benzene

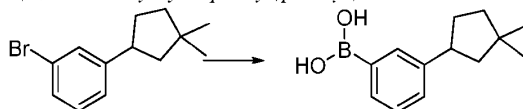


[248] To a solution of 3-(3,3-dimethylcyclopentyl)aniline (700 mg, 3.33 mmol) in anhydrous MeCN (20 mL) were added CuBr₂ (445 mg, 2.00 mmol) and *tert*-butyl nitrite (343 mg, 3.33 mmol) at room temperature. The resulting mixture was stirred at reflux for 15 min. The reaction was quenched with water (80 mL). The aqueous layer was extracted with ethyl acetate (80 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column

chromatography (eluting with PE : EA = 50 : 1) to give the title compound (478 mg, 53.9 %) as a yellow oil.

¹HNMR (400 MHz, chloroform-*d*): δ 7.41-7.13 (m, 4H), 3.57-3.12 (m, 1H), 2.17-1.50 (m, 6H), 1.12 (s, 3H), 1.10 (s, 3H) ppm.

Step 5. Synthesis of (3-(3,3-dimethylcyclopentyl)phenyl)boronic acid

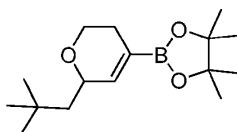


[249] To a cooled and stirred solution of 1-bromo-3-(3,3-dimethylcyclopentyl)benzene (470 mg, 1.67 mmol) in anhydrous tetrahydrofuran (20 mL) was added *n*-butyllithium (1.34 mL, 3.34 mmol, 2.5 M solution in hexanes) dropwise at -78 °C. After completion of the addition, the reaction mixture was stirred at -78 °C for 0.5 h. Next, trimethyl borate (347 mg, 3.34 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h. The reaction was then gradually warmed to room temperature over 2 h. To this solution was added hydrochloric acid (6.0 N, 5 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction was diluted with water (50 mL). The aqueous phase was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic extracts were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (400 mg, crude) as a yellow solid.

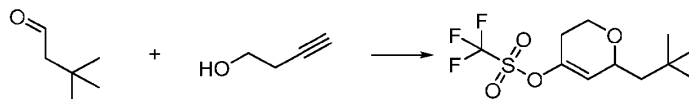
¹HNMR (400 MHz, chloroform-*d*): δ 7.68-7.23 (m, 4H), 3.20-3.15 (m, 1H), 2.07-1.30 (m, 6H), 1.16 (s, 3H), 1.14 (s, 3H) ppm.

Intermediate B-16:

4,4,5,5-Tetramethyl-2-(6-neopentyl-3,6-dihydro-2H-pyran-4-yl)-1,3,2-dioxaborolane



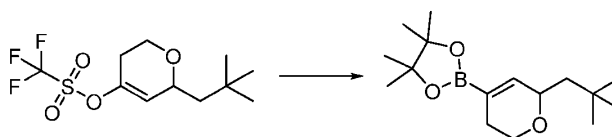
Step 1. Synthesis of 6-neopentyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate



[250] To a stirred solution of 3,3-dimethylbutanal (1.0 g, 9.98 mmol) in dry dichloromethane (50.0 mL) was added dropwise at 0 °C trifluoromethanesulfonic acid (1.8 g, 12.0 mmol), followed by but-3-yn-1-ol (1.05 g, 15.0 mmol). The reaction mixture was stirred at room

temperature for 12 h. After completion of the reaction, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (100 mL) and extracted with DCM (80 mL $\times$ 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated to dryness. The residue was purified by flash column chromatography (eluting with PE: EA= 10: 1) to give the title compound (1.70 g, 56.3%) as a yellow oil.

Step 2. Synthesis of 4,4,5,5-tetramethyl-2-(6-neopentyl-3,6-dihydro-2H-pyran-4-yl)-1,3,2-dioxaborolane.

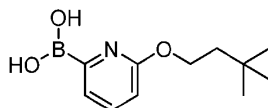


[251] A mixture of 6-neopentyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (1.7 g, 5.62 mmol), bis (pinacolato)diboron (2.14 g, 8.44 mmol), CH_3COOK (1.10 g, 11.2 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (411 mg, 0.562 mmol) and 1,4-dioxane (60 mL) was heated overnight at 80 °C under Ar. The reaction mixture was concentrated to afford the crude title compound (0.87 g, 56.3%) as a yellow oil.

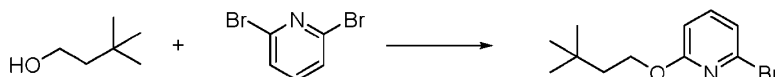
LCMS (Method 1): LC retention time = 2.50 min. MS (ESI) m/z 281.0 $[\text{M}+\text{H}]^+$.

Intermediate B-17:

(6-(3,3-Dimethylbutoxy)pyridin-2-yl)boronic acid



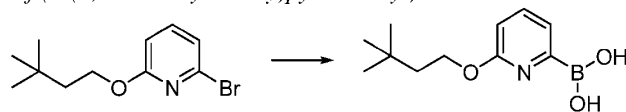
Step 1. Synthesis of 2-bromo-6-(3,3-dimethylbutoxy)pyridine



[252] To a cooled (0 °C) and stirred solution of 3,3-dimethylbutan-1-ol (500 mg, 4.89 mmol) in dry THF (10 mL) was added NaH (293.58 mg, 7.34 mmol, 60% dispersion in oil). The reaction mixture was stirred at room temperature for 0.5 h. To the reaction mixture was added 2,6-dibromopyridine (1.16 g, 4.89 mmol), and stirring at room temperature continued for 12 h. The reaction was diluted with EA (20 mL), and washed with water (10 mL $\times$ 2). The EA extract was dried over Na_2SO_4 , filtered, and concentrated to dryness to give the crude product which was purified by silica gel chromatography (petroleum ether eluent) to give the title compound (1.8 g, 71% two batches) as a colorless oil.

LCMS (Method 1): MS (ESI) m/z 258, 260 $[\text{M} + \text{H}]^+$

Step 2. Synthesis of (6-(3,3-dimethylbutoxy)pyridin-2-yl)boronic acid

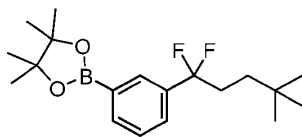


[253] To the stirred solution of 2-bromo-6-(3,3-dimethylbutoxy)pyridine (0.5 g, 1.93 mmol) in THF (6 mL) was added n-butyllithium (1.42 mL, 2.9 mmol) at -78 °C under a N₂ atmosphere. The reaction was stirred at this temperature for 1 h, then triisopropyl borate (436.3 mg, 2.32 mmol) was added. The mixture was warmed to room temperature and stirred at this temperature for 13 h. TLC (silica, PE/EA = 8/1) showed that the starting material was consumed. To the mixture was added MeOH (3 mL), the pH adjusted to 3 with aqueous HCl (2 M), the organics removed under reduced pressure, and the pH adjusted to 7 with aqueous NaHCO₃. The aqueous mixture was extracted with EA (15 mL × 3). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was suspended in PE (10 mL) and filtered to give the title compound (0.2 g, 46.3%) as a yellow solid.

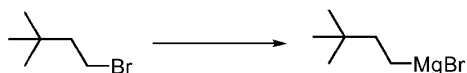
¹H NMR (400 MHz, methanol-*d*) δ 8.19 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 4.46 (t, *J* = 7.2 Hz, 2H), 1.97-1.81 (m, 2H), 1.06 (s, 9H) ppm.

Intermediate B-18:

2-(3-(1,1-Difluoro-4,4-dimethylpentyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

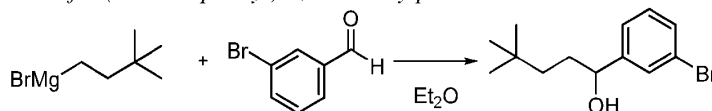


Step 1. Synthesis of (3,3-dimethylbutyl)magnesium bromide



[254] Magnesium turnings (2.10 g, 86.42 mmol) were added to 60 mL of Et₂O. A small amount of iodine was added, followed by the slow addition of a solution of 1-bromo-3,3-dimethylbutane (17.500 g, 106 mmol) in 10 mL of Et₂O. The reaction mixture was stirred under reflux for 2 h. After cooling to rt, the reaction solution containing the desired 3,3-dimethylbutyl)magnesium bromide was used directly in the next step.

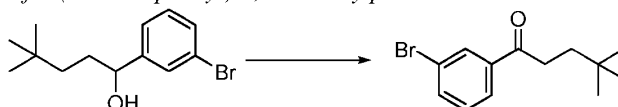
Step 2. Synthesis of 1-(3-bromophenyl)-4,4-dimethylpentan-1-ol



[255] To a solution of 3-bromobenzaldehyde (5.42 g, 29.3 mmol) in anhydrous Et₂O (30 mL) was added under N₂ at room temperature (3,3-dimethylbutyl)magnesium bromide (70 mL, 86.42 mmol). The resulting mixture was stirred at room temperature for 2 h. The mixture was poured into a saturated aqueous ammonium chloride solution (50 mL) and extracted with DCM (30 mL × 2). The extracts were washed with brine (20 mL × 2), dried over sodium sulfate, and filtered. The filtrate was used directly in the next step.

LCMS (Method 1): LC retention time = 2.34 min. MS (ESI) *m/z* 271, 273 [M+H]⁺.

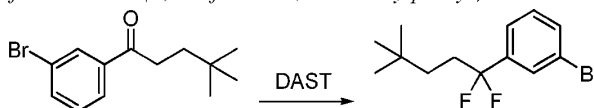
Step 3. Synthesis of 1-(3-bromophenyl)-4,4-dimethylpentan-1-one



[256] To a stirred solution of 1-(3-bromophenyl)-4,4-dimethylpentan-1-ol (7.95 g, 29.3 mmol) in dry DCM (150 mL) was added at 0 °C under nitrogen PCC (17.60 g, 81.7 mmol). The resulting mixture was stirred at room temperature for 12 h. The mixture was filtered, and the filtrate concentrated. The residue was purified by silica gel chromatography (eluting with PE/EA = 98/2) to give the title compound (6.95 g, 88 % yield over 3 steps) as a light-yellow oil.

LCMS (Method 1): LC retention time = 2.33 min. MS (ESI) *m/z* 269, 271 [M+H]⁺.

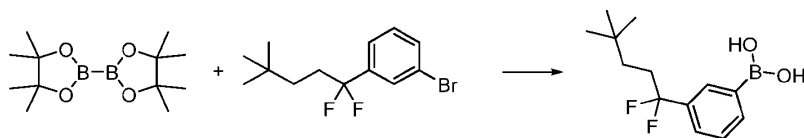
Step 4. Synthesis of 1-bromo-3-(1,1-difluoro-4,4-dimethylpentyl)benzene



[257] To a stirred solution of 1-(3-bromophenyl)-4,4-dimethylpentan-1-one (1.74 g, 6.84 mmol) in DCM (20 mL) was added DAST (4.50 g, 27.9 mmol) at room temperature under nitrogen. The reaction mixture was stirred at 86 °C for 14 h. The mixture was poured into ice water. The pH of the aqueous phase was adjusted to 8. The aqueous phase was extracted with EA (10 mL × 3). The organic extracts were combined, dried over Na₂SO₄, filtered and concentrated. The crude residue was purified via flash chromatography (eluting with PE) to afford the title compound (1.59 g, 79.9%) as a colorless oil.

¹H NMR (400 MHz, Chloroform-d) δ 7.64 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 2.11-2.03 (m, 2H), 1.35-1.30 (m, 2H), 0.90 (s, 9H) ppm.

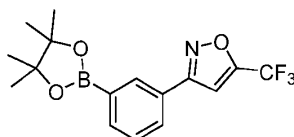
Step 5. Synthesis of (3-(1,1-difluoro-4,4-dimethylpentyl)phenyl)boronic acid



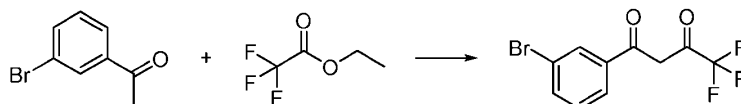
[258] A mixture of 1-bromo-3-(1,1-difluoro-4,4-dimethylpentyl)benzene (266 mg, 0.913 mmol), potassium acetate (270mg, 2.75 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (255 mg, 1.0 mmol), tricyclohexylphosphane (27 mg, 0.096 mmol) and $\text{Pd}_2(\text{dba})_3$ (84 mg, 0.092 mmol) in 1,4-dioxane (10 mL) was stirred at 85 °C under N_2 for 20 h. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated to give the title compound (235 mg, 100%) as a colorless oil. LCMS: LC retention time = 2.19 min. MS (ESI) m/z 256.8 $[\text{M}+\text{H}]^+$.

Intermediate B-19:

3-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(trifluoromethyl)isoxazole



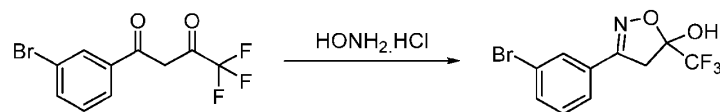
Step 1. Synthesis of 1-(3-bromophenyl)-4,4,4-trifluoro-butane-1,3-dione



[259] Sodium (347 mg, 15.1 mmol) was dissolved in ethanol (10 mL) under nitrogen. To this solution was added a solution of ethyl 2,2,2-trifluoroacetate (2.86 g, 20.1 mmol) in ethanol (10 mL), followed by a solution of 1-(3-bromophenyl)ethanone (2.00 g, 10.0 mmol) in ethanol (10 mL). The reaction mixture was refluxed at 85 °C overnight. After the completion of the reaction, the reaction was quenched with aqueous HCl (1 N) (30 mL). The aqueous mixture was extracted with ethyl acetate (50 mL). The EA extract was washed with brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with 15 % ethyl acetate in petroleum ether) to afford the title compound (2.12 g, 7.19 mmol, 71.9% yield) as a red oil.

LCMS (Method 1): LC retention time = 1.18 min. MS (ESI) m/z 295, 296 $[\text{M}+\text{H}]^+$.

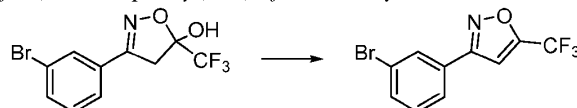
Step 2. Synthesis of 3-(3-bromophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol



[260] To a solution of hydroxylamine hydrochloride (236 mg, 3.39 mmol) in aqueous NaOH (142 mg, 3.56 mmol) was added 1-(3-bromophenyl)-4,4,4-trifluoro-butane-1,3-dione (1 g, 3.39 mmol) over 1 h at 20-30 °C. The resulting mixture was refluxed for 45 min. After cooling to room temperature, the mixture was poured into ice water (50 mL). The precipitate was filtered off. The filtrate was extracted with ethyl acetate (30 mL), the EA extract dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford the title compound (810 mg, 77.1 % yield).

LCMS (Method 1): LC retention time = 2.02 min. MS (ESI) *m/z* 310, 312 [M+H]⁺.

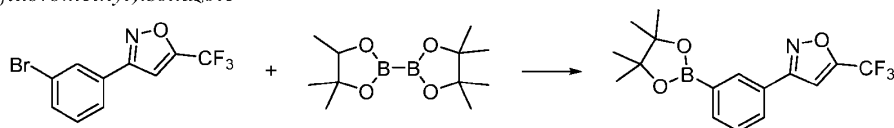
Step 3. Synthesis of 3-(3-bromophenyl)-5-(trifluoromethyl)isoxazole



[261] A solution of 3-(3-bromophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (810 mg, 3.36 mmol) in trifluoroacetic acid (20 mL) was refluxed overnight. After completion of the reaction, the reaction was quenched with saturated aqueous NaHCO₃ (40 mL). The aqueous phase was extracted with ethyl acetate (40 mL). The organic extract was then washed with water (30 mL), dried over anhydrous Na₂SO₄ and filtered. The resulting solution was concentrated under reduced pressure to yield the crude product which was purified by silica gel chromatography (11 % ethyl acetate in petroleum ether) to afford the title compound (190 mg).

LCMS: LC retention time = 1.54 min. MS (ESI) *m/z*: no signal observed.

Step 4. Synthesis of 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(trifluoromethyl)isoxazole

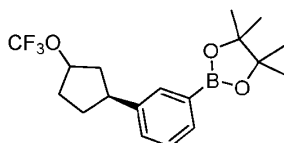


[262] To a solution of 3-(3-bromophenyl)-5-(trifluoromethyl)isoxazole (200 mg, 0.685 mmol) in 1,4-dioxane (10 mL) were added under a nitrogen atmosphere 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (174 mg, 0.685 mmol), Pd(dppf)Cl₂ (25.1 mg, 0.034 mmol) and potassium acetate (134 mg, 1.37 mmol). The reaction

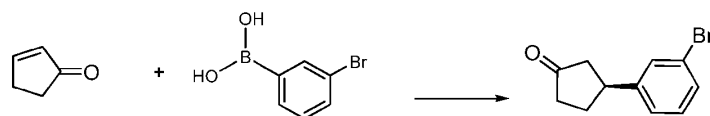
was stirred at 80 °C overnight. After completion of the reaction, the mixture was filtered, and the filtrate was extracted with ethyl acetate (25 mL). The organic extract was washed with water (25 mL) and brine (25 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title compound as a brown oil. LCMS (Method 1): LC retention time = 1.59 min. MS (ESI) m/z 340 [M+H]⁺.

Intermediate B-20:

4,4,5,5-Tetramethyl-2-(3-((1S)-3-(trifluoromethoxy)cyclopentyl)phenyl)-1,3,2-dioxaborolane

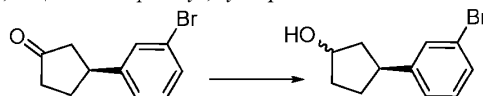


Step 1. Synthesis of (S)-3-(3-bromophenyl)cyclopentan-1-one



[263] To a solution of (3-bromophenyl)boronic acid (6.84 g, 34.2 mmol) in 40 mL of dioxane and 4 mL of H₂O were added under nitrogen acetylacetonatobis(ethylene)rhodium (I) (188.6 mg, 0.74 mmol), *S*-BINAP (455 mg, 0.74 mmol), and cyclopent-2-en-1-one (2.0 g, 24.4 mmol). After refluxing for 5.0 h, the reaction mixture was cooled and concentrated. The residue was partitioned between 100 mL of EA and 100 mL of 1N aqueous NaHCO₃. After phase separation, the organic layer was washed with 100 mL of brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (eluting with PE : EA = 5 : 1) to afford the title compound (4.70 g, 80.6 % yield) as a light-yellow solid. LCMS (Method 1): LC retention time = 2.14 min. MS (ESI) m/z 239, 241 [M+H]⁺.

Step 2. Synthesis of (3S)-3-(3-bromophenyl)cyclopentan-1-ol

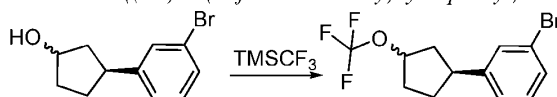


[264] A solution of (S)-3-(3-bromophenyl)cyclopentan-1-one (4.58 g, 19.2 mmol) in anhydrous tetrahydrofuran (40.0 mL) was cooled to -78 °C under an argon atmosphere. To this solution was added DIBAL (1M in toluene) (76.7 mL) while maintaining the original temperature. The reaction mixture was allowed to warm slowly to room temperature and stirring continued at room temperature overnight. Saturated potassium sodium tartrate tetrahydrate solution (80 mL) was added and stirred for another 1 h. The mixture was filtered

through a Celite plug. The filtrate was concentrated under reduced pressure to give the crude product which was purified by reverse phase column chromatography to afford the title compound (3.25 g, 70.4 %) as a colorless oil.

LCMS (Method 1): LC retention time = 2.05 min. MS (ESI) m/z 223, 225 $[M-H_2O]^+$.

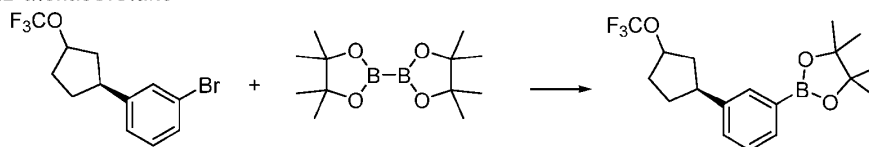
Step 3. Synthesis of 1-bromo-3-((1S)-3-(trifluoromethoxy)cyclopentyl)benzene



[265] A flask was charged with silver trifluoromethanesulfonate (3.20 g, 12.4 mmol), Select-F® (2.20 g, 6.22 mmol), KF (964 mg, 16.6 mmol), and (3S)-3-(3-bromophenyl)cyclopentan-1-ol (1.0 g, 4.15 mmol). The flask was purged with argon, then ethyl acetate (20 mL) was added, followed by $TMSCF_3$ (1.77 g, 12.4 mmol) and 2-fluoropyridine (1.21 g, 12.4 mmol). The reaction mixture was stirred overnight at room temperature under argon. The reaction mixture was filtered through a Celite pad. The filtrate was concentrated. The residue was purified by silica gel column chromatography (eluting with PE) to afford the title compound (402 mg, 31.4 %) as a colorless oil.

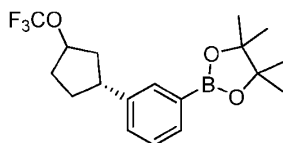
1H NMR (400 MHz, chloroform- d) δ 7.36 (m, 2H), 7.16 (m, 2H), 4.85 (m, 1H), 3.39-2.95 (m, 1H), 2.61-2.21 (m, 2H), 2.16-1.59 (m, 5H) ppm.

Step 4. Synthesis of 4,4,5,5-tetramethyl-2-[3-[(1S)-3-(trifluoromethoxy)cyclopentyl]phenyl]-1,3,2-dioxaborolane

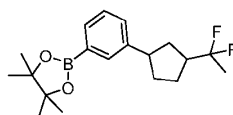


[266] To a solution of 1-bromo-3-[(1S)-3-(trifluoromethoxy) cyclopentyl]benzene (1.0 g, 3.23 mmol) in dioxane (20 mL) were added 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane (1.38 g, 4.85 mmol), KOAc (793 mg, 8.09 mmol), and $Pd(dppf)Cl_2$ (70.9 mg, 9.70×10^{-5} mol). The reaction was stirred at 90 °C overnight under argon. The mixture was concentrated and extracted with EA (10 mL $\times$ 3), the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (eluting with PE: EA = 10: 1) to give the title compound (720 mg, 62.5% yield) as a light oil.

LCMS (acidic): LC retention time = 2.41, MS (ESI): m/z 357 $[M+H]^+$.

Intermediate B-21:*1-Bromo-3-((1R)-3-(trifluoromethoxy)cyclopentyl)benzene*

[267] **Intermediate B-21** was prepared in the same manner as **Intermediate B-20**, except using *R*-BINAP in Step 1 instead of *S*-BINAP.

Intermediate B-22:*2-(3-(3-(1,1-Difluoroethyl)cyclopentyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane*

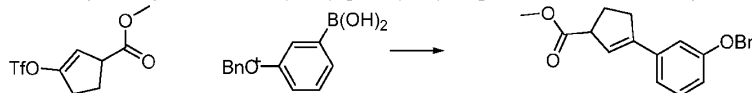
Step 1. Synthesis of methyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-ene-1-carboxylate



[268] To a solution of methyl 3-oxocyclopentane-1-carboxylate (2.56 g, 18.0 mmol) in toluene (50 mL) was added at room temperature under a N₂ atmosphere DIEA (9.35 g, 72.3 mmol). The solution was then chilled to 0 °C and triflic anhydride (12.80 g, 45.4 mmol) added. The resulting mixture was stirred at 50 °C for 2 h. The mixture was poured into water (400 mL) and extracted with ethyl acetate (100 mL × 2). The combined organic extracts were washed with water (100 mL × 2), dried over sodium sulfate, and concentrated. The crude product was purified by silica gel chromatography (eluting with PE : EA = 10 : 1) to afford the title compound (4.93 g, 100 %) as a yellow oil.

¹H NMR (400 MHz, chloroform-*d*) δ 5.74-5.61 (m, 1H), 3.75 (s, 3H), 3.82-3.62 (m, 1H), 3.35-2.96 (m, 1H), 2.87-2.64 (m, 2H), 2.37-2.30 (m, 1H) ppm.

Step 2. Synthesis of methyl 3-(3-(benzyloxy)phenyl)cyclopent-2-ene-1-carboxylate

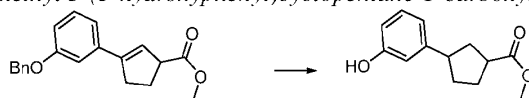


[269] To a solution of methyl 3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-ene-1-carboxylate (4930 mg, 18.0 mmol) in 1,2-dimethoxyethane /H₂O (60 mL, v/v = 5/1) were

added (3-(benzyloxy)phenyl)boronic acid (4.18 g, 18.3 mmol), $\text{Pd}(\text{Ph}_3\text{P})_4$ (520 mg, 0.45 mmol), and NaHCO_3 (4.57 g, 54.49 mmol). The resulting mixture was stirred at 80 °C under an argon atmosphere for 16 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was suspended in water (200 mL). The aqueous mixture was extracted with ethyl acetate (20 mL $\times$ 2). The EA extracts were combined, dried over anhydrous Na_2SO_4 , filtered, and concentrated to dryness under reduced pressure. The crude product was purified by silica gel chromatography (eluting with PE : EA = 10 : 1) to afford the title compound (2.63 g, 47.5% yield over 2 steps) as a yellow oil.

LCMS (Method 1): LC retention time = 2.27 min. MS (ESI) m/z 309 $[\text{M}+\text{H}]^+$.

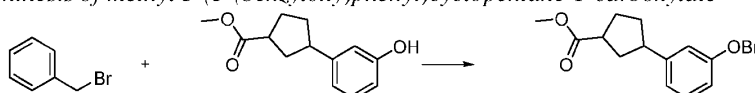
Step 3. Synthesis of methyl 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylate



[270] To a solution of methyl 3-(3-(benzyloxy)phenyl)cyclopent-2-ene-1-carboxylate (2.63 g, 8.53 mmol) in MeOH (150 mL) was added Pd/C (1210 mg). The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The reaction mixture was filtered through a Celite plug. The filtrate was concentrated and purified by silica gel chromatography (eluting with PE : EA = 5 : 1) to give the title compound (1450 mg, 77.2%) as a yellow oil.

LCMS (Method 1): LC retention time = 1.54 min. MS (ESI) m/z 221 $[\text{M}+\text{H}]^+$.

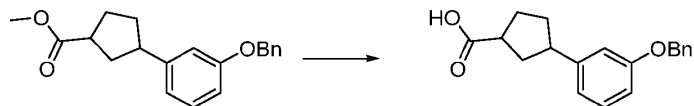
Step 4. Synthesis of methyl 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylate



[271] To a solution of methyl 3-(3-hydroxyphenyl)cyclopentane-1-carboxylate (1.45 g, 6.58 mmol) in acetone (30 mL) were added (bromomethyl)benzene (2220 mg, 12.98 mmol) and K_2CO_3 (2735 mg, 19.79 mmol). The resulting mixture was stirred at 55 °C under a N_2 atmosphere for 16 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 2). The combined EA extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated to dryness under reduced pressure. The crude product was purified by silica gel chromatography (eluting with PE : EA = 10 : 1) to give the title compound (2.04 g, 100 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 2.26 min. MS (ESI) m/z 333 $[\text{M}+\text{Na}]^+$.

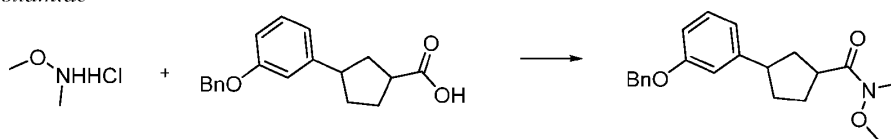
Step 5. Synthesis of 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylic acid



[272] To a stirred solution of methyl 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylate (2.04 g, 6.57 mmol) in THF (8 mL), MeOH (4 mL) and water (0.75 mL) was added at room temperature LiOH·H₂O (2060 mg, 49.05 mmol). Stirring at room temperature was continued for 16 h. Hydrochloric acid (2N) was added to the solution until the pH reached 4. The mixture was extracted with ethyl acetate (50 mL × 2). The combined EA extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give the title compound (2.17 g, 100 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.38 min. MS (ESI) *m/z* 297 [M+H]⁺.

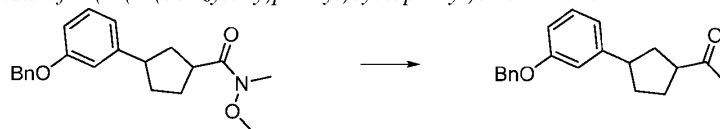
Step 6. Synthesis of 3-(3-(benzyloxy)phenyl)-N-methoxy-N-methylcyclopentane-1-carboxamide



[273] To a solution of 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylic acid (2175 mg, 7.34 mmol) in DCM (40 mL) were added at room temperature HATU (5580 mg, 14.68 mmol), N,O-dimethylhydroxylamine hydrochloride (1.08 g, 11.12 mmol) and DIEA (2850 mg, 22.05 mmol). The resulting mixture was stirred at the same temperature for 16 h. The mixture was poured into water (100 mL) and extracted with ethyl acetate (100 mL × 2). The extracts were combined and washed with water (100 mL × 2), dried over sodium sulfate, and evaporated. The crude product was purified by silica gel chromatography (eluting with PE : EA = 10 : 1) to give the title compound (2.19 g, 88.0 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.16 min. MS (ESI) *m/z* 340.1 [M+H]⁺.

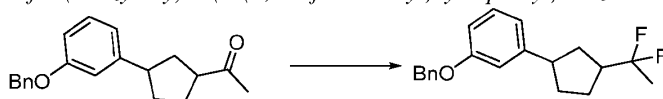
Step 7. Synthesis of 1-(3-(3-(benzyloxy)phenyl)cyclopentyl)ethan-1-one



[274] To a solution of 3-(3-(benzyloxy)phenyl)-N-methoxy-N-methylcyclopentane-1-carboxamide (2690 mg, 7.92 mmol) in THF (20 mL) was added CH₃MgBr (7.9 mL, 23.7 mmol,

3.0 M) under N₂ at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The mixture was poured into water (50 mL) and extracted with ethyl acetate (100 mL × 2). The combined organic extracts were washed with water (100 mL × 2), dried over sodium sulfate, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with PE : EA = 10 : 1) to afford the title compound (2.31 g, 99.0 % yield) as a colorless oil. LCMS (Method 1): LC retention time = 2.22 min. MS (ESI) *m/z* 295 [M+H]⁺.

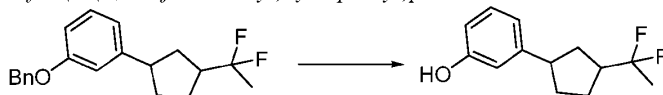
Step 8. Synthesis of 1-(3-(3-(benzyloxy)phenyl)cyclopentyl)ethan-1-one



[275] To a stirred solution of 1-(3-(3-(benzyloxy)phenyl)cyclopentyl)ethan-1-one (1.50 g, 5.1 mmol) in DCM (15 mL) was added DAST (4.0 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 16 h. The mixture was poured into water (100 mL) and extracted with ethyl acetate (100 mL × 2). The extracts were washed with water (100 mL × 2), dried over sodium sulfate, and concentrated. The crude product was purified by silica gel chromatography (eluting with PE : EA = 95 : 5) to give the title compound (1.36 g, 84.9 % yield) as a colorless oil.

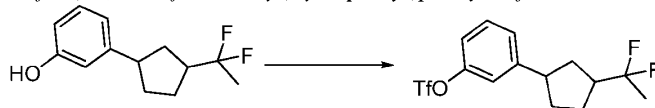
MS (Method 1): LC retention time = 2.47 min. MS (ESI) *m/z* 317.0 [M+H]⁺.

Step 9. Synthesis of 3-(3-(1,1-difluoroethyl)cyclopentyl)phenol



To a solution of 1-(benzyloxy)-3-(3-(1,1-difluoroethyl)cyclopentyl)benzene (2.04 g, 6.46 mmol) in EA (50 mL) was added Pd/C (1.04 g). The resulting mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. The mixture was filtered through a Celite plug. The filtrate was concentrated and purified by silica gel chromatography (eluting with PE : EA = 6 : 1) to give the title compound (1.25 g, 85.6% yield) as a yellow oil. LCMS (Method 1): LC retention time = 2.03 min. MS (ESI) *m/z* 227.0 [M+H]⁺.

Step 10. Synthesis of 3-(3-(1,1-difluoroethyl)cyclopentyl)phenyl trifluoromethanesulfonate

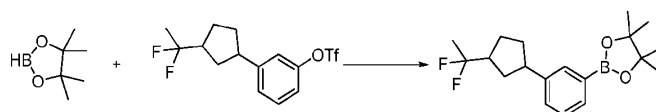


[276] To a solution of 3-(3-(1,1-difluoroethyl)cyclopentyl)phenol (223 mg, 0.986 mmol) in DCM (2.5 mL) were added at 0 °C pyridine (80 mg, 1.01 mmol) and triflic anhydride (335 mg,

1.19 mmol). The reaction mixture was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EA (20 mL $\times$ 3). The organic phases were combined, washed with saturated aqueous NaHCO₃ (10 mL) and brine (20 mL), dried over anhydrous Na₂SO₄. The solvent was evaporated and the residue purified by silica gel column chromatography (eluting with 5 % EA in PE) to afford the title compound (171 mg, 48.4% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.37 min. MS (ESI) m/z 381.0 [M+Na]⁺.

Step 11. Synthesis of 2-(3-(3-(1,1-difluoroethyl)cyclopentyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

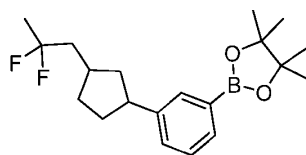


[277] To a solution of 3-(3-(1,1-difluoroethyl)cyclopentyl)phenyl trifluoromethanesulfonate (171 mg, 0.48 mmol) in dioxane (2.5 mL) were added at room temperature 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (108 mg, 0.84 mmol), TEA (145 mg, 1.43 mmol) and PdCl₂(dppf) (22 mg, 0.03 mmol). The reaction was refluxed for 16 h until TLC indicated that the starting material had been consumed. The mixture was extracted with EA (30 mL $\times$ 2). The combined organic extracts were washed with brine (30 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered, and concentrated to give the title compound (195 mg, 100% yield) as a yellow solid.

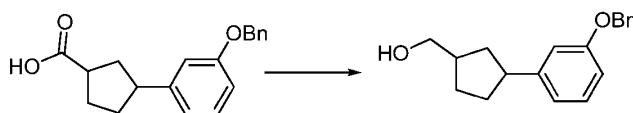
LCMS (Method 1): LC retention time = 1.96 min. MS (ESI) m/z 337.0 [M+H]⁺.

Intermediate B-23:

2-(3-(3-(2,2-Difluoropropyl)cyclopentyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. Synthesis of (3-(3-(benzyloxy)phenyl)cyclopentyl)methanol

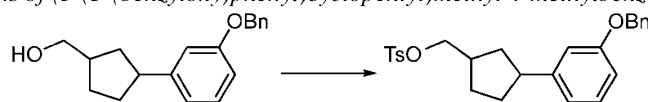


[278] To a solution of 3-(3-(benzyloxy)phenyl)cyclopentane-1-carboxylic acid (from Step 5, **Intermediate B-22**) (2.10 g, 7.09 mmol) in anhydrous THF (60 mL) was slowly added LiAlH₄ (808 mg, 21.3 mmol) at 0 °C under an argon atmosphere. After addition, the mixture was

allowed to warm to room temperature and stirred for 1 h. LCMS analysis showed that the starting material was consumed. The mixture was cooled to 0 °C, and Na₂SO₄·10H₂O, and water were added. The mixture was stirred for another 1 h, being allowed to warm to rt. The mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (150 mL). The organic extract was washed with water (100 mL) and brine (150 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude which was purified by flash chromatography column (eluting with PE/EA = 5/1) to afford the title compound (1.66 g, 83.0% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.15 min. MS (ESI) m/z 283.0 [M+H]⁺.

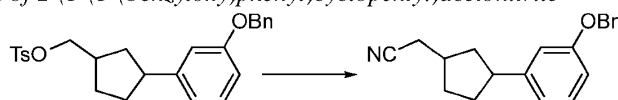
Step 2. Synthesis of (3-(3-(benzyloxy)phenyl)cyclopentyl)methyl 4-methylbenzenesulfonate



[279] To a solution of (3-(3-(benzyloxy)phenyl)cyclopentyl)methanol (1.66 g, 5.88 mmol) in DCM (30 mL) were added under an argon atmosphere at 0 °C DMAP (71.8 mg, 0.59 mmol), Et₃N (1.78 g, 17.6 mmol), and TsCl (1.68 g, 8.82 mmol). The mixture was allowed to warm to room temperature and stirred at the same temperature overnight. The mixture was poured into ice-water (100 mL) and extracted with DCM (60 mL). The DCM solution was washed with saturated aqueous NaHCO₃ (30 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the title compound (2.47 g, 96.2 % yield) as a yellow oil.

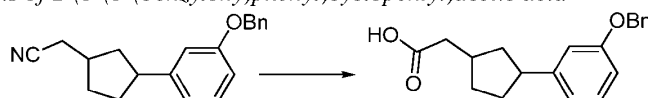
LCMS (Method 1): LC retention time = 2.38 min. MS (ESI) m/z 459 [M+Na]⁺.

Step 3. Synthesis of 2-(3-(3-(benzyloxy)phenyl)cyclopentyl)acetonitrile



[280] To a solution of (3-(3-(benzyloxy)phenyl)cyclopentyl)methyl 4-methylbenzenesulfonate (2.47 g, 5.66 mmol) in DMF (30.0 mL) were added 18-Crown-6 (2.24 g, 8.49 mmol) and KCN (552 mg, 8.49 mmol). The solution was stirred at 55 °C overnight. The resulting solution was cooled to rt, diluted with ethyl acetate (150 mL), washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude was purified by flash chromatography column (eluting with PE : EA = 5 : 1) to give the title compound (1.49 g, 90.4% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.22 min. MS (ESI) m/z 292 [M+H]⁺.

Step 4. Synthesis of 2-(3-(3-(benzyloxy)phenyl)cyclopentyl)acetic acid

[281] To a solution of 2-(3-(3-(benzyloxy)phenyl)cyclopentyl)acetonitrile (1.49 g, 5.11 mmol) in ethanol (30 mL) and H₂O (3.0 mL) was added sodium hydroxide (4.09 g, 100.3 mg). The reaction was stirred at 80 °C for 12 h. The resulting mixture was concentrated under vacuum. The residue was dissolved in water (60 mL). The pH was adjusted to 4 with hydrochloric acid (1N). The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the title compound (1.48 g) as a light-yellow solid.

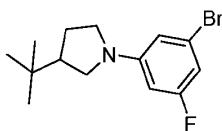
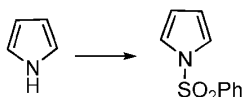
LCMS (Method 1): LC retention time = 2.13 min. MS (ESI) m/z 311.1 [M+H]⁺.

[282] The rest of the steps were carried out by following procedures of Steps 6 to 11, **Preparation of Intermediate 22**, to obtain **Intermediate 23**.

LCMS (Method 1): LC retention time = 2.45 min. MS (ESI) m/z 351.0 [M+H]⁺.

Intermediate B-24:

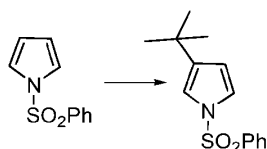
1-(3-Bromo-5-fluorophenyl)-3-(tert-butyl)pyrrolidine

*Step 1. Synthesis of 1-(phenylsulfonyl)-1H-pyrrole*

[283] To a suspension of NaH (8.05 g, 201 mmol, 60% dispersion in oil) in THF (100 mL) was added at 0 °C a solution of pyrrole (9.0 g, 134 mmol) in THF (100 mL). After 30 min, benzenesulfonyl chloride (23.70 g, 134 mmol) in THF (50 mL) was added. The mixture was stirred at rt for 5 h. The reaction was quenched with water (200 mL). THF was evaporated under reduced pressure. The resulting suspension was filtered, and the filter cake was washed with water and dried to obtain the title compound (26.00 g, 89.8% yield) as a white solid.

LCMS (Method 1): LC retention time = 2.04 min. MS (ESI) m/z 208.2 [M+H]⁺.

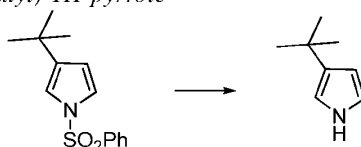
Step 2. Synthesis of 3-(tert-butyl)-1-(phenylsulfonyl)-1H-pyrrole



[284] To a solution of 1-(phenylsulfonyl)-1H-pyrrole (9.0 g, 43.4 mmol) and 2-chloro-2-methylpropane (4.79 g, 52.1 mmol) in DCM (150 mL) was added AlCl₃ (8.68 g, 65.1 mmol) at 0 °C. After addition, the mixture was stirred at rt for 6 h. The reaction was quenched with water (150 mL). The aqueous mixture was extracted with DCM (100 mL). The organic phase was washed with water (100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with PE : EA = 2:1) to give the title compound (6.0 g, 49.8% yield) as a yellow oil.

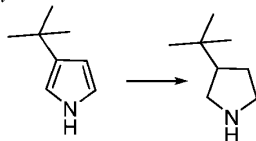
LCMS (Method 1): LC retention time = 2.25 min. MS (ESI) *m/z* 264.2 [M+H]⁺.

Step 3. Synthesis of 3-(tert-butyl)-1H-pyrrole



[285] To a solution of 3-(tert-Butyl)-1-(phenylsulfonyl)-1H-pyrrole (6.0 g, 22.8 mmol) in EtOH/H₂O (60 mL/60 mL) was added KOH (12.8 g, 228 mmol). The mixture was refluxed for 5 h. The solvent was removed under reduced pressure. The residue was suspended in water (50 mL). The resulting aqueous mixture was extracted with DCM (20 mL × 3). The organic extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with PE : EA = 5 : 1) to give the title compound (2.20 g, 78.4% yield) as a yellow oil.

Step 4. Synthesis of 3-(tert-butyl)pyrrolidine

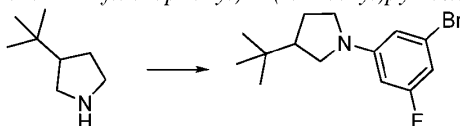


[286] To a solution of 3-(tert-butyl)-1H-pyrrole (2.20 g, 17.9 mmol) in EtOH (100 mL) was added aqueous HCl (1N, 1.0 mL) and PtO₂ (203 mg) at room temperature under an Ar atmosphere. The flask was purged with hydrogen and stirring continued at rt under a hydrogen atmosphere for 16 h. The reaction mixture was filtered and the solids washed with ether. The

combined filtrate was concentrated in *vacuo* to afford the title compound (1.80 g, 79.2% yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.43 min. MS (ESI) m/z 128.1 $[M+H]^+$

Step 5. Synthesis of 1-(3-bromo-5-fluorophenyl)-3-(tert-butyl)pyrrolidine

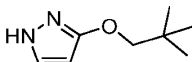


[287] To a solution of 1-bromo-3,5-difluorobenzene (2.0 g, 10.4 mmol) in NMP (10.0 mL) placed in a reaction tube were added 3-(*tert*-butyl)pyrrolidine (1.45 g, 11.4 mmol) and DIPEA (6.68 g, 51.8 mmol). The tube was sealed and heated at 100 °C while stirring overnight. Upon cooling, the reaction mixture was diluted with water and ethyl acetate (10 mL each). The aqueous layer was back extracted with ethyl acetate (30 mL $\times$ 3). The combined organic extracts were washed with H₂O (150 mL), brine (150 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with PE) to obtain the title compound (2.40 g, 51.7% yield) as a colorless oil.

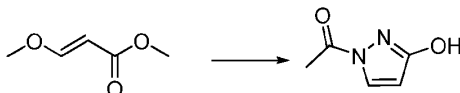
LCMS (Method 1): LC retention time = 3.04 min. MS (ESI) m/z 300, 302.0 $[M+H]^+$.

Intermediate B-25:

3-(Neopentyloxy)-1H-pyrazole

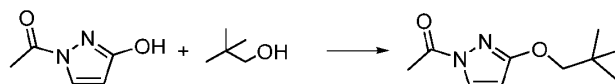


Step 1. Synthesis of 1-(3-hydroxy-1H-pyrazol-1-yl)ethan-1-one



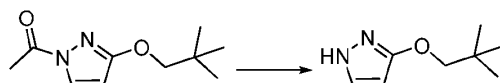
[288] To a stirred solution of methyl (*E*)-3-methoxyacrylate (6.00 g, 51.72 mmol) in MeOH (50 mL) was added hydrazine hydrate (30 mL) at room temperature. The solution was stirred under reflux for 16 h. After the reaction was complete, the solvent was removed under reduced pressure. The residue was dissolved in pyridine (30 mL) and Ac₂O (4.7 g, 46.12 mmol) was added slowly at 95 °C. Stirring was continued at 95 °C for 2 h. The solvent was removed under reduced pressure and the residue was suspended in Et₂O (60 mL). The resulting slurry was stirred overnight at room temperature. The solid was collected via filtration and rinsed with Et₂O (30 mL) to afford the title compound (4.32 g, 78% yield) as a light-yellow solid.

LCMS (Method 1): MS (ESI) m/z 127.0 $[M+H]^+$.

Step 2. Synthesis of 1-(3-(neopentyloxy)-1H-pyrazol-1-yl)ethan-1-one

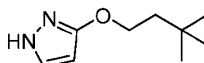
[289] To a stirred solution of 1-(3-hydroxy-1H-pyrazol-1-yl)ethan-1-one (4.32 g, 34.29 mmol) in THF (100 mL) were added at room temperature 2,2-dimethylpropan-1-ol (3.00 g, 34.29 mmol), PPh₃ (9.88 g, 37.72 mmol) and DIAD (7.62 g, 37.72 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with water (50 mL) and extracted with EA (30 mL × 3). The combined organic extracts were washed with brine (20 mL × 2), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with EA:PE = 1:10) to afford the title compound (3.3 g, 49% yield) as a light-yellow solid.

LCMS (Method 1): MS (ESI) *m/z* 197 [M+H]⁺.

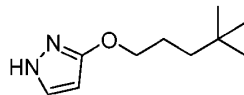
Step 3. Synthesis of 3-(neopentyloxy)-1H-pyrazole

[290] To a stirred solution of 1-(3-(neopentyloxy)-1H-pyrazol-1-yl)ethan-1-one (3.3 g, 16.84 mmol) in MeOH/H₂O (30 mL/ 3 mL) was added NaOH (673 mg, 16.84 mmol) at room temperature. The solution was stirred at room temperature for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (20 mL × 3). The combined organic extracts were washed with brine (20 mL × 2), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with EA : PE = 1 : 5) to afford the title compound (2.0 g, 80% yield) as a yellow oil.

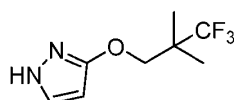
LCMS (Method 1): MS (ESI) *m/z* 155 [M+H]⁺.

Intermediate B-26:*3-(3,3-Dimethylbutoxy)-1H-pyrazole*

[291] **Intermediate B-26** was prepared from 1-(3-hydroxy-1H-pyrazol-1-yl)ethan-1-one (from Step 1, preparation of **Intermediate B-25**) by following the procedures of Steps 2 and 3 above, except for using 2,2-dimethylpropan-1-ol instead of 2,2-dimethylpropan-1-ol in Step 2. LCMS (Method 1): MS (ESI) *m/z* 169.1 [M+H]⁺.

Intermediate B-27:*3-((4,4-Dimethylpentyl)oxy)-1H-pyrazole*

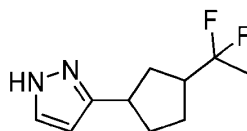
[292] **Intermediate B-27** was prepared from 1-(3-hydroxy-1H-pyrazol-1-yl)ethan-1-one (from Step 1, preparation of **Intermediate B-25**) by following the procedures of Steps 2 and 3 above, except for using 4,4-dimethylpentan-1-ol instead of 2,2-dimethylpropan-1-ol in Step 2. LCMS: MS (ESI) m/z 183 [M+H]⁺.

Intermediate B-28:*3-(3,3,3-Trifluoro-2,2-dimethylpropoxy)-1H-pyrazole*

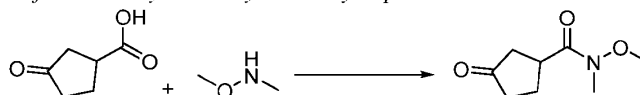
[293] **Intermediate B-28** was prepared from 1-(3-hydroxy-1H-pyrazol-1-yl)ethan-1-one (from Step 1, preparation of **Intermediate B-25**) by following the procedures of Steps 2 to 3 above, except for using 3,3,3-trifluoro-2,2-dimethylpropan-1-ol instead of 2,2-dimethylpropan-1-ol in Step 2.

LCMS (Method 1): LC retention time = 1.58 min. MS (ESI) m/z 208.8 [M+H]⁺.

¹H NMR (400 MHz, chloroform-*d*) δ 7.37 (s, 1H), 5.76 (s, 1H), 4.13 (s, 2H), 1.26 (s, 6H) ppm.

Intermediate B-29:*3-(3-(1,1-Difluoroethyl)cyclopentyl)-1H-pyrazole*

Step 1. Synthesis of N-methoxy-N-methyl-3-oxocyclopentane-1-carboxamide



[294] To a stirred solution of 3-oxocyclopentane-1-carboxylic acid (3.50 g, 27.3 mmol) in DCM (20 mL) were added oxalyl chloride (6.93 g, 54.6 mol) and DMF (0.2 mL). After the reaction was stirred at rt for 2 h, the solvent was removed. The residue was dissolved in DCM (30 mL). To this solution were added DIPEA (7.06 g, 54.6 mol) and N,O-

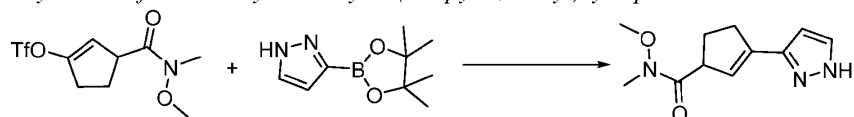
dimethylhydroxylamine (2.00 g, 32.8 mmol). The reaction was stirred at rt for 16 h and concentrated in *vacuo* to afford the title compound (4.20 g, 89.8% yield) as a yellow solid. The crude product was used immediately in the next step without further purification and characterization.

Step 2. Synthesis of 3-(methoxy(methyl)carbamoyl)cyclopent-1-en-1-yl trifluoromethanesulfonate



[295] To a solution of N-methoxy-N-methyl-3-oxocyclopentane-1-carboxamide (3.60 g, 0.021 mol) in anhydrous THF (150 mL) was slowly added LDA (27 mL, 1M in THF, 27 mol) at -78 °C. The mixture was stirred at -78 °C for 2 h. A solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (9.02 g, 25.2 mmol) in anhydrous THF (50 mL) was added. The mixture was warmed to 0 °C and stirred overnight. The mixture was poured into saturated aqueous NH₄Cl (30 mL) and extracted with Et₂O (80 mL × 3). The combined organic extracts were washed with water (50 mL) and brine (80 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to afford the title compound (5.00 g, 78.5 % yield) as a yellow solid. The crude product was used immediately in the next step without further purification and characterization.

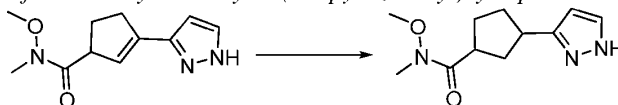
Step 3. Synthesis of N-methoxy-N-methyl-3-(1H-pyrazol-3-yl)cyclopent-2-ene-1-carboxamide



[296] To a stirred solution of 3-(methoxy(methyl)carbamoyl)cyclopent-1-en-1-yl trifluoromethanesulfonate (3.5 g, 11.5 mmol) in toluene/ethanol/H₂O (175 mL, v/v/v = 4/2/1) were added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.79 g, 9.23 mmol), Pd(Ph₃P)₄ (1.33 g, 1.15 mmol) and K₂CO₃ (3.19 g, 23.1 mmol). The resulting mixture was stirred overnight at 80 °C under an argon atmosphere. The mixture was filtered, and the filtrate was concentrated in *vacuo*. The residue was suspended in water (100 mL) and brine (100 mL). The aqueous mixture was extracted with ethyl acetate (100 mL × 3), the combined extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated. The crude product was purified by reverse phase flash column chromatography to afford the title compound (1.3 g, 50.9% over 3 steps) as a light-yellow oil.

LCMS (Method 1): MS (ESI) *m/z* 222.0 [M+H]⁺.

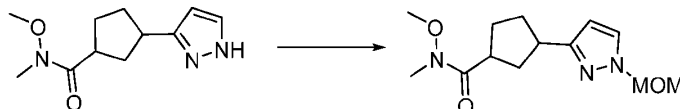
Step 4. Synthesis of N-methoxy-N-methyl-3-(1H-pyrazol-3-yl)cyclopentane-1-carboxamide



[297] To a stirred solution of N-methoxy-N-methyl-3-(1H-pyrazol-3-yl)cyclopent-2-ene-1-carboxamide (1.3 g, 5.88 mmol) in ethyl acetate (20 mL) was added Pd/C (0.0625 g, 0.588 mmol). The reaction was stirred at rt under H₂ for 16 h. The solids were filtered off and the filtrate was evaporated to afford the title compound (1.1 g, 83.9% yield) as a yellow solid.

LCMS (Method 1): MS *m/z* 224.1 [M+H]⁺.

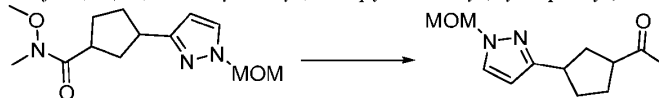
Step 5. Synthesis of N-methoxy-3-(1-(methoxymethyl)-1H-pyrazol-3-yl)-N-methylcyclopentane-1-carboxamide



[298] To a stirred solution of N-methoxy-N-methyl-3-(1H-pyrazol-3-yl)cyclopentane-1-carboxamide (1.1 g, 0.00493 mol) in DMF (20 mL) were added potassium carbonate (1.36 g, 9.85 mmol) and MOM-Br (0.739 g, 5.91 mmol). The reaction mixture was stirred at rt for 16 h, cooled and concentrated to dryness. The residue was purified by prep-HPLC to afford the title compound (1.20 g, 91% yield) as a yellow solid.

LCMS (Method 1): MS (ESI) *m/z* 268.0 [M+H]⁺.

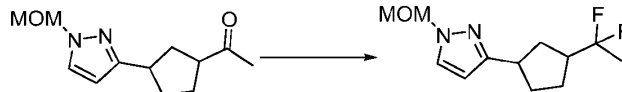
Step 6. Synthesis of 1-(3-(1-(methoxymethyl)-1H-pyrazol-3-yl)cyclopentyl)ethan-1-one



[299] To a stirred solution of N-methoxy-3-(1-(methoxymethyl)-1H-pyrazol-3-yl)-N-methylcyclopentane-1-carboxamide (1.20 g, 4.49 mmol) in THF (50 mL) was slowly added CH₃MgBr (4.49 mL, 13.5 mol) at 0 °C. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The residue was purified by prep-HPLC to afford the title compound (0.83 g, 83.0% yield) as a yellow solid.

LCMS (Method 1): MS (ESI) *m/z* 223.0 [M+H]⁺.

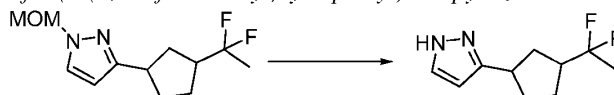
Step 7. Synthesis of 3-(3-(1,1-difluoroethyl)cyclopentyl)-1-(methoxymethyl)-1H-pyrazole



[300] To a stirred solution of 1-(3-(1-(methoxymethyl)-1H-pyrazol-3-yl)cyclopentyl)ethan-1-one (0.73 g, 3.28 mmol) in DCM (5 mL) was added DAST (2.18 g, 9.85 mol). The reaction mixture was stirred at rt for 16 h, the solvent was evaporated, and the residue was purified by prep-HPLC to afford the title compound (0.25 g, 31.0% yield) as a yellow solid.

LCMS (Method 1): MS (ESI) m/z 245 $[M+H]^+$.

Step 8. Synthesis of 3-(3-(1,1-difluoroethyl)cyclopentyl)-1H-pyrazole

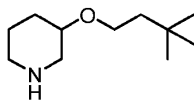


[301] To a stirred solution of 3-(3-(1,1-difluoroethyl)cyclopentyl)-1-(methoxymethyl)-1H-pyrazole (0.2 g, 0.819 mmol) in MeOH (5 mL) was added aqueous dilute HCl (0.5 mL). The reaction mixture was stirred at 60 °C for 16 h, concentrated, and the residue purified by prep-HPLC to afford the title compound (0.11 g, 67.1% yield) as a yellow solid.

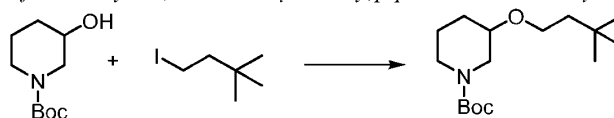
LCMS (Method 1): MS (ESI) m/z 201.0 $[M+H]^+$.

Intermediate B-30:

3-(3,3-Dimethylbutoxy)piperidine



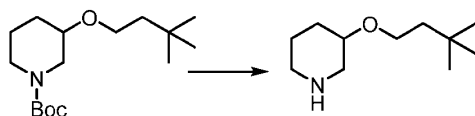
Step 1. Synthesis of *tert*-butyl 3-(3,3-dimethylbutoxy)piperidine-1-carboxylate



[302] To a chilled (0 °C) solution of *tert*-butyl 3-hydroxypiperidine-1-carboxylate (1.00 g, 5.0 mmol) in DMF (10 mL) was added NaH (400 mg, 10.0 mmol, 60% dispersion in oil). The reaction mixture was stirred at rt for 30 min and 1-iodo-3,3-dimethylbutane (1.40 g, 6.5 mmol) was added. The stirred mixture was allowed to warm from 0 °C to rt over 16 h. To the reaction mixture was added water (50 mL). The aqueous solution was extracted with EA (50 mL x 2). The organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography using PE : EA (10 : 1) as eluent to give the title compound (130 mg, 7.0 % yield) as a colorless oil.

LCMS (Method 1): MS (ESI) m/z 308 $[M+Na]^+$.

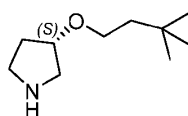
Step 2. Synthesis of 3-(3,3-dimethylbutoxy)piperidine



[303] To a stirred solution of *tert*-butyl 3-(3,3-dimethylbutoxy)piperidine-1-carboxylate (130 mg, 0.5 mmol) in DCM (2 mL) was added HCl in dioxane (4M, 2 mL). The reaction mixture was stirred at rt for 1 h, and concentrated to afford the title compound (80 mg, 95% yield) as a white solid.

Intermediate B-31:

(S)-3-(3,3-Dimethylbutoxy)pyrrolidine hydrochloride

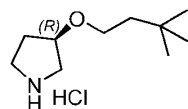


[304] **Intermediate B-31** was prepared by following the procedure for the preparation of **Intermediate B-30** except for using *tert*-butyl (S)-3-hydroxypyrrolidine-1-carboxylate instead of *tert*-butyl 3-hydroxypiperidine-1-carboxylate in Step 1.

LCMS (Method 1): MS (ESI) m/z 172.0 [M+H]⁺

Intermediate B-32:

(R)-3-(3,3-Dimethylbutoxy)pyrrolidine hydrochloride

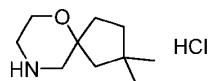


[305] **Intermediate B-32** was prepared by following the procedure for the preparation of **Intermediate B-30** except for using *tert*-butyl (R)-3-hydroxypyrrolidine-1-carboxylate instead of *tert*-butyl 3-hydroxypiperidine-1-carboxylate in Step 1.

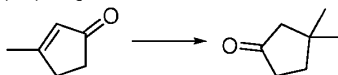
LCMS (Method 1): MS (ESI) m/z 172.0 [M+H]⁺.

Intermediate B-33:

2,2-Dimethyl-6-oxa-9-azaspiro[4.5]decane hydrochloride

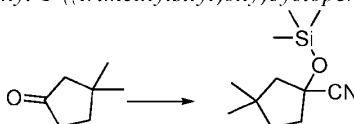


Step 1. Synthesis of 3,3-dimethylcyclopentan-1-one



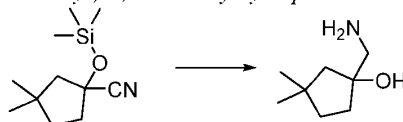
[306] To a suspension of CuI (6.85 g, 36.0 mmol) in anhydrous ether (100 mL) was added a solution of methyllithium in diethoxy methane (1.6 M, 47 mL, 75 mmol) at 0 °C over a period of 30 min. The mixture was stirred at 0 °C for 30 min. To the above mixture was added 3-methylcyclopent-2-en-1-one (2.88 g, 30.0 mmol) dropwise over a period of 30 min at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction was then quenched with saturated aqueous NH₄Cl (150 mL) and filtered. The filtrate was extracted with ether (100 mL × 2). The combined organic extracts were dried over anhydrous Mg₂SO₄ and filtered. The filtrate was evaporated under reduced pressure to obtain the title compound. This crude product was used immediately in the next step without further purification and characterization.

Step 2. Synthesis of 3,3-dimethyl-1-((trimethylsilyl)oxy)cyclopentane-1-carbonitrile



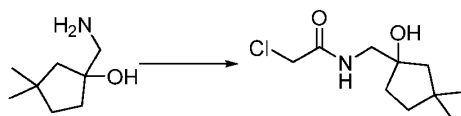
[307] To a solution of 3,3-dimethylcyclopentan-1-one (2.52 g, 22.5 mmol) in 30 mL of THF were added at 0 °C trimethylsilylformonitrile (3.35 g, 33.8 mmol) and ZnI₂ (72 mg, 0.225 mmol). The mixture was stirred for 3 hours at 0 °C and for 3 hours at 60 °C. The resulting solids were filtered off. The filtrate was concentrated to obtain the title compound. This crude product was used immediately in the next step without further purification and characterization.

Step 3. Synthesis of 1-(aminomethyl)-3,3-dimethylcyclopentan-1-ol



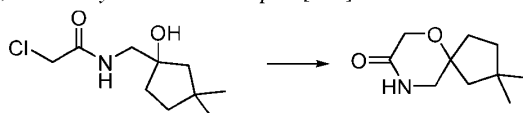
[308] To a solution of 3,3-dimethyl-1-((trimethylsilyl)oxy)cyclopentane-1-carbonitrile (4.76 g, 22.5 mmol) in 50 mL of THF was added a solution of lithium aluminum hydride in THF (27 mL, 1 M, 27 mmol) dropwise at 0 °C under an argon atmosphere. After stirring for 16 h at room temperature, an aqueous sodium hydroxide solution (20 %) was added slowly with cooling. The solid was filtered off after dilution with ethyl acetate (30 mL). The filtrate was evaporated to give the title compound (3.23 g, 22.6 mmol, 100% yield) as a semi-solid. LCMS (Method 1): LC retention time = 1.314 min. MS (ESI) m/z 144 [M+H]⁺.

Step 4. Synthesis of 2-chloro-N-((1-hydroxy-3,3-dimethylcyclopentyl)methyl)acetamide



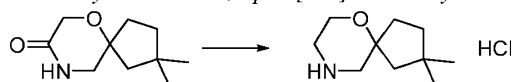
[309] To a solution of potassium carbonate (6.22 g, 45.1 mmol) in water (30 mL) was added to a solution of 1-(aminomethyl)-3,3-dimethylcyclopentan-1-ol (3.23 g, 22.6 mmol) in ethyl acetate (30 mL). The mixture was cooled to 0 °C, and then treated dropwise with 2-chloroacetyl chloride (2.8 g, 24.8 mmol). After completion of the addition, the reaction mixture was warmed to 25 °C and allowed to stir for 16 h. The aqueous solution was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in *vacuo* to give the title compound. This crude product was used immediately in the next step without further purification and characterization.

Step 5. Synthesis of 2,2-dimethyl-6-oxa-9-azaspiro[4.5]decan-8-one



[310] To a suspension of tBuOK in *tert*-butanol (40 mL) was added 2-chloro-N-((1-hydroxy-3,3-dimethylcyclopentyl)methyl)acetamide (4.95 g, 22.5 mmol) in THF (30 mL) over 30 min. The resulting mixture was stirred at room temperature for 16 h before it was concentrated. The residue was diluted with EA and water, the organic layer was separated, washed with brine, and concentrated to give the title compound. This crude product was used immediately in the next step without further purification and characterization.

Step 6. Synthesis of 2,2-dimethyl-6-oxa-9-azaspiro[4.5]decane hydrochloride



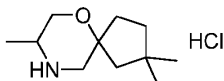
[311] To a solution of 2,2-dimethyl-6-oxa-9-azaspiro[4.5]decan-8-one (4.13 g, 22.5 mmol) in THF (50 mL) was added at room temperature borane-tetrahydrofuran (7.75 g, 90.2 mmol). The reaction mixture was then refluxed for 2 h and cooled to room temperature. MeOH was carefully added. The mixture was concentrated under reduced pressure. To the residue was added MeOH (50 mL) and N,N,N',N'-tetramethylethylenediamine (10.5 g, 90.2 mmol), and the reaction was stirred at 78°C overnight. The reaction mixture was concentrated, and the residue was diluted with ethyl acetate and water. The organic phase was separated, washed with brine, and concentrated in *vacuo* to give a crude product. To the crude product was added HCl-

dioxane (5 mL) and stirring continued at rt for 1 h. Concentration of the resulting mixture afforded the title compound (566 mg, 7 % yield over 6 steps) as a yellow solid.

LCMS (acidic): LC retention time = 1.421 min. MS (ESI): m/z 170 $[M+H]^+$.

Intermediate B-34:

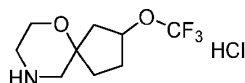
2,2,8-Trimethyl-6-oxa-9-azaspiro[4.5]decane hydrochloride



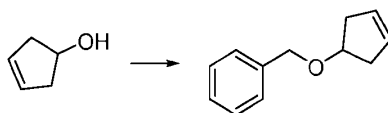
[312] **Intermediate B-34** was synthesized in same manner as **Intermediate B-33**.

Intermediate B-35:

2-(Trifluoromethoxy)-6-oxa-9-azaspiro[4.5]decane hydrochloride



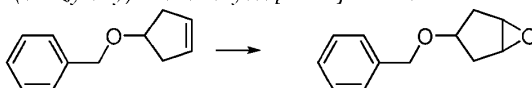
Step 1. Synthesis of ((cyclopent-3-en-1-yloxy)methyl)benzene



[313] To a cooled and stirred suspension of sodium hydride (2.85 g, 71.3 mmol, 60% in paraffin oil) in 30 mL dry toluene was added slowly under a N_2 atmosphere a solution of cyclopent-3-en-1-ol (4.00 g, 47.6 mmol) in toluene (10 mL). After gas evolution ceased, a solution of benzyl bromide (8.94 g, 52.3 mmol) in toluene (20 mL) was added dropwise and the resulting mixture was refluxed for 12 h. Methanol in toluene was added in small portions to decompose residual NaH. The reaction mixture was partitioned between water and ethyl acetate (20 mL each) and the two phases were separated. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (eluting with PE) to afford the title compound (8.0 g, 96.6% yield) as a yellow oil.

LCMS (acidic): LC retention time = 2.179 min; MS (ESI) signal not observed.

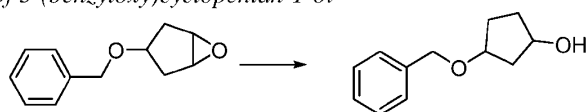
Step 2. Synthesis of 3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane



[314] To a stirred solution of [(cyclopent-3-en-1-yloxy)methyl]benzene (8.00 g, 45.9 mmol) in DCM (80 mL) at 0 °C was added meta-chloroperoxybenzoic acid (8.69 g, 50.5 mmol) in

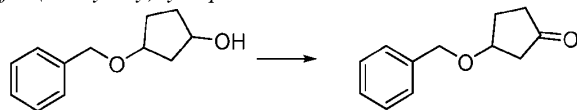
one portion. The reaction mixture was stirred at 0 °C for 2 h before it was slowly warmed to room temperature. The reaction mixture was slowly quenched with a 1:1 mixture of saturated aqueous NaHSO₃ and NaHCO₃ solutions (150 mL), diluted with ethyl acetate and the two phases were separated. The aqueous phase was extracted with ethyl acetate (100 mL × 2). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with a 0-5% EA in PE gradient) to afford the title compound (7.06 g, 80.8%) as a yellow oil. LCMS (acidic): LC retention time = 1.875, 1.948 min. MS (ESI) *m/z* 213 [M+Na]⁺.

Step 3. Synthesis of 3-(benzyloxy)cyclopentan-1-ol



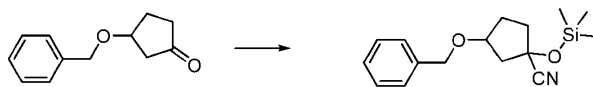
[315] To a solution of 3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane (7.06 g, 37.1 mmol) in 80 mL of THF was added a solution of LiAlH₄ (44.5 mL, 44.5 mmol, 1.0 M in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quickly warmed to room temperature over 5 min. To this mixture was added Celite/Na₂SO₄·10H₂O (1:1, 100 g) until gas stopped evolving. The solid was dissolved in diethyl ether and filtered through a plug of Celite. The filtrate was concentrated to give the title compound (3.44 g, 48.2%) as a yellow oil. LCMS (acidic): LC retention time = 1.83 min. MS (ESI) *m/z* 193 [M+H]⁺.

Step 4. Synthesis of 3-(benzyloxy)cyclopentan-1-one



[316] To a stirred solution of 3-(benzyloxy)cyclopentan-1-ol (3.44 g, 17.9 mmol) in 40 mL of THF was added Dess-Martin periodinane (15.20 g, 35.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched slowly with a mixture of saturated aqueous NaHSO₃ and NaHCO₃ solutions (1:1, 100 mL), diluted with ethyl acetate, and the two phases were separated. The aqueous phase was extracted with ethyl acetate (150 mL × 2). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford the title compound (2.67 g, 78.5%) as a yellow oil. LCMS (acidic): LC retention time = 1.896 min. MS (ESI) *m/z* 191 [M+H]⁺.

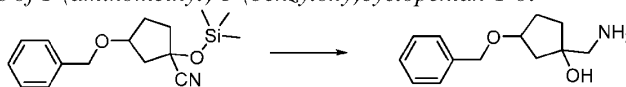
Step 5. Synthesis of 3-(benzyloxy)-1-((trimethylsilyl)oxy)cyclopentane-1-carbonitrile



[317] To a solution of 3-(benzyloxy)cyclopentan-1-one (2.10 g, 11.0 mmol) in 25 mL of THF were added at 0 °C trimethylsilylformonitrile (1.75 g, 17.7 mmol) and ZnI₂ (352 mg, 1.10 mmol). The mixture was stirred at 0 °C for 6 h and at 60 °C for 16 h. The solids were filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluting with PE: EA = 20: 1) to give the title compound (2.25 g, 70.4%) as a yellow oil.

LCMS (acidic): LC retention time = 2.66 min. MS (ESI) m/z 312 [M+Na]⁺.

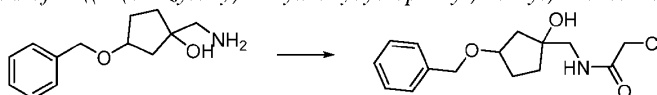
Step 6. Synthesis of 1-(aminomethyl)-3-(benzyloxy)cyclopentan-1-ol



[318] To a solution of 3-(benzyloxy)-1-((trimethylsilyl)oxy)cyclopentane-1-carbonitrile (2.25 g, 7.77 mmol) in 15 mL of tetrahydrofuran was added dropwise under an argon atmosphere at 0 °C a solution of lithium aluminum hydride in tetrahydrofuran (9.33 mL, 9.33 mmol). After stirring for 16 h at room temperature, an aqueous sodium hydroxide solution (20 %) was added slowly with cooling. The solids were filtered off after dilution with ethyl acetate and the filtrate was concentrated to give the title compound (1.60 g, 93.0%) as a yellow oil.

LCMS (acidic): LC retention time = 1.296 min. MS (ESI) m/z 222 [M+H]⁺.

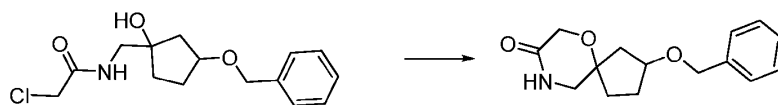
Step 7. Synthesis of N-((3-(benzyloxy)-1-hydroxycyclopentyl)methyl)-2-chloroacetamide



[319] To a solution of potassium carbonate (2.0 g, 14.5 mmol) in water (15 mL) was added to a solution of 1-(aminomethyl)-3-(benzyloxy)cyclopentan-1-ol (1.60 g, 7.23 mmol) in ethyl acetate (15 mL). The mixture was cooled to 0 °C, and then treated with 2-chloroacetyl chloride (980 mg, 8.68 mmol). After completion of the addition, the reaction mixture was warmed to 25 °C and allowed to stir for 16 h. The aqueous solution was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (1.90 g, 88.2%) as a yellow oil.

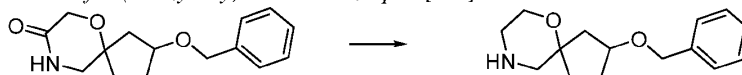
LCMS (acidic): LC retention time = 1.86 min. MS (ESI) m/z 298 [M+H]⁺.

Step 8. Synthesis of 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decan-8-one



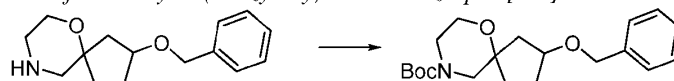
[320] To a solution of potassium *tert*-butoxide (1.43 g, 12.8 mmol) in *tert*-butanol (15 mL) was added N-((3-(benzyloxy)-1-hydroxycyclopentyl)methyl)-2-chloroacetamide (1.90 g, 6.38 mmol) in THF (15 mL) over 10 min, and the resulting mixture was stirred for 16 h at room temperature before it was concentrated. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was isolated, washed with brine (50 mL $\times$ 2), and concentrated to provide the title compound (1.50 g, 90.0%) as a light-yellow oil. LCMS (acidic): LC retention time = 1.81, 1.84 min (mixture of 2 diastereomers). MS (ESI) m/z 262 [M+H]⁺.

Step 9. Synthesis of 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decane



[321] To a solution of 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decane-8-one (1.30 g, 4.97 mmol) in THF (15 mL) was added at room temperature borane-tetrahydrofuran (14.9 mL, 14.9 mmol). The reaction mixture was refluxed for 2 h, then cooled to room temperature. MeOH was carefully added, and the solvent was evaporated under reduced pressure. To the residue was added MeOH (15 mL) and N,N,N',N'-tetramethylethylenediamine (2.31 g, 19.9 mmol). The reaction was stirred at 75 °C overnight. The reaction mixture was concentrated, and the residue was diluted with ethyl acetate (50 mL) and water (50 mL), and the two phases were separated. The organic phase was washed with brine (50 mL $\times$ 2) and concentrated in *vacuo* to give the title compound (1.15 g, 93.5%) as a yellow oil. LCMS (acidic): LC retention time = 1.531, 1.558 min (mixture of 2 diastereomers). MS (ESI) m/z 248 [M+H]⁺.

Step 10. Synthesis of tert-butyl 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decane-9-carboxylate

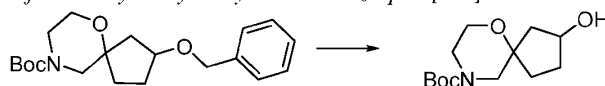


[322] To a solution of 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decane (1.20 g, 4.85 mmol) in 1,4-dioxane (10 mL) and H₂O (10 mL) were added di-*tert*-butyl dicarbonate (3.18 g, 14.6 mmol) and Na₂CO₃ (1.54 g, 14.6 mmol). The resulting mixture was stirred at room temperature overnight. The reaction solution was concentrated. The residue was dissolved in EA (50 mL). The EA solution was washed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated.

The residue was purified by silica gel column chromatography (eluting with PE: EA = 5: 1) to give the title compound (1.20 g, 71.2%) as a yellow oil.

LCMS (acidic): LC retention time = 2.205, 2.242 min (mixture of 2 diastereomers). MS (ESI) m/z 292 [M-tBu]⁺

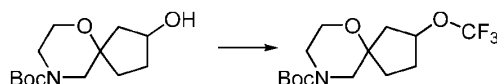
Step 11. Synthesis of tert-butyl 2-hydroxy-6-oxa-9-azaspiro[4.5]decane-9-carboxylate



[323] To a solution of *tert*-butyl 2-(benzyloxy)-6-oxa-9-azaspiro[4.5]decane-9-carboxylate (1.20 g, 3.45 mmol) in ethyl acetate (25 mL) was added Pd/C. The flask was attached to a hydrogenation apparatus. The flask was agitated under a hydrogen atmosphere for 5 h. The catalyst was filtered off. The filtrate was concentrated to give the title compound (810 mg, 91.1%) as a colorless oil.

LCMS (acidic): LC retention time = 1.736 min. MS (ESI) m/z 202 [M-t-Bu]⁺.

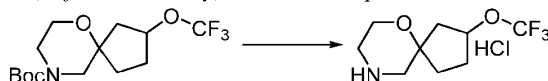
Step 12. Synthesis of tert-butyl 2-(trifluoromethoxy)-6-oxa-9-azaspiro[4.5]decane-9-carboxylate



[324] A flask was charged with silver triflate (1.65 g, 6.41 mmol), Select-F[®] (1.14 g, 3.21 mmol), KF (497 mg, 8.55 mmol) and *tert*-butyl 2-hydroxy-6-oxa-9-azaspiro[4.5]decane-9-carboxylate (550 mg, 2.14 mmol). The flask was purged with argon. Ethyl acetate (15 mL) was added, followed by TMSCF₃ (912 mg, 6.41 mmol) and 2-fluoropyridine (623 mg, 6.41 mmol). The reaction mixture was stirred at room temperature overnight under an argon atmosphere, then filtered through a Celite pad. The filtrate was concentrated and purified by flash chromatography on silica gel (eluting with PE) to afford the title compound (420 mg, 60.4 %) as a yellow oil.

LCMS: LC retention time = 2.170 min. MS (ESI) m/z 270 [M-t-Bu]⁺.

Step 13. Synthesis of 2-(trifluoromethoxy)-6-oxa-9-azaspiro[4.5]decane hydrochloride



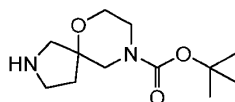
[325] To a solution of *tert*-butyl 2-(trifluoromethoxy)-6-oxa-9-azaspiro[4.5]decane-9-carboxylate (650 mg, 2.0 mmol) in dioxane (1 mL) was added HCl-dioxane (10 mL). The

solution was stirred at room temperature for 2 h. The mixture was concentrated to give the title compound (523 mg, 100% yield) as a yellow oil.

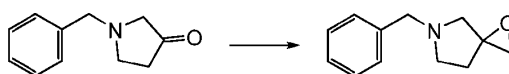
LCMS (Method 1): LC retention time = 1.28 min. MS (ESI) m/z 226 [M+H]⁺.

Intermediate B-36:

tert-Butyl 6-oxa-2,9-diazaspiro[4.5]decane-9-carboxylate



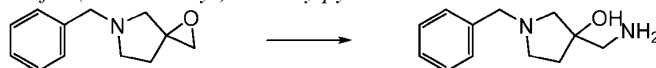
Step 1. Synthesis of 5-benzyl-1-oxa-5-azaspiro[2.4]heptane



[326] To a suspension of NaH (3.01 g, 60% dispersion in oil, 75.33 mmol) in DMSO (120 mL) was added trimethylsulfoxonium iodide (19.59 g, 89.03 mmol) followed by 1-benzylpyrrolidin-3-one (12.00 g, 68.48 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched by the addition of water (500 mL) and extracted with ethyl acetate (500 mL $\times$ 2). The combined extracts were washed with water (300 mL $\times$ 2), dried over Na₂SO₄, filtered, and concentrated to afford the title compound (12.00 g, 92.6 %) as a brown oil.

LCMS: LC retention time = 1.370 min. MS (ESI) m/z 190 [M+H]⁺.

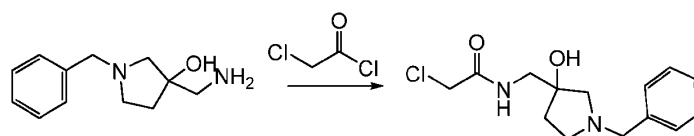
Step 2. Synthesis of 3-(aminomethyl)-1-benzylpyrrolidin-3-ol



[327] To a solution of 5-benzyl-1-oxa-5-azaspiro[2.4]heptane (12.00 g, 63.4 mmol) in 60 mL of MeOH was added dropwise at 0 °C 90 mL of 28% aqueous NH₄OH. The reaction mixture was stirred at room temperature overnight, concentrated, and diluted with 500 mL of ethyl acetate. The two phases were separated, and the organic phase was washed with water (200 mL $\times$ 2), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica (eluting with a 0-10% gradient of MeOH in DCM) to give the title compound (5.93 g, 45.3 %) as a yellow oil.

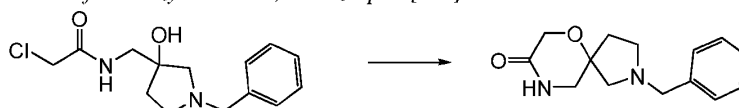
LCMS (Method 1): LC retention time = 1.10 min. MS (ESI) m/z 207 [M+H]⁺.

Step 3. Synthesis of N-((1-benzyl-3-hydroxypyrrolidin-3-yl)methyl)-2-chloroacetamide



[328] Triethylamine was added dropwise under Ar to a stirred, chilled (-20 °C) solution of 3-(aminomethyl)-1-benzylpyrrolidin-3-ol (6.08 g, 29.5 mmol) in DCM (50 mL) (8.95 g, 88.4 mmol) followed by 2-chloroacetyl chloride (3.33 g, 29.5 mmol). The reaction mixture was stirred at -20 °C for 0.5 h and then warmed to r.t for 1 h. The reaction mixture was diluted with DCM (100 mL) and washed with saturated aqueous NH₄Cl solution (100 mL), and brine (100 mL). The organic phase was dried (Na₂SO₄) and concentrated in *vacuo* to give the crude product which was purified by flash column chromatography on silica (eluting with 0-5% MeOH in DCM) to give the title compound (4.70 g, 56% yield) as a yellow oil. LCMS (Method 1): LC retention time = 0.578 min. MS (ESI) *m/z* 283 [M+H]⁺.

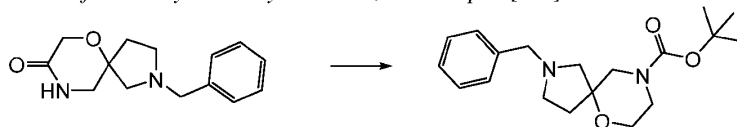
Step 4. Synthesis of 2-benzyl-6-oxa-2,9-diazaspiro[4.5]decan-8-one



[329] To a solution of N-((1-benzyl-3-hydroxypyrrolidin-3-yl)methyl)-2-chloroacetamide (0.35 g, 1.24 mmol, 1.0 eq) in THF (5 mL) was added at 0 °C under Ar a solution of t-BuOK in THF (1.0 M, 1.49 mL, 1.49 mmol, 1.2 eq). The mixture was stirred at the same temperature for 15 min and then at rt for 1 h. The reaction was diluted with H₂O (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated in *vacuo* to give the crude product which was purified by flash chromatography on silica (eluting with 0-5% MeOH in DCM) to give the title compound (178 mg, 58.0% yield) as a white solid.

LCMS (Method 1): LC retention time = 1.251 min. MS (ESI) *m/z* 247 [M+H]⁺.

Step 5. Synthesis of tert-butyl 2-benzyl-6-oxa-2,9-diazaspiro[4.5]decane-9-carboxylate

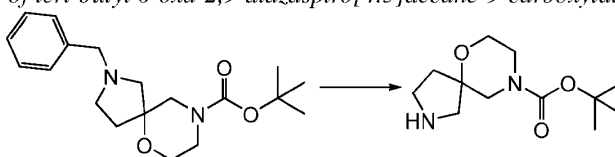


[330] To a stirred solution of 2-benzyl-6-oxa-2,9-diazaspiro[4.5]decan-8-one (2.36 g, 9.58 mmol, 1.0 eq) in THF (150 mL) was added at 0 °C under Ar LiAlH₄ (14.4 mL, 1 M, 14.4 mmol,

1.5 eq) in THF. The mixture was refluxed for 1 h, cooled to 0 °C and quenched by the addition of H₂O (5 mL) and Na₂CO₃ (2.03 g, 19.2 mmol, 2.0 eq). To this solution was added (Boc)₂O (4.18 g, 19.2 mmol, 2.0 eq). The mixture was stirred at rt for 3 h, then diluted with H₂O (200 mL) and extracted with ethyl acetate (200 mL × 2). The combined extracts were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography (eluting with 0-20% ethyl acetate in heptane) to give the title compound (2.59 g, 82.0% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.484 min. MS (ESI) *m/z* 333 [M+H]⁺.

Step 6. Synthesis of tert-butyl 6-oxa-2,9-diazaspiro[4.5]decane-9-carboxylate

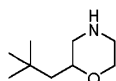


[331] To a solution of *tert*-butyl 2-benzyl-6-oxa-2,9-diazaspiro[4.5]decane-9-carboxylate (3.00 g, 9.0 mmol, 1.0 eq) in MeOH (50 mL) was added at rt Pd/C (10 wt. %, 2.0 g) and ammonium formate (4.00 g, 63.4 mmol, 7.0 eq). The mixture was refluxed for 1 h. The catalyst was removed by filtration and the filtrate was concentrated in *vacuo* to give the title compound (2.0 g, 91.5% yield) as a colorless oil.

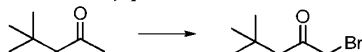
LCMS (Method 1): LC retention time = 1.417 min. MS (ESI) *m/z* 243 [M+H]⁺.

Intermediate B-37:

2-Neopentylmorpholine

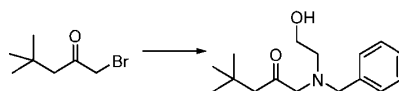


Step 1. Synthesis of 1-bromo-4,4-dimethylpentan-2-one



[332] To a chilled (0 °C) solution of 4,4-dimethylpentan-2-one (1.0 g, 8.76 mmol) in 15 mL of MeOH was added dropwise Br₂ (1.40 g, 8.76 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated to afford the title compound (1.69 g, 100%) as a brown oil. This crude product was used immediately in the next step of the reaction without further purification and characterization.

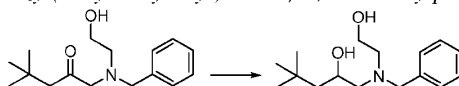
Step 2. Synthesis of 1-(benzyl(2-hydroxyethyl)amino)-4,4-dimethylpentan-2-one



[333] To a solution of 1-bromo-4,4-dimethylpentan-2-one (1.69 g, 8.75 mmol) in 40 mL of CH₃CN were added 2-(benzylamino)ethanol (1.99 g, 13.1 mmol) and K₂CO₃ (1.81 g, 13.1 mmol). The reaction was then heated at 80 °C overnight. The reaction mixture was cooled to rt and concentrated. The residue was dissolved in ethyl acetate (100 mL), the ethyl acetate solution was washed with water (50 mL), brine (50 mL), dried (Na₂SO₄), filtered and concentrated. The residue was purified by prep-TLC to afford the title compound (500 mg, 21.7%) as a yellow oil.

LCMS (Method 1): LC retention time = 1.624 min. MS (ESI) m/z 264 [M+H]⁺.

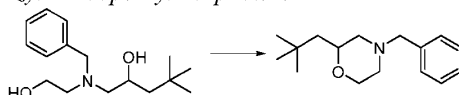
Step 3. Synthesis of 1-(benzyl(2-hydroxyethyl)amino)-4,4-dimethylpentan-2-ol



[334] To a solution of 1-(benzyl(2-hydroxyethyl)amino)-4,4-dimethylpentan-2-one (500 mg, 1.90 mmol) in 10 mL of MeOH was added NaBH₄ (351mg, 9.49 mmol) in portions. The reaction mixture was stirred at room temperature for 5 h, quenched with aqueous NH₄Cl, concentrated, and extracted with ethyl acetate (20 mL × 4). The combined organic extracts were washed with brine, water, dried over Na₂SO₄, filtered, and concentrated to afford the title compound (430 mg, 85.3%) as a yellow oil.

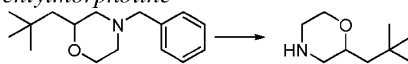
LCMS (Method 1): LC retention time = 1.555 min. MS (ESI) m/z 266 [M+H]⁺.

Step 4. Synthesis of 4-benzyl-2-neopentylmorpholine



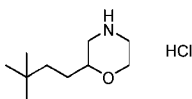
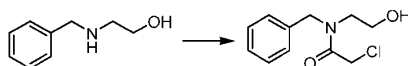
[335] To a solution of 1-(benzyl(2-hydroxyethyl)amino)-4,4-dimethylpentan-2-ol (400 mg, 1.51 mmol) in 10 mL of THF was added at room temperature Ph₃P (1.19 g, 4.52 mmol), followed by the dropwise addition of DIAD (913 mg, 4.52 mmol). The reaction mixture was stirred at room temperature overnight, then quenched through the addition of aqueous NH₄Cl. The aqueous mixture was extracted with ethyl acetate (20 mL × 4). The EA extracts were concentrated to dryness and redissolved in ethyl acetate (50 mL). The solid formed was filtered off. The filtrate was concentrated and purified by silica gel Prep-TLC (eluting with PE: EA = 3:1) to afford the title compound (100 mg, 26.7% yield) as a pink oil.

LCMS (Method 1): LC retention time = 2.047 min. MS (ESI) m/z 248 [M+H]⁺.

Step 5. Synthesis of 2-neopentylmorpholine

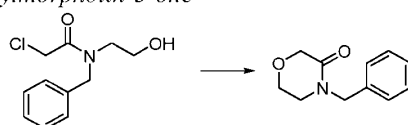
[336] To a solution of 4-benzyl-2-neopentylmorpholine (100 mg, 0.404 mmol) in 30 mL of MeOH was added Pd/C (100 mg, 10 wt. %). The reaction was stirred at room temperature under H₂ for 4 h, the solids were filtered off and the filtrate concentrated to afford 2-neopentylmorpholine (45 mg, 70.8%) as a pink oil.

LCMS (Method 1): LC retention time = 1.529 min. MS (ESI) m/z 158 [M+H]⁺.

Intermediate B-38:*2-(3,3-Dimethylbutyl)morpholine hydrochloride**Step 1. Synthesis of N-benzyl-2-chloro-N-(2-hydroxyethyl)acetamide*

[337] To a solution of 2-(benzylamino)ethan-1-ol (20.00 g, 132 mmol) in 50 mL of DCM were added dropwise a solution of NaOH (5.29 g, 132 mmol) in 50 mL of H₂O and 2-chloroacetyl chloride (14.9 g, 132 mmol). The reaction mixture was stirred at room temperature overnight. The two phases were separated, and the organic layer was washed with water (50 mL). The organic solution was dried over Na₂SO₄, filtered, and concentrated to afford the title compound (29.00 g, 96%) as a yellow oil.

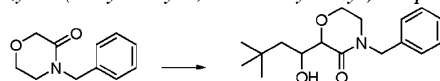
LCMS: LC retention time = 1.523 min. MS (ESI) m/z 228 [M+H]⁺.

Step 2. Synthesis of 4-benzylmorpholin-3-one

[338] To a suspension of t-BuOK (23.70 g, 211 mmol) in 100 mL of t-BuOH was added dropwise a solution of N-benzyl-2-chloro-N-(2-hydroxyethyl)acetamide (24.00 g, 105 mmol) in 100 mL of THF. The reaction mixture was stirred at room temperature for 2 h, and diluted with 180 mL of ethyl acetate. The ethyl acetate solution was washed with water (100 mL × 2), dried over Na₂SO₄, filtered, and concentrated to afford the title compound (18.00 g, 89.3%) as a yellow oil.

LCMS: LC retention time = 1.512 min. MS (ESI) m/z 192 [M+H]⁺.

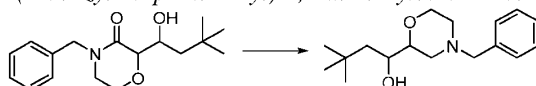
Step 3. Synthesis of 4-benzyl-2-(1-hydroxy-3,3-dimethylbutyl)morpholin-3-one



[339] To a solution of 4-benzylmorpholin-3-one (5.00 g, 26.1 mmol) in 60 mL of THF was added n-BuLi (2.5M in hexane, 12.6 mL, 31.4 mmol) at -78 °C. After stirring at -78 °C for 45 min, 3,3-dimethylbutanal (3.14 g, 31.4 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h, then allowed to warm to room temperature overnight. The reaction mixture was quenched by addition of aqueous NH₄Cl (50 mL). The aqueous suspension was extracted with EA (100 mL × 2). The organic extract was concentrated and the residue purified by flash column chromatography on silica (eluting with a 0-100% EA in PE gradient) to afford the title compound (3.78 g, 49.1 % yield) as a yellow oil.

LCMS: LC retention time = 2.006 min. MS (ESI) m/z 292 [M+H]⁺.

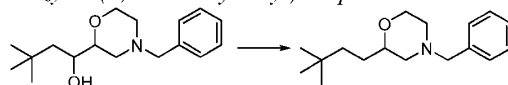
Step 4. Synthesis of 1-(4-benzylmorpholin-2-yl)-3,3-dimethylbutan-1-ol



[340] To a solution of 4-benzyl-2-(1-hydroxy-3,3-dimethylbutyl)morpholin-3-one (3.48 g, 11.9 mmol) in 20 mL of THF was added BH₃·THF (1M in THF, 35.8 mL, 35.8 mmol). The reaction mixture was heated at 55 °C for 2 h, cooled to room temperature, quenched with MeOH (1 mL), and concentrated. The residue was dissolved in MeOH (30 mL). To the methanol solution was added TMEDA (5.54 g, 47.8 mmol), and the solution heated at 80 °C overnight. After cooling to rt, the mixture was concentrated. The residue was dissolved in ethyl acetate (100 mL), the ethyl acetate solution was washed with brine (80 mL × 2), dried (Na₂SO₄), filtered, and concentrated to afford the title compound (3.0 g, 90%) as a yellow oil.

LCMS (Method 1): LC retention time = 1.526 min. MS (ESI) m/z 278 [M+H]⁺.

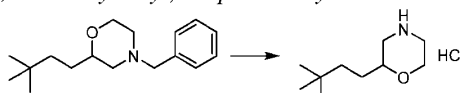
Step 5. Synthesis of 4-benzyl-2-(3,3-dimethylbutyl)morpholine



[341] To a solution of 1-(4-benzylmorpholin-2-yl)-3,3-dimethylbutan-1-ol (1.0 g, 3.60 mmol) in DCM (10 mL) was added DMAP (88 mg, 0.721 mmol) and TEA (728 mg, 7.21 mmol). The reaction mixture was cooled to 0 °C. Tosyl chloride (825 mg, 4.33 mmol) was added in portions. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with water (20 mL), extracted with DCM (30 mL × 2), the DCM extract was washed with water and concentrated. The residue was dissolved in THF (5

mL). To this solution was added LiAlH_4 (1M in THF, 5.84 mL) at 0 °C. The reaction mixture was refluxed overnight, cooled to room temperature, quenched with aqueous Na_2SO_4 solution (2 mL), and filtered. The filter cake was washed with ethyl acetate. The combined filtrates were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by Prep-TLC (eluting with PE: EA = 4:1) to afford the title compound (283 mg, 55.6%) as a yellow oil. LCMS (Method 1): LC retention time = 1.661 min. MS (ESI) m/z 262 $[\text{M}+\text{H}]^+$.

Step 6. Synthesis of 2-(3,3-dimethylbutyl)morpholine hydrochloride

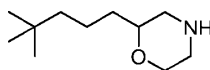


[342] To a solution of 4-benzyl-2-(3,3-dimethylbutyl)morpholine (283 mg, 1.08 mmol) in 50 mL of MeOH was added 500 mg of Pd/C (10 wt. %). The reaction mixture was stirred overnight at room temperature under H_2 . The solids were filtered off, and the filtrate was concentrated. The residue was dissolved in 2 mL of DCM and 5 mL of 4M HCl in dioxane was added. The reaction mixture was stirred at room temperature for 20 min and concentrated, to afford the title compound (200 mg, 88.9%) as a white solid.

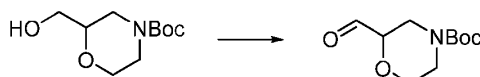
LCMS (Method 1): LC retention time = 1.488 min. MS (ESI) m/z 172 $[\text{M}+\text{H}]^+$.

Intermediate B-39:

2-(4,4-Dimethylpentyl)morpholine



Step 1. Synthesis of tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate

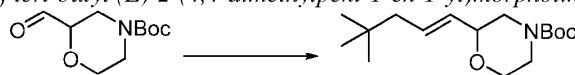


[343] To a stirred solution of oxalyl chloride (1.93 g, 15.2 mmol) in DCM (40 mL) was slowly added DMSO (0.79 mL, 11.0 mmol) at -78 °C. The resulting mixture was stirred for 30 min at this temperature. A solution of *tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (3.00 g, 13.8 mmol) in DCM (10 mL) was added slowly over 10 min and stirred for 1 h. Then TEA (6.29 g, 62.1 mmol) was added dropwise and stirring continued for 0.5 h. The reaction mixture was allowed to warm slowly to rt and quenched with water (30 mL). After extraction with DCM (20 mL $\times$ 3), the combined organic extracts were washed successively with HCl (1 M, 10 mL), saturated aqueous Na_2CO_3 (30 mL), and brine (30 mL). The organic phase was dried

over anhydrous Na_2SO_4 and concentrated in *vacuo* to afford the title compound as a yellow oil (2.0 g, 67.0 % yield).

LCMS (Method 1): LC retention time = 1.49 min; MS (ESI) m/z 160 $[\text{M}-t\text{-Bu}]^+$.

Step 2. Synthesis of tert-butyl (E)-2-(4,4-dimethylpent-1-en-1-yl)morpholine-4-carboxylate

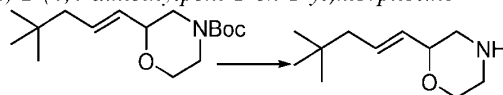


[344] To a chilled (0 °C) solution of (3,3-dimethylbutyl) (triphenyl)phosphonium methanesulfonate (2.05 g, 4.6 mmol) in THF (30 mL) was added sodium hydride (60% dispersion in mineral oil, 223 mg, 9.2 mmol). The mixture was stirred for 30 min. To the reaction mixture was added dropwise a solution of *tert*-butyl 2-formylmorpholine-4-carboxylate (1.0 g, 4.6 mmol) in THF (10 mL), and the mixture was stirred at 50 °C for 4 h. Hydrochloric acid (1N) was added, and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica gel chromatography using PE : EA (20 : 1) as eluent to give the title compound (490 mg, 37.0% yield) as a colorless oil.

LCMS: LC retention time = 2.30 min; MS (ESI) m/z 228 $[\text{M}-t\text{-Bu}]^+$.

^1H NMR (400 MHz, chloroform- d) δ 5.72-7.65 (m, 1H), 5.43-5.38 (m, 1 H), 4.13 (t, J = 8.4 Hz, 1H), 3.88-3.52 (m, 4H), 2.94 (t, J = 11.2 Hz, 1H), 2.68 (s, 1H), 2.01 (d, J = 8.0 Hz, 2H), 1.47 (s, 9H), 0.90 (s, 9H) ppm.

Step 3. Synthesis of (E)-2-(4,4-dimethylpent-1-en-1-yl)morpholine



[345] To a stirred solution of *tert*-butyl (E)-2-(4,4-dimethylpent-1-en-1-yl)morpholine-4-carboxylate (430 mg, 1.4 mmol) in DCM (3 mL) was added HCl/dioxane (4 mL). The reaction was stirred at rt for 1 h and concentrated to give the title compound (250 mg, 90% yield) as a white solid.

LCMS (Method 1): LC retention time = 1.48 min. MS (ESI) m/z 184 $[\text{M}+\text{H}]^+$.

Step 4. Synthesis of 2-(4,4-dimethylpentyl)morpholine

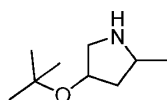


[346] To a solution of (E)-2-(4,4-dimethylpent-1-en-1-yl)morpholine (250 mg, 0.77 mmol) in MeOH (6 mL) were added Pd/C (10%, 100 mg). The reaction mixture was stirred at rt under H₂ for 1 h, the solids filtered off, and the filtrate concentrated to give the title compound (220 mg, 87% yield) as a white solid.

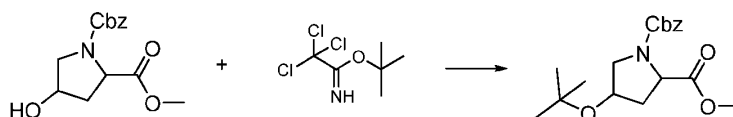
LCMS (Method 1): LC retention time = 1.54 min. MS (ESI) m/z 186 [M+H]⁺.

Intermediate B-40:

4-(tert-Butoxy)-2-methylpyrrolidine



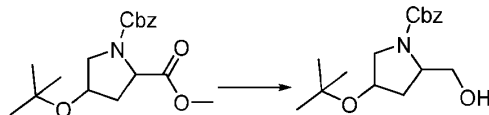
Step 1. Synthesis of 1-benzyl 2-methyl 4-(tert-butoxy)pyrrolidine-1,2-dicarboxylate



[347] To a stirred solution of 1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (5.67 g, 20.3 mmol) in THF (60 mL) was added *tert*-butyl 2,2,2-trichloroethanimidate (3.6 mL). The mixture was stirred at room temperature for 3 h, then additional *tert*-butyl 2,2,2-trichloroethanimidate (3.6 mL) was added and stirring continued for 0.5 h. The remaining amount of *tert*-butyl 2,2,2-trichloroethanimidate (29.1 mL) was added portion wise. After addition was completed, the solution was stirred at room temperature for 48 h. To the reaction mixture was added DCM (60 mL). The mixture was filtered through a Celite plug and the filtrate was concentrated to dryness under reduced pressure to give the crude which was purified by reversed phase silica gel column chromatography to afford the title compound (1.75 g, 25.7 %) as a colorless oil.

LCMS (Method 1): LC retention time = 2.12 min. MS (ESI) m/z 336 [M+H]⁺.

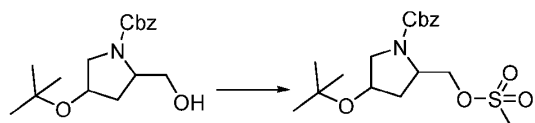
Step 2. Synthesis of benzyl 4-(tert-butoxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate



[348] To a stirred solution of 1-benzyl 2-methyl 4-(*tert*-butoxy)pyrrolidine-1,2-dicarboxylate (1.75 g, 4.17 mmol) in anhydrous tetrahydrofuran (40.0 mL) was added diisobutylaluminum hydride (1M in toluene, 20.9 mL) at -78 °C under an argon atmosphere. The mixture was allowed to warm slowly to room temperature and stirred overnight. Saturated aqueous

potassium sodium tartrate tetrahydrate solution (40 mL) was added and stirring continued for 1 h. The mixture was filtered through a Celite plug. The filtrate was concentrated under reduced pressure. The crude was purified by flash column chromatography on silica (eluting with PE : EA = 2:1) to give the title compound (850 mg, 53.0% yield) as a light-yellow oil. LCMS: LC retention time = 1.99 min. MS (ESI) m/z 308 $[M + H]^+$.

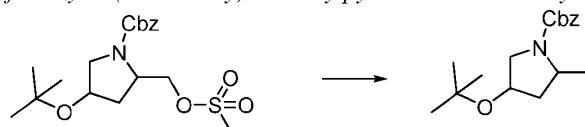
Step 3. Synthesis of benzyl 4-(tert-butoxy)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate



[349] To a chilled (0 °C) solution of benzyl 4-(tert-butoxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (700 mg, 2.28 mmol) in DCM (30 mL) were added mesityl chloride (521 mg, 4.55 mmol) and Et₃N (690 mg, 6.83 mmol). The mixture was stirred at room temperature overnight, concentrated to dryness in *vacuo*, and the residue was dissolved in ethyl acetate (80 mL). The ethyl acetate solution was washed with a saturated aqueous NaHCO₃ solution (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give the crude which was purified by flash column chromatography on silica (eluting with PE : EA = 2 : 1) to afford the title compound (860 mg, 98.0 %) as a colorless oil.

LCMS (Method 1): LC retention time = 2.08 min. MS (ESI) m/z 386 $[M+H]^+$.

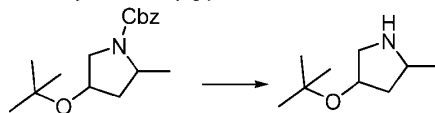
Step 4. Synthesis of benzyl 4-(tert-butoxy)-2-methylpyrrolidine-1-carboxylate



[350] To a solution of benzyl 4-(tert-butoxy)-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (860 mg, 2.23 mmol) in dioxane (30 mL) was added under an argon atmosphere (Bu₄N)BH₄ (2.29 g, 9.92 mmol). The reaction mixture was stirred at 100 °C for 5 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (150 mL). The ethyl acetate solution was washed with water (80 mL) and brine (150 mL). The aqueous phase was back extracted with ethyl acetate (80 mL × 2). The combined organic phases were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give the crude which was purified by silica gel chromatography (eluting with PE : EA = 5 : 1) to afford the title compound (530 mg, 81.5% yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.22 min. MS (ESI) m/z 314 $[M+Na]^+$.

Step 5. Synthesis of 4-(tert-butoxy)-2-methylpyrrolidine

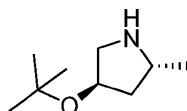


[351] To a solution of benzyl 4-(tert-butoxy)-2-methylpyrrolidine-1-carboxylate (530 mg, 1.82 mmol) in MeOH (20 mL) was added $Pd(OH)_2$ (150 mg). The mixture was stirred at room temperature overnight under a hydrogen atmosphere. The mixture was diluted with MeOH (20 mL) and filtered through a Celite plug. The filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography (eluting with EA) to give the title compound (70 mg, 24.5%) as a light-yellow oil.

LCMS (Method 1): LC retention time = 1.35 min. MS (ESI) m/z 158 $[M+H]^+$.

Intermediate B-41:

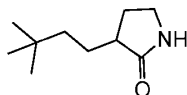
(2R,4R)-4-(tert-Butoxy)-2-methylpyrrolidine



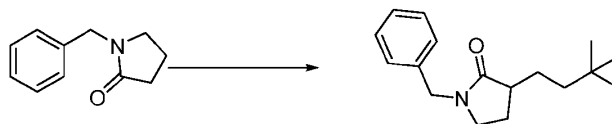
[352] **Intermediate B-41** was prepared in essentially the same way as **Intermediate B-40** described above except for using 1-benzyl 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate instead of 1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate in Step 1.

Intermediate B-42:

3-(3,3-Dimethylbutyl)pyrrolidin-2-one



Step 1. Synthesis of 1-benzyl-3-(3,3-dimethylbutyl)pyrrolidin-2-one

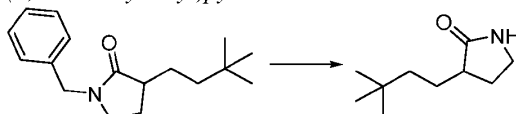


[353] To a solution of diisopropylamine (3.18 g, 31.4 mmol) in THF (50 mL) was added n-BuLi (13.7 mL, 34.2 mmol) at 0 °C and stirred for 0.5 h. The mixture was cooled to -78 °C and 1-benzylpyrrolidin-2-one (5 g, 28.5 mmol) was added. The mixture was stirred for 0.5 h, 1-bromo-3,3-dimethyl-butane (7.07 g, 42.8 mmol) was added, and the reaction was allowed to

warm up slowly to rt with stirring over 16 h. The reaction was quenched with water (2 mL), extracted with ethyl acetate (50 mL). The ethyl acetate extract was washed with brine (50 mL $\times$ 2). The aqueous phase was back extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with EA in PE = 0-10%) to give the title compound (2.90 g, 39.2% yield) as a yellow oil.

LCMS (Method 1): LC retention time = 2.21 min. MS (ESI) m/z 260 $[M+H]^+$.

Step 2. Synthesis of 3-(3,3-dimethylbutyl)pyrrolidin-2-one

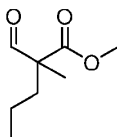


[354] To a solution of 1-benzyl-3-(3,3-dimethylbutyl)pyrrolidin-2-one (1.8 g, 6.9 mmol) in toluene (6 mL) was added trifluoromethanesulfonic acid (4.17 g, 27.8 mmol). The reaction mixture was heated at 195 °C for 40 min in a microwave oven. The mixture was cooled to rt and poured into a saturated aqueous NaHCO_3 solution (10 mL). The resulting suspension was extracted with EA (50 mL). The EA extract was washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with a 60%-100% EA in PE gradient) to give the title compound (500 mg, 42.6% yield) as a yellow solid.

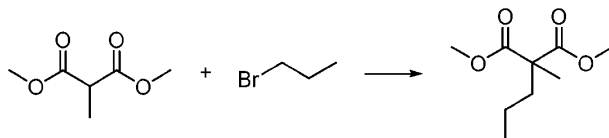
LCMS (Method 1): LC retention time = 1.89 min. MS (ESI) m/z 170 $[M+H]^+$.

Intermediate D-1:

Methyl 2-formyl-2-methyl-pentanoate



Step 1. Synthesis of dimethyl 2-methyl-2-propyl-propanedioate

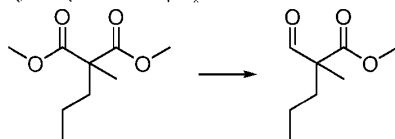


[355] To a solution of dimethyl 2-methylpropanedioate (1.00 eq, 14.00 g, 95.8 mmol) in THF (200 mL) was added sodium hydride (5748 mg, 239 mmol) (60%) at 0 °C. The mixture was stirred for 30 min and 1-bromopropane (23565 mg, 192 mmol) was added to the mixture. The

mixture was stirred at rt for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (200 mL) at 0 °C and extracted with EA (200 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure at 0-10 °C. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 10:1) to give dimethyl 2-methyl-2-propyl-propanedioate (9.50 g, 50.5 mmol, 52.7 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.97 min. MS (ESI) m/z 189.3 $[\text{M}+\text{H}]^+$.

Step 2. Synthesis of methyl 2-formyl-2-methyl-pentanoate

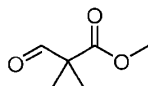


[356] To a solution of dimethyl 2-methyl-2-propyl-propanedioate (20.00 g, 106 mmol) in DCM (200 mL) was added diisobutylaluminum hydride (30224 mL, 213 mmol) (1.0 M in hexanes) at -78 °C under nitrogen. The mixture was stirred at -78°C for 1 h. The reaction was quenched with MeOH (10 mL), diluted with 2M aqueous HCl (200 mL) and extracted with DCM (200 mL). The organic extract was dried over Na_2SO_4 , filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 10:1) to give methyl 2-formyl-2-methyl-pentanoate (6.00 g, 37.9 mmol, 35.7 % yield) as a colorless oil.

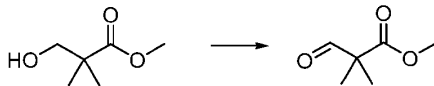
LCMS (Method 1): LC retention time = 2.10 min. MS (ESI) m/z 159.1 $[\text{M}+\text{H}]^+$.

Intermediate D-2:

Methyl 2,2-dimethyl-3-oxo-propanoate



Step 1. Synthesis of methyl 2,2-dimethyl-3-oxo-propanoate



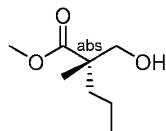
[357] To a solution of methyl 3-hydroxy-2,2-dimethyl-propanoate (CAS# 14002-80-3, 26.00 g, 197 mmol) in DCM (100 mL) was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benzodioxol-3-(1H)-one (83.44 g, 197 mmol) at °C. The mixture was stirred at r.t for 16 h. Then, the solid was filtered off. The filtration cake was washed with DCM. The filtrate was

concentrated in vacuo. The residue was dissolved in hexane. The solid was filtered off again. The filtrate was concentrated in vacuo to give methyl 2,2-dimethyl-3-oxo-propanoate (26.00 g, 160 mmol, 81.2 % yield) as a colorless oil.

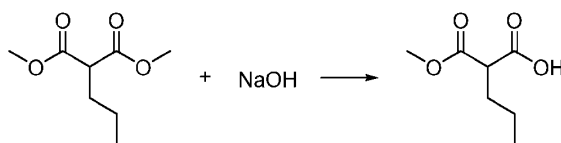
^1H NMR (400 MHz, DMSO- d_6) δ : 9.60 (s, 1H), 3.72 – 3.63 (s, 3H), 1.27 (s, 6H).

Intermediate D-3:

Methyl (2S)-2-(hydroxymethyl)-2-methyl-pentanoate



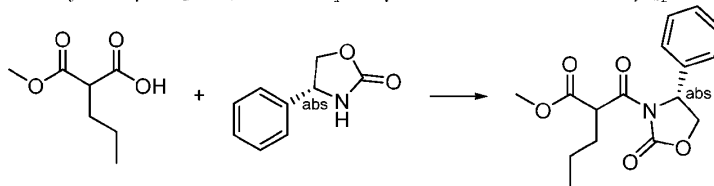
Step 1. Synthesis of 2-methoxycarbonylpentanoic acid



[358] To a solution of dimethyl 2-propylpropanedioate (5000 mg, 28.7 mmol) in methanol (50 mL) and water (10 mL) was added sodium hydroxide (5741 mg, 144 mmol). The mixture was stirred at rt for 16 h. Then solvent was evaporated, and water (30 mL) was added. The pH was adjusted to < 2. The aqueous solution was then extracted with EA (40 mL x 2). The combined organic extracts were washed with brine (30 mL) and concentrated to afford 2-methoxycarbonylpentanoic acid (4500 mg, 28.1 mmol, 97.9 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 1.61 min. MS (ESI) m/z 161.1 $[\text{M}+\text{H}]^+$.

Step 2. Synthesis of methyl 2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate

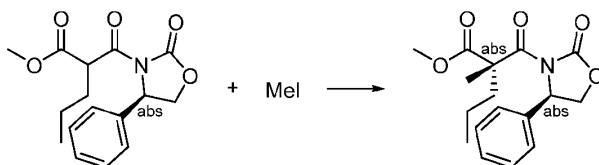


[359] To a solution of 2-methoxycarbonylpentanoic acid (4500 mg, 28.1 mmol) in DCM (50 mL) was added thionyl chloride (4.1 mL, 56.2 mmol). The reaction mixture was stirred at 45 °C for 16 h and concentrated under reduced pressure. The residue was dissolved in DCM (50 mL). To this solution was added (4R)-4-phenyloxazolidin-2-one (5501 mg, 33.7 mmol) and triethylamine (12 mL, 84.3 mmol). The mixture was stirred at rt for 1h and diluted with water (50 mL). The aqueous suspension was extracted with DCM (40 mL x 2). The combined organic extracts were washed with brine (30 mL) and concentrated. The residue was purified by

column chromatography on silica gel (eluting with 0-30% EA in PE) to give methyl 2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate (6000 mg, 19.7 mmol, 69.9 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 1.63 min. MS (ESI) m/z 306.3 [M+H]⁺.

Step 3. Synthesis of methyl (2S)-2-methyl-2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate

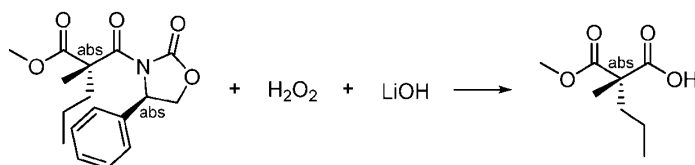


[360] To a suspension of methyl 2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate (10000 mg, 32.8 mmol) and cesium carbonate (26678 mg, 81.9 mmol) in MeCN (100 mL) was added methyl iodide (4.1 mL, 65.5 mmol). The mixture was stirred at 80 °C for 16 h, cooled and diluted with water (50 mL). The aqueous solution was extracted with EA (50 mL × 3). The combined organic extracts were washed with brine (50 mL), and concentrated. The residue was purified by column chromatography on silica gel (eluting with 0-16% EA in PE) to give methyl (2S)-2-methyl-2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate (4000 mg, 12.5 mmol, 38.2 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 1.69 min. MS (ESI) m/z 320.3 [M+H]⁺.

Chiral purity: 97.6%

Step 4. Synthesis of (2S)-2-methoxycarbonyl-2-methyl-pentanoic acid

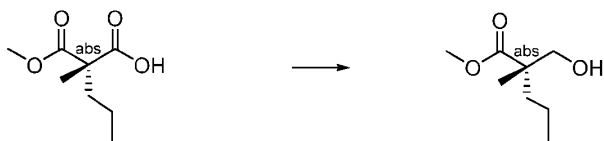


[361] To a solution of methyl (2S)-2-methyl-2-[(4R)-2-oxo-4-phenyl-oxazolidine-3-carbonyl]pentanoate (1000 mg, 3.13 mmol) in THF (9 mL) and water (3 mL) was added hydrogen peroxide (0.38 mL, 12.5 mmol). The mixture was stirred at rt for 1 h and lithium hydroxide (150 mg, 6.26 mmol) was added. The mixture was stirred at rt for 4 h. The reaction was quenched by the addition of saturated aqueous NaHSO₃ (4 mL) and saturated aqueous NaHCO₃ (5 mL). The volatiles were removed under reduced pressure and the residue

was taken up in water (20 mL). The aqueous mixture was then extracted with EA (20 mL $\times$ 2) and discarded. The pH of the aqueous phase was adjusted to < 1 with 2N hydrochloric acid. This aqueous mixture was extracted with EA (30 mL $\times$ 3), the extracts were dried over Na_2SO_4 , and concentrated in vacuo to give (2S)-2-methoxycarbonyl-2-methyl-pentanoic acid (450 mg, 1.29 mmol, 41.3 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 0.77 min. MS (ESI) m/z 175.3 $[\text{M}+\text{H}]^+$.

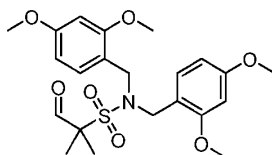
Step 5. Synthesis of methyl (2S)-2-(hydroxymethyl)-2-methyl-pentanoate



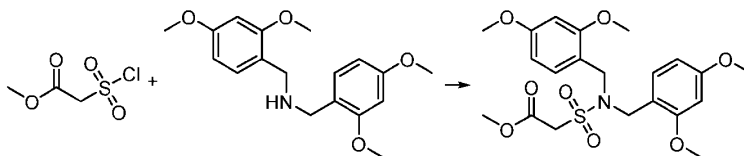
[362] To a solution of (2S)-2-methoxycarbonyl-2-methyl-pentanoic acid (571 mg, 2.30 mmol) and N-methylmorpholine (0.63 mL, 5.74 mmol) in THF (10 mL) was added isobutyl chloroformate (0.60 mL, 4.59 mmol). The mixture was stirred at rt for 4 h. To this solution was slowly added sodium borohydride (434 mg, 11.5 mmol). The reaction mixture was stirred at rt for 6 h then quenched with saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with EA (30 mL $\times$ 3). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography on silica gel (eluting with 0-25% EA in PE) to give methyl (2S)-2-(hydroxymethyl)-2-methyl-pentanoate as a colorless oil (100 mg, 0.624 mmol, 27.2 % yield). LCMS (Method 4): LC retention time = 1.62 min. MS (ESI) m/z 161.2 $[\text{M}+\text{H}]^+$.

Intermediate D-4:

N,N-bis(2,4-dimethoxybenzyl)-2-methyl-1-oxopropane-2-sulfonamide



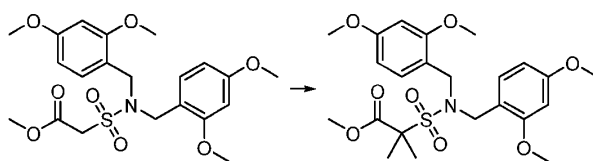
Step 1. Synthesis of methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]acetate



[363] To a solution of methyl 2-chlorosulfonylacetate (1000 mg, 5.79 mmol) in DCM (20 mL) was added 1-(2,4-dimethoxyphenyl)-N-[(2,4-dimethoxyphenyl)methyl]methanamine (1839 mg, 5.79 mmol) and triethylamine (2.4 mL, 17.4 mmol). The reaction was stirred at 0 °C for 30 min, then at 25 °C for 3 h. The reaction was quenched with water (50 mL). The aqueous mixture was extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (40 g silica gel column, eluting with 30% ethyl acetate in petroleum ether) to afford methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]acetate (1400 mg, 3.09 mmol, 53.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.90 min. Molecular ion was not observed.

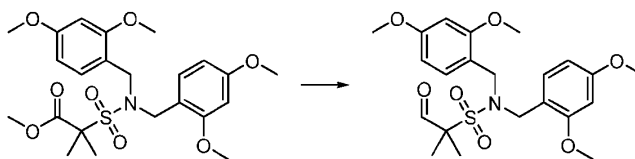
Step 2. Synthesis of methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propanoate



[364] To a solution of methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]acetate (1000 mg, 2.21 mmol) in DMF (10 mL) were added sodium hydride (132 mg, 5.51 mmol) and methyl iodide (0.14 mL, 2.21 mmol). The reaction was stirred at 0°C for 3 h and quenched with water (50 mL). The aqueous was extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column eluting with 30% ethyl acetate in petroleum ether) to yield methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propanoate (980 mg, 2.04 mmol, 92.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.90 min. Molecular ion was not observed.

Step 3. Synthesis of N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-1-oxo-propane-2-sulfonamide

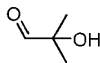


[365] To a solution of methyl 2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propanoate (100 mg, 0.208 mmol) in DCM (10 mL) was added diisobutylaluminum hydride (44 mg, 0.311 mmol) at -78°C . The reaction was stirred at -78°C for 3 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column eluting with 30% ethyl acetate in petroleum ether) to yield N, N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-1-oxo-propane-2-sulfonamide (30 mg, 0.0664 mmol, 32.0 % yield) as a yellow solid.

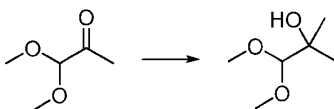
LCMS (Method 1): LC retention time = 1.93 min. Molecular ion was not observed.

Intermediate D-5:

2-Hydroxy-2-methyl-propanal

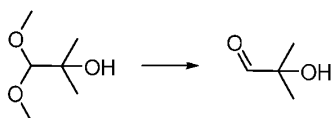


Step 1. Synthesis of 1,1-dimethoxy-2-methyl-propan-2-ol



[366] To a solution of 1,1-dimethoxypropan-2-one (2500 mg, 21.2 mmol) in THF (20 mL) was added methylmagnesium bromide (21 mL, 63.5 mmol) at 0°C . The mixture was stirred at 0°C for 1 h. The reaction was quenched by adding 4 N hydrochloric acid until all solids were dissolved. The aqueous solution was extracted with dichloromethane (20 mL x 3). The combined organic extracts were concentrated to give 1,1-dimethoxy-2-methyl-propan-2-ol (2500 mg, 11.2 mmol, 52.8 % yield) as an off-yellow oil which was used in the next step without further purification.

Step 2. Synthesis of 2-hydroxy-2-methyl-propanal

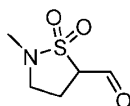


[367] To a solution of 1,1-dimethoxy-2-methylpropan-2-ol (200 mg, 1.49 mmol) in water (0.4 mL) was added trifluoroacetic acid (0.15 mL, 1.94 mmol). The reaction was stirred at 50 °C for 10 h. The reaction was cooled to rt. To this mixture was added triethylamine (0.21 mL, 1.49 mmol). The solution was concentrated to afford the title compound in quantitative yield.

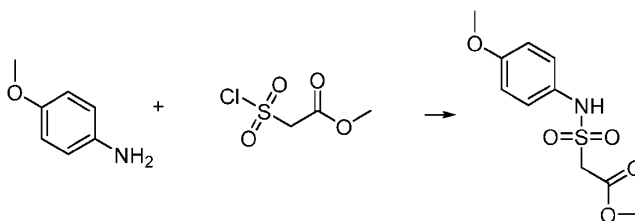
The compound is UV inactive. No LCMS signal detected.

Intermediate D-6:

2-Methylisothiazolidine-5-carbaldehyde 1,1-dioxide



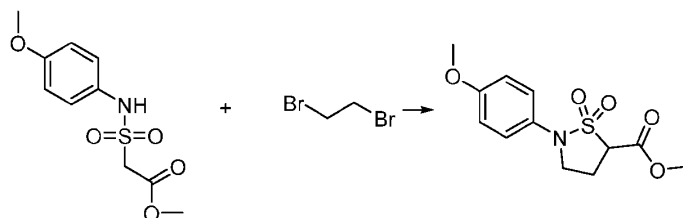
Step 1. Synthesis of methyl 2-[(4-methoxyphenyl)sulfamoyl]acetate



[368] To a solution of 4-methoxyaniline (30 mg, 0.244 mmol) and pyridine (0.059 mL, 0.731 mmol) in MeCN (3 mL) was added dropwise methyl 2-chlorosulfonylacetate (0.800 eq, 34 mg, 0.195 mmol) at 0 °C under a nitrogen over a period of 10 min. The reaction was monitored by LCMS. Upon completion, water (100 mL) was added at 0 °C and the resulting mixture was extracted with EA (100 mL $\times$ 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 5:1) to give methyl 2-[(4-methoxyphenyl)sulfamoyl]acetate (20 mg, 0.0771 mmol, 31.7 % yield) as a colorless oil.

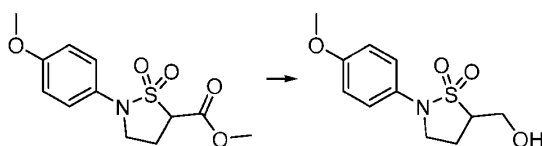
LCMS (Method 4): LC retention time = 1.54 min. MS (ESI) m/z 259.8[M+H]⁺.

Step 2. Synthesis of methyl 2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidine-5-carboxylate



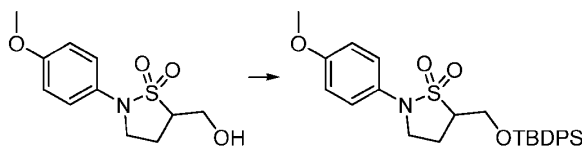
[369] To a solution of methyl 2-[(4-methoxyphenyl)sulfamoyl]acetate (200 mg, 0.771 mmol) and 1,2-dibromoethane (0.080 mL, 0.926 mmol) in DMF (3 mL) was added potassium carbonate (320 mg, 2.31 mmol) portion wise. The mixture was stirred for 0.5 h at rt. The mixture was concentrated under reduced pressure. To this residue was added EA (50 mL) and saturated aqueous Na₂CO₃ (30 mL). The two phases were separated, and the organic phase was dried over Na₂SO₄, filtered, and concentrated to give methyl 2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidine-5-carboxylate (150 mg, 0.526 mmol, 68.2 % yield) as a yellow solid. LCMS (Method 4): LC retention time = 1.67 min. MS (ESI) *m/z* 285.9 [M+H]⁺.

Step 3. Synthesis of [2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methanol



[370] To a solution of methyl 2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidine-5-carboxylate (1100 mg, 3.86 mmol) in methanol (5 mL) was added sodium borohydride (175 mg, 4.63 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was diluted with DCM (30 mL). the two layers were separated and the organic phase was washed with brine, dried (Na₂SO₄), filtered, and concentrated under vacuum to give [2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methanol (700 mg, 2.72 mmol, 70.6 % yield) as a colorless oil. LCMS (Method 4): LC retention time = 1.50 min. MS (ESI) *m/z* 258.1 [M+H]⁺.

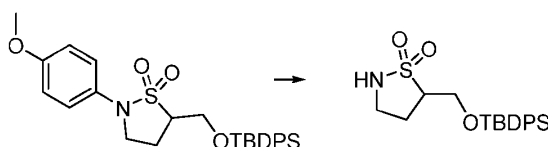
Step 4. Synthesis of tert-butyl-[[2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methoxy]-diphenyl-silane



[371] To a solution of [2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methanol (700 mg, 2.72 mmol) and triethylamine (1.1 mL, 8.16 mmol) in DMF (3 mL) was added tert-butyl-diphenylchlorosilane (1.4 mL, 5.44 mmol). The mixture was stirred at rt for 24 h under N₂. The reaction was quenched with water (50 mL) at 0 °C. The two phases were separated, and the aqueous phase was extracted with EA (50 mL x 3). The organic extracts were combined and washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with PE : EA = 5:1) to give tert-butyl-[[2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methoxy]-diphenyl-silane (900 mg, 1.82 mmol, 66.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.14 min. MS (ESI) m/z 513.2 [M+H₂O]⁺.

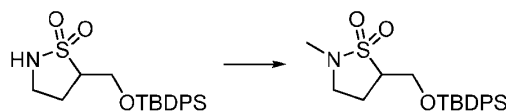
Step 5. Synthesis of tert-butyl-[(1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane



[372] To a solution of tert-butyl-[[2-(4-methoxyphenyl)-1,1-dioxo-1,2-thiazolidin-5-yl]methoxy]-diphenyl-silane (50 mg, 0.101 mmol) in ether (5 mL) and water (1 mL) was added ceric ammonium nitrate (276 mg, 0.504 mmol). The reaction was stirred at rt for 3 h under nitrogen. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield tert-butyl-[(1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane (3.0 mg, 0.0077 mmol, 7.6 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.28 min. MS (ESI) m/z 412.1 [M+Na]⁺.

Step 6. Synthesis of tert-butyl-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane



[373] To a solution of tert-butyl-[(1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane (900 mg, 2.31 mmol), sodium hydride (166 mg, 6.93 mmol) in DMF (10 mL) was

added methyl iodide (0.29 mL, 4.62 mmol). The mixture was stirred at 0 °C for 15 min under N₂, diluted with water (50 mL) at 0 °C and extracted with EA (50 mL × 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluting with PE : EA = 5:1) to give tert-butyl-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane (580 mg, 1.44 mmol, 62.2 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.28 min. MS (ESI) *m/z* 404.1 [M+H]⁺.

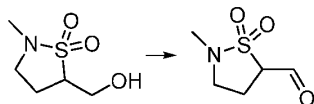
Step 7. Synthesis of (2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methanol



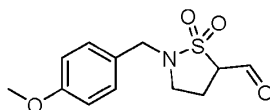
[374] To a solution of tert-butyl-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methoxy]-diphenyl-silane (300 mg, 0.743 mmol) in THF (4 mL) was added tetra-*n*-butylammonium fluoride (194 mg, 0.743 mmol). The reaction was stirred at rt for 1 h under nitrogen, quenched with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield (2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methanol (30 mg, 0.182 mmol, 24.4 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 0.36 min. MS (ESI) *m/z* 166.1 [M+H₂O]⁺.

Step 8. Synthesis of 2-methyl-1,1-dioxo-1,2-thiazolidine-5-carbaldehyde

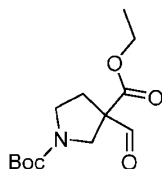


[375] To a solution of (2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methanol (100 mg, 0.605 mmol) in toluene (3 mL) was added 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (169 mg, 0.605 mmol). The reaction mixture was stirred at 60 °C for 16 h under N₂. The reaction was monitored by LCMS. Upon reaction completion, the reaction mixture was filtered through a fritted funnel. The filter cake was washed with DCM. The combined filtrate was concentrated under reduced pressure to afford 2-methyl-1,1-dioxo-1,2-thiazolidine-5-carbaldehyde (100 mg, 0.613 mmol, 101.2 % yield) as a black oil which was used for the next step without purification.

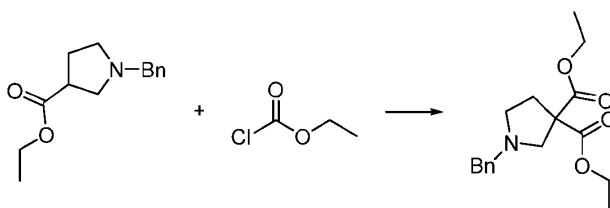
Intermediate D-7:*2-[(4-Methoxyphenyl)methyl]-1,1-dioxo-1,2-thiazolidine-5-carbaldehyde*

[376] **Intermediate D-7** was synthesized by following the procedures of Step 7 and Step 8 in the synthesis of **Intermediate D-6** by using the product from Step 5 described immediately above.

LCMS (Method 1): LC retention time = 1.40 min. MS (ESI) m/z 292.1 $[M+Na]^+$.

Intermediate D-8:*1-(tert-Butyl) 3-ethyl 3-formylpyrrolidine-1,3-dicarboxylate*

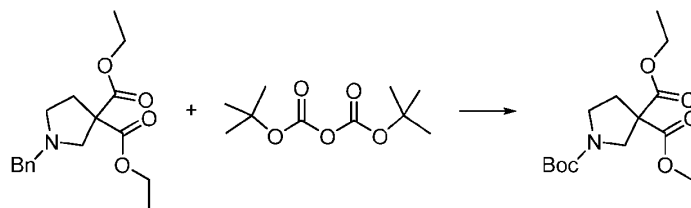
Step 1. Synthesis of diethyl 1-benzylpyrrolidine-3,3-dicarboxylate



[377] To a solution of ethyl 1-benzylpyrrolidine-3-carboxylate (10.00 g, 42.9 mmol) in THF (80 mL) was added LDA (1M in THF, 34 mL) dropwise at -78 °C under a nitrogen atmosphere, and stirring was continued for 40 min. Ethyl chloroformate (5.4 mL, 55.7 mmol) was added at -78 °C and the reaction was stirred for another 40 min. The mixture was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with EA (100 mL $\times$ 3). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with PE : EA = 5 : 1) to give diethyl 1-benzylpyrrolidine-3,3-dicarboxylate (6.50 g, 21.3 mmol, 49.7 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 2.11 min. MS (ESI) m/z 306.2 $[M+H]^+$.

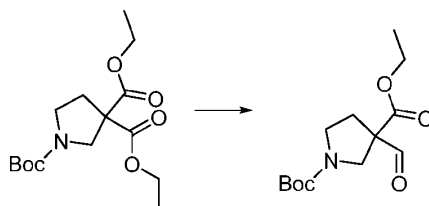
Step 2. Synthesis of 1-(tert-butyl) 3,3-diethyl pyrrolidine-1,3,3-tricarboxylate



[378] To a solution of diethyl 1-benzylpyrrolidine-3,3-dicarboxylate (5.00 g, 16.4 mmol) in methanol (30 mL) was added Pd/C (1 g, 30%w/w). The mixture was stirred at rt under H₂ for 3 h. The reaction was monitored by LCMS. Upon reaction completion, the mixture was filtered through a Celite pad. The filtrate was concentrated, and the residue was dissolved in DCM (30 mL). Di-tert-butyl decarbonate (4.29 g, 19.65 mmol) was added and the mixture was stirred at rt for 1 h, then concentrated to dryness. The crude product was purified by reverse-phase flash chromatography (C18, 0.1% NH₄HCO₃ in water, 10-100 % MeCN) to give 1-(tert-butyl) 3,3-diethyl pyrrolidine-1,3,3-tricarboxylate (3.40 g, 10.8 mmol, 65.8 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 2.03 min. MS (ESI) m/z 216.1 [M+H-Boc]⁺.

Step 3. Synthesis of 1-(tert-butyl) 3-ethyl 3-formylpyrrolidine-1,3-dicarboxylate

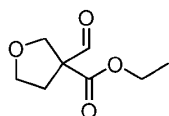


[379] To a solution of 1-(tert-butyl) 3,3-diethyl pyrrolidine-1,3,3-tricarboxylate (2.40 g, 7.61 mmol) in DCM (30 mL) was added diisobutylaluminum hydride (1M in THF, 11 mL, 11.4 mmol) at -78 °C. The mixture was stirred at -78 °C for 3 h. A saturated aqueous Rochelle salt solution was added slowly to the reaction mixture and stirring at rt was continued for 30 min. The two phases were separated and the aqueous phase was extracted with DCM (50 mL × 3). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 1-(tert-butyl) 3-ethyl 3-formylpyrrolidine-1,3-dicarboxylate (1.80 g, 6.63 mmol, 87.2 % yield) as a colorless oil.

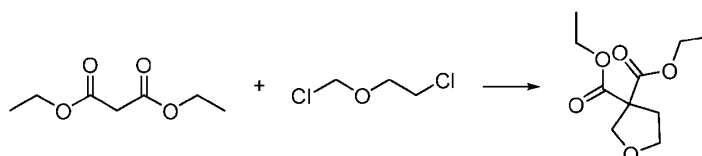
LCMS (Method 4): LC retention time = 1.89 min. MS (ESI) m/z 172.1 [M+H-Boc]⁺.

Intermediate D-9:

Ethyl 3-formyltetrahydrofuran-3-carboxylate



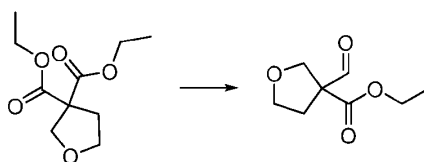
Step 1. Synthesis of diethyl tetrahydrofuran-3,3-dicarboxylate



[380] To a solution of diethyl malonate (4.8 mL, 31.2 mmol) in DMF (50 mL) was added sodium hydride (3122 mg, 78.0 mmol) at 0 °C under N₂. The mixture was stirred at 0 °C for 0.5 h, 1-chloro-2-(chloromethoxy)ethane (4429 mg, 34.3 mmol) was added, and the mixture was stirred at rt for 2 h. The reaction was quenched with saturated aqueous NH₄Cl solution (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic extracts were concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 5:1) to obtain diethyl tetrahydrofuran-3,3-dicarboxylate (2000 mg, 8.88 mmol, 28.4 % yield) as an off-white oil.

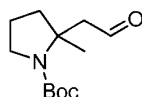
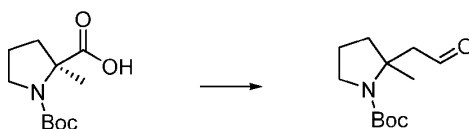
LCMS (Method 1): LC retention time = 2.02 min. MS (ESI) m/z 217.1 [M+H]⁺.

Step 2. Synthesis of ethyl 3-formyltetrahydrofuran-3-carboxylate



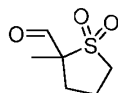
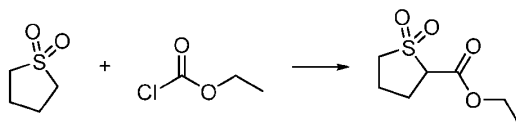
[381] To a solution of diethyl tetrahydrofuran-3,3-dicarboxylate (2000 mg, 9.25 mmol) in DCM (20 mL) was added diisobutylaluminum hydride (14 mL, 13.9 mmol) at -78 °C under N₂. The mixture was stirred at -78 °C for 2 h. The reaction was quenched with methanol (15 mL) and extracted with dichloromethane (50 mL × 3). The combined organic extracts were concentrated to give ethyl 3-formyltetrahydrofuran-3-carboxylate (1000 mg, 2.90 mmol, 31.4 % yield) as a light-yellow oil.

LCMS (Method 1): LC retention time = 1.21 min. MS (ESI) m/z 173.1 [M+H]⁺.

Intermediate D-10:*tert*-Butyl 2-methyl-2-(2-oxoethyl)pyrrolidine-1-carboxylate*Step 1. Synthesis of tert-butyl 2-methyl-2-(2-oxoethyl)pyrrolidine-1-carboxylate*

[382] To the mixture of (2S)-1-tert-butoxycarbonyl-2-methylpyrrolidine-2-carboxylic acid (229 mg, 0.999 mmol) in DMA (10 mL) was added 1,3-dioxol-2-one (103 mg, 1.20 mmol), 1,5-bis(diphenylphosphino)pentane (CAS# 27721-02-4, 48 mg, 0.110 mmol), dibromo[1,2-di(methoxy- κ O)ethane]nickel (CSA# 28923-39-9, 0.100 eq, 31 mg, 0.0999 mmol), Iridium(I) [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- κ N1, κ N1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- κ N]phenyl- κ C] hexafluorophosphate (CAS# 870987-63-6, 11 mg, 0.00999 mmol), and potassium hydroxide (56 mg, 0.999 mmol). The reaction was stirred at rt under blue light for 16 h. The reaction mixture was poured into water (20 mL) and extracted with EA (100 mL x 3). The combined organic extracts were concentrated and the crude was purified by flash column chromatography on silica gel (EtOAc in PE: 0-30% for 40 min) to get *tert*-butyl 2-methyl-2-(2-oxoethyl)pyrrolidine-1-carboxylate (100 mg, 0.440 mmol, 44.1 % yield) as a colorless oil.

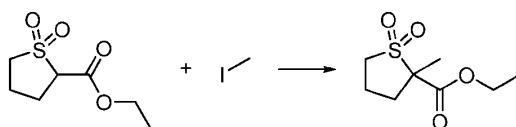
LCMS (Method 1): LC retention time = 1.94 min. MS (ESI) m/z 172.01 [M+H-tBu]⁺.

Intermediate D-11:*2-Methyl-1,1-dioxo-thiolane-2-carbaldehyde**Step 1. Synthesis of ethyl 1,1-dioxothioline-2-carboxylate*

[383] To a solution of sulfolane (3.9 mL, 41.6 mmol) in THF (100 mL) was added N-butyllithium (17 mL, 41.6 mmol) at -78 °C. The reaction was stirred at -78 °C for 1 h. Ethyl chloroformate (2.0 mL, 20.8 mmol) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous NH₄Cl solution (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic extracts were concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 3:1) to obtain ethyl 1,1-dioxothiolane-2-carboxylate (2000 mg, 9.36 mmol, 22.5 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.30 min. MS (ESI) m/z 193.0 [M+H]⁺.

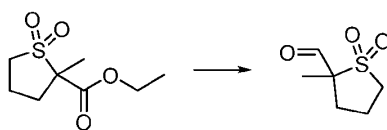
Step 2. Synthesis of ethyl 2-methyl-1,1-dioxo-thiolane-2-carboxylate



[384] To a solution of ethyl 1,1-dioxothiolane-2-carboxylate (0.16 mL, 1.04 mmol) in THF (10 mL) was added sodium hydride (50 mg, 1.25 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. Methyl iodide (0.078 mL, 1.25 mmol) was added and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phases were concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 3:1) to obtain ethyl 2-methyl-1,1-dioxo-thiolane-2-carboxylate (100 mg, 0.461 mmol, 44.3 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.57 min. MS (ESI) m/z 207.1 [M+H]⁺.

Step 3. Synthesis of 2-methyl-1,1-dioxo-thiolane-2-carbaldehyde



[385] This step of the reaction was carried out by following the procedures for synthesis of **Intermediate D-9**, Step 2.

LCMS (Method 1): LC retention time = 1.73 min. MS (ESI) m/z 163.0 [M+H]⁺.

Intermediate D-12 to Intermediate D-19:

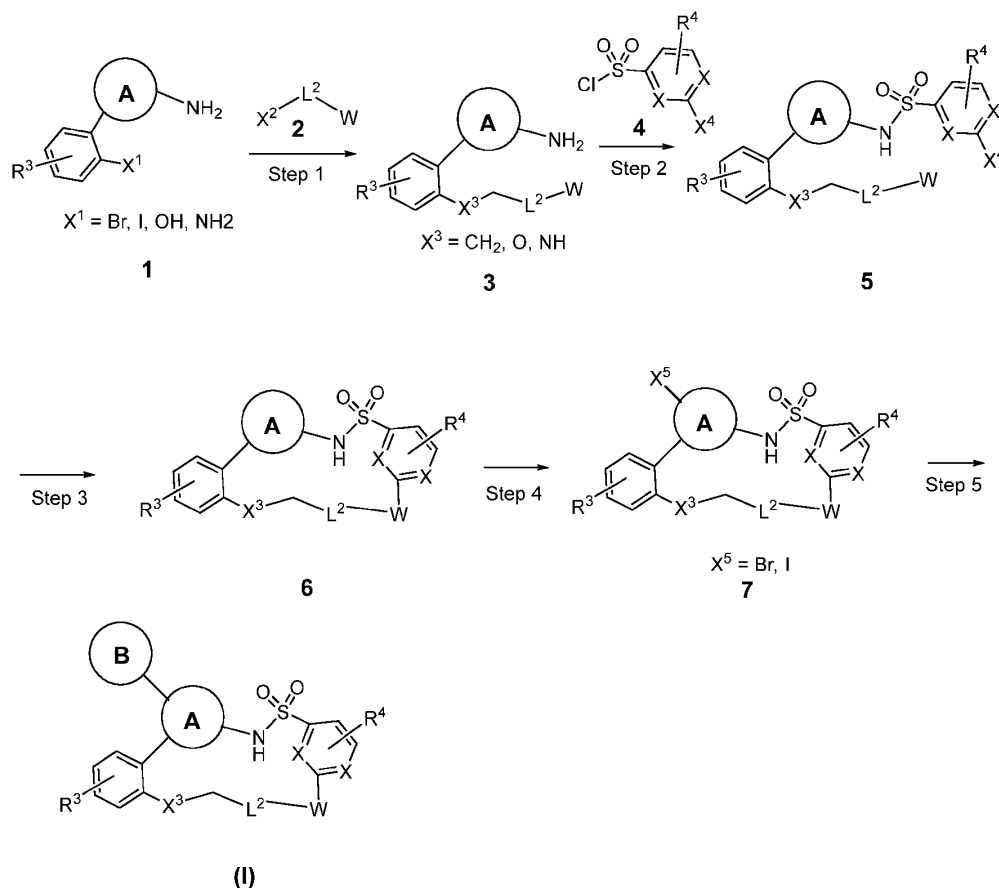
[386] The following intermediates (**Intermediate D-12** to **Intermediate D-19**) were prepared similarly by following the procedures detailed in preparation of **Intermediate D-1** to **Intermediate D-11**:

Intermediate	Structure	Name	Analytical
D-12		Ethyl 1-formylcyclohexane carboxylate	LCMS (Method 1): Rt 1.97 min. MS (ESI) m/z 185.2 $[M+H]^+$.
D-13		Methyl 2-cyclohexyl-2-methyl-3-oxo-propanoate	LCMS (Method 2): Rt 1.97 min MS (ESI) m/z 199.3 $[M+H]^+$
D-14		Ethyl 2-formyl-2,3,3-trimethyl-butanoate	LCMS (Method 1): Rt 2.24 min MS (ESI) m/z not observed
D-15		tert-Butyl 2-formyl-2-methyl-pyrrolidine-1-carboxylate	LCMS (Method 1): Rt 1.90 min. MS (ESI) m/z 158.2 $[M+H-tBu]^+$ 1H NMR (400 MHz, DMSO- D_6) δ : 9.28 (d, J = 9.9 Hz, 1H), 3.54–3.38 (m, 2H), 2.07–1.82 (m, 3H), 1.65–1.50 (m, 1H), 1.36 (m, 9H), 1.27 (d, J = 5.9 Hz, 3H)
D-16		2-Methyl-2-methylsulfonyl-propanal	LCMS (Method 1): Rt 1.77 min. MS (ESI) m/z 151.0 $[M+H]^+$
D-17		tert-Butyl N-(2,2-dimethyl-3-oxo-propyl)carbamate	LCMS (Method 4): Rt 1.97 min. MS (ESI) m/z 147.1 $[M+H-tBu]^+$
D-18		2-(Trifluoromethylsulfonyl)acetaldehyde	LCMS (Method 4): Rt 1.07 min MS (ESI) m/z 175 (M-H) $^-$

General Schemes

[387] The following general synthetic schemes illustrate how the examples in this disclosure were synthesized by using the intermediates described above and should not be deemed to narrow the scope of the disclosure.

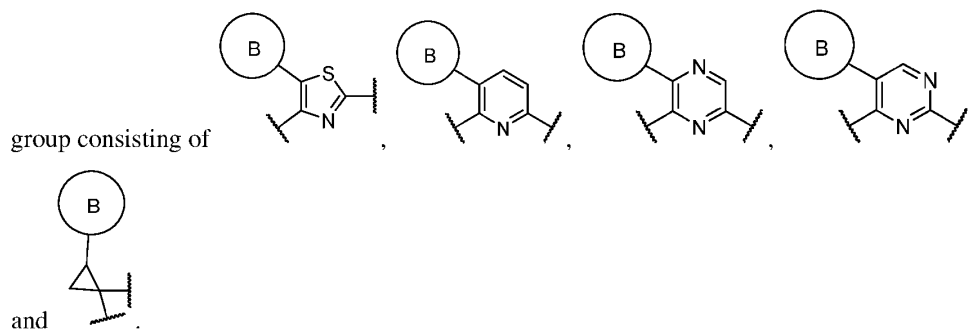
General Scheme 1: Representative scheme for the synthesis of exemplary compounds of the disclosure



[388] **Scheme 1** is a representative scheme for synthesis of some of the exemplary compounds of the disclosure. In Step 1, starting material **Compound 1** is coupled with a properly substituted **Compound 2**. Selection of the coupling reaction conditions is dictated by the functional groups in **Compound 1** and **Compound 2**. If X^2 in **Compound 2** is a carbon, Sonogashira coupling reaction (terminal acetylene **Compound 2** couples with halide **Compound 1** where X^1 is Br, I) or Suzuki coupling reaction (boronic acid or boronic ester **Compound 2** couples with halide **Compound 1** where X^1 is Br, I) is ideal. If X^3 requires oxygen or nitrogen, then the starting material **Compound 1** should be a phenol or aniline ($X^1 = \text{OH or NH}_2$), **Compound 2** should bear a leaving group ($X^2 = \text{leaving group}$), such as OTs, OMs, Cl, Br, or I, and simple halogen replacement conditions are applied to obtain **Compound 3**. In Step 2, sulfonamide formation is carried out by using sulfonyl chloride (**Compound 4**) in dry pyridine or an aprotic solvent catalyzed by pyridine with heat in a good yield to obtain

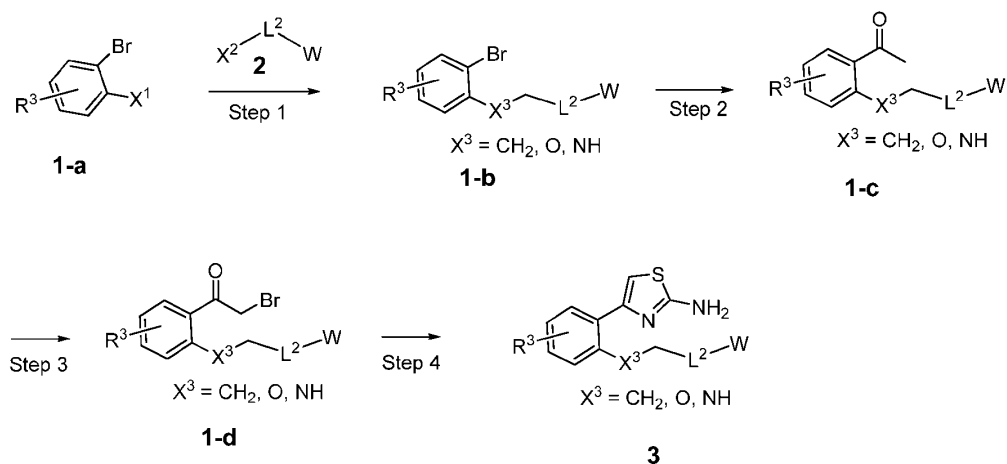
Compound 5. Selection of sulfonyl chloride (**Compound 4**) is determined by X (X = N or -CH= or -CF=) to ensure that Step 3 is feasible. If X = N, then X⁴ should be fluoride.

[389] At this stage, group W can be functionalized to the desired functional group. For example, if W = NH₂, then, reductive amination of **Compound 5** with an aldehyde, **Intermediates D (Intermediate D-1, D-2, or D4-D19)**, see the “*Synthesis of the Intermediates*” section) to install the desired functional groups. Also, a simple alkylation reaction can be used to install the required functional groups. The macrocyclization reaction can be achieved via a fluoride replacement reaction (where W = -NH₂, -NHR²) (Step 3). If X = -CH= or -CF=, then X⁴ should be NH₂ or NHR², such that the Buchwald coupling reaction conditions are applied (Step 3). Halogen (X⁵ = Br, I) is introduced onto **Ring-A** (Step 4) under standard conditions. For example, **Compound 6** in THF is treated with NIS to yield iodide **Compound 7** in 70% - 80% yield in one instance. Coupling of **Compound 7** with **Ring B (Intermediate B1-B42, see the “*Synthesis of the Intermediates*” section)** (Step 5) is accomplished via a Suzuki coupling reaction (if **Ring B** is connected to **Ring A** through a carbon atom) or a halogen substitution reaction (if **Ring B** connected to **Ring A** via a nitrogen atom) to form the compound of formula (I), where **Ring A** is selected from the



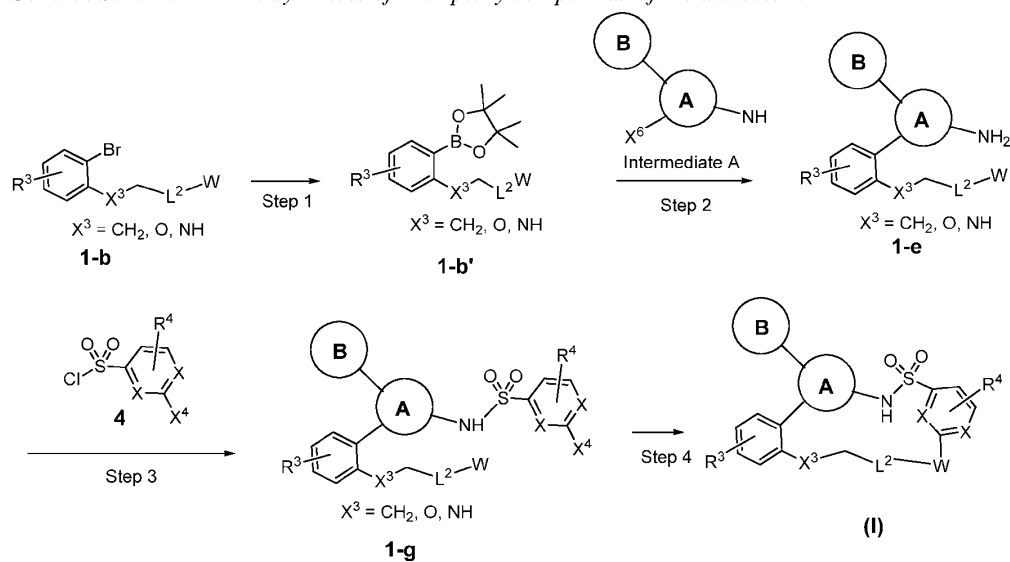
[390] It should be understandable that sometime, the sequence of the reaction shall be adjusted based on the requirements of the functional groups and the selection of the reactions. For example, Step 2 can be carried out first followed by Step 1.

General Scheme 1A.:The synthesis of exemplary compounds of the disclosure



[391] **Scheme 1A** is a representative scheme for synthesis of some of the exemplary compounds of the disclosure in an alternative sequence of the reactions. Step 1 is the same as described in **Scheme 1**, Step 1. In Step 2, aryl bromide **1-b** (**Intermediate 1-7**, see the “*Synthesis of the Intermediates*” section) is converted into methyl aryl ketone **1-c** via a palladium catalyzed reaction, such as Stelle coupling reaction, in a good yield. Then, a simple bromination reaction gives a bromide **1-d** (Step 3). Condensation of the bromoketone **1-d** with thiourea to obtain amino-thiazole **3**. By following the procedures in Scheme 1, **Compound 3** can be further transformed into the final desired compound of formula (I).

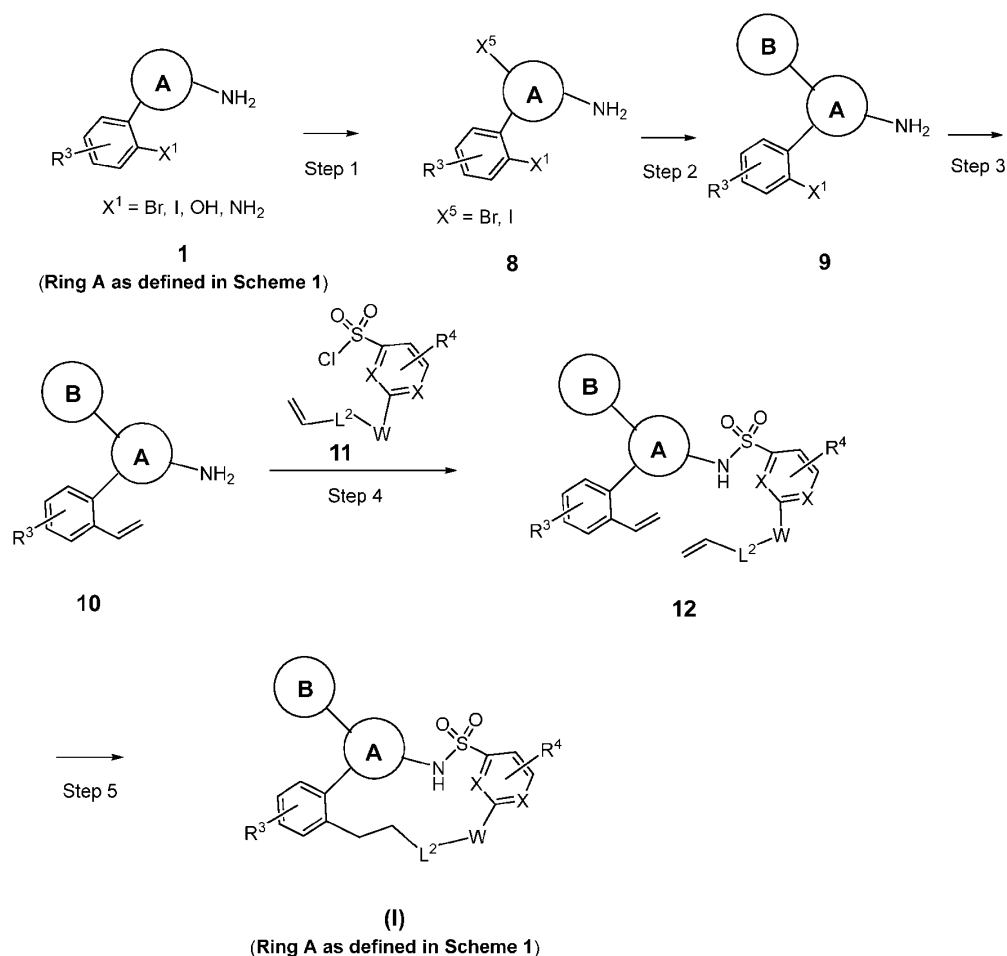
General Scheme 1B: The synthesis of exemplary compounds of the disclosure



[392] **Scheme 1B** is a representative scheme for synthesis of some of the exemplary compounds of the disclosure in an alternative sequence of the reactions to meet the needs for the functional groups and selections of the reactions. Bromide **1-b** (**Intermediate 1** through **Intermediate 7**) from **Scheme 1A** is coupled with bis(pinacolato)diboron to form boronic ester **1-b'** (**Intermediate 1A** through **Intermediate 6A**) under standard conditions in good yield. Then, the boronic ester **1b'** is coupled with **Intermediate A** (**Intermediate A-3** through **Intermediate A-12**) to obtain **compound 1-e** (Step 2) under Suzuki coupling reaction conditions. Sulfonamide formation is carried out by using sulfonyl chloride (**Compound 4**) in dry pyridine or an aprotic solvent catalyzed by pyridine with heat in a good yield to obtain **Compound 1-g** (Step 3). At this stage, **Compound 1-g** ($W = \text{NH}_2$) can be further functionalized into the desired precursor **1-g** ($W = \text{NR}_2$). For example, if $W = \text{NH}_2$, then, reductive amination of

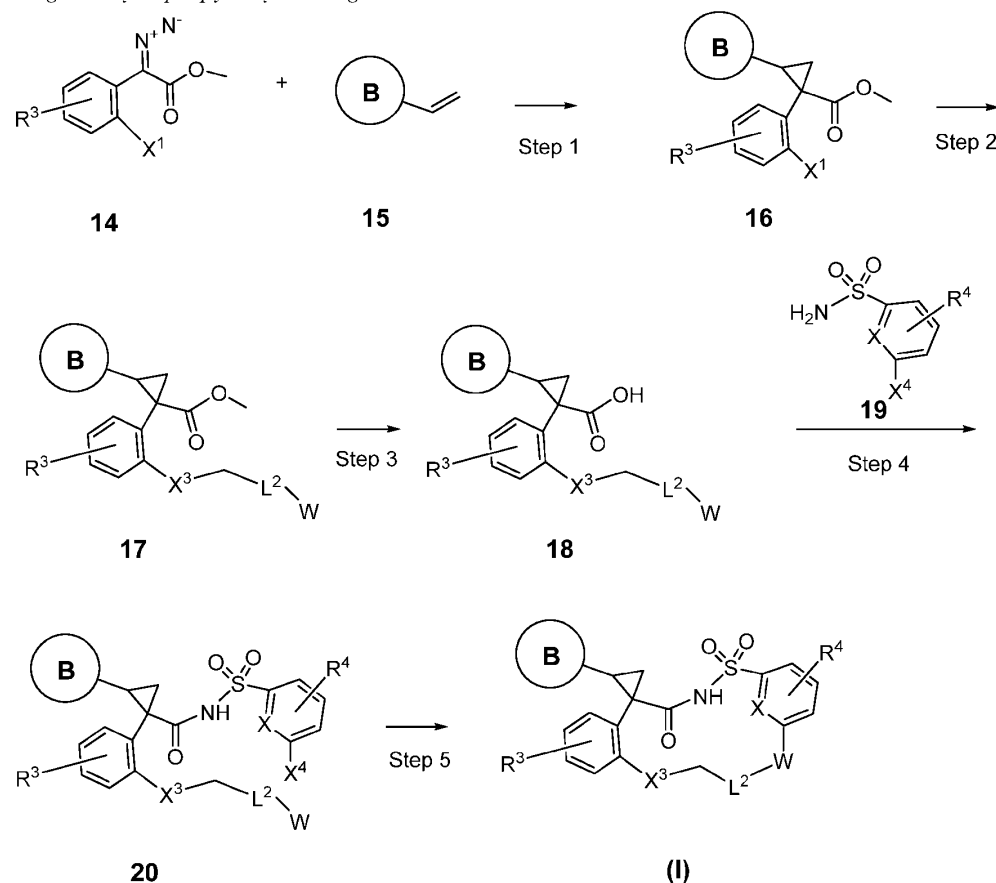
[393] **Compound 1-g** with an aldehydes **Intermediates D** (**Intermediate D1-D19**, see the “*Synthesis of the Intermediates*” section) to install the desired functional group. Also, a simple alkylation reaction can be used to install the required functional group. For definition of $W = \text{NR}_2$, see “Detailed Description”. Macrocyclization is achieved via amine fluoride displacement reaction (step 4) to obtain compound of formula (**I**) of this disclosure.

General Scheme 2: Alternative method for the synthesis of exemplary compounds of the disclosure



[394] **Scheme 2** illustrates an alternative method for synthesis of exemplary compounds of the disclosure. Starting material **Compound 1** is subjected to a halogenation reaction conditions, such as treatment of **Compound 1** in THF with N-iodosuccinimide or N-bromosuccinimide at ambient or elevated temperature (Step 1) to yield a halide **Compound 8**. **Compound 8** is coupled with **Ring B (Intermediate B1-B42)** in the same manner as described in **Scheme 1**, Step 5 to obtain **Compound 9**. This compound is then coupled with a reagent, such as trifluoro(vinyl)boron, catalyzed by Pd(0)-based catalyst (Step 3), to yield **Compound 10**. The reaction of **Compound 10** with a functionalized sulfonyl chloride (**Compound 11**) (Step 4) is carried out in the same manner as described in **Scheme 1**, Step 2 to obtain **Compound 12**. Finally, **Compound 12** is cyclized via Grubbs ring closing metathesis (Step 5), followed by hydrogenation to realize the compound of formula **(I)**.

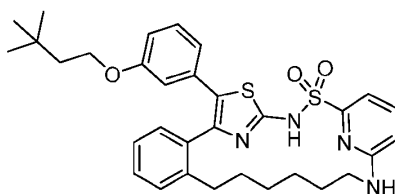
General Scheme 3: Representative scheme for the synthesis of exemplary compounds where Ring A is cyclopropyl acyl analogs.



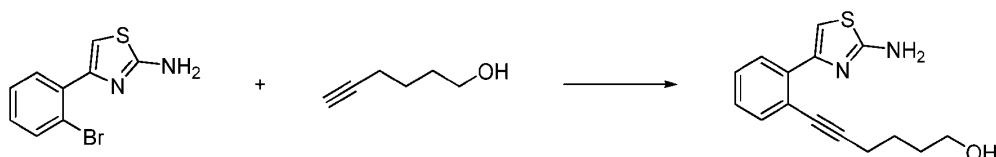
[395] **Scheme 3** illustrates the synthesis of exemplary compounds where **Ring A** is cyclopropyl acyl. In Step 1, the insertion of diazoacetate analog **Compound 14** into the alkene (**Compound 15**) to form a cyclopropyl **Compound 16** is carried out via a blue-light-mediated cyclopropanation reaction (Ref.: Synthesis **2019**, *51*(4), 889-898). The sidechain is installed onto **Compound 16** through the procedures as described in **Scheme 1**, Step 1, to obtain **Compound 17** (Step 2). The ester **Compound 17** is converted into an acid (**Compound 18**) (Step 3) under base catalyzed hydrolysis conditions. This acid is then condensed with sulfonamide **Compound 19** (Step 4) to form an acyl sulfonamide **Compound 20** under the standard conditions well known to a person skilled in the art. Cyclization of the precursor **Compound 20** is carried out (Step 5) in essentially the same manner as described in **Scheme 1**, Step 3 to obtain the compound of formula (I) (**Ring A** = cyclopropyl acyl).

[396] *Disclaimer:* The chirality of the stereoisomers in this disclosure was not determined and was unknown. The stereoisomers are *arbitrarily* designated as **P1** and **P2** and displayed *arbitrarily* as *R* and *S* in structural display. The stereo isomers **P1** and **P2** are for differentiation purposes only. There is no association of **P1** or **P2** with *R* or *S* designation and *vice versa*.

EXAMPLE 1. Preparation of 6-[3-(3,3-Dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

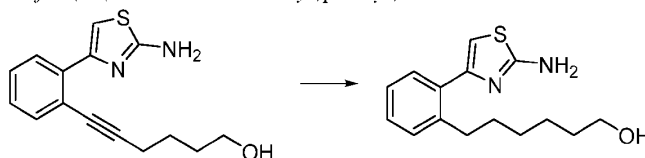


Step 1. Synthesis of 6-(2-(2-aminothiazol-4-yl)phenyl)hex-5-yn-1-ol



[397] To a solution of 4-(2-bromophenyl)thiazol-2-amine (**Intermediate A-1**) (1.00 eq, 2200 mg, 8.62 mmol), hex-5-yn-1-ol (1.20 eq, 1016 mg, 10.3 mmol), triphenylphosphine (0.1000 eq, 226 mg, 0.862 mmol) and copper (I) iodide (0.10 eq, 164 mg, 0.862 mmol) in triethylamine (20.8 eq, 25 mL, 179 mmol) was added tetrakis(triphenylphosphine)palladium(0) (0.050 eq, 498 mg, 0.431 mmol) under N₂. The mixture was stirred at 60 °C overnight. Then water (50 mL) was added. The aqueous solution was extracted with EA (30 mL × 3). The combined EA solution was washed with brine (30 mL) and dried over Na₂SO₄. The solution was filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-10% MeOH in DCM) to give the title compound (1100 mg, 46.8 % yield) as a brown oil. LCMS (Method 1): LCMS: LC retention time = 1.70 min. MS (ESI) *m/z* 273.0 [M+H]⁺.

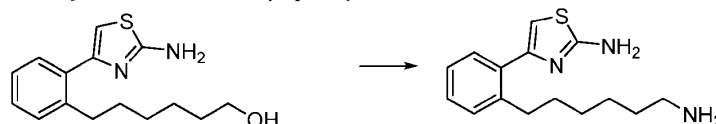
Step 2. Synthesis of 6-(2-(2-aminothiazol-4-yl)phenyl)hexan-1-ol



[398] To a solution of 6-[2-(2-aminothiazol-4-yl)phenyl]hex-5-yn-1-ol (1.00 eq, 1100 mg, 4.04 mmol) in methanol (30 mL) was added palladium on carbon (10 wt. %, 0.0512 eq, 220 mg, 0.207 mmol). The mixture was stirred at 40 °C overnight under a hydrogen atmosphere. Additional palladium on carbon (0.0512 eq, 220 mg, 0.207 mmol) was added and stirring continued at 40 °C overnight. The mixture was filtered, and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (eluting with 0-7% MeOH in DCM) to give the title compound (300 mg, 0.988 mmol, 24.5 % yield) as a brown solid.

LCMS (Method 1): LC retention time = 2.18 min. MS (ESI) m/z 277.2 $[M+H]^+$.

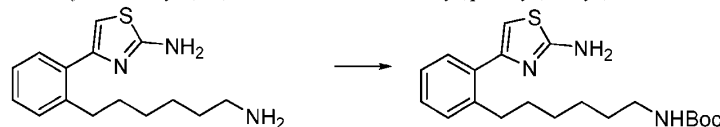
Step 3. Synthesis of 4-(2-(6-aminohexyl)phenyl)thiazol-2-amine



[399] To a solution of 6-[2-(2-aminothiazol-4-yl)phenyl]hexan-1-ol (1.00 eq, 300 mg, 1.09 mmol) and triethylamine (2.50 eq, 0.38 mL, 2.71 mmol) in DCM (10 mL) was added methanesulfonyl chloride (1.10 eq, 0.093 mL, 1.19 mmol). The mixture was stirred at 20 °C for 2 h and then water (20 mL) was added. The aqueous suspension was extracted with DCM (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude product was dissolved in 1,4-dioxane (2 mL). To this solution was added concentrated aqueous ammonia (47.8 eq, 2.0 mL, 51.9 mmol). The mixture was stirred at 45 °C overnight, cooled to rt, then water (20 mL) was added, followed by extraction with EA (20 mL x 2). The combined EA extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated in *vacuo* to give the title compound (240 mg, 0.680 mmol, 62.6 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.63 min. MS (ESI) m/z 276.1 $[M+H]^+$.

Step 4. Synthesis of tert-butyl (6-(2-(2-aminothiazol-4-yl)phenyl)hexyl)carbamate

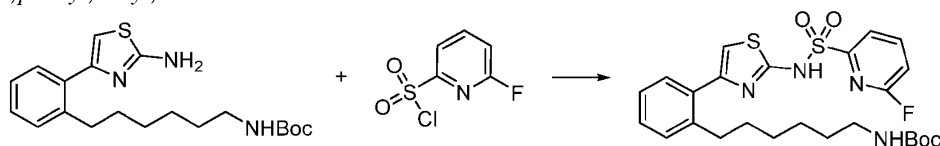


[400] To a solution of 4-[2-(6-aminohexyl)phenyl]thiazol-2-amine (1.00 eq, 240 mg, 0.871 mmol) and triethylamine (2.50 eq, 0.30 mL, 2.18 mmol) in DCM (5 mL) was added di-*tert*-butyl dicarbonate (1.00 eq, 0.20 mL, 0.871 mmol). The mixture was stirred at 20 °C overnight,

then water (20 mL) was added, followed by extraction with DCM (20 mL $\times$ 2). The DCM phase was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (eluting with 0-70% ethyl acetate in heptane) to give the title compound (260 mg, 0.692 mmol, 79.5 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.07 min. MS (ESI) m/z 376.0 [M+H]⁺.

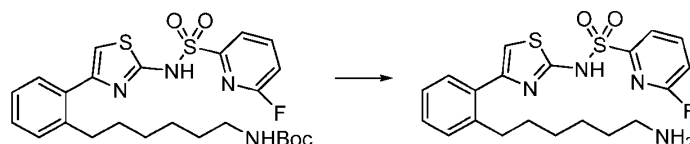
Step 5. Synthesis of tert-butyl (6-(2-(2-((6-fluoropyridine)-2-sulfonylamido)thiazol-4-yl)phenyl)hexyl)carbamate



[401] To a solution of tert-butyl N-[6-[2-(2-aminothiazol-4-yl)phenyl]hexyl]carbamate (1.20 eq, 260 mg, 0.692 mmol) in dry-pyridine (2 mL) was added 6-fluoropyridine-2-sulfonyl chloride (1.20 eq, 163 mg, 0.831 mmol). The mixture was stirred at 100 °C overnight. The mixture was concentrated in *vacuo*. The residue was purified by combi-flash (A: water (10 mmol/L NH₄HCO₃) B: ACN) to give the title compound (240 mg, 0.449 mmol, 64.8 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.82 min. MS (ESI) m/z 535.1 [M+H]⁺.

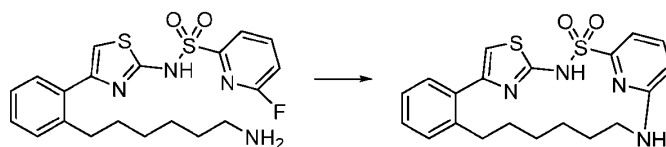
Step 6. Synthesis of N-(4-(2-(6-aminohexyl)phenyl)thiazol-2-yl)-6-fluoropyridine-2-sulfonamide



[402] To a solution of tert-butyl N-[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexyl]carbamate (1.00 eq, 240 mg, 0.449 mmol) in DCM (5 mL) was added trifluoroacetic acid (14.5 eq, 0.50 mL, 6.49 mmol). The mixture was stirred at 20 °C for 2 h then concentrated in *vacuo*. DCM (5 mL) was added, and the solution concentrated again to give the title compound (150 mg, 0.345 mmol, 76.9 % yield) as a brown oil.

LCMS (Method 4): LC retention time = 1.72 min. MS (ESI) m/z 435.0 [M+H]⁺.

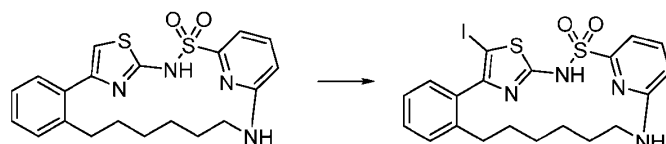
Step 7. Synthesis of 2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



[403] To a solution of N-[4-[2-(6-aminoheptyl)phenyl]thiazol-2-yl]-6-fluoropyridine-2-sulfonamide (1.00 eq, 150 mg, 0.345 mmol) in DMSO (3 mL) was added cesium fluoride (5.00 eq, 262 mg, 1.73 mmol). The mixture was stirred at 100 °C overnight, cooled to rt and treated with water (20 mL). The aqueous solution was extracted with EA (20 mL × 2). The combined EA extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-10% MeOH in DCM) to give the title compound (110 mg, 0.265 mmol, 76.8 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.76 min. MS (ESI) *m/z* 415.1 [M+H]⁺.

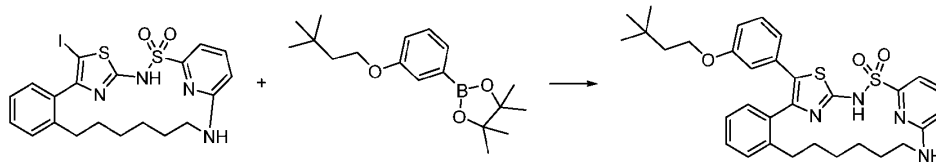
Step 8. Synthesis of 6-iodo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



[404] To a solution of (Z)-4-thia-3,6-diaza-2(4,2)-thiazola-5(2,6)-pyridina-1(1,2)-benzenacyclododecaphane 4,4-dioxide (1.00 eq, 80 mg, 0.193 mmol) in THF (2 mL) was added N-iodosuccinimide (1.10 eq, 48 mg, 0.212 mmol). The reaction was stirred at room temperature for 1 h. Then quenched with Na₂SO₃aq (5 mL). The aqueous solution was extracted with DCM (20 mL × 2). The combined DCM solution was washed with brine (10 mL × 2). Then the organic solution was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-10% MeOH in DCM) to give the title compound (75 mg, 0.139 mmol, 71.9 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.75 min. MS (ESI) *m/z* 540.8 [M+H]⁺.

Step 9. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

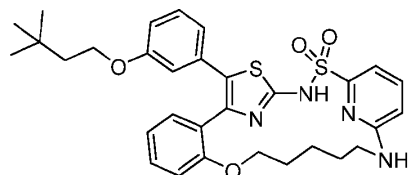


[405] To a solution of 6-iodo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (1.00 eq, 80 mg, 0.148 mmol) in 1,4-dioxane (2 mL) and water (0.50 mL), were added cesium carbonate (2.00 eq, 96 mg, 0.296 mmol), 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate B-2a) (1.20 eq, 54 mg, 0.178 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.200 eq, 34 mg, 0.0296 mmol) under N₂. The reaction was stirred at 100 °C overnight. Then water (20 mL) was added. The aqueous solution was extracted with EA (20 mL × 2). The EA solution was washed with brine (20 mL), then concentrated under vacuum. The residue was purified by combi-flash (eluting with A: water with 10 mmol/L NH₄HCO₃; B: ACN) to give the title compound (20 mg, 0.0338 mmol, 22.8 % yield) as a white solid.

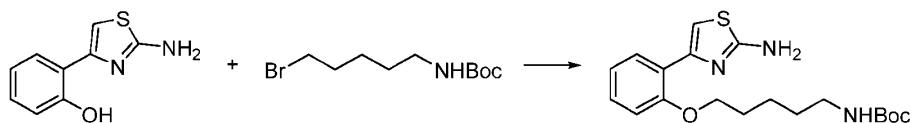
LCMS (Method 4): LC retention time = 2.69 min. MS (ESI) *m/z* 591.3 [M+H]⁺.

¹H NMR (500 MHz, DMSO-*d*₆) δ: 12.95 (s, 1H), 7.52-7.45 (m, 1H), 7.41 (s, 2H), 7.33 (t, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.78 (dd, *J* = 17.2, 8.4 Hz, 2H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.43 (s, 1H), 3.71-3.55 (m, 3H), 2.85 (s, 1H), 2.36 (s, 1H), 2.23 (s, 1H), 1.54-1.38 (m, 4H), 1.32-1.02 (m, 6H), 0.88 (s, 9H).

EXAMPLE 2. Preparation of 6-[3-(3,3-dimethylbutoxy)phenyl]-14-oxa-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



Step 1. Synthesis of tert-butyl N-[5-[2-(2-aminothiazol-4-yl)phenoxy]pentyl]carbamate

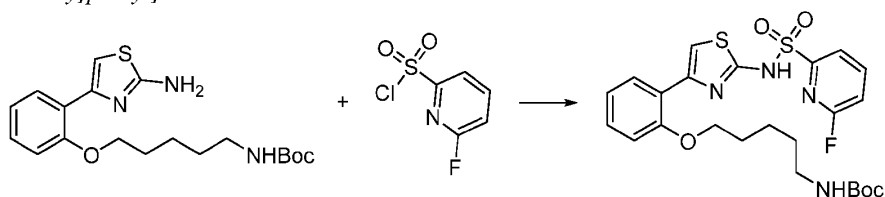


[406] To a solution of 2-(2-aminothiazol-4-yl)phenol (**Intermediate A-2**) (1.00 eq, 1000 mg, 5.20 mmol) in DMF (10 mL) were added *tert*-butyl N-(5-bromopentyl)carbamate (1.10 eq, 1523 mg, 5.72 mmol) and potassium carbonate (3.00 eq, 2157 mg, 15.6 mmol). Then the reaction was stirred at 65 °C overnight. The reaction solution was filtered and the solid was washed with EA (100 mL). The filtrate was poured into water (80 mL) and extracted with EA

(200 mL × 3). The yellow organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude was then purified by silica gel flash column chromatography (eluting with 0-100% ethyl acetate in PE) to obtain the title compound (1200 mg, 3.18 mmol, 61.1 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.78 min. MS (ESI) m/z 378.0 [M+H]⁺.

Step 2. Synthesis of tert-butyl N-[5-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenoxy]pentyl]carbamate



[407] To a solution of *tert*-butyl N-[5-[2-(2-aminothiazol-4-yl)phenoxy]pentyl]carbamate (1.00 eq, 500 mg, 1.32 mmol) in pyridine (5 mL) was added 6-fluoropyridine-2-sulfonyl chloride (1.20 eq, 311 mg, 1.59 mmol). The reaction was stirred at rt for 3 h. The reaction mixture was concentrated in *vacuo*. The residue was purified by flash column chromatography eluting with 20% ethyl acetate in petroleum ether to give the title compound (580 mg, 1.08 mmol, 81.6 % yield) as a yellow solid.

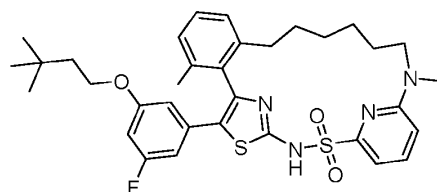
LCMS (Method 1): LC retention time = 2.26 min. MS (ESI) m/z 537.0 [M+H]⁺.

[408] The rest of the steps (Step 3 through Step 6) were performed by following the procedures of Step 6 through Step 9 of **Example 1**. The title compound was obtained in 51.9 % yield as a white solid.

LCMS (Method 3): LC retention time = 2.17 min. MS (ESI) m/z 593.0 [M+H]⁺.

¹H NMR (400 MHz, CH₃OH-*d*₄) δ 7.49-7.38 (m, 2H), 7.23-7.09 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 2H), 4.10 (t, *J* = 5.1 Hz, 2H), 3.70 (t, *J* = 7.2 Hz, 2H), 3.25 (s, 2H), 1.74-1.65 (m, 2H), 1.59 (t, *J* = 7.1 Hz, 2H), 1.56-1.36 (m, 4H), 0.94 (s, 9H).

EXAMPLE 3. Preparation of 6-[3-(3,3-Dimethylbutoxy)-5-fluoro-phenyl]-9,20-dimethyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(24),4(26),6,8(13),9,11,21(25),22-octaene 2,2-dioxide

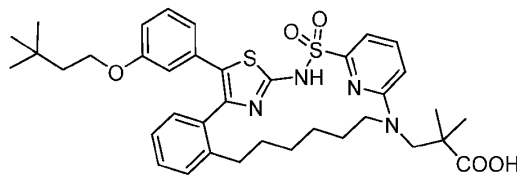


[409] The title compound was synthesized by following protocols similar to those described in **EXAMPLE 1** except for using 4-(2-bromo-6-methyl-phenyl)thiazol-2-amine (**Intermediate A-1a**) instead of 4-(2-bromophenyl)thiazol-2-amine (**Intermediate A-1**) and *tert*-butyl N-hex-5-ynyl-N-methyl-carbamate instead of hex-5-yn-1-ol in step 1.

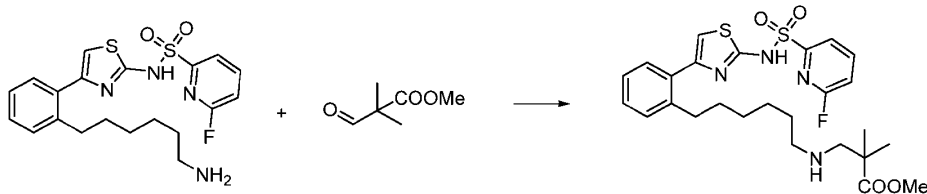
LCMS (Method 1): LC retention time = 3.49 min. MS (ESI) m/z 637.2 $[M+H]^+$.

^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 7.70-7.54 (m, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.25-7.12 (m, 3H), 6.72 (d, $J = 8.7$ Hz, 1H), 6.51 (m, 2H), 6.33 (s, 1H), 4.42 (dt, $J = 14.8, 7.6$ Hz, 1H), 3.72-3.57 (m, 2H), 3.00 (d, $J = 11.9$ Hz, 4H), 2.42 (dd, $J = 10.5, 5.9$ Hz, 1H), 2.32-2.15 (m, 4H), 1.55 (m, 2H), 1.31 (m, 6H), 1.19-1.02 (m, 2H), 0.91 (s, 9H).

EXAMPLE 4. Preparation of 3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethyl-propanoic acid



Step 1. Synthesis of methyl 3-[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate

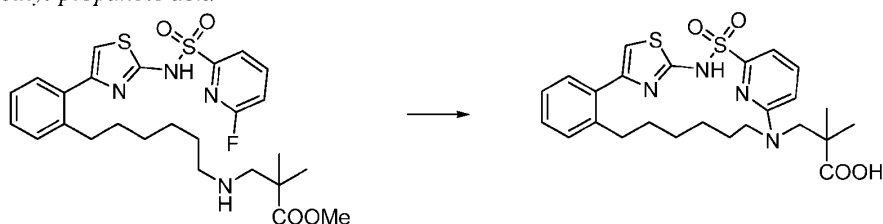


[410] To a solution of N-[4-[2-(6-aminohexyl)phenyl]thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide (from Step 6, **Example 1**) (1.00 eq, 800 mg, 1.84 mmol) and methyl 2,2-dimethyl-3-oxo-propanoate (1.20 eq, 288 mg, 2.21 mmol) in DCE (10 mL) was added acetic acid (1.90 eq, 0.20 mL, 3.49 mmol). The solution was stirred for 1 h. Then sodium triacetoxyborohydride (2.00 eq, 780 mg, 3.68 mmol) was added and stirred at 20 °C overnight. To the reaction mixture was added water (20 mL) and extracted with EA (20 mL $\times$ 2). The organic extracts were washed

with brine (20 mL), dried (Na_2SO_4), and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (eluting with 0-5% MeOH in DCM) to give the title compound (680 mg, 1.24 mmol, 67.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.51 min. MS (ESI) m/z 549.3 $[\text{M}+\text{H}]^+$.

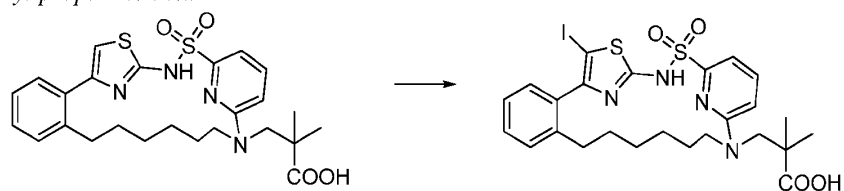
Step 2. Synthesis of 3-(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)-2,2-dimethyl-propanoic acid



[411] To a solution of methyl 3-[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (1.00 eq, 680 mg, 1.24 mmol) in DMSO (5 mL) and water (0.1 mL) was added cesium fluoride (5.00 eq, 941 mg, 6.20 mmol). The reaction solution was stirred at 100 °C for 48 h. Then water (30 mL) was added. The aqueous solution was extracted with DCM (30 mL $\times$ 3). The organic layer was washed with brine (30 mL $\times$ 2), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (eluting with 0-7% MeOH in DCM) to give the title compound (200 mg, 0.389 mmol, 31.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.01 min. MS (ESI) m/z 515.2 $[\text{M}+\text{H}]^+$.

Step 3. Synthesis of 3-(6-iodo-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)-2,2-dimethyl-propanoic acid

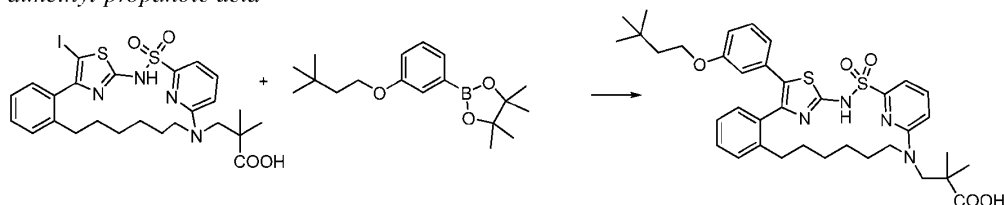


[412] To a solution of 3-(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)-2,2-dimethyl-propanoic acid (1.00 eq, 200 mg, 0.389 mmol) in THF (5 mL) was added N-iodosuccinimide (1.10 eq, 96 mg, 0.427 mmol). The mixture was stirred at 20 °C for 1 h. Then quenched with saturated aqueous Na_2SO_3 (5 mL) and water (20 mL). The aqueous solution was

extracted with DCM (30 mL $\times$ 3). The combined DCM solutions were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (eluting with 0-7% MeOH in DCM) to give the title compound (180 mg, 0.281 mmol, 72.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.11 min. MS (ESI) m/z 641.1 $[\text{M}+\text{H}]^+$.

Step 4. Synthesis 3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethyl-propanoic acid

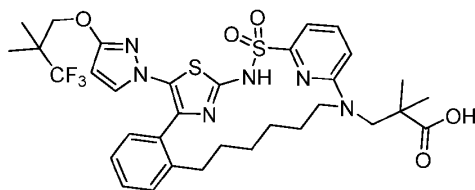


[413] To a solution of 3-(6-iodo-2,2-dioxo-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)-2,2-dimethyl-propanoic acid (1.00 eq, 50 mg, 0.0781 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) were added 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate B-2a**) (1.20 eq, 28 mg, 0.0937 mmol), cesium carbonate (2.50 eq, 64 mg, 0.195 mmol), and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.200 eq, 11 mg, 0.0156 mmol). The mixture was stirred at 100 °C overnight. Then water (20 mL) was added. The pH was adjusted to 3.0. The aqueous solution was then extracted with DCM (30 mL $\times$ 3). The DCM solution was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuum to obtain the residue which was purified by flash column chromatography (TFA) to give the title compound (15 mg, 0.0220 mmol, 28.2 % yield) as an off-white solid.

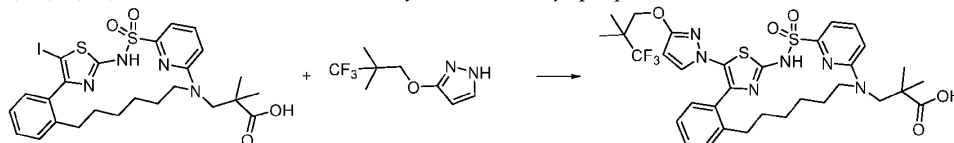
LCMS (Method 1): LC retention time = 2.60 min. MS (ESI) m/z 691.4 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ : 7.59 (dd, J = 8.7, 7.3 Hz, 1H), 7.46-7.33 (m, 3H), 7.31 (d, J = 7.7 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.79 (dd, J = 8.1, 2.2 Hz, 1H), 6.54-6.50 (m, 1H), 4.19 (br, 1H), 3.67 (m, 4H), 2.98 (br, 1H), 2.32 (br, 2H), 1.56 (t, J = 7.2 Hz, 2H), 1.48 (br, 2H), 1.39-0.95 (m, 12H), 0.92 (s, 9H).

EXAMPLE 5. Preparation of 3-[2,2-Dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-

2,2-dimethyl-propanoic acid

Step 1. Synthesis of 3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2,2-dimethyl-propanoic acid

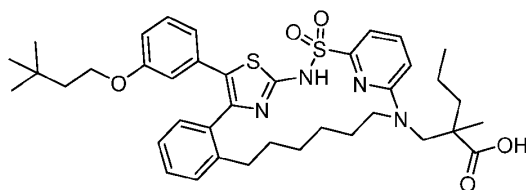


[414] To a suspension of 3-(6-iodo-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)-2,2-dimethyl-propanoic acid (from Step 4 of **Example 4**) (1.00 eq, 380 mg, 0.593 mmol), 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (**Intermediate B-28**) (1.50 eq, 185 mg, 0.890 mmol) and potassium carbonate (3.00 eq, 246 mg, 1.78 mmol) in DMF (2 mL) were added copper (I) iodide (0.500 eq, 56 mg, 0.297 mmol) and potassium carbonate (3.00 eq, 246 mg, 1.78 mmol) under N₂. The mixture was stirred at 120 °C overnight. The reaction was quenched with water (20 mL) and aqueous NH₄OH (2 mL). The aqueous solution was extracted with DCM (20 mL × 2). The DCM solution was washed with brine (20 mL), dried (Na₂SO₄), filtered, and then concentrated under vacuum. The residue was purified by combi-flash (NH₄HCO₃) to give the title compound (32 mg, 0.0437 mmol, 7.4 % yield) as a white solid.

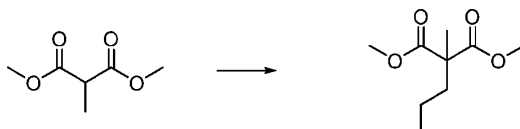
LCMS (Method 1): LC retention time = 2.37 min. MS (ESI) m/z 721.3 [M+H]⁺.

¹H NMR (400 MHz, MeOH-*d*₄) δ: 7.50 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.27-7.11 (m, 4H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 5.65 (d, *J* = 2.5 Hz, 1H), 4.08 (m, 2H), 3.72 (br, 2H), 3.63 (s, 2H), 2.49 (t, *J* = 7.4 Hz, 2H), 1.44 (m, 4H), 1.19 (m, 16H).

EXAMPLE 6. Preparation of 2-[[6-[3-(3,3-Dimethylbutoxy)phenyl]-2,2-dioxo-2,6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid



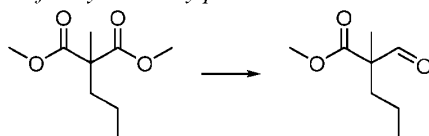
Step 1. Synthesis of dimethyl 2-methyl-2-propyl-propanedioate



[415] To a solution of dimethyl 2-methylpropanedioate (1.00 eq, 10.00 g, 68.4 mmol) and 1-bromopropane (1.20 eq, 10.10 g, 82.1 mmol) in DMF (70 mL) was added sodium hydride (2.50 eq, 4.11 g, 171 mmol). The mixture was stirred at 100 °C overnight. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous solution was extracted with EA (30 mL $\times$ 3). The EA solution was washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-10% ethyl acetate in heptane) to obtain the title compound (10.60 g, 56.3 mmol, 82.3 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.93 min. MS (ESI) m/z 189.1 $[\text{M}+\text{H}]^+$.

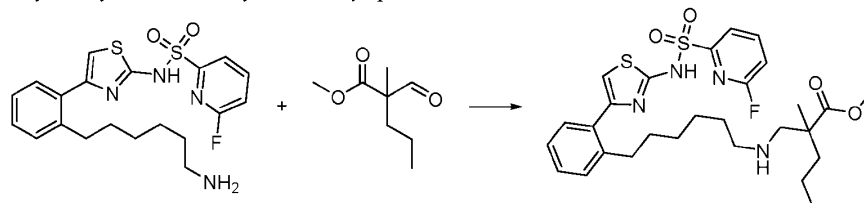
Step 2. Synthesis of methyl 2-formyl-2-methylpentanoate



[416] To a solution of dimethyl 2-methyl-2-propylpropanedioate (1.00 eq, 5.00 g, 26.6 mmol) in DCM (80 mL) was added diisobutylaluminum hydride (1M in toluene) (2.00 eq, 53 mL, 53.1 mmol) dropwise at 0 °C under N_2 . The mixture was stirred at 0 °C for 6 h. The reaction was quenched with saturated aqueous ammonium chloride (50 mL). The cold bath was removed. Aqueous hydrochloric acid (1.0 M, 150 mL) and *dl*-tartaric acid (6 g) were added sequentially, and the mixture was allowed to warm to 25 °C over 2 h with vigorous stirring. The biphasic mixture was then partitioned between 1.0 M aqueous hydrochloric acid solution (70 mL) and dichloromethane (150 mL). The organic layer was separated, dried over sodium sulfate, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-10% EA in heptane) to give the title compound (1.70 g, 10.7 mmol, 40.4 % yield) as a colorless oil.

LCMS (Method 1): LCMS: LC retention time = 1.81 min. MS (ESI) m/z 159.2 $[M+H]^+$.

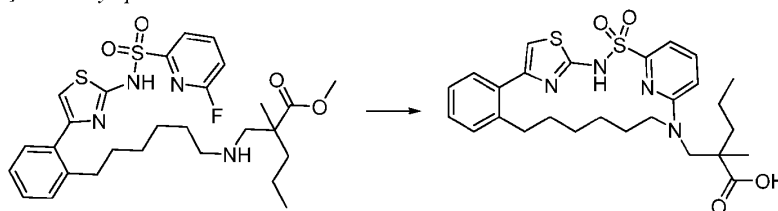
Step 3. Synthesis of methyl 2-[[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexylamino]methyl]-2-methyl-pentanoate



[417] To a solution of N-[4-[2-(6-aminohexyl)phenyl]thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide (from Step 6, **Example 1**) (1.00 eq, 600 mg, 1.38 mmol) and methyl 2-formyl-2-methyl-pentanoate (1.20 eq, 262 mg, 1.66 mmol) in DCE (8 mL) was added acetic acid (1.27 eq, 0.10 mL, 1.75 mmol). The mixture was stirred at 20 °C for 0.5 h, then sodium triacetoxyborohydride (2.00 eq, 585 mg, 2.76 mmol) was added and the mixture was stirred overnight. Then water (30 mL) was added. The aqueous solution was extracted with EA (30 mL $\times$ 3). The combined EA solutions were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-7% MeOH in DCM) to give the title compound (450 mg, 0.780 mmol, 56.5 % yield) as a white solid.

LCMS (Method 1): LCMS: LC retention time = 1.65 min. MS (ESI) m/z 577.3 $[M+H]^+$.

Step 4. Synthesis of 2-[(2,2-dioxo-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid

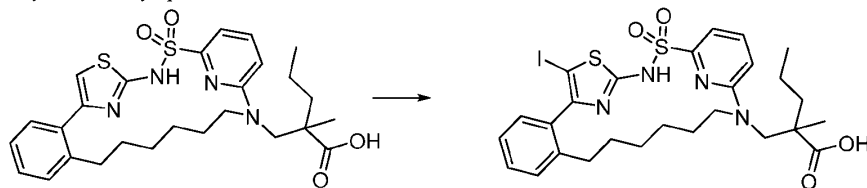


[418] To a solution of methyl 2-[[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexylamino]methyl]-2-methyl-pentanoate (1.00 eq, 380 mg, 0.659 mmol) in DMSO (5 mL) and water (0.5 mL) was added cesium fluoride (5.00 eq, 500 mg, 3.29 mmol). The mixture was stirred at 100 °C for 48 h. Then water (30 mL) was added. The acidity of the solution to was adjusted to pH 3 by adding 1N HCl. The aqueous solution was extracted with DCM (30 mL $\times$ 3). The DCM solution was washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. The residue was purified by silica gel column

chromatography (0-7% MeOH in DCM) to give the title compound (160 mg, 0.295 mmol, 44.8 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.17 min. MS (ESI) m/z 543.3 $[M+H]^+$.

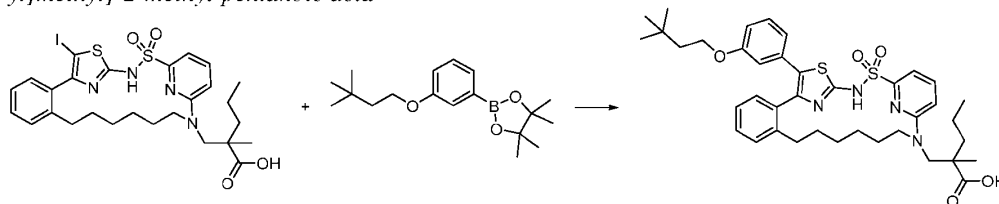
Step 5. Synthesis of 2-[(6-iodo-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid



[419] To a solution of 2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (1.00 eq, 160 mg, 0.295 mmol) in THF (4 mL) was added N-iodosuccinimide (1.00 eq, 66 mg, 0.295 mmol). The mixture was stirred at 20 °C for 1 h. Then quenched with saturated aqueous Na₂SO₃ (10 mL) and water (10 mL). The aqueous solution was extracted with DCM (30 mL × 3). The DCM solution was washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-7% MeOH in DCM) to give the title compound (150 mg, 0.224 mmol, 76.1 % yield) as a yellow solid.

LCMS (Method 1): LCMS: LC retention time = 2.27 min. MS (ESI) m/z 669.2 $[M+H]^+$.

Step 6. Synthesis of 2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid



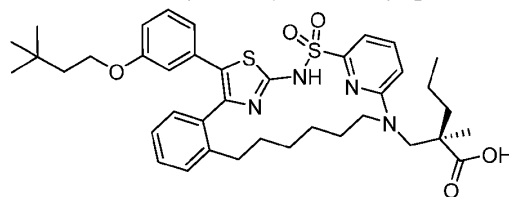
[420] To a solution of 2-[(6-iodo-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (1.00 eq, 70 mg, 0.105 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) were added cesium carbonate (2.50 eq, 85 mg, 0.262 mmol), 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate B-2a**) (1.20 eq, 38 mg, 0.126 mmol), and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II)

dichloromethane complex (0.200 eq, 15 mg, 0.0209 mmol) under N₂. The reaction was stirred at 100 °C overnight. Then water (10 mL) was added. The acidity of the solution was adjusted to pH ~3 with 1N HCl. The aqueous solution was extracted with DCM (30 mL × 3). The DCM solution was washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by prep-HPLC (TFA) to give the title compound (16 mg, 0.0225 mmol, 21.5 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.73 min. MS (ESI) *m/z* 719.4 [M+H]⁺.

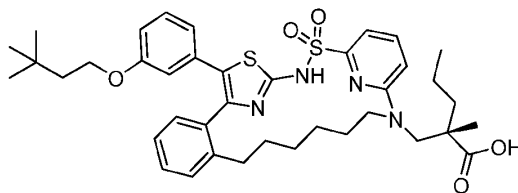
¹H NMR (400 MHz, MeOH-*d*₄) δ: 7.59 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.46-7.27 (m, 4H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.52 (s, 1H), 4.15 (br, 1H), 3.65 (m, 4H), 2.92 (br, 1H), 2.33 (br, 2H), 1.81-1.31 (m, 8H), 1.25-1.00 (m, 9H), 0.92 (s, 12H).

EXAMPLE 7 (P1 and P2). Preparation of (2R)-2-[[6-[3-(3,3-Dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid (P1)

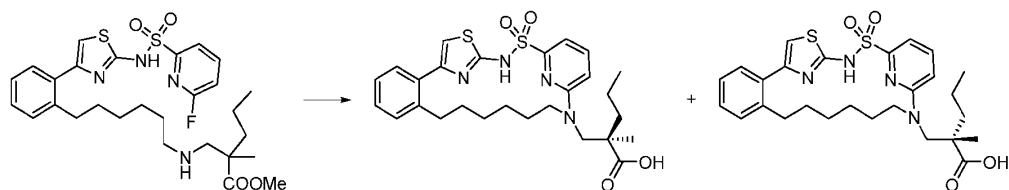


and

(2S)-2-[[6-[3-(3,3-Dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid (P2)



Step 1. Synthesis of (2R)-2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (P1) and (2S)-2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (P2)



[421] To a solution of methyl 2-[[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]hexylamino]methyl]-2-methyl-pentanoate (from Step 3, **Example 6**) (1.00 eq, 200 mg, 0.347 mmol) in DMSO (5 mL) and water (0.15 mL) was added cesium fluoride (5.00 eq, 263 mg, 1.73 mmol). The mixture was stirred at 100 °C for 72 h. Then water (20 mL) was added. The acidity of the solution was adjusted to pH < 3 with 2N HCl. The aqueous solution was extracted with DCM (20 mL × 2). DCM solution was washed with brine (20 mL × 3), dried (N₂SO₄), filtered, and concentrated in *vacuo*. The residue was purified by Combi-flash (A: water (10 mmol/L NH₄HCO₃); B: acetonitrile) to yield the title compound (120 mg) as an enantiomeric mixture.

LCMS (Method 4): LC retention time = 1.64 min. MS (ESI) *m/z* 543.2 [M+H]⁺.

[422] The enantiomeric mixture obtained above was then purified by SFC to give (2R)-2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (50 mg, 0.0921 mmol, 26.5 % yield) (**P1**) as a yellow solid and (2S)-2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (50 mg, 0.0921 mmol, 26.5 % yield) (**P2**) as a yellow solid.

P1: ee: 100%; **P2**: ee: 97.68%

SFC conditions:

Instrument: SFC-150 (Waters)

Column: IG 25 × 250 mm, 10 μm (Daicel)

Column temperature: 35 °C

Mobile phase: CO₂/ EtOH 0.2% NH₃ (7M in MeOH) = 60/40

Flow rate: 100 mL/min

Back pressure: 100 bar

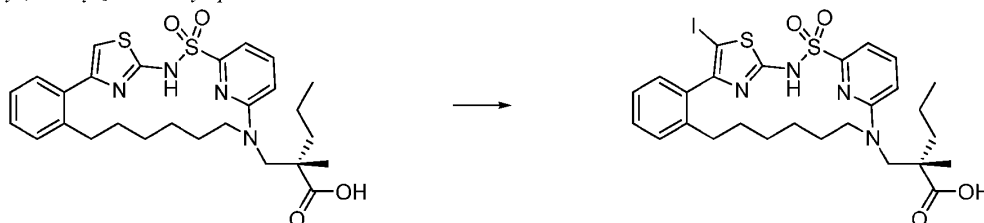
Detection wavelength: 214 nm

Cycle time: 3.81 min

Sample solution: 100 mg dissolved in 27 ml methanol.

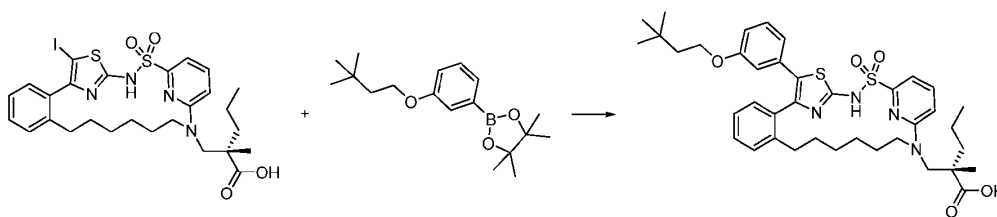
Injection volume: 4.8 mL

Step 2. Synthesis of (2S)-2-[(6-iodo-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid



[423] To a solution of (2S)-2-[(2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (1.00 eq, 50 mg, 0.0921 mmol) in THF (2mL) was added N-iodosuccinimide (1.10 eq, 23 mg, 0.101 mmol). The mixture was stirred at rt for 1 h. Then the mixture was quenched with saturated aqueous Na₂SO₃. The acidity of the solution was adjusted to pH < 2 with 2N HCl and then extracted with DCM (20 mL × 3). The combined DCM solution was washed with brine (20 mL), dried (Na₂SO₄), filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (0-7% MeOH in DCM) to yield the title compound (38 mg, 0.0568 mmol, 61.7 % yield) as yellow solid. LCMS (Method 4): LC retention time = 1.36 min. MS (ESI) m/z 669.2 [M+H]⁺.

Step 3. Synthesis (2S)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid



[424] To a solution of (2S)-2-[(6-iodo-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methyl-pentanoic acid (1.00 eq, 38 mg, 0.0568 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) were added 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane (**Intermediate B-2a**) (1.10 eq, 19 mg, 0.0625 mmol) and cesium carbonate (2.00 eq, 37 mg, 0.114 mmol) under N₂. The mixture was stirred at 100 °C for 16 h. Then water (20 mL) was added. The acidity of the solution was adjusted to pH < 3 by adding 2N HCl, then extracted with DCM (20 mL × 3). The DCM solution was washed with brine (20 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (A: water with 10 mmol/L formic acid); B: ACN) to give the title compound (**P1**) (14 mg, 0.0195 mmol, 34.3 % yield) as an off-white solid.

LCMS (Method 1): LC retention time = 2.33 min. MS (ESI) m/z 719.3 [M+H]⁺.

¹H NMR (400 MHz, MeOH-d₄) δ : 7.59 (dd, J = 8.6, 7.3 Hz, 1H), 7.46-7.27 (m, 4H), 7.21 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.79 (dd, J = 8.3, 1.9 Hz, 1H), 6.52 (s, 1H), 4.15 (br, 1H), 3.65 (m, 4H), 2.92 (br, 1H), 2.33 (br, 2H), 1.81-1.31 (m, 8H), 1.25-1.00 (m, 9H), 0.92 (s, 12H).

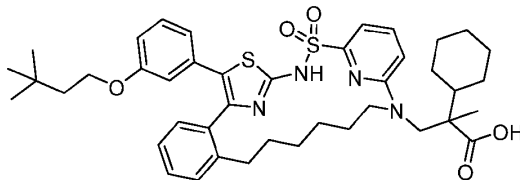
[425] The title compound of **P2** was synthesized following the same procedures of Step 2 and Step 3 after Step 1.

LCMS (Method 1): LC retention time = 2.33 min. MS (ESI) m/z 719.3 [M+H]⁺.

¹H NMR (400 MHz, MeOH-d₄) δ : 7.59 (dd, J = 8.6, 7.3 Hz, 1H), 7.48-7.27 (m, 4H), 7.21 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.79 (dd, J = 8.3, 1.9 Hz, 1H), 6.52 (s, 1H), 4.15 (br, 1H), 3.65 (m, 4H), 2.92 (br, 1H), 2.33 (br, 2H), 1.81-1.31 (m, 8H), 1.25-1.00 (m, 9H), 0.92 (s, 12H).

[426] To emphasize the disclaimer at the beginning of the section that the chirality of the stereoisomers in this disclosure was not determined and was unknown. The stereoisomers are *arbitrarily* designated as **P1** and **P2** and displayed *arbitrarily* as *R* and *S* in structural display. The stereo isomers **P1** and **P2** are for differentiation purposes only. There is no association of **P1** or **P2** with *R* or *S* designation and *vice versa*.

EXAMPLE 8. Preparation of 2-Cyclohexyl-3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-methyl-propanoic acid

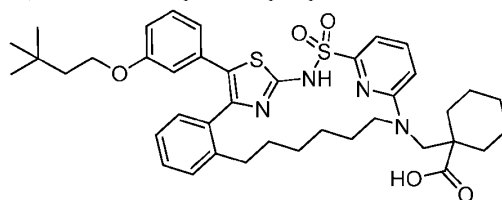


[427] The title compound was synthesized similarly by following the procedures for synthesis of **Example 6** except using methyl 2-cyclohexyl-2-methyl-3-oxo-propanoate instead of methyl 2-formyl-2-methyl-pentanoate in Step 3.

LCMS (Method 1): LC retention time = 2.33 min. MS (ESI) m/z 760.3 $[M+H]^+$.

^1H NMR (400 MHz, MeOH- d_4) δ 7.58 (t, J = 8.0 Hz, 1H), 7.36 (m, 4H), 7.21 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.81 (m, 3H), 6.52 (s, 1H), 3.91 (s, 1H), 3.57 (m, 4H), 3.00 (m, 1H), 2.45 (s, 1H), 2.19 (s, 1H), 1.92-1.40 (m, 11H), 1.22 (m, 10H), 0.99 (s, 3H), 0.92 (s, 9H).

EXAMPLE 9. Preparation of 1-[[6-[3-(3,3-Dimethylbutoxy)phenyl]-2,2-dioxo-2 λ 6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]cyclohexanecarboxylic acid

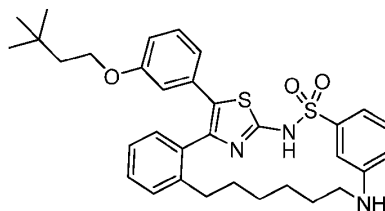


[428] The title compound was synthesized similarly by following the procedures for synthesis of **Example 6** except using ethyl 1-formylcyclohexanecarboxylate instead of methyl 2-formyl-2-methyl-pentanoate in Step 3.

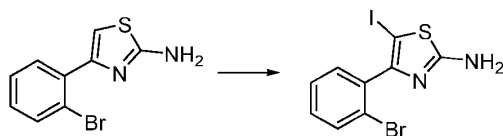
LCMS (Method 1): LC retention time = 2.27 min. MS (ESI) m/z 731.4 $[M+H]^+$.

^1H NMR (400 MHz, MeOH- d_4) δ 7.60-7.53 (m, 1H), 7.45-7.28 (m, 4H), 7.21 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.81 (m, 2H), 6.53 (s, 1H), 4.34-3.95 (m, 1H), 3.56 (s, 4H), 3.13-2.93 (m, 1H), 2.46 (s, 1H), 2.11 (s, 3H), 1.54 (m, 8H), 1.31 (m, 10H), 0.92 (s, 9H).

EXAMPLE 10. Preparation of 6-[3-(3,3-Dimethylbutoxy)phenyl]-2 λ 6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

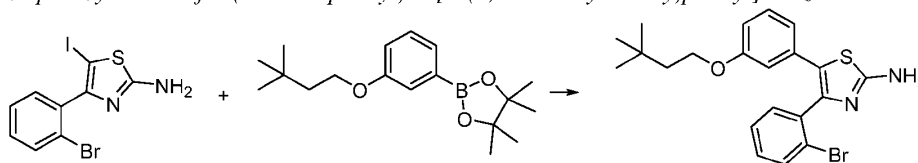


Step 1. Synthesis of 4-(2-bromophenyl)-5-iodo-thiazol-2-amine



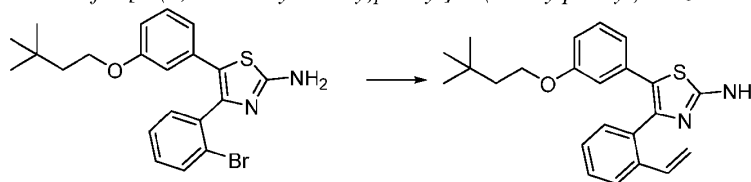
[429] To a solution of 4-(2-bromophenyl)thiazol-2-amine (**Intermediate A-1**) (1.00 eq, 20.00 g, 78.4 mmol) in THF (200 mL) was added N-iodosuccinimide (1.10 eq, 19.40 g, 86.2 mmol). The mixture was stirred at 25 °C overnight. The mixture was concentrated to dryness. The crude was then purified by silica gel flash column chromatography (EA in PE: 0-100% for 40 min) to get the title compound in two benches (25.00 g, 65.6 mmol, 83.7 % yield) and (114.0 g, 90.1 %), respectively, both are yellow oils. LCMS (Method 4): LC retention time = 1.88 min. MS (ESI) m/z 380.8, 382.8 [M+H]⁺.

Step 2. Synthesis of 4-(2-bromophenyl)-5-[3-(3,3-dimethylbutoxy)phenyl]thiazol-2-amine



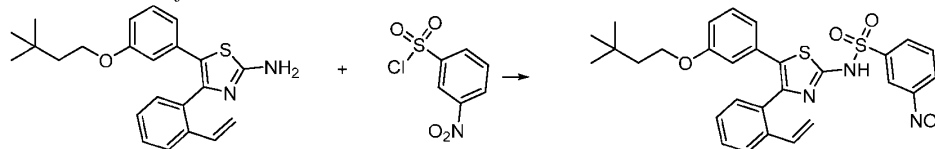
[430] To a solution of 4-(2-bromophenyl)-5-iodo-thiazol-2-amine (1.00 eq, 10.00 g, 26.2 mmol) in 1,4-dioxane (100 mL) and water (10 mL) were added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.100 eq, 1920 mg, 2.62 mmol), 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate B-2a**) (1.00 eq, 7984 mg, 26.2 mmol), and potassium carbonate (3.00 eq, 10.88 g, 78.7 mmol). Then the mixture was stirred at 100 °C overnight under Ar atmosphere. After cooled to room temperature, the reaction solution was filtered and the solid was washed with EA (1 L). The filtrate was concentrated in *vacuo*. The crude was then purified by silica gel flash column chromatography (EA in PE: 0-25% for 40 min, 25% hold 1 h) to get the title compound (8.00 g, 18.5 mmol, 70.7 % yield) as a yellow solid. LCMS (Method 4): LC retention time = 2.29 min. MS (ESI) m/z 431.0, 433.0 [M+H]⁺.

Step 3. Synthesis of 5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-amine



[431] To a solution of 4-(2-bromophenyl)-5-[3-(3,3-dimethylbutoxy)phenyl]thiazol-2-amine (1.00 eq, 8.00 g, 18.5 mmol) in 1,4-dioxane (80 mL) and water (8 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.100 eq, 1357 mg, 1.85 mmol), potassium carbonate (3.00 eq, 7689 mg, 55.6 mmol), and trifluoro(vinyl)boron (1.50 eq, 2638 mg, 27.8 mmol). The mixture was stirred at 100 °C overnight under Ar atmosphere. After cooled to room temperature, the reaction solution was filtered and the solid was washed with EA (200 mL). The filtrate was concentrated in *vacuo*. The crude was then purified by flash silica gel column chromatography (ethyl acetate in PE (0-55% for 40 min) to get the title compound (7.00 g, 16.7 mmol, 90.2 % yield) as a yellow solid. LCMS (Method 4): LC retention time = 2.30 min. MS (ESI) m/z 379.1 [M+H]⁺.

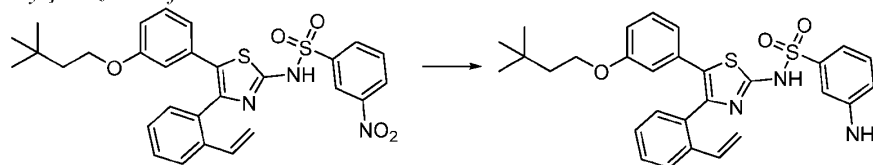
Step 4. Synthesis of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-nitro-benzenesulfonamide



[432] To a solution of 5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-amine (1.00 eq, 7.00 g, 18.5 mmol) in pyridine (70 mL) was added 3-nitrobenzenesulfonyl chloride (1.50 eq, 6147 mg, 27.7 mmol). Then the mixture was stirred at rt for 12 h. The mixture was concentrated, and the crude was then purified by flash silica gel column chromatography (EA in PE: 0-100% for 50 min) to get the title compound (7.50 g, 13.3 mmol, 71.9 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.98 min. MS (ESI) m/z 564.0 [M+H]⁺.

Step 5. Synthesis of 3-amino-N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]benzenesulfonamide

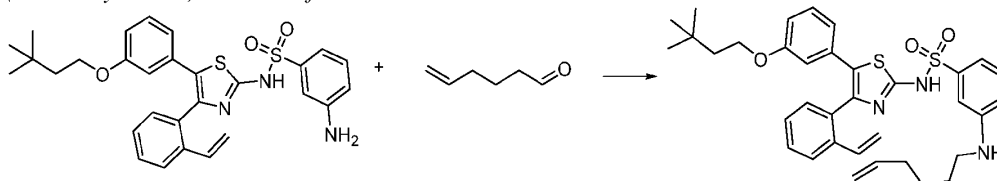


[433] To a solution of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-nitro-benzenesulfonamide (1.00 eq, 7.00 g, 12.4 mmol) in ethanol (60 mL) and water (12 mL) were added iron (3.00 eq, 2081 mg, 37.3 mmol) and ammonium chloride (3.00 eq, 1993 mg, 37.3 mmol). Then the mixture was stirred at 80 °C overnight under Ar atmosphere. After cooled to room temperature, the reaction solution was filtered and the solid was washed with

EA (1 L). The filtrate was concentrated *in vacuo*. The crude was then purified by flash silica gel column chromatography (EA in PE: 0-100% for 40 min) to get the title compound (6.00 g, 11.2 mmol, 90.5 % yield) as a yellow oil.

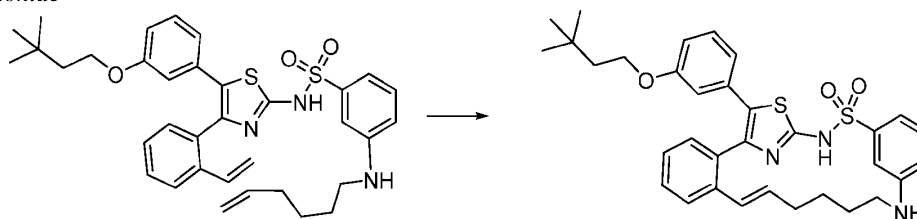
LCMS (Method 1): LC retention time = 2.54 min. MS (ESI) m/z 534.2 $[M+H]^+$.

Step 6. Synthesis of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-(hex-5-enylamino)benzenesulfonamide



[434] To a solution of 3-amino-N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]benzenesulfonamide (1.00 eq, 1.00 g, 1.87 mmol) in DCM (30 mL) was added hex-5-enal (1.00 eq, 184 mg, 1.87 mmol), and AcOH (1 mL). Then the mixture was stirred at rt for 0.5 h, and sodium triacetoxyborohydride (3.00 eq, 1191 mg, 5.62 mmol) was added portion wise at 0 °C. The mixture was stirred at rt for 2 h, and then concentrated to dryness. The residue was purified by flash silica gel column chromatography (EA in PE: 0-100% for 20 min) to get the title compound (700 mg, 1.14 mmol, 60.7 % yield) as a white solid. LCMS (Method 4): LC retention time = 1.99 min. MS (ESI) m/z 616.3 $[M+H]^+$.

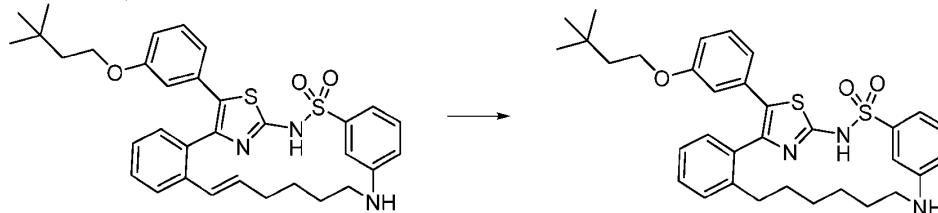
Step 7. Synthesis of (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,14,21,23-nonaene 2,2-dioxide



[435] To a solution of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-(hex-5-enylamino)benzenesulfonamide (1.00 eq, 700 mg, 1.14 mmol) in DCE (5 mL) was added Grubbs catalyst 2nd Generation (10 mg). Then the mixture was stirred at rt for 1 h. The mixture was concentrated and the residue was then purified by flash silica gel column chromatography (EA in PE: 0-100% for 20 min) to get the title compound (20 mg, 0.034 mmol, 3 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.06 min. MS (ESI) m/z 588.1 $[M+H]^+$.

Step 8. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

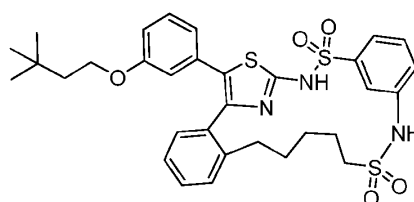


[436] To a solution of (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,14,21,23-nonaene 2,2-dioxide (1.00 eq, 20 mg, 0.0340 mmol) in methanol (5 mL) was added Pd/C (10 mg)). The mixture was stirred at 25 °C overnight under H₂ atmosphere. The reaction solution was filtered and the solid was washed with EA (10 mL). The filtrate was concentrated under *vacuo*. The residue was purified by pre-HPLC. After freeze-drying, the title compound (2.1 mg, 0.00356 mmol, 10.5 % yield) was obtained as a white solid.

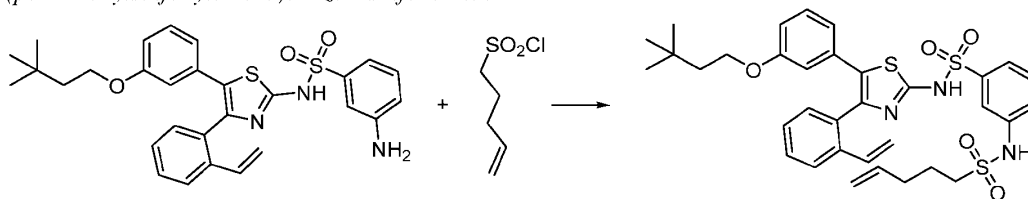
LCMS (Method 4): LC retention time = 2.08 min. MS (ESI) *m/z* 588.3 [M-H]⁻.

¹H NMR (400 MHz, MeOH-*d*₄) δ 7.46-7.26 (m, 4H), 7.22-7.08 (m, 3H), 7.02 (s, 1H), 6.85-6.69 (m, 3H), 6.49 (d, *J* = 2.0 Hz, 1H), 3.61 (s, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 2H), 1.55 (t, *J* = 7.2 Hz, 2H), 1.50-1.35 (m, 5H), 1.23 (s, 3H), 0.91 (s, 9H).

EXAMPLE 11. Preparation of 6-[3-(3,3-Dimethylbutoxy)phenyl]-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide



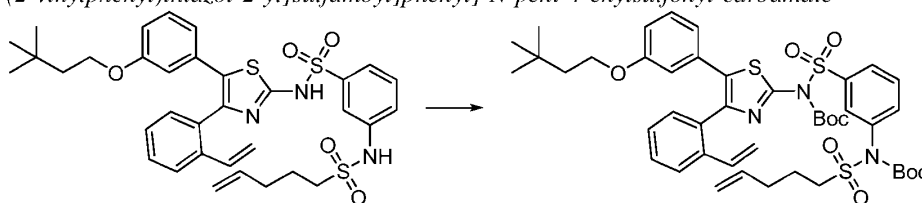
Step 1. Synthesis of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-(pent-4-enylsulfonylamino)benzenesulfonamide



[437] To a solution of 3-amino-N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]benzenesulfonamide (from Step 5 of **Example 10**) (1.00 eq, 300 mg, 0.562 mmol) in pyridine (2 mL) was added pent-4-ene-1-sulfonyl chloride (1.58 eq, 150 mg, 0.889 mmol). The mixture was stirred at 60 °C for 12 h and the desired product was detected by LCMS. The mixture was washed with water (50.0 mL) and back extracted with ethyl acetate (50 mL × 3). The combined organic phases were concentrated to give a residue which was purified by flash column chromatography (petroleum ether : ethyl acetate = 3 : 1) to obtain the title compound (150 mg, 0.214 mmol, 38.1 % yield) as a tan solid.

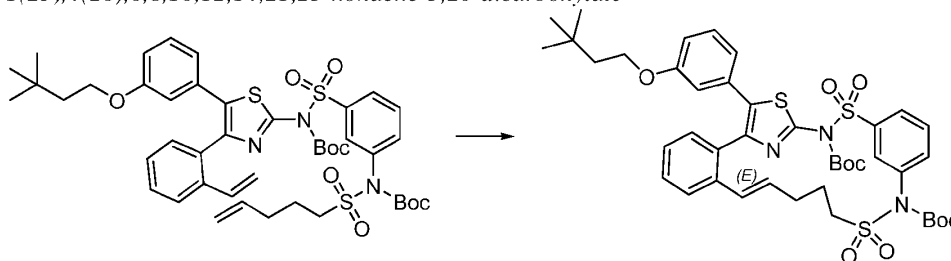
LCMS (Method 4): LC retention time = 2.06 min. MS (ESI) m/z 666.2 $[M+H]^+$.

Step 2. Synthesis of tert-butyl N-[3-[tert-butoxycarbonyl-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]sulfamoyl]phenyl]-N-pent-4-enylsulfonyl-carbamate



[438] To a solution of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-3-(pent-4-enylsulfonylamino)benzenesulfonamide (1.00 eq, 50 mg, 0.0751 mmol) in DCM (5 mL) was added di-*tert*-butyl dicarbonate (9.76 eq, 0.17 mL, 0.733 mmol) and 4-dimethylaminopyridine (0.545 eq, 5.0 mg, 0.0409 mmol). The mixture was stirred at 50 °C for 12 h and the desired product was detected by LCMS. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether : ethyl acetate = 5 : 1) to obtain the title compound (40 mg, 0.0439 mmol, 58.4 % yield) as a light-yellow solid. LCMS (Method 1): Retention time 3.82 min. MS (ESI) m/z 766.3 $[M+H]^+$.

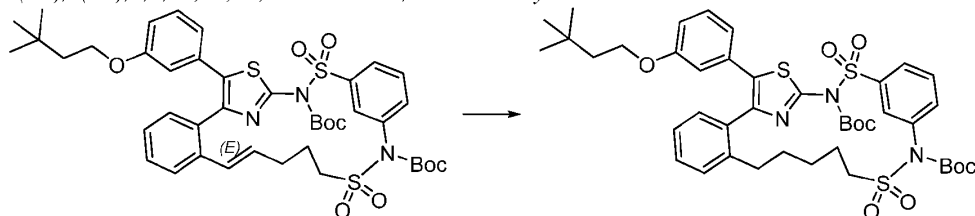
Step 3. Synthesis of di-tert-butyl (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,14,21,23-nonaene-3,20-dicarboxylate



[439] To a solution of *tert*-butyl N-[3-[*tert*-butoxycarbonyl]-5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]sulfamoyl]phenyl]-N-pent-4-enylsulfonfyl-carbamate (1.00 eq, 40 mg, 0.0462 mmol) in DCE (2 mL) was added [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine) ruthenium (0.204 eq, 8.0 mg, 0.00942 mmol) under N₂. The mixture was stirred at 80 °C for 2 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 5 : 1) to obtain the title compound (20 mg, 0.0227 mmol, 49.1 % yield) as light-yellow solid.

LCMS (Method 1): LC retention time = 3.64 min. MS (ESI) *m/z* 738.3 [M+H-Boc]⁺.

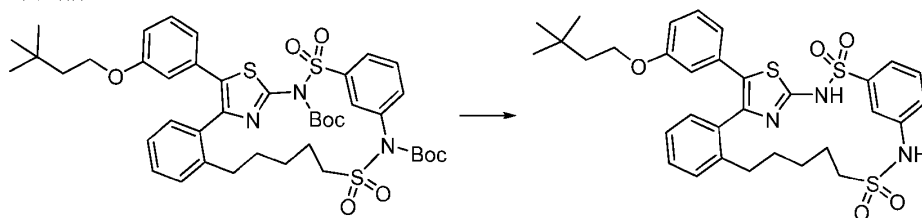
Step 4. Synthesis of di-tert-butyl 6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene-3,20-dicarboxylate



[440] To a solution of di-*tert*-butyl (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,14,21,23-nonaene-3,20-dicarboxylate (1.00 eq, 20 mg, 0.0239 mmol) in methanol (10 mL) was added Pd/C (5.0 mg). The mixture was stirred at room temperature for 2 h under H₂ atmosphere. The mixture was filtered, and the filtrate was concentrated to give the title compound (10 mg, 0.0113 mmol, 47.4 % yield) as an off-white oil.

LCMS (Method 1): LC retention time = 3.35 min. MS (ESI) *m/z* 640.3 [M+H-2Boc]⁺.

Step 5. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide

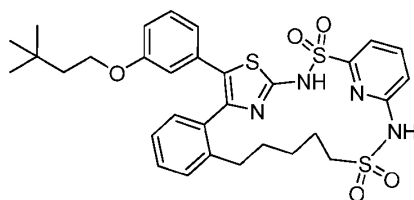


[441] To a solution of di-*tert*-butyl 6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2 λ 6,5,19 λ 6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene-3,20-dicarboxylate (1.00 eq, 10 mg, 0.0119 mmol) in DCM (5 mL) was added trifluoroacetic acid (2.95 eq, 0.0027 mL, 0.0351 mmol). The mixture was stirred at 50 °C for 12 h. The mixture was concentrated to give a residue which was taken in NaHCO₃ saturate solution (10 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phases were concentrated to give a residue which was purified by silica gel flash column chromatography (dichloromethane : methanol = 10 : 1) to obtain the title compound (4.2 mg, 0.00650 mmol, 54.6 % yield) as a white solid.

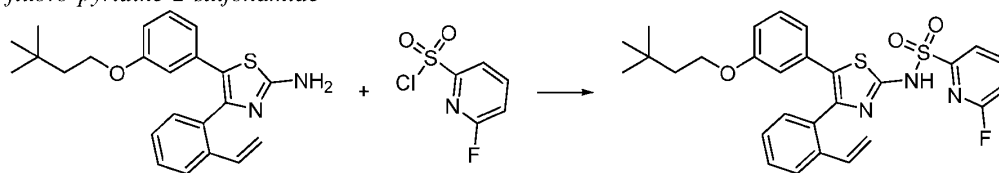
LCMS (Method 4): LC retention time = 1.97 min. MS (ESI) m/z 638.3 [M-H]⁻.

¹H NMR (500 MHz, MeOH-*d*₄) δ 8.06 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.51-7.33 (m, 5H), 7.28-7.23 (m, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.83-6.74 (m, 2H), 6.61-6.58 (m, 1H), 3.67 (s, 2H), 3.08-2.96 (m, 2H), 2.33-2.17 (m, 2H), 1.58-1.45 (m, 5H), 1.23 (m, 3H), 0.93 (s, 9H).

EXAMPLE 12. Preparation of 6-[3-(3,3-Dimethylbutoxy)phenyl]-2 λ 6,5,19 λ 6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide



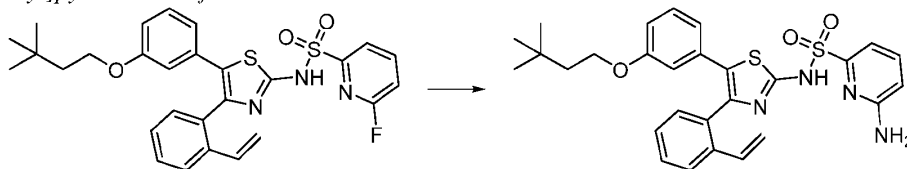
Step 1. Synthesis of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide



[442] To a test tube containing 5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-amine (from **Example 10**, Step 3) (1.00 eq, 300 mg, 0.793 mmol) in pyridine (2 mL) was added 6-fluoropyridine-2-sulfonyl chloride (1.29 eq, 200 mg, 1.02 mmol). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether / ethyl acetate = 5/1) to obtain the title compound (300 mg, 0.530 mmol, 66.8 % yield) as a light-yellow solid.

LCMS (Method 1): LC retention time = 2.32 min. MS (ESI) m/z 538.1 $[M+H]^+$.

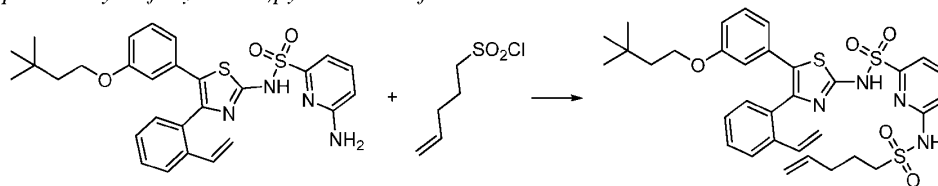
Step 2. Synthesis of 6-amino-N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]pyridine-2-sulfonamide



[443] To a solution of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide (1.00 eq, 300 mg, 0.558 mmol) in 1,4-dioxane (1 mL) was added aqueous ammonia (5.0 mL). The mixture was stirred at 80 °C for 3 days and the desired product was detected by LCMS. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 5 : 1) to obtain the title compound (150 mg, 0.267 mmol, 47.7 % yield) as a light-yellow solid.

LCMS (Method 1): LC retention time = 2.24 min. MS (ESI) m/z 535.2 $[M+H]^+$.

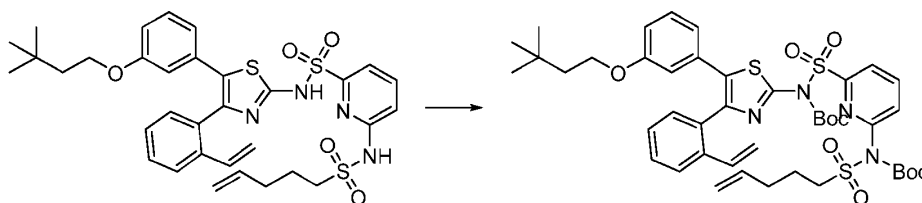
Step 3. Synthesis of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-6-(pent-4-enylsulfonylamino)pyridine-2-sulfonamide



[444] To a solution of 6-amino-N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]pyridine-2-sulfonamide (1.00 eq, 150 mg, 0.281 mmol) in DCM (5 mL) was added pent-4-ene-1-sulfonyl chloride (1.52 eq, 72 mg, 0.427 mmol) and triethylamine (3.17 eq, 0.12 mL, 0.889 mmol). The mixture was stirred at 30 °C for 12 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 5 : 1) to obtain the title compound (70 mg, 0.0997 mmol, 35.5 % yield) as an off-white solid.

LCMS (Method 2): LC retention time = 2.02 min. MS (ESI) m/z 667.2 $[M+H]^+$.

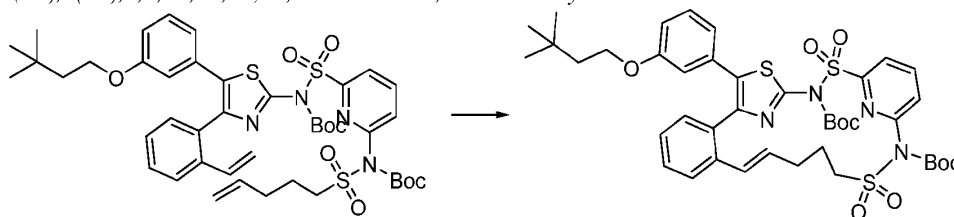
Step 4. Synthesis of tert-butyl N-[6-[tert-butoxycarbonyl]-5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]sulfamoyl]-2-pyridyl]-N-pent-4-enylsulfonyl-carbamate



[445] To a solution of N-[5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]-6-(pent-4-enylsulfonylamino)pyridine-2-sulfonamide (1.00 eq, 60 mg, 0.0900 mmol) in DCM (5 mL) was added 4-dimethylaminopyridine (0.273 eq, 3.0 mg, 0.0246 mmol) and di-*tert*-butyl di-carbonate (5.09 eq, 0.11 mL, 0.458 mmol). The mixture was stirred at 50 °C for 12 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 5 : 1) to obtain the title compound (50 mg, 0.0548 mmol, 60.8 % yield) as a light-yellow solid.

LCMS (Method 1): LC retention time = 3.58 min. MS (ESI) m/z 768.3 [M-BOC+H]⁺

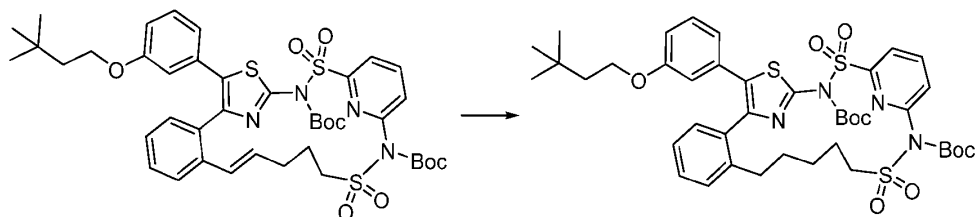
Step 5. Synthesis of di-tert-butyl (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2λ6,5,19λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosal(25),4(26),6,8,10,12,14,21,23-nonaene-3,20-dicarboxylate



[446] To a solution of *tert*-butyl N-[6-[*tert*-butoxycarbonyl]-5-[3-(3,3-dimethylbutoxy)phenyl]-4-(2-vinylphenyl)thiazol-2-yl]sulfamoyl]-2-pyridyl]-N-pent-4-enylsulfonyl-carbamate (1.00 eq, 50 mg, 0.0577 mmol) in DCE (2 mL) was added [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene) (tricyclohexylphosphine) ruthenium (0.204 eq, 10 mg, 0.0118 mmol) under N₂. The mixture was stirred at 80 °C for 2 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 5 : 1) to obtain the title compound (20 mg, 0.0226 mmol, 39.2 % yield) as a light-yellow solid.

LCMS (Method 1): LC retention time = 3.57 min. MS (ESI) m/z 739.3 [M+H-Boc]⁺.

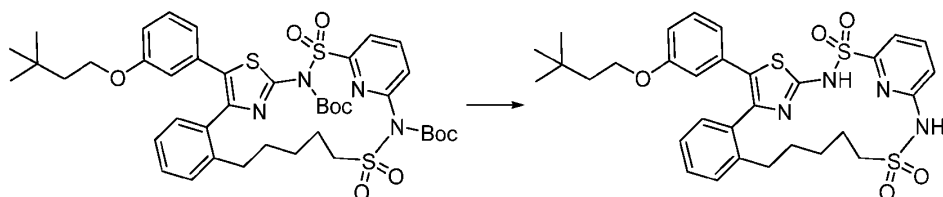
Step 6. Synthesis of di-tert-butyl 6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2λ6,5,19λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosal(25),4(26),6,8,10,12,21,23-octaene-3,20-dicarboxylate



[447] To a solution of di-*tert*-butyl (14E)-6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2 λ 6,5,19 λ 6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,14,21,23-nonaene-3,20-dicarboxylate (1.00 eq, 20 mg, 0.0238 mmol) in methanol (10 mL) was added Pd/C (5.0 mg). The mixture was stirred under H₂ atmosphere at room temperature for 2 h. The mixture was filtered, and the filtrate was concentrated to give the title compound (15 mg, 0.0169 mmol, 71.1 % yield) as a light-yellow oil.

LCMS (Method 1): LC retention time = 4.14 min. MS (ESI) *m/z* 741.2 [M+H-Boc]⁺.

Step 7. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-2 λ 6,5,19 λ 6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide



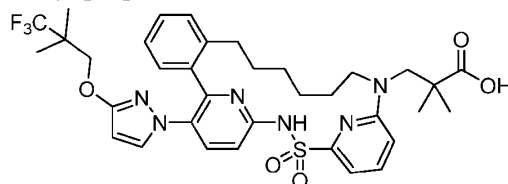
[448] To a solution of di-*tert*-butyl 6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,19,19-tetraoxo-2 λ 6,5,19 λ 6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene-3,20-dicarboxylate (1.00 eq, 15 mg, 0.0178 mmol) in DCM (5 mL) was added trifluoroacetic acid (2.95 eq, 0.0041 mL, 0.0526 mmol). The mixture was stirred at 50 °C for 12 h. The mixture was concentrated. The residue was neutralized with NaHCO₃ saturate aqueous solution (10.0 mL) and back extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phases were concentrated to give a residue which was purified by flash column chromatography (dichloromethane: methanol = 10 : 1) to obtain the title compound (7.0 mg, 0.0108 mmol, 60.6 % yield) as a white solid.

LCMS (Method 2): LC retention time = 1.83 min. MS (ESI) *m/z* 639.0 [M-H]⁻.

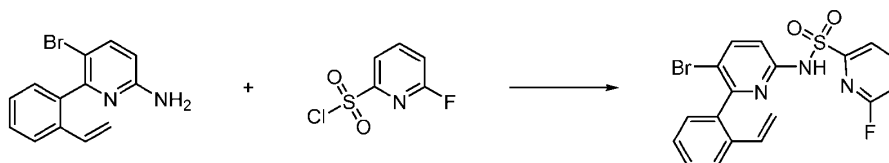
¹H NMR (400 MHz, MeOH-*d*₄) δ 7.91 (t, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.46-7.34 (m, 3H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 6.75 (d, *J* = 8.8 Hz,

1H), 6.58 (s, 1H), 3.65 (t, $J = 7.1$ Hz, 2H), 3.27-3.17 (m, 2H), 2.31 (s, 2H), 1.72-1.61 (m, 2H), 1.56 (t, $J = 7.1$ Hz, 2H), 1.39 (d, $J = 6.8$ Hz, 2H), 1.33-1.22 (m, 2H), 0.92 (s, 9H).

EXAMPLE 13. Preparation of 3-[20,20-Dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid



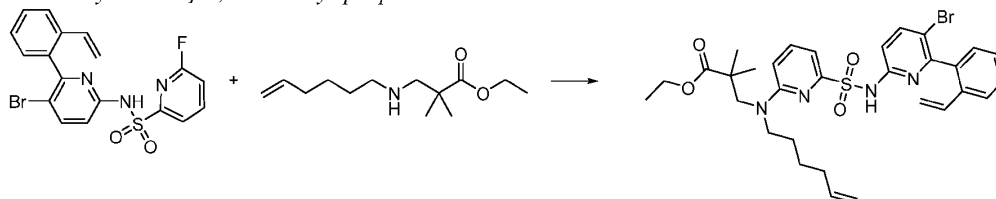
Step 1. Synthesis of N-[5-bromo-6-(2-vinylphenyl)-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide



[449] To a solution of 5-bromo-6-(2-vinylphenyl)pyridin-2-amine (**Intermediate A-3**) (1.00 eq, 5000 mg, 18.2 mmol) in pyridine (50mL) was added 6-fluoropyridine-2-sulfonyl chloride (1.13 eq, 4000 mg, 20.4 mmol) slowly at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated to give a residue which was purified by flash column chromatography (petroleum ether: ethyl acetate = 3 : 1) to obtain the title compound (4.0 g, 8.75 mmol, 48.2 % yield) as a light-yellow solid.

LCMS (Method 4): LC retention time = 1.69 min. MS (ESI) m/z 434.0, 436.0 $[M+H]^+$.

Step 2. Synthesis of ethyl 3-[[6-[[5-bromo-6-(2-vinylphenyl)-2-pyridyl]sulfamoyl]-2-pyridyl]-hex-5-enyl-amino]-2,2-dimethyl-propanoate

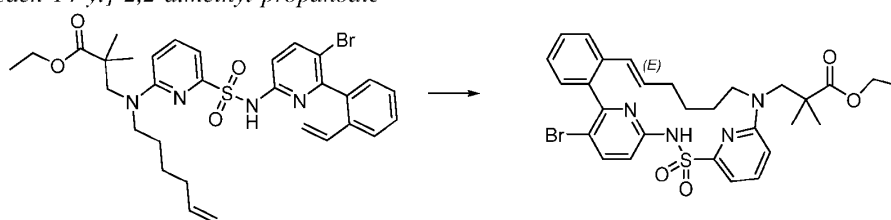


[450] To a mixture of ethyl 3-(hex-5-enylamino)-2,2-dimethyl-propanoate (1.00 eq, 500 mg, 2.20 mmol) in DMSO (10 mL) were added N-[5-bromo-6-(2-vinylphenyl)-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (1.20 eq, 1146 mg, 2.64 mmol) and N,N-diisopropylethylamine (3.00 eq, 1.1 mL, 6.60 mmol). The mixture was stirred at 150 °C for 48 h under N₂. The

reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reversed phase flash chromatography to give the title compound (160 mg, 0.249 mmol, 11.3 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.34 min. MS (ESI) m/z 641, 643 $[M+H]^+$.

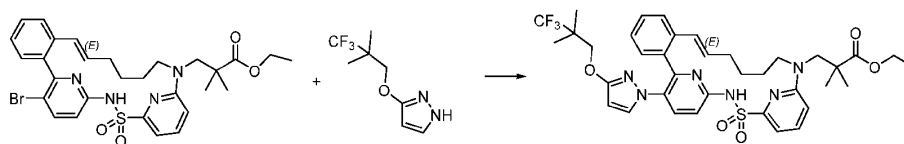
Step 3. Synthesis of ethyl 3-[(8E)-25-bromo-20,20-dioxo-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,8,15(27),16,18,22(26),23-decaen-14-yl]-2,2-dimethyl-propanoate



[451] To a solution of ethyl 3-[[6-[[5-bromo-6-(2-vinylphenyl)-2-pyridyl]sulfamoyl]-2-pyridyl]-hex-5-enyl-amino]-2,2-dimethyl-propanoate (1.00 eq, 160 mg, 0.249 mmol) in DCE (5 mL) was added [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (0.100 eq, 21 mg, 0.0249 mmol). The mixture was stirred at 65 °C for 16 h under N_2 . The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography eluting with 15 % EA in petroleum ether to give the title compound (80 mg, 0.130 mmol, 52.3 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.25 min. MS (ESI) m/z 613, 615 $[M+H]^+$.

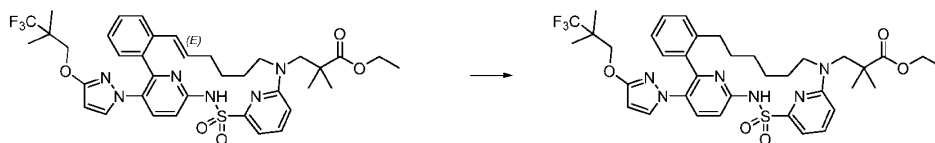
Step 4. Synthesis of ethyl 3-[(8E)-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,8,15(27),16,18,22(26),23-decaen-14-yl]-2,2-dimethyl-propanoate



[452] To a solution of ethyl 3-[(8E)-25-bromo-20,20-dioxo-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacos-1(25),2,4,6,8,15(27),16,18,22(26),23-decaen-14-yl]-2,2-dimethyl-propanoate (1.00 eq, 50 mg, 0.0815 mmol) in DMF (1.5 mL) were added 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (**Intermediate B-28**) (2.00 eq, 34 mg, 0.163 mmol), N,N'-dimethylethane-1,2-diamine (5.00 eq, 36 mg, 0.407 mmol) and copper (I) iodide (1.00 eq, 16 mg, 0.0815 mmol). The mixture was stirred at 120 °C for 24 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography eluting with 5 % EA in petroleum ether to give the title compound (70 mg, 0.0227 mmol, 27.8 % yield) as a white solid.

LCMS (Method 2): LC retention time = 2.41 min. MS (ESI) m/z 741.0 [M+H]⁺.

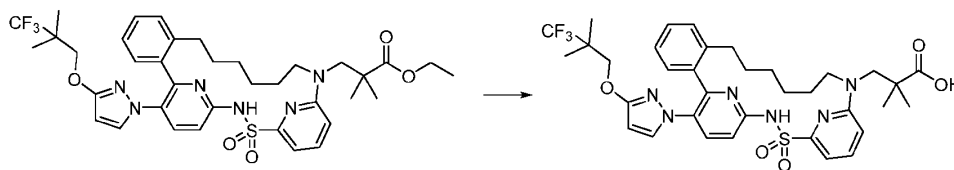
Step 5. Synthesis of ethyl 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoate



[453] To a solution of ethyl 3-[(8E)-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacos-1(25),2,4,6,8,15(27),16,18,22(26),23-decaen-14-yl]-2,2-dimethyl-propanoate (1.00 eq, 70 mg, 0.0227 mmol) in methanol (5 mL) was added platinum (IV) oxide (1.00 eq, 5.1 mg, 0.0227 mmol). The suspension was stirred at rt for 3 h under H₂ atmosphere. The reaction mixture was filtered and concentrated in *vacuo* to give the title compound (60 mg, 0.0186 mmol, 81.9 % yield) as a white solid.

LCMS (Method 2): LCMS: LC retention time = 2.46 min. MS (ESI) m/z 743.0 [M+H]⁺.

Step 6. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid

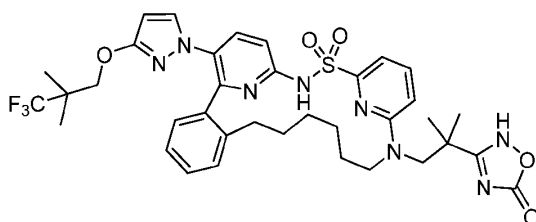


[454] To a solution of ethyl 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoate (1.00 eq, 60 mg, 0.0186 mmol) in methanol (2 mL) and THF (2 mL) was added sodium hydroxide (363 eq, 1.1 mL, 6.75 mmol). The mixture was stirred at rt for 13 h. The reaction mixture was poured into water (50 mL), and adjusted pH to 6-7 with citric acid and extracted with ethyl acetate (30 mL × 3). The combined organic phases were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified by reversed phase flash column chromatography to give the title compound (5.6 mg, 0.00783 mmol, 42.2 % yield) as a white solid.

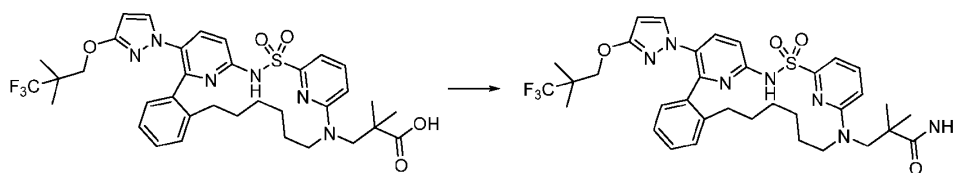
LCMS (Method 4): LCMS: LC retention time = 1.92 min. MS (ESI) m/z 715.0 $[M+H]^+$.

^1H NMR (500 MHz, MeOH-d_4) δ 7.93 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.60 (dd, J = 8.6, 7.3 Hz, 1H), 7.27 (td, J = 7.3, 1.8 Hz, 1H), 7.24-7.14 (m, 4H), 6.93 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.03 (s, 2H), 3.79-3.47 (m, 4H), 2.44-2.11 (m, 2H), 1.43-1.27 (m, 4H), 1.20 (s, 6H), 1.16 (s, 6H), 1.12-1.03 (m, 2H), 0.90 (s, 2H).

EXAMPLE 14. Preparation of 3-[2-[20,20-Dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-1,1-dimethyl-ethyl]-2H-1,2,4-oxadiazol-5-one



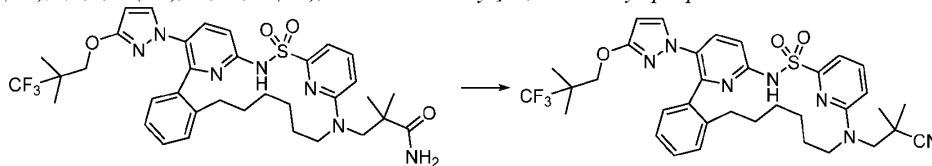
Step 1. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide



[455] To a solution of **Example 13** (1.00 eq, 35 mg, 0.0490 mmol) in DMF (2 mL) was added ammonium chloride (10.0 eq, 26 mg, 0.490 mmol), N,N-diisopropylethylamine (3.00 eq, 0.026 mL, 0.147 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.50 eq, 28 mg, 0.0734 mmol). The reaction mixture was stirred at rt for 2 h. The mixture was poured into water (30 mL). The resulting aqueous solution was extracted with ethyl acetate (30 mL $\times$ 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulted residue was purified by reversed phase flash chromatography to give the title compound (30 mg, 0.0420 mmol, 85.8 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.14 min. MS (ESI) m/z 714.0 [M+H]⁺.

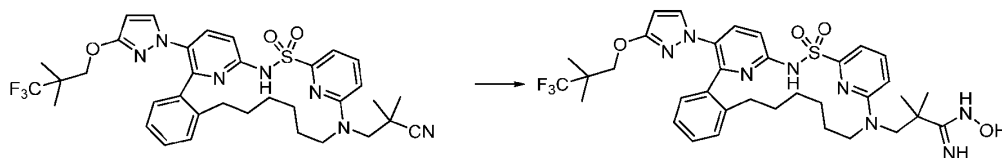
Step 2. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanenitrile



[456] To a solution of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide (1.00 eq, 30 mg, 0.0420 mmol) in DCM (5 mL) was added N,N-diethyl-N-[(methoxycarbonyl)amino]sulfonyl]ethanaminium inner salt (5.00 eq, 50 mg, 0.210 mmol). The reaction mixture was stirred at rt for 4 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% EA in petroleum ether to give the title compound (28 mg, 0.0402 mmol, 95.8 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.17 min. MS (ESI) m/z 696.0 [M+H]⁺.

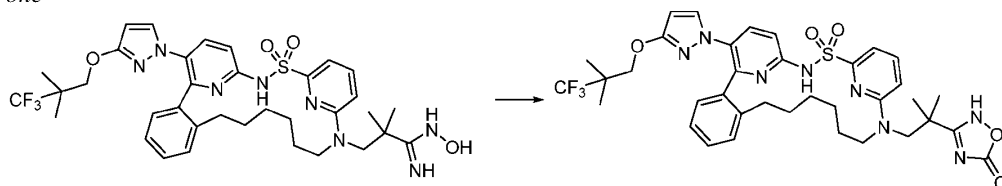
Step 3. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-N-hydroxy-2,2-dimethyl-propanamidine



[457] To a solution of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanenitrile (1.00 eq, 28 mg, 0.0402 mmol) in ethanol (3 mL) was added hydroxylamine (50wt.% in water, 0.5 mL). The reaction was stirred at 65 °C for 4 h. The reaction mixture was concentrated in vacuo. The residue was purified by reversed phase flash chromatography to give the title compound (20 mg, 0.0274 mmol, 68.2 % yield) as a white solid.

LCMS (Method 3): LC retention time = 1.76 min. MS (ESI) m/z 729.0 [M+H]⁺.

Step 4. Synthesis of 3-[2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-1,1-dimethyl-ethyl]-2H-1,2,4-oxadiazol-5-one



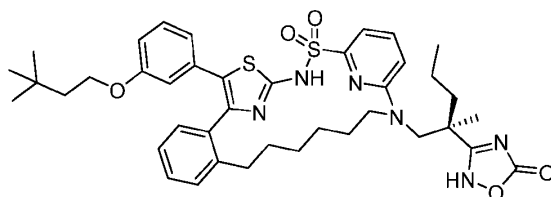
[458] To a solution of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-N-hydroxy-2,2-dimethyl-propanamidine (1.00 eq, 20 mg, 0.0274 mmol) in ethyl acetate (10 mL) was added N,N'-carbonyldiimidazole (10.0 eq, 44 mg, 0.274 mmol). The reaction was stirred at 70 °C for 12 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by reversed phase flash chromatography to give the title compound (4.2 mg, 0.00556 mmol, 20.3 % yield) as a white solid.

LCMS (Method 2): LC retention time = 2.28 min. MS (ESI) m/z 755.3 [M+H]⁺.

¹H NMR (400 MHz, MeOH-*d*₄) δ 7.93 (d, *J* = 8.9 Hz, 1H), 7.76-7.66 (m, 1H), 7.62 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.33-7.10 (m, 5H), 6.93-6.84 (m, 2H), 5.63 (d, *J* = 2.6 Hz, 1H), 4.02 (s, 2H),

3.83-3.36 (m, 4H), 2.35-2.05 (m, 2H), 1.45-1.15 (m, 16H), 1.14-1.03 (m, 2H), 0.97-0.81 (m, 2H).

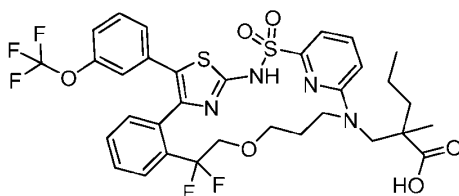
EXAMPLE 15. Preparation of 3-[(1R)-1-[[6-[3-(3,3-Dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-1-methyl-butyl]-2H-1,2,4-oxadiazol-5-one



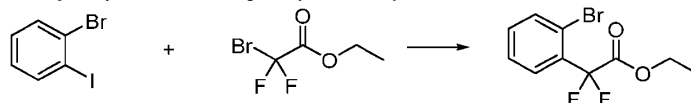
[459] The title compound was synthesized in essentially the same manner as **Example 14** except using **Example 7 (P1)** as the starting material instead of **Example 13**.

LCMS (Method 4): LC retention time = 1.99 min. MS(ESI) m/z 758 [M-H]⁻. ¹H NMR (400 MHz, MeOH-*d*₄) δ: 7.68-7.55 (m, 1H), 7.51-7.27 (m, 4H), 7.27-7.09 (m, 2H), 6.94-6.64 (m, 3H), 6.52 (s, 1H), 4.50-3.51 (m, 5H), 2.86 (br, 1H), 2.32 (m, 2H), 1.90-0.81 (m, 29H).

EXAMPLE 16. Preparation of 2-[[14,14-Difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-16-oxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid



Step 1. Synthesis of ethyl 2-(2-bromophenyl)-2,2-difluoro-acetate

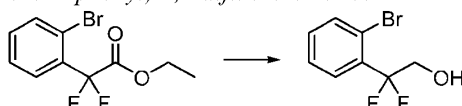


[460] To a solution of 1-bromo-2-iodobenzene (1.00 eq, 9.1 mL, 70.7 mmol) and ethyl bromodifluoroacetate (1.00 eq, 9.1 mL, 70.7 mmol) in DMSO (150 mL) was added copper (powder, 300 mesh) (2.60 eq, 11.68 g, 184 mmol). The mixture was stirred at 50 °C for 16 h under nitrogen. After cooling to rt, the mixture was filtered, and the filtrate was washed with water (150 mL). The aqueous was extracted with EA (100 mL × 3). The organic layers were combined and washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum.

The residue was purified by flash column chromatography (PE: EA = 15: 1) to give the title compound (14.00 g, 50.2 mmol, 71.0 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.96 min. MS (ESI) m/z 279.0, 281.0 $[M+H]^+$.

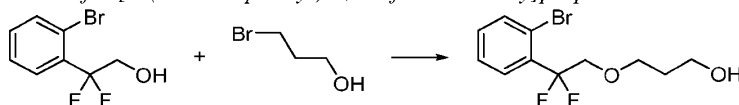
Step 2. Synthesis of 2-(2-bromophenyl)-2,2-difluoro-ethanol



[461] To a solution of ethyl 2-(2-bromophenyl)-2,2-difluoroacetate (1.00 eq, 10.00 g, 35.8 mmol) in methanol (100 mL) was added sodium borohydride (1.20 eq, 1.63 g, 43.0 mmol) in five portions at 0 °C, the mixture was stirred at 0 °C for 30 min. Water (150 mL) was added and the resultant aqueous solution was extracted with EA (100 mL $\times$ 3). The combined organic layers were washed with brine and dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by reversed-phase flash chromatography (C18) (A: 0.1% NH_4HCO_3 in water, B: MeCN, 10-100%) to give the title compound (7.50 g, 31.6 mmol, 88.3 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.77 min. MS (ESI) m/z 237.1, 239.1 $[M+H]^+$.

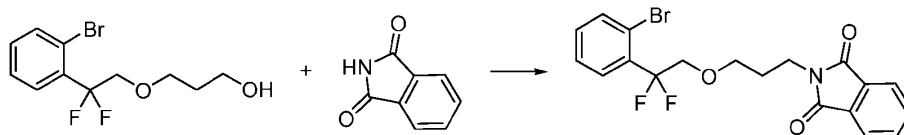
Step 3. Synthesis of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-ol



[462] To a solution of 2-(2-bromophenyl)-2,2-difluoroethanol (1.00 eq, 5.60 g, 23.6 mmol) and 3-bromo-1-propanol (1.20 eq, 2.5 mL, 28.3 mmol) in 1,4-dioxane (20 mL) was added 33% NaOH (5 mL). The mixture was stirred at room temperature under nitrogen for 16 h and concentrated. The residue was purified by flash column chromatography (PE: EA= 4: 1) to give the title compound (6.00 g, 20.3 mmol, 86.1 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 1.55 min. MS (ESI) m/z 295.1, 297.1 $[M+H]^+$.

Step 4. Synthesis of 2-[3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl]isoindoline-1,3-dione

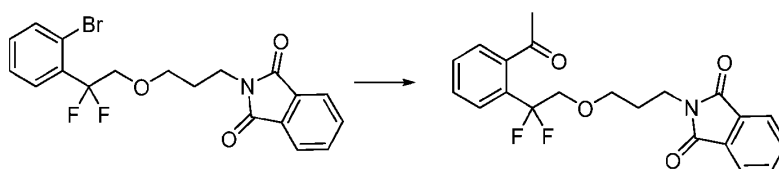


[463] To a solution of 3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propan-1-ol (1.00 eq, 6.00 g, 20.3 mmol) in dry THF (12 mL) were added phthalimide (1.50 eq, 4.49 g, 30.5 mmol) and

triphenylphosphine (1.50 eq, 8.00 g, 30.5 mmol). The reaction was stirred at 0 °C under nitrogen. To this mixture was added dropwise diethyl azodicarboxylate (1.50 eq, 4.8 mL, 30.5 mmol) over a period of 10 min, and the reaction was monitored by LCMS. After completing, the reaction mixture was concentrated and the residue was purified by flash column chromatography (PE: EA = 10 : 1) to give the title compound (6.80 g, 16.0 mmol, 78.8 % yield) as a colorless oil.

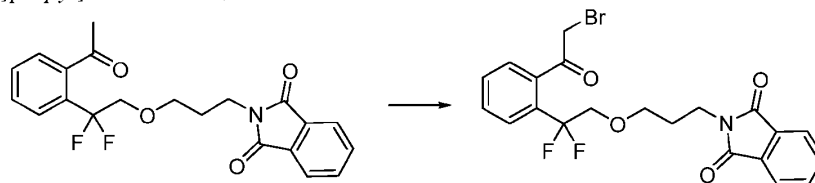
LCMS (Method 1): LC retention time = 2.09 min. MS (ESI) m/z 424.1, 426.1 $[M+H]^+$.

Step 5. Synthesis of 2-[3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl]isoindoline-1,3-dione



[464] To a solution of 2-[3-[2-(2-bromophenyl)-2,2-difluoro-ethoxy]propyl]isoindoline-1,3-dione (1.00 eq, 6.80 g, 16.0 mmol) and 1-ethoxyvinyltri-*n*-butyltin (2.00 eq, 11 mL, 32.1 mmol) in dry toluene (20 mL) was added bis(triphenylphosphine)palladium(II) chloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$) (0.10 eq, 1.13 g, 1.60 mmol). The reaction mixture was stirred at 80 °C for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was dissolved in THF (15 mL) and 2N HCl (5 mL) and stirred at rt for 30 min. Then the mixture was concentrated and the residue was purified by flash column chromatography (PE : EA = 5 : 1) to give the title compound (5.10 g, 13.2 mmol, 82.1 % yield) as a white solid. LCMS (Method 1): LC retention time = 1.97 min. MS (ESI) m/z 388.2 $[M+H]^+$.

Step 6. Synthesis of 2-[3-[2-[2-(2-bromoacetyl)phenyl]-2,2-difluoro-ethoxy]propyl]isoindoline-1,3-dione

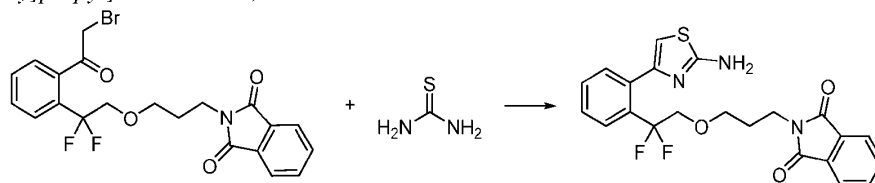


[465] To a solution of 2-[3-[2-(2-acetylphenyl)-2,2-difluoro-ethoxy]propyl]isoindoline-1,3-dione (1.00 eq, 5.10 g, 13.2 mmol) in MeCN (10 mL) and THF (10 mL) was added dibromo- λ 3-bromane-pyridine (1.50 eq, 6.32 g, 19.7 mmol) in three portions. The reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated and purified by flash column

chromatography (PE: EA = 1: 1) to give the partially purified title compound (9.6 g) as a yellow oil.

LCMS (Method 1): LC retention time = 2.01 min. MS (ESI) m/z 466.1, 468.1 $[M+H]^+$.

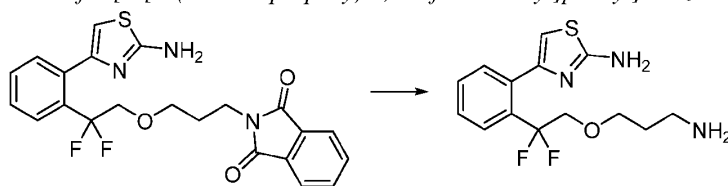
Step 7. Synthesis of 2-[3-[2-[2-(2-aminothiazol-4-yl)phenyl]-2,2-difluoroethoxy]propyl]isoindoline-1,3-dione



[466] To a solution of 2-[3-[2-[2-(2-bromoacetyl)phenyl]-2,2-difluoroethoxy]propyl]isoindoline-1,3-dione (9.6 g) in ethanol (25 mL) was added thiourea (1.50 eq, 387 mg, 5.09 mmol). The mixture was stirred at 80 °C for 1 h and concentrated. The residue was purified by reversed-phase flash chromatography (C18) (A: 0.1% NH_4HCO_3 in water, B: MeCN, 10-100%) to give the title compound (6.0 g) as a colorless oil.

LCMS (Method 1): LC retention time = 1.63 min. MS (ESI) m/z 444.2 $[M+H]^+$.

Step 8. Synthesis of 4-[2-[2-(3-aminopropoxy)-1,1-difluoro-ethyl]phenyl]thiazol-2-amine



[467] To a solution of 2-[3-[2-[2-(2-aminothiazol-4-yl)phenyl]-2,2-difluoroethoxy]propyl]isoindoline-1,3-dione (1.00 eq, 4.00 g, 9.02 mmol) in methanol (15 mL) and THF (5 mL) was added hydrazine hydrate ($\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$) (10.0 eq, 4.4 mL, 90.2 mmol). The reaction was stirred at 80 °C for 4 h. The mixture was cooled to rt and concentrated under reduced pressure to dryness. The residue was purified by reversed-phase flash chromatography (C18) (A: 0.1% NH_4HCO_3 in water, B: MeCN, 10-100%) to give the title compound (2.70 g, 8.62 mmol, 95.5 % yield) as a colorless oil.

LCMS (Method 4): LC retention time = 1.31 min. MS (ESI) m/z 314.2 $[M+H]^+$.

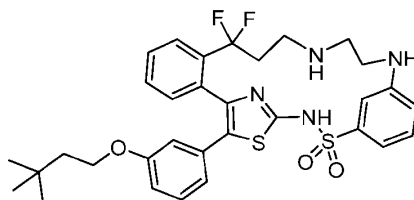
[468] The rest of the steps (Step 9 to Step 12) were performed by following Step 3 to Step 6 of **Example 6** except using 4-[2-[2-(3-aminopropoxy)-1,1-difluoro-ethyl]phenyl]thiazol-2-

amine instead of N-[4-[2-(6-aminohexyl)phenyl]thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide in Step 9.

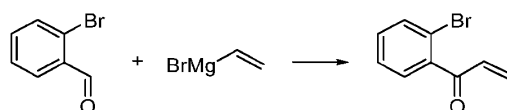
LCMS (Method 1): LC retention time = 2.07 min. MS (ESI) m/z 741.2 $[M+H]^+$.

1H NMR (400 MHz, MeOH- d_4) δ 7.72 (d, J = 7.6 Hz, 1H), 7.68-7.56 (m, 3H), 7.48 (s, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.98-6.82 (m, 2H), 3.97-3.34 (m, 8H), 2.07-1.55 (m, 3H), 1.44-1.12 (m, 3H), 1.09 (s, 3H), 0.97-0.69 (m, 3H).

EXAMPLE 17. Preparation of 6-[3-(3,3-Dimethylbutoxy)phenyl]-14,14-difluoro-2 λ 6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



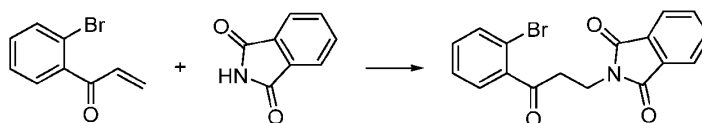
Step 1. Synthesis of 1-(2-bromophenyl)prop-2-en-1-one



[469] To a solution of 2-bromobenzaldehyde (1.00 eq, 16 mL, 135 mmol) in dry THF (250 mL) was added vinyl magnesium bromide (1.00 eq, 135 mL, 135 mmol) dropwise over 30 min at 0 °C. Then saturated NH_4Cl aqueous solution (150 mL) was added slowly while keeping the temperature at 0 °C. The aqueous solution was extracted with EA (100 mL $\times$ 3). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4 , filtered, and concentrated. The crude product was dissolved in DCM (150 mL). Then, Dess-Martin periodinane (2.00 eq, 114.62 g, 270 mmol) was added in five portions to the mixture at 0 °C and stirred for 30 min. The mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (PE : EA = 20 : 1) to give the title compound (15.00 g, 56.9 mmol, 42.1 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 2.74 min. MS (ESI) m/z 211, 213 $[M+H]^+$.

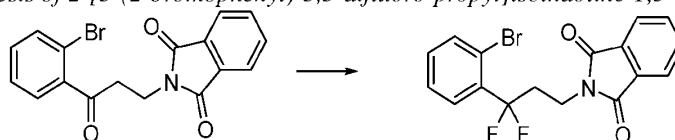
Step 2. Synthesis of 2-[3-(2-bromophenyl)-3-oxo-propyl]isoindoline-1,3-dione



[470] To a solution of 1-(2-bromophenyl)prop-2-en-1-one (1.00 eq, 10.00 g, 47.4 mmol) and phthalimide (1.00 eq, 6.97 g, 47.4 mmol) in ethyl acetate (100 mL) was added sodium ethoxide (0.200 eq, 0.64 g, 9.48 mmol). The reaction was stirred at 78 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by reversed-phase flash chromatography (C18 column; A: water with 0.1% NH₄HCO₃; B: 10-100% MeCN) to give the title compound (7.00 g, 19.5 mmol, 41.3 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.99 min. MS (ESI) m/z 358.0, 360.0 [M+H]⁺.

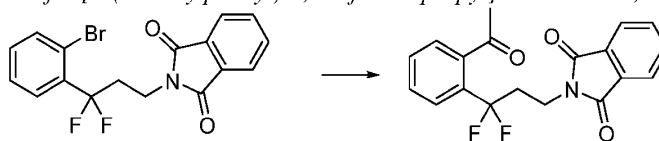
Step 3. Synthesis of 2-[3-(2-bromophenyl)-3,3-difluoro-propyl]isoindoline-1,3-dione



[471] To a solution of 2-[3-(2-bromophenyl)-3-oxo-propyl]isoindoline-1,3-dione (1.00 eq, 7.00 g, 19.5 mmol) in Chloroform (20 mL) was added diethylaminosulfur trifluoride (13.6 eq, 35 mL, 265 mmol). The reaction was stirred at 60 °C for 3 days. Then the mixture was diluted with saturated NaHCO₃ (500 mL) and extracted with DCM (100 mL × 3). The organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (PE: EA = 5 : 1) to give the title compound (2.90 g, 7.63 mmol, 39.0 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.65 min. MS (ESI) m/z 398.2, 400.2 [M+H₂O]⁺.

Step 4. Synthesis of 2-[3-(2-acetylphenyl)-3,3-difluoro-propyl]isoindoline-1,3-dione

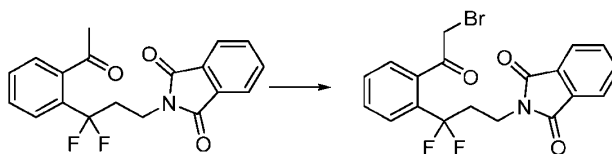


[472] To a solution of 2-[3-(2-bromophenyl)-3,3-difluoro-propyl]isoindoline-1,3-dione (1.00 eq, 3.00 g, 7.89 mmol) and 1-ethoxyvinyltri-n-butyltin (2.00 eq, 5.4 mL, 15.8 mmol) in toluene (20 mL) was added bis(triphenylphosphine)palladium(II) chloride (0.100 eq, 554 mg, 0.789 mmol) (Pd(PPh₃)₂Cl₂). The reaction was stirred at 80 °C for 6 h under N₂ and concentrated

under reduced pressure. The residue was dissolved in THF (15 mL) and 2N HCl (2 mL) was added while stirring at rt for 30 min. The mixture was concentrated to dryness. The residue was purified by flash column chromatography (PE : EA = 5 : 1) four times to give the title compound (1.30 g, 3.79 mmol, 48.0 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.90 min. MS (ESI) m/z 344.1 [M+H]⁺.

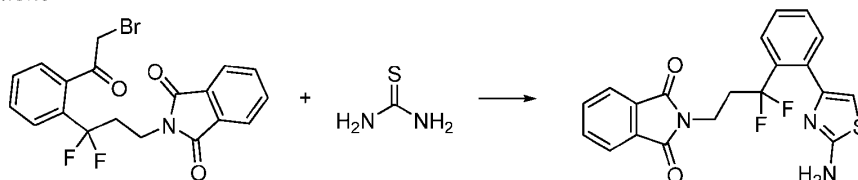
Step 5. Synthesis of 2-[3-[2-(2-bromoacetyl)phenyl]-3,3-difluoro-propyl]isoindoline-1,3-dione



[473] To a solution of 2-[3-(2-acetylphenyl)-3,3-difluoro-propyl]isoindoline-1,3-dione (1.00 eq, 1.30 g, 3.79 mmol) in acetonitrile (15 mL) was added pyridinium hydrogen tribromide (1.00 eq, 1.21 g, 3.79 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography (PE: EA = 1:1) to give the title compound (1.79 g, 2.97 mmol, 78.4 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.97 min. MS (ESI) m/z 444.0, 446.0 [M+Na]⁺.

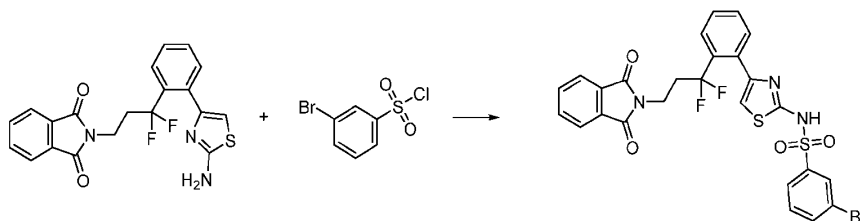
Step 6. Synthesis of 2-[3-[2-(2-aminothiazol-4-yl)phenyl]-3,3-difluoro-propyl]isoindoline-1,3-dione



[474] To a solution of 2-[3-[2-(2-bromoacetyl)phenyl]-3,3-difluoro-propyl]isoindoline-1,3-dione (1.00 eq, 1.79 g, 4.24 mmol) in ethanol (15 mL) was added thiourea (1.20 eq, 387 mg, 5.09 mmol). The reaction mixture was stirred at 80 °C for 1 h. Then the mixture was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography (column: C18; eluent: A: water with 0.1% NH₄HCO₃, B: MeCN; program: 10-100%) to give the title compound (1.22 g, 3.05 mmol, 72.1 % yield) as a colorless oil.

LCMS (Method 1): LC retention time = 1.62 min. MS (ESI) m/z 400.0 [M+H]⁺.

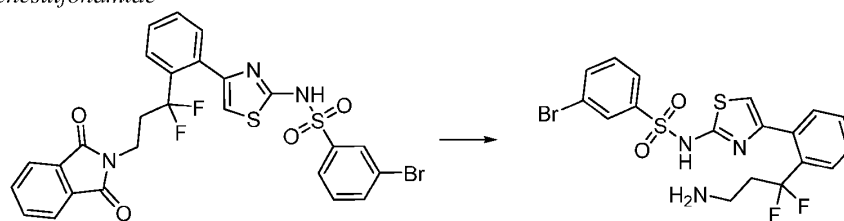
Step 7. Synthesis of 3-bromo-N-[4-[2-[3-(1,3-dioxoisindolin-2-yl)-1,1-difluoro-propyl]phenyl]thiazol-2-yl]benzenesulfonamide



[475] To a solution of 2-[3-[2-(2-aminothiazol-4-yl)phenyl]-3,3-difluoro-propyl]isindoline-1,3-dione (1.00 eq, 1.22 g, 3.05 mmol) in pyridine (10 mL) was added 3-bromobenzenesulfonyl chloride (1.20 eq, 937 mg, 3.67 mmol) in three portions at rt. The reaction was stirred at rt for 16 h. The mixture was concentrated under reduced pressure to dryness. The residue was purified by reversed-phase flash chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) to give the title compound (1.85 g, 2.99 mmol, 97.9 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.99 min. MS (ESI) m/z 618.0, 620.0 $[\text{M}+\text{H}]^+$.

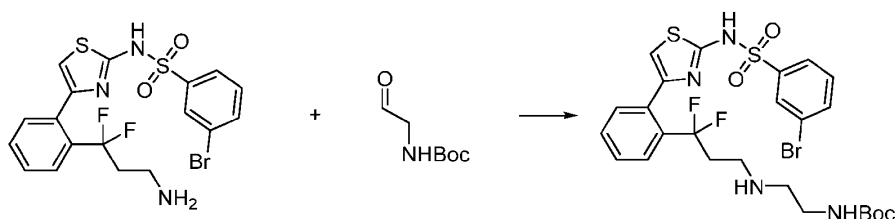
Step 8. Synthesis of N-[4-[2-(3-amino-1,1-difluoro-propyl)phenyl]thiazol-2-yl]-3-bromobenzenesulfonamide



[476] To a solution of 3-bromo-N-[4-[2-[3-(1,3-dioxoisindolin-2-yl)-1,1-difluoro-propyl]phenyl]thiazol-2-yl]benzenesulfonamide (1.00 eq, 1.85 g, 2.99 mmol) in methanol (15 mL) was added hydrazine hydrate (13.4 eq, 1.9 mL, 40.0 mmol). The reaction was stirred at 80 °C for 4 h. The mixture was concentrated under a vacuum. The residue was purified by reversed-phase flash chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) to give the title compound (1.22 g, 2.50 mmol, 83.5 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.49 min. MS (ESI) m/z 488.0, 490.0 $[\text{M}+\text{H}]^+$.

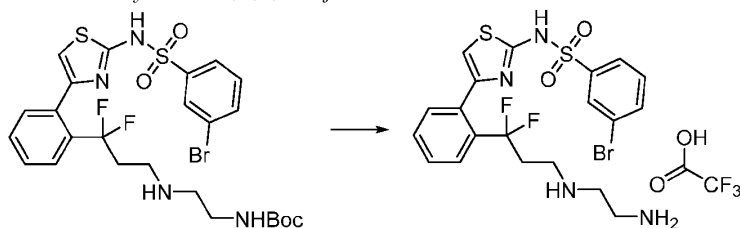
Step 9. Synthesis of tert-butyl N-[2-[[3-[2-[2-[(3-bromophenyl)sulfonylamino]thiazol-4-yl]phenyl]-3,3-difluoro-propyl]amino]ethyl]carbamate



[477] To a solution of N-[4-[2-(3-amino-1,1-difluoro-propyl)phenyl]thiazol-2-yl]-3-bromobenzenesulfonamide (1.00 eq, 1.00 g, 2.05 mmol) in DCM (10 mL) and methanol (10 mL) were added tert-butyl N-(2-oxoethyl)carbamate (1.50 eq, 489 mg, 3.07 mmol) and sodium triacetoxyborohydride (5.00 eq, 2.17 g, 10.2 mmol) at 0 °C. The reaction was stirred at 0 °C for 8 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) to give the title compound (400 mg, 0.633 mmol, 30.9 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.60 min. MS (ESI) m/z 631.2, 633.2 $[\text{M}+\text{H}]^+$.

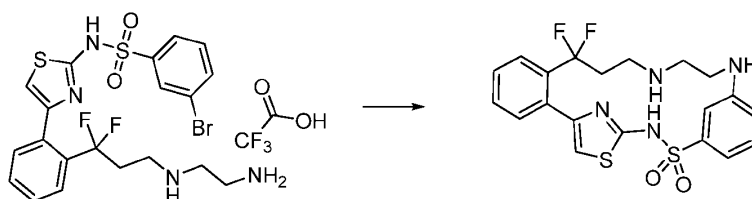
Step 10. Synthesis of N-[4-[2-[3-(2-aminoethylamino)-1,1-difluoro-propyl]phenyl]thiazol-2-yl]-3-bromobenzenesulfonamide; 2,2,2-trifluoroacetic acid



[478] To a solution of tert-butyl N-[2-[3-[2-[2-[(3-bromophenyl)sulfonylamino]thiazol-4-yl]phenyl]-3,3-difluoro-propyl]amino]ethyl]carbamate (1.00 eq, 400 mg, 0.633 mmol) in DCM (10 mL) was added trifluoroacetic acid (41.0 eq, 2.0 mL, 26.0 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the title compound (500 mg, 0.775 mmol, 122.31 % yield) as an oil. This sample was used directly for the next step reaction without further purification.

LCMS (Method 4): LC retention time = 1.48 min. MS (ESI) m/z 531.1, 533.1 $[\text{M}+\text{H}]^+$.

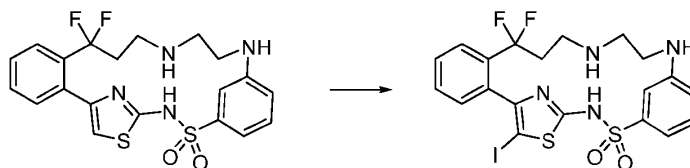
Step 11. Synthesis of 14,14-difluoro-2λ6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



[479] To a solution of N-[4-[2-[3-(2-aminoethylamino)-1,1-difluoro-propyl]phenyl]thiazol-2-yl]-3-bromo-benzenesulfonamide 2,2,2-trifluoroacetic acid (1.00 eq, 500 mg, 0.775 mmol) in 1,4-dioxane (3 mL) were added cesium carbonate (10.0 eq, 2.52 g, 7.75 mmol) and BrettPhos Pd G3 (CAS No.: 1470372-59-8) (0.500 eq, 351 mg, 0.387 mmol). The reaction mixture was stirred at 90 °C for 1.5 h under a nitrogen atmosphere. The mixture was concentrated and purified by reversed-phase flash chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) to give the title compound (65 mg, 0.144 mmol, 18.6 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.30 min. MS (ESI) m/z 451.2 $[\text{M}+\text{H}]^+$.

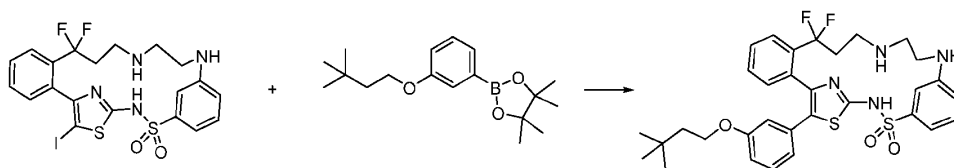
Step 12. Synthesis of 14,14-difluoro-6-iodo-2,6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



[480] To a solution of 14,14-difluoro-2,6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (1.00 eq, 75 mg, 0.166 mmol) in DMF (3 mL) was added N-iodosuccinimide (1.20 eq, 45 mg, 0.200 mmol). The reaction mixture was stirred at rt for 5 min. and concentrated under vacuum. The residue was purified by reversed-phase chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) to give the title compound (30 mg, 0.0520 mmol, 31.3 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.38 min. MS (ESI) m/z 577.1 $[\text{M}+\text{H}]^+$.

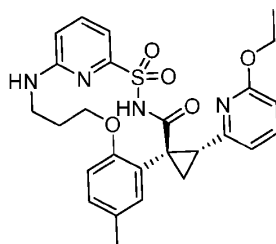
Step 13. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2,6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



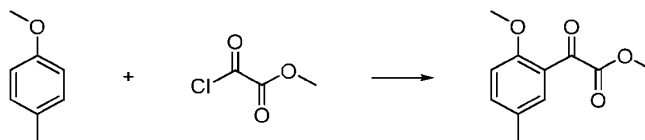
[481] To a solution of 14,14-difluoro-6-iodo-2λ6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (1.00 eq, 65 mg, 0.113 mmol) and 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate B-2a**) (1.20 eq, 41 mg, 0.135 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) were added potassium carbonate (1.00 eq, 16 mg, 0.113 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex ($\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$) (0.05 eq, 4.6 mg, 0.00564 mmol). The reaction was stirred at 100 °C for 1 h under N_2 . The reaction mixture was concentrated to dryness. The residue was purified by reversed-phase chromatography (column: C18; eluent: water with 0.1% NH_4HCO_3 , 10-100% MeCN) twice to give the title compound (10 mg, 0.0160 mmol, 14.1 % yield) as a white solid. LCMS (Method 1): LC retention time = 1.63 min. MS (ESI) m/z 627.3 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 7.76-7.61 (m, 3H), 7.60-7.51 (m, 1H), 7.32-7.23 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 7.10 (s, 1H), 6.94 (dt, J = 7.6, 2.0 Hz, 1H), 6.83 (dd, J = 7.7, 0.7 Hz, 1H), 6.78 (dd, J = 8.3, 1.9 Hz, 1H), 6.52-6.39 (m, 1H), 3.62 (t, J = 6.9 Hz, 4H), 3.31 (s, 2H), 3.12 (bs, 2H), 2.47-2.23 (m, 2H), 1.55 (t, J = 7.1 Hz, 2H), 0.92 (s, 9H).

EXAMPLE 18. Preparation of (2'R,5R)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicosa-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one

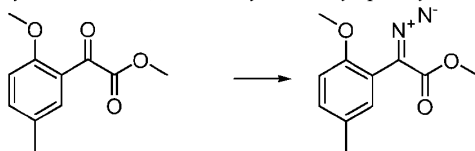


Step 1. Synthesis of methyl 2-(2-methoxy-5-methyl-phenyl)-2-oxo-acetate



[482] To a suspension of aluminum chloride (1.20 eq, 23.58 g, 177 mmol) in DCM (30 mL) at 0 °C was added 1-methoxy-4-methylbenzene (1.00 eq, 18.00 g, 147 mmol). After stirring for 10 min, methyl oxalyl chloride (1.20 eq, 16 mL, 177 mmol) was added dropwise. The reaction was stirred and allowed to slowly warm to ambient temperature. After 16 h, the reaction was quenched with 1.0 M hydrochloric acid (60 mL) and vigorously stirred for 15 min. The two layers were separated, and the organic phase was washed with saturated NaHCO₃ (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (120 g silica gel column, eluted with 0-30% ethyl acetate in petroleum ether) to give the title compound (25.00 g, 120 mmol, 81.5 % yield) as a light-yellow oil. LCMS (Method 1): LC retention time = 1.80 min. MS (ESI) m/z 209.1 [M+H]⁺.

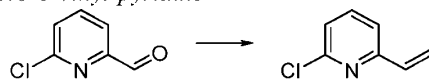
Step 2. Synthesis of methyl 2-diazo-2-(2-methoxy-5-methyl-phenyl)acetate



[483] A mixture of methyl 2-(2-methoxy-5-methyl-phenyl)-2-oxo-acetate (1.00 eq, 2.00 g, 9.61 mmol) and p-toluenesulfonylhydrazide (1.00 eq, 1.79 g, 9.61 mmol) in toluene (30 mL) was refluxed with stirring for 16 h. The reaction mixture was concentrated under reduced pressure. DCM (30 mL) and triethylamine (1.20 eq, 1.6 mL, 11.5 mmol) were added to the resulting residue. After stirring at 40 °C for 16 h, the reaction was washed with saturated aqueous NaHCO₃ (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (120 g silica gel column, eluted with 0-30% ethyl acetate in petroleum ether) to give the title compound (1.20 g, 5.45 mmol, 56.7 % yield) as a yellow solid.

LCMS (Method 3): LC retention time = 2.01 min. MS (ESI) m/z 193.1 [M-N₂+H]⁺.

Step 3. Synthesis of 2-chloro-6-vinyl-pyridine

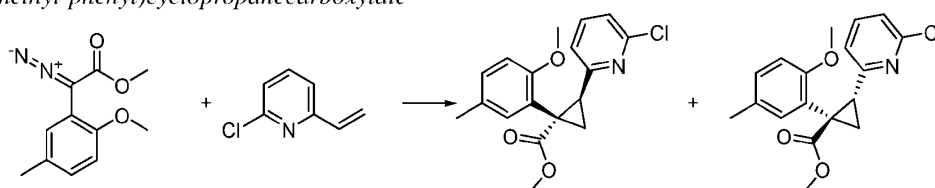


[484] To a suspension of methyltriphenylphosphonium bromide (1.20 eq, 15.14 g, 42.4 mmol) in THF (30 mL) at 0 °C was added potassium tert-butoxide (1.50 eq, 53 mL, 53.0 mmol) in THF dropwise. After stirring for 30 min, 6-chloropyridine-2-carbaldehyde (1.00 eq, 5.00 g, 35.3 mmol) was added. The reaction was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (60 mL) and was stirred vigorously for

15 min. The two layers were separated. The aqueous layer was extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (120 g silica gel column, eluted with 0-30% ethyl acetate in petroleum ether) to give the title compound (2.00 g, 14.3 mmol, 40.6 % yield) as a light-yellow oil.

LCMS (Method 1): LC retention time = 1.80 min. MS (ESI) m/z 140.1 $[M+H]^+$.

Step 4. Synthesis of methyl (1S,2S)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate and methyl (1R,2R)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate



[485] A mixture of methyl 2-diazo-2-(2-methoxy-5-methyl-phenyl)acetate (from Step 2) (1.00 eq, 600 mg, 2.72 mmol) and 2-chloro-6-vinyl-pyridine (from Step 3) (1.50 eq, 570 mg, 4.09 mmol) in DCM (18 mL) was irradiated with blue light (Penn PHD, Photoreactor m2) at 25 °C. After 22 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (12 g silica gel column, eluted with 0-20% ethyl acetate in petroleum ether) to give methyl 2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate (500 mg, 1.51 mmol, 55.3 % yield) as a white solid.

LCMS (Method 3): LC retention time = 2.05 min. MS (ESI) m/z 332.1 $[M+H]^+$.

[486] The diastereomeric mixture of methyl 2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate (1.00 eq, 1.50 g, 4.52 mmol) obtained above was separated by SFC to give methyl (1S,2S)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate, the first eluent designated as **P1**, (620 mg, 1.87 mmol, 41.3 % yield) and methyl (1R,2R)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate, the second eluent designated as **P2**, (600 mg, 1.81 mmol, 40.0 % yield) as white solids.

P1:

LCMS (Method 1): LC retention time = 2.00 min. MS (ESI) m/z 332.1 $[M+H]^+$.

Chiral HPLC retention time = 0.832 min. 100% ee.

P2:

LCMS (Method 1): LC retention time = 2.00 min. MS (ESI) m/z 332.1 $[M+H]^+$.

Chiral HPLC retention time = 1.252 min. 99.20% ee.

SFC conditions:

Instrument: SFC-150 (Waters)

Column: IG 20×250 mm, 10 μm (REGIS)

Column temperature: 35 °C

Mobile phase: CO₂/MeOH (0.2% NH₃ (7M in MeOH) = 80/20

Flow rate: 100 mL/min

Back pressure: 100 bar

Detection wavelength: 214 nm

Cycle time: 4 min

Sample solution 1500 mg dissolved in 120 ml methanol

Injection volume: 2 mL

Analytical Chiral-HPLC conditions:

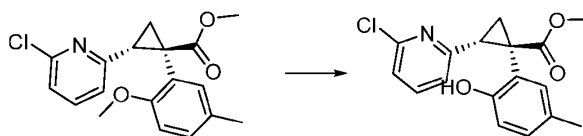
Column Name: IK 4.6×100 mm 5 μm; Acq. Method Set: 10% B1; Co Solvent: MeOH [0.2%

NH₃ (7M in MeOH)]; Injection Volume: 7.00 μL; Run Time: 4.0 min.; Proc. Flow rate: 3.0

mL/min; CST Back Pressure: 2000 psi; Column Temperature: 40 °C.

It is confirmed that the two enantiomers were separated under these conditions.

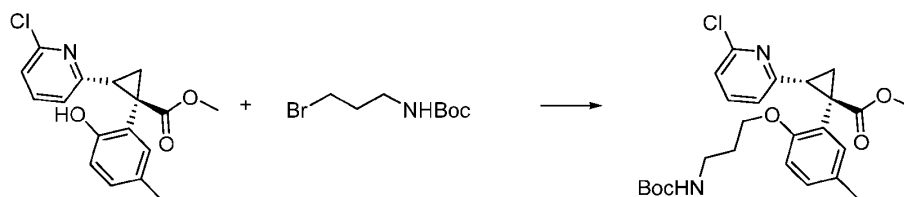
Step 5. Synthesis of methyl (1R,2R)-2-(6-chloropyridin-2-yl)-1-(2-hydroxy-5-methylphenyl)cyclopropane-1-carboxylate



[487] To a solution of methyl (1R,2R)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methylphenyl)cyclopropanecarboxylate (**P2**, step 4) (1.00 eq, 250 mg, 0.753 mmol) in DCM (10 mL) was added boron tribromide (1.50 eq, 1.1 mL, 1.13 mmol) at 0 °C. the mixture was stirred for 1 h. Then, the reaction was quenched with MeOH (1 mL) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (0-35% EA in PE) to give the title compound (230 mg, 0.724 mmol, 96.1 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.63 min. MS (ESI) *m/z* 318.2 [M+H]⁺.

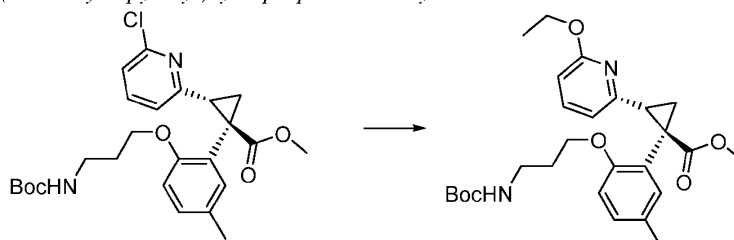
Step 6. Synthesis of methyl (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methylphenyl]-2-(6-chloro-2-pyridyl)cyclopropanecarboxylate



[488] To a solution of methyl (1R,2R)-2-(6-chloro-2-pyridyl)-1-(2-hydroxy-5-methyl-phenyl)cyclopropanecarboxylate (1.00 eq, 230 mg, 0.724 mmol) and tert-butyl N-(3-bromopropyl)carbamate (2.50 eq, 431 mg, 1.81 mmol) in DMF (5 mL) was added potassium carbonate (3.00 eq, 300 mg, 2.17 mmol). The mixture was stirred at rt for 72 h. Then water (20 mL) was added. The aqueous solution was extracted with EA (20 mL $\times$ 2). The EA combined solutions were washed with brine (20 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (0-35% EA in PE) to give the title compound (300 mg, 0.632 mmol, 87.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.84 min. MS (ESI) m/z 475.3 [M+H]⁺.

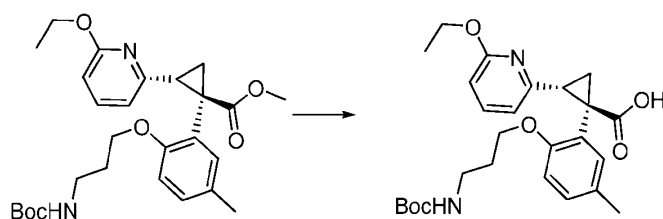
Step 7. Synthesis of methyl (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)cyclopropanecarboxylate



[489] To a solution of methyl (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methyl-phenyl]-2-(6-chloro-2-pyridyl)cyclopropanecarboxylate (1.00 eq, 300 mg, 0.632 mmol), 5-[bis(1,1-dimethylethyl)phosphino]-1',3',5'-triphenyl-1,4'-bi-1H-pyrazole (CAS: 894086-00-1) (0.200 eq, 64 mg, 0.126 mmol) and cesium carbonate (3.00 eq, 617 mg, 1.89 mmol) in ethanol (5 mL) was added palladium(II) acetate (0.100 eq, 14 mg, 0.0632 mmol) under N₂. The mixture was stirred at rt for 1 h and concentrated. The residue was purified by silica gel column chromatography (0-40% EA in PE) to give the title compound (250 mg, 0.516 mmol, 81.7 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.70 min. MS (ESI) m/z 485.3 [M+H]⁺.

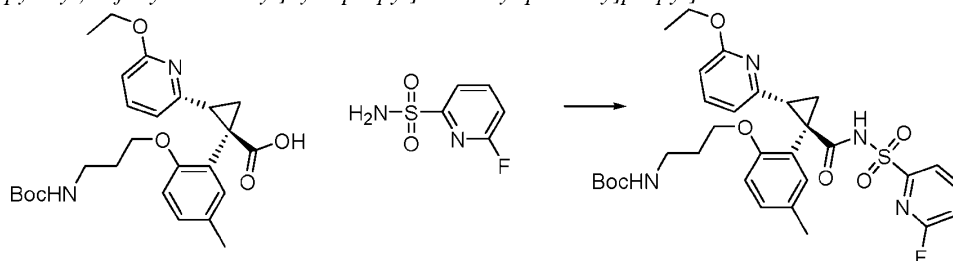
Step 8. Synthesis of (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)cyclopropanecarboxylic acid



[490] To a test tube containing methyl (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)cyclopropanecarboxylate (1.00 eq, 100 mg, 0.206 mmol) in methanol (5 mL) and water (5 mL) was added potassium hydroxide (5.18 eq, 60 mg, 1.07 mmol). The mixture was stirred at 60 °C for 12 h. The mixture was concentrated. The residue was taken in water (10.0 mL) and acidified to pH of 5-6 with citric acid. The aqueous solution was extracted with ethyl acetate (10 mL × 3). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. This residue was purified by flash column chromatography (petroleum ether / ethyl acetate = 1/1) to obtain the title compound (80 mg, 0.162 mmol, 78.3 % yield) as a light-yellow solid.

LCMS (Method 1): LC retention time = 2.47 min. MS (ESI) m/z 471.3 [M+H]⁺.

Step 9. Synthesis of tert-butyl N-[3-[2-[(1R,2R)-2-(6-ethoxy-2-pyridyl)-1-[(6-fluoro-2-pyridyl)sulfonyl]cyclopropyl]-4-methyl-phenoxy]propyl]carbamate

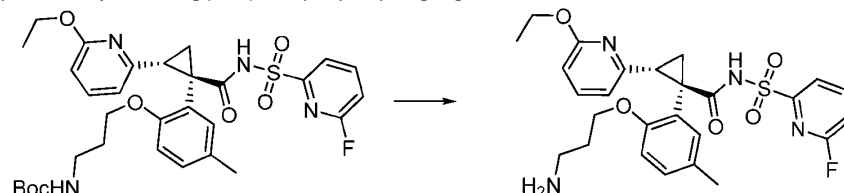


[491] To a solution of (1R,2R)-1-[2-[3-(tert-butoxycarbonylamino)propoxy]-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)cyclopropanecarboxylic acid (1.00 eq, 120 mg, 0.255 mmol), 6-fluoropyridine-2-sulfonamide (1.20 eq, 54 mg, 0.306 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.50 eq, 73 mg, 0.383 mmol) in DCM (8 mL) was added 4-dimethylaminopyridine (0.500 eq, 16 mg, 0.128 mmol). The mixture was stirred at rt for 8 h. Then water (20 mL) was added. The aqueous solution was extracted with DCM (20 mL × 2). The combined DCM solution was washed with brine (20 mL) and concentrated under vacuum. The residue was purified by silica gel column

chromatography (0-30% EA in PE) to give the title compound (140 mg, 0.223 mmol, 87.3 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.51 min. MS (ESI) m/z 629.4 [M+H]⁺.

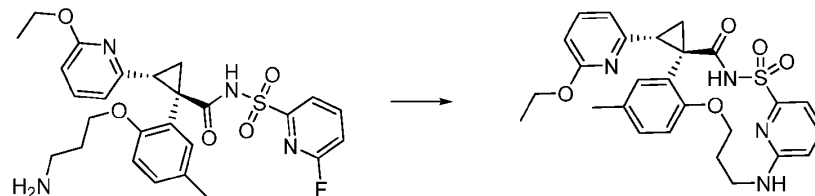
Step 10. Synthesis of (1R,2R)-1-[2-(3-aminopropoxy)-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)-N-[(6-fluoro-2-pyridyl)sulfonyl]cyclopropanecarboxamide



[492] To a solution of tert-butyl N-[3-[2-[(1R,2R)-2-(6-ethoxy-2-pyridyl)-1-[(6-fluoro-2-pyridyl)sulfonyl]cyclopropyl]-4-methyl-phenoxy]propyl]carbamate (1.00 eq, 130 mg, 0.207 mmol) in DCM (5 mL) was added TFA (98.5 eq, 1.3 mL, 20.4 mmol). The mixture was stirred at rt for 1 h. Then the mixture was concentrated under vacuum to give the title compound (85 mg, 0.161 mmol, 77.8 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.49 min. MS (ESI) m/z 529.3 [M+H]⁺.

Step 11. Synthesis of (2'R,5R)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicosa-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one



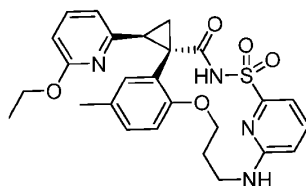
[493] To a solution of (1R,2R)-1-[2-(3-aminopropoxy)-5-methyl-phenyl]-2-(6-ethoxy-2-pyridyl)-N-[(6-fluoro-2-pyridyl)sulfonyl]cyclopropanecarboxamide (1.00 eq, 85 mg, 0.161 mmol) in DMSO (5 mL) was added cesium fluoride (5.00 eq, 122 mg, 0.804 mmol). The reaction was stirred at 100 °C for 8 h. Then water (20 mL) was added. The aqueous solution was extracted with EA (20 mL × 2). The combined EA solution was washed with brine (20 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was purified by prep-HPLC (A: water with 10 mmol/L NH₄HCO₃) B: ACN) to give the title compound (11 mg, 0.0222 mmol, 13.8 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.44 min. MS (ESI) m/z 509.3 [M+H]⁺.

Chiral HPLC retention time = 1.211 min. 97.50 % ee.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.30 (s, 1H), 7.43 (m, 2H), 7.31-6.39 (m, 7H), 6.31 (d, *J* = 7.6 Hz, 1H), 4.04 (br, 1H), 3.73 (m, 2H), 3.34 (s, 3H), 3.19 (s, 1H), 2.12 (br, 4H), 1.80 (s, 2H), 1.57 (s, 1H), 1.05 (t, *J* = 7.1 Hz, 3H).

EXAMPLE 19. Preparation of (2'S,5S)-2'-(6-Ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.0_{6,11}]henicosa-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one



[494] From methyl (1S,2S)-2-(6-chloro-2-pyridyl)-1-(2-methoxy-5-methyl-phenyl)cyclopropanecarboxylate (**P1**, step 4), following the same protocol of Step 5 to Step 11 to obtain the title compound.

LCMS (Method 2): LC retention time = 1.75 min. MS (ESI) *m/z* 507.2 [M-H]⁻.

Chiral HPLC retention time = 0.803 min. 99.88 % ee.

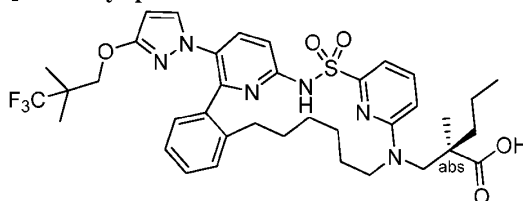
¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.27 (s, 1H), 7.46 (m, 2H), 7.31-6.39 (m, 7H), 6.32 (d, *J* = 7.6 Hz, 1H), 4.04 (br, 1H), 3.73 (m, 2H), 3.34 (s, 3H), 3.19 (s, 1H), 2.12 (br, 4H), 1.80 (s, 2H), 1.57 (s, 1H), 1.05 (t, *J* = 7.1 Hz, 3H).

Analytical Chiral-HPLC conditions:

Column Name: IK 4.6×100 mm 5 μm; Acq. Method Set: 10% B1; Co Solvent: MeOH [0.2% NH₃ (7M in MeOH)]; Injection Volume: 7.00 μL; Run Time: 4.0 min.; Proc. Flow rate: 3.0 mL/min; CST Back Pressure: 2000 psi; Column temperature: 40 °C.

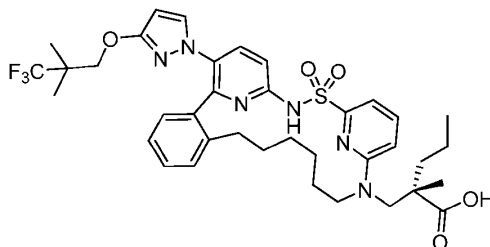
It is confirmed that the two enantiomers were separated under these conditions.

EXAMPLE 20 (P1 and P2). Preparation of (2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid

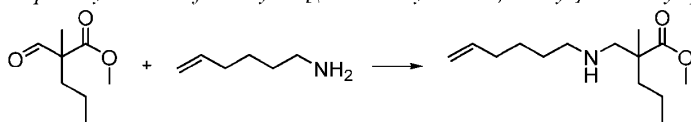


and

(2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid



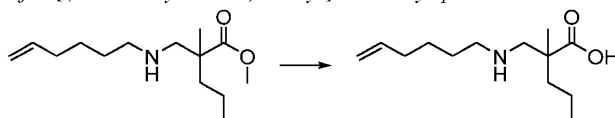
Step 1. Synthesis of methyl 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoate



[495] To a solution of methyl 2-formyl-2-methyl-pentanoate (**Intermediate D-1**, 2000 mg, 12.6 mmol) in DCM (50 mL) was added hex-5-en-1-amine hydrochloride (1600 mg, 11.8 mmol), acetic acid (0.095 mL, 1.67 mmol), and sodium triacetoxyborohydride (14000 mg, 66.1 mmol). The mixture was stirred at room temperature for 2 h, the solids were filtered off and the filtrate was concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 3:1) to obtain methyl 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoate (2000 mg, 7.46 mmol, 59.0 % yield) as a light-yellow oil.

LCMS (Method 1): RT 1.52 min. MS (ESI) m/z 242.3 [M+H]⁺.

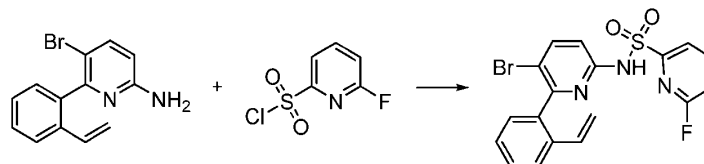
Step 2. Synthesis of 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoic acid



[496] To a solution of methyl 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoate (2000 mg, 8.29 mmol) in methanol (10 mL), THF (10 mL) and water (5mL) was added potassium hydroxide (1400 mg, 25.0 mmol). The mixture was stirred at 50 °C for 24 h, and concentrated to afford a residue which was washed with water (50 mL) and acidified to pH 5-6 with aqueous citric acid. The resulting mixture was extracted with ethyl acetate (200 mL × 3), and the combined organic extracts were concentrated to give 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoic acid (1500 mg, 5.94 mmol, 71.7 % yield).

LCMS (Method 1): RT 1.46 min. MS (ESI) m/z 228.3 $[M+H]^+$.

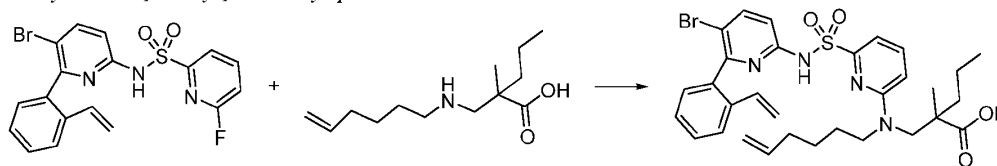
Step 3. Synthesis of N-[5-bromo-6-(2-vinylphenyl)-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide



[497] To a solution of 5-bromo-6-(2-vinylphenyl)pyridin-2-amine (**Intermediate A-3**, 3000 mg, 10.9 mmol) in pyridine (50 mL) was added 6-fluoropyridine-2-sulfonyl chloride (2400 mg, 12.3 mmol) slowly at 0 °C. The mixture was stirred at rt for 2 h, and concentrated to give a residue which was purified by column flash (petroleum ether : ethyl acetate = 3:1) to afford N-[5-bromo-6-(2-vinylphenyl)-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (2000 mg, 4.38 mmol, 40.1 % yield) as a light yellow solid.

LCMS (Method 1): RT = 2.23 min. MS (ESI) m/z 434, 436 $[M+H]^+$.

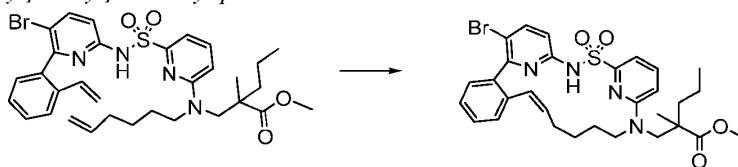
Step 4. Synthesis of 2-[[[6-[[5-bromo-6-(2-vinylphenyl)-2-pyridyl]sulfamoyl]-2-pyridyl]-hex-5-enyl-amino]methyl]-2-methyl-pentanoic acid



[498] To a reaction tube containing a solution of N-[5-bromo-6-(2-vinylphenyl)-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (2000 mg, 4.61 mmol) in DMSO (5 mL) was added 2-[(hex-5-enylamino)methyl]-2-methyl-pentanoic acid (3000 mg, 13.2 mmol) and cesium fluoride (7000 mg, 46.1 mmol). The mixture was stirred at 100 °C for 7 days and the desired product was detected by LCMS. The mixture was taken up in water (500 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The combined organic extracts were concentrated to afford a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 1:1) to obtain 2-[[[6-[[5-bromo-6-(2-vinylphenyl)-2-pyridyl]sulfamoyl]-2-pyridyl]-hex-5-enyl-amino]methyl]-2-methyl-pentanoic acid (1500 mg, 2.22 mmol, 48.2 % yield) as a light yellow solid.

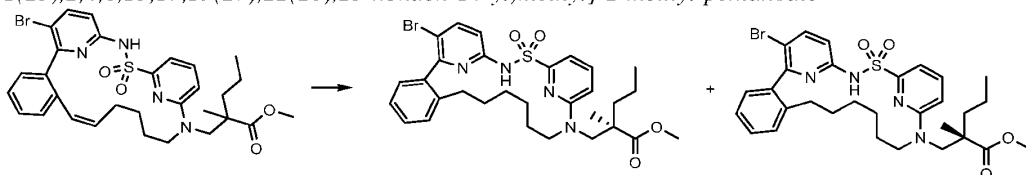
LCMS (Method 1): RT 2.95 min. MS (ESI) m/z 641.2, 643.2 $[M+H]^+$.

Step 5. Synthesis of methyl 2-[[[(8E)-25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,8,15,17,19(27),22(26),23-decaen-14-yl]methyl]-2-methyl-pentanoate



[499] To a solution of methyl 2-[[[6-[[5-bromo-6-(2-vinylphenyl)-2-pyridyl]sulfamoyl]-2-pyridyl]-hex-5-enyl-amino]methyl]-2-methyl-pentanoate (1200 mg, 1.83 mmol) in DCE (20 mL) was added [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene) (tricyclohexylphosphine)ruthenium (CAS# **246047-72-3**, 180 mg, 0.212 mmol) under N₂. The mixture was stirred at 70 °C for 12 h. The mixture was concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 5:1) to obtain the desired product, methyl 2-[[[(8E)-25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,8,15,17,19(27),22(26),23-decaen-14-yl]methyl]-2-methyl-pentanoate (900 mg, 1.36 mmol, 74.4 % yield) as a light yellow solid. LCMS (Method 1): RT 2.86 min. MS (ESI) *m/z* 627.2, 629.2 [M+H]⁺.

Step 6. Synthesis of methyl (2R)-2-[(25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate and methyl (2S)-2-[(25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate



[500] To a solution of methyl 2-[[[(8E)-25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,8,15,17,19(27),22(26),23-decaen-14-yl]methyl]-2-methyl-pentanoate (900 mg, 1.43 mmol) in methanol (20 mL) was added platinum (IV) oxide (70 mg, 0.308 mmol). The reaction mixture was stirred at rt under H₂ for 12 h. The mixture was filtered and the filtrate was concentrated to give methyl 2-[(25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-

1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate (600 mg, 0.905 mmol, 63.1 % yield) as a light yellow oil.

LCMS (Method 2): RT 2.83 min. MS (ESI) m/z 629.3 [M+H]⁺.

[501] This sample was separated by SFC to give two enantiomeric products, labeled **P1** and **P2**. Enantiomer P1 was arbitrarily designated as methyl (2R)-2-[(25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-

1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate (260 mg, 0.392 mmol, 41.2 % yield, a white solid) and enantiomer P2 was designated as methyl (2S)-2-[(25-bromo-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate (260 mg, 0.392 mmol, 41.2 % yield, a white solid).

P1: LCMS (Method 1): Rt 2.44 min. MS (ESI) m/z 629.0 [M+H]⁺.

P2: LCMS (Method 1): Rt 2.45 min. MS (ESI) m/z 629.2 [M+H]⁺.

SFC separation conditions:

Instrument: SFC-150 (Waters)

Column: AD 25*250 mm, 10 μm

Column temperature: 35 °C

Mobile phase: CO₂/EtOH[0.2%NH₃(7M in MeOH)] = 65/35

Flow rate: 100 ml/min

Back pressure: 100 bar

Detection wavelength: 214 nm

Cycle time: 8.0 min

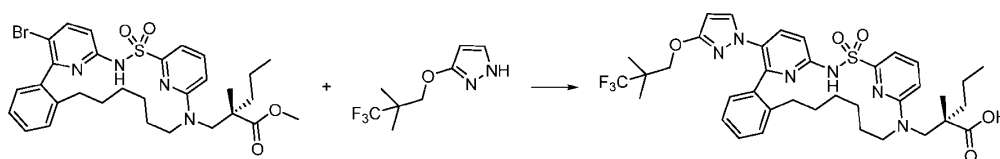
Sample solution: 600 mg dissolved in 30 ml methanol

Injection volume: 2.5 ml

P1 : RT 1.72 min. chiral purity: 99.96%;

P2 : RT 2.29 min. chiral purity: 99.86%

Step 7. Synthesis of (2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoic acid



[502] To a reaction tube containing a solution of methyl (2R)-2-[(25-bromo-20,20-dioxo-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoate (100 mg, 0.159 mmol, Enantiomer **P1** from previous step) in DMF (2 mL) were added 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (70 mg, 0.336 mmol), copper (I) iodide (100 mg, 0.525 mmol), potassium carbonate (200 mg, 1.45 mmol), and N,N'-dimethyl-1,2-ethanediamine (CAS# 110-70-3) (excess) under N₂. The mixture was stirred at 120 °C for 72 h. The mixture was concentrated to give a residue which was purified by flash column chromatography on silica gel (eluting with petroleum ether : ethyl acetate = 1:1) to obtain (2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoic acid (2.9 mg, 0.00386 mmol, 2.4 % yield) as a white solid. This reaction product was labeled as **P1**.

[503] The same procedure was employed to obtain (2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1¹⁵,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl)methyl]-2-methyl-pentanoic acid (3.1 mg, 0.00413 mmol, 2.6 % yield) as a white solid (labeled as **P2**).

P1:

LCMS (Method 2): Rt 1.87 min. MS (ESI) m/z 741.3 [M-H]⁺.

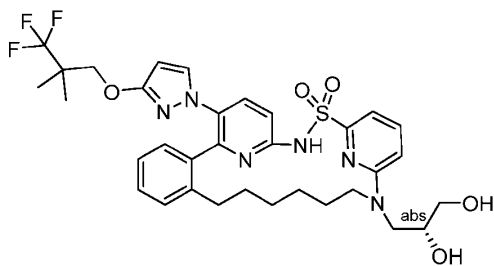
¹H NMR (500 MHz, CD₃OD) δ 7.93 (d, J = 8.9 Hz, 1H), 7.76-7.55 (m, 2H), 7.22 (m, 5H), 6.89 (m, 2H), 5.63 (d, J = 2.6 Hz, 1H), 4.04 (s, 2H), 3.49 (m, 4H), 2.25 (s, 2H), 1.67 (dd, J = 13.4, 9.2 Hz, 1H), 1.35 (m, 6H), 1.20 (s, 7H), 1.07 (s, 5H), 0.90 (t, J = 7.1 Hz, 5H).

P2:

LCMS (Method 2): Rt 1.87 min. MS (ESI) m/z 741.3 [M-H]⁺.

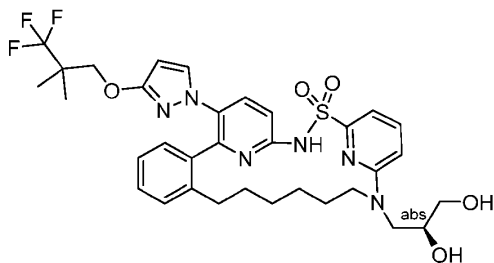
^1H NMR (500 MHz, CD_3OD) δ 7.93 (d, J = 8.9 Hz, 1H), 7.76-7.55 (m, 2H), 7.22 (m, 5H), 6.89 (m, 2H), 5.63 (d, J = 2.6 Hz, 1H), 4.04 (s, 2H), 3.49 (m, 4H), 2.25 (s, 2H), 1.67 (dd, J = 13.4, 9.2 Hz, 1H), 1.35 (m, 6H), 1.20 (s, 7H), 1.07 (s, 5H), 0.90 (t, J = 7.1 Hz, 5H).

EXAMPLE 21 (P1 and P2). Preparation of (2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol

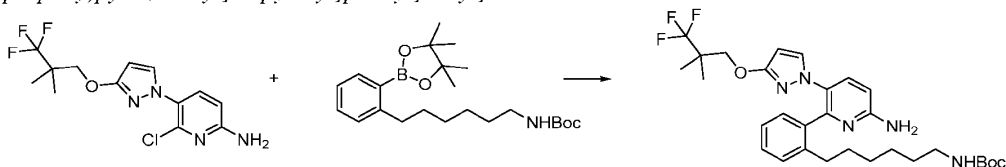


and

(2S)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol



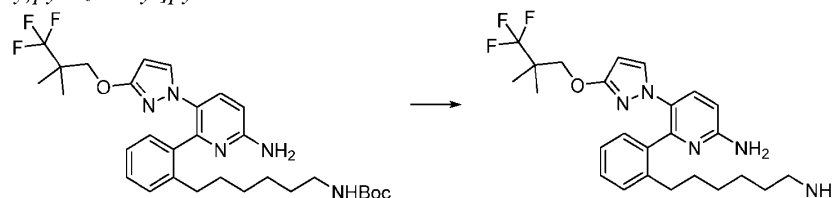
Step 1. Synthesis of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate



[504] To a solution of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (**Intermediate A-4**, 1000 mg, 2.99 mmol), tert-butyl N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexylcarbamate (**Intermediate 1A**, 1446 mg, 3.58 mmol) and potassium phosphate (2220 mg, 10.5 mmol) in THF (16 mL) and water (4 mL)

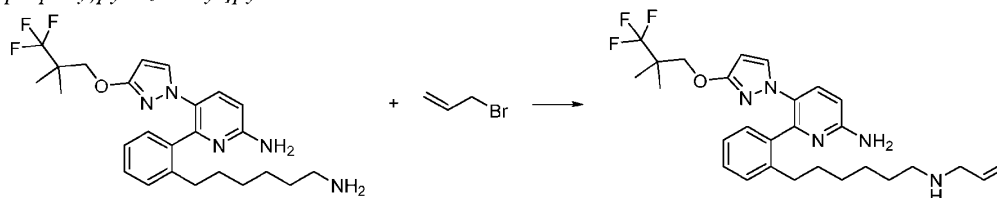
was added [2'-(amino- κ N)[1,1'-biphenyl]-2-yl- κ C][butylbis(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phosphine](methanesulfonato- κ O Palladium (II) (CAS# 1651823-59-4, 436 mg, 0.597 mmol) under N₂. The mixture was stirred at 80 °C for 16 h, quenched with water (50 mL) and extracted with EA (40 mL $\times$ 3). The combined organic extracts were washed with brine (40 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluting with 0-50 % EA in PE) to obtain tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (1400 mg, 2.31 mmol, 77.3 % yield) as an off-white solid. LCMS (Method 1): LC retention time = 1.85 min. MS (ESI) m/z 576.3 [M+H]⁺.

Step 2. Synthesis of 6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine



[505] To a solution of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (1300 mg, 2.26 mmol) in DCM (10 mL) was added trifluoroacetic acid (3.0 mL, 38.9 mmol). The reaction was stirred at rt for 1 h. The mixture was concentrated, and the residue taken up in water (30 mL). The aqueous mixture was extracted with EA (30 mL $\times$ 3). The combined organic extracts were washed with saturated aqueous NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo to give 6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (1000 mg, 2.06 mmol, 91.3 % yield) as a yellow solid. LCMS (Method 4): LC retention time = 1.73 min. MS (ESI) m/z 476.4 [M+H]⁺.

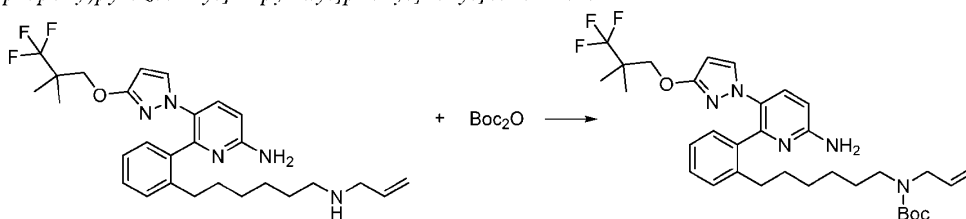
Step 3. Synthesis of 6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine



[506] To a solution of 6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (1500 mg, 3.15 mmol) and allyl bromide (0.30 mL,

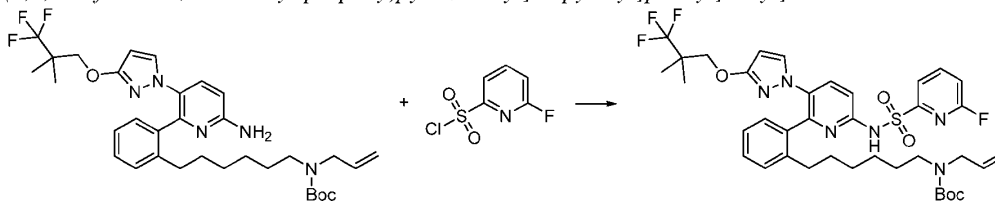
3.47 mmol) in MeCN (20 mL) was added N,N-diisopropylethylamine (1.6 mL, 9.46 mmol). The mixture was stirred at 60 °C for 18 h. The mixture was concentrated under reduced pressure to give 6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (1500 mg, 0.727 mmol, 23.1 % yield) as a yellow oil. LCMS (Method 4): LC retention time = 1.75 min. MS (ESI) m/z 516.0 [M+H]⁺.

Step 4. Synthesis of tert-butyl N-allyl-N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate



[507] To a solution of 6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (1500 mg, 0.727 mmol) and di-tert-butyl dicarbonate (0.25 mL, 1.09 mmol) in DCM (20 mL) was added triethylamine (0.30 mL, 2.18 mmol). The reaction was stirred at rt for 1 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 0-70 % EA in PE) to afford tert-butyl N-allyl-N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (365 mg, 0.581 mmol, 79.9 % yield) as a yellow solid. LCMS (Method 4): LC retention time = 1.81 min. MS (ESI) m/z 616.4 [M+H]⁺.

Step 5. Synthesis of tert-butyl N-allyl-N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate

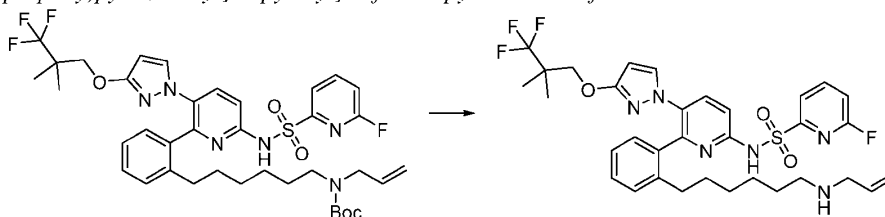


[508] To a mixture of tert-butyl N-allyl-N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (365 mg, 0.593 mmol) and 4A molecular sieves in pyridine (3 mL) was added 6-fluoropyridine-2-sulfonyl chloride (139 mg, 0.711 mmol). The reaction was stirred at rt for 2 h and was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 0-60% EA in PE) to give tert-butyl N-allyl-N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-

(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (400 mg, 0.501 mmol, 84.5 % yield) as a yellow solid.

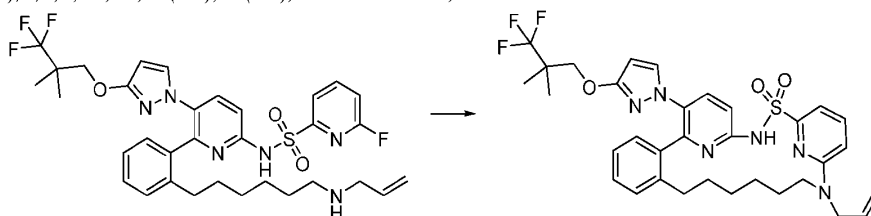
LCMS (Method 1): LC retention time = 2.36 min. MS (ESI) m/z 775.3 [M+H]⁺.

Step 6. Synthesis of N-[6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide



[509] To a solution of tert-butyl N-allyl-N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (380 mg, 0.490 mmol) in DCM (5 mL) was added trifluoroacetic acid (0.038 mL, 0.490 mmol). The reaction was stirred at rt for 1 h, and concentrated to afford N-[6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (320 mg, 0.451 mmol, 91.9 % yield) as a yellow oil. LCMS (Method 1): LC retention time = 1.65 min. MS (ESI) m/z 675.3 [M+H]⁺.

Step 7. Synthesis of 14-allyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosal(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

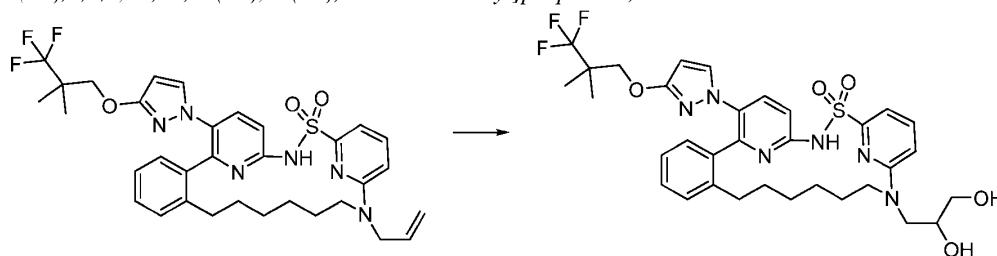


[510] To a solution of N-[6-[2-[6-(allylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (320 mg, 0.451 mmol) in DMSO (10 mL) was added cesium fluoride (684 mg, 4.51 mmol). The mixture was stirred at 100 °C for 4 days. The reaction was cooled to ambient temperature and water was added (30 mL). The aqueous mixture was extracted with EA (30 mL × 3), the combined extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel (eluting with 0-75% EA in PE) to give 14-allyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-

tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (250 mg, 0.374 mmol, 83.1 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.10 min. MS (ESI) m/z 655.3 [M+H]⁺.

Step 8. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol



[511] To a solution of 14-allyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (250 mg, 0.382 mmol) and 4-methylmorpholine n-oxide (58 mg, 0.496 mmol) in THF (5 mL) and water (1 mL) was added potassium osmate dihydrate (14 mg, 0.0382 mmol). The reaction was stirred at rt for 16 h and quenched with water (30 mL). The aqueous mixture was extracted with EA (30 mL × 3), the combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 0-10% MeOH in DCM) to give 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol (200 mg, 0.279 mmol, 73.0 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.07 min. MS (ESI) m/z 689.3 [M+H]⁺.

[512] 100 mg of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol (100 mg, 0.145 mmol) in methanol (1 mL) was separated into its constituent enantiomers by chiral-HPLC, and further purified by prep-HPLC (formic acid) to give (2S)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-

14-yl]propane-1,2-diol (31 mg, 0.0448 mmol, 30.9 % yield), labeled as **P1**, as a white solid and (2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.1.15,19.02,7]heptacosal(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol (32 mg, 0.0454 mmol, 31.3 % yield), labeled as **P2**, as a white solid.

SFC conditions:

Instrument: SFC-150 (Waters)

Column: AD 25*250 mm, 10 μm

Column temperature: room temperature

Mobile phase: CO₂/EtOH[0.5% NH₃ (7M in MeOH)] = 80/20

Flow rate: 100 mL/min.

Back pressure: 100 bar.

Detection wavelength: 214 nm.

Cycle time: 5.3 min.

Sample solution: 100 mg dissolved in 17 mL ethanol.

Injection volume: 2.0 mL

P1:

LCMS (Method 1): LC retention time = 2.09 min. MS (ESI) m/z 689.3 [M+H]⁺.

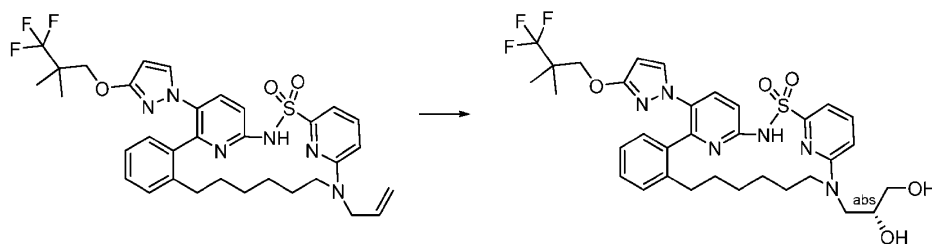
¹H NMR (400 MHz, CD₃OD) δ: 7.91 (d, J = 8.9 Hz, 1H), 7.61 (dt, J = 14.8, 7.4 Hz, 2H), 7.26 (m, 2H), 7.21-7.05 (m, 3H), 6.88 (dd, J = 11.0, 5.7 Hz, 2H), 5.63 (d, J = 2.6 Hz, 1H), 4.02 (s, 2H), 3.88-3.78 (m, 1H), 3.70-3.43 (m, 5H), 3.34 (brs, 1H), 2.31 (brs, 2H), 1.49-1.25 (m, 4H), 1.19 (s, 6H), 1.16-1.05 (m, 2H), 1.00-0.89 (m, 2H).

P2:

LCMS (Method 1): LC retention time = 2.07 min. MS (ESI) m/z 689.3 [M+H]⁺.

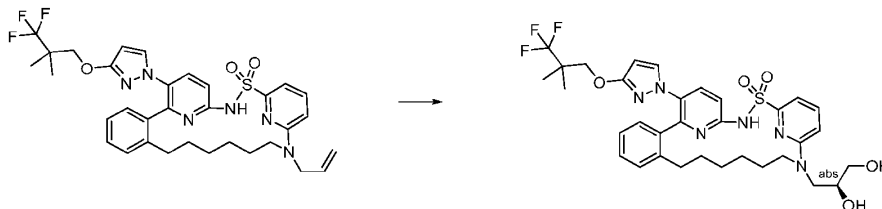
¹H NMR (400 MHz, CD₃OD) δ: 7.91 (d, J = 8.8 Hz, 1H), 7.61 (dt, J = 14.8, 7.4 Hz, 2H), 7.26 (m, 2H), 7.21-7.05 (m, 3H), 6.88 (dd, J = 11.0, 5.7 Hz, 2H), 5.63 (d, J = 2.6 Hz, 1H), 4.02 (s, 2H), 3.90-3.78 (m, 1H), 3.68-3.43 (m, 5H), 3.34 (brs, 1H), 2.31 (brs, 2H), 1.49-1.25 (m, 4H), 1.19 (s, 6H), 1.16-1.05 (m, 2H), 1.00-0.89 (m, 2H).

EXAMPLE 21 (P1 and P2) were also prepared by an alternative method as described below.



[513] To a solution of 14-allyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (Intermediate from Step 7 above, 15 mg, 0.0229 mmol) and methanesulfonamide (6.5 mg, 0.0687 mmol) in tert-butanol (2 mL) and water (2 mL) was added AD-mix- β (CAS# 148618-32-0) (300 mg). The mixture was stirred at rt for 28 h, and then diluted with water (20 mL). The aqueous mixture was extracted with EA (20 mL $\times$ 3). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, then concentrated. The residue was purified by prep-HPLC (formic acid) (to give (2*R*)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol (2.0 mg, 0.00287 mmol, 12.6 % yield, a white solid), labeled as **P1** .

Chiral-purity: 67.4%,



[514] To a solution of 14-allyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (10 mg, 0.0153 mmol) in DMSO (2 mL) was added AD-mix- α (CAS#:153130-59-7, 10 mg.). The reaction mixture was stirred at rt for 16 h, then concentrated to dryness, and the residue was purified by reverse-phase chromatography(C18) (0.1% FA in water,10-100% ACN) to give (2*S*)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-

tetrazatetracyclo[20.3.1.1.15,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol (5.0 mg, 0.00726 mmol, 47.5 % yield, a white solid), labeled as **P2**.

Chiral-purity: 31.93%,

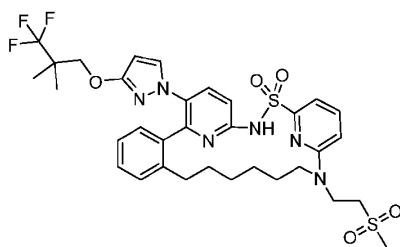
The above P1 and P2 samples were individually purified further by chiral SFC, as described above to afford the pure title compounds.

P1: ee: 100%

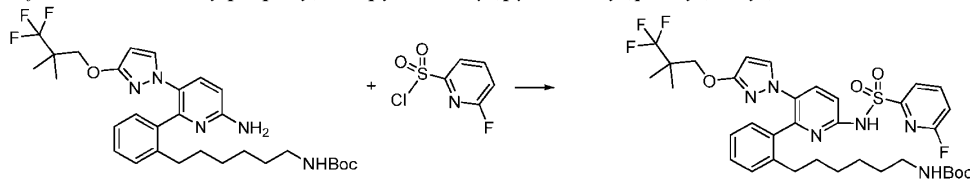
P2: ee: 98.98%

The analytical of both samples were identical with the corresponding compounds obtained as above.

EXAMPLE 22. Preparation of 14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,26-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide



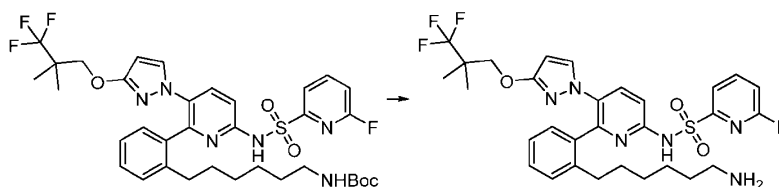
Step 1. Synthesis of tert-butyl (6-(2-(6-((6-fluoropyridine)-2-sulfonamido)-3-(3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl)pyridin-2-yl)phenyl)hexyl)carbamate



[515] To a solution of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (Intermediate from **EXAMPLE 21**, step 1, 2200 mg, 3.82 mmol) in pyridine (10 mL) was added 6-fluoropyridine-2-sulfonyl chloride (972 mg, 4.97 mmol). The reaction was stirred at rt for 12 h, concentrated under reduced pressure, and the crude was purified by flash column chromatography on silica gel (eluting with EtOAc in PE: 0-50%) to get tert-butyl N-[6-[2-[6-((6-fluoro-2-

pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (2500 mg, 3.40 mmol, 89.0 % yield) as a yellow oil.
LCMS (Method 4): LC retention time = 2.04 min. MS (ESI) m/z 735.0 [M+H]⁺.

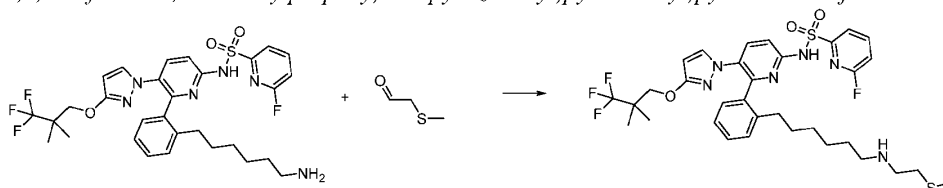
Step 2. Synthesis of N-(6-(2-(6-aminohexyl)phenyl)-5-(3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl)pyridin-2-yl)-6-fluoropyridine-2-sulfonamide



[516] To a solution of tert-butyl N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]phenyl]hexyl]carbamate (100 mg, 0.136 mmol) in DCM (5 mL) was added trifluoroacetic acid (0.50 mL, 6.49 mmol). The reaction was stirred at 25 °C for 3 h, quenched with saturated aqueous NaHCO₃ (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated to afford N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (90 mg, 0.142 mmol, 104.2 % yield) as a yellow solid which was used in the next step without purification.

LCMS (Method 1): LC retention time = 1.84 min. MS (ESI) m/z 635.2 [M+H]⁺.

Step 3. Synthesis of 6-fluoro-N-(6-(2-(6-((2-(methylthio)ethyl)amino)hexyl)phenyl)-5-(3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl)pyridin-2-yl)pyridine-2-sulfonamide

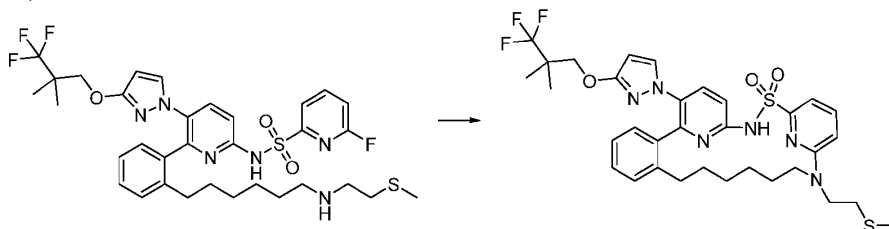


[517] To a solution of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (500 mg, 0.788 mmol) in THF (5 mL) was added sodium triacetoxyborohydride (668 mg, 3.15 mmol) and 2-methylsulfanylacetaldehyde (CAS#: 23328-62-3, 71 mg, 0.788 mmol). The reaction was stirred at 25°C for 3 h, quenched with saturated aqueous NaHCO₃ (50 mL), and extracted with

ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40g silica gel column, eluting with 30% ethyl acetate in petroleum ether) to yield 6-fluoro-N-[6-[2-[6-(2-methylsulfonylethylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]pyridine-2-sulfonamide (365 mg, 0.515 mmol, 65.4 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.18 min. MS (ESI) m/z 709.2 [M+H]⁺.

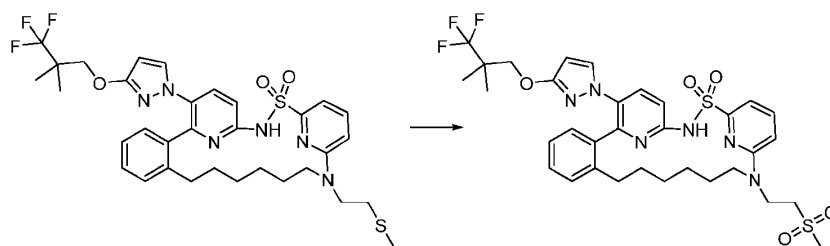
Step 4. Synthesis of 14-(2-methylsulfonylethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide



[518] To a solution of 6-fluoro-N-[6-[2-[6-(2-methylsulfonylethylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]pyridine-2-sulfonamide (355 mg, 0.501 mmol) in DMSO (10 mL) was added cesium fluoride (1521 mg, 10.0 mmol). The reaction was stirred at 100 °C for 16 h under nitrogen. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield 14-(2-methylsulfonylethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (165 mg, 0.240 mmol, 47.8 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.46 min. MS (ESI) m/z 689.2 [M+H]⁺.

Step 5. Synthesis of 14-(2-methylsulfonylethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

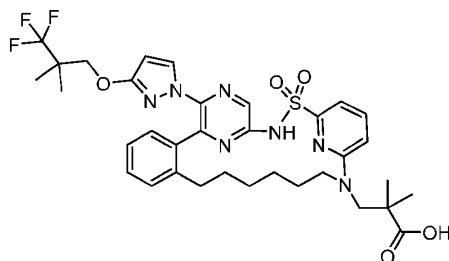


[519] To a solution of 14-(2-methylsulfanylethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (355 mg, 0.515 mmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (89 mg, 0.515 mmol). The reaction was stirred at rt for 6 h, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with water (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by Combi-flash reversed-phase chromatography (C18, Boston ODS 120 g Flash) eluting with 0.1% TFA in water, 10-100% ACN) to give 14-(2-methylsulfonylethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide (300 mg, 0.416 mmol, 80.8 % yield) as a yellow solid.

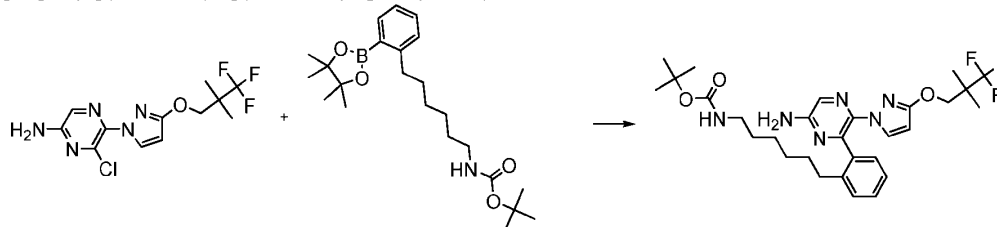
LCMS (Method 1): LC retention time = 2.10 min. MS (ESI) m/z 721.2 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 7.92 (d, J = 8.9 Hz, 1H), 7.72-7.59 (m, 2H), 7.34-7.25 (m, 2H), 7.23-7.09 (m, 3H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.00 (s, 2H), 3.82 (s, 2H), 3.60 (s, 2H), 3.41 (s, 2H), 2.87 (s, 3H), 2.14 (s, 2H), 1.55-1.33 (m, 4H), 1.23-1.09 (m, 8H), 0.97 (s, 2H).

EXAMPLE 23. Preparation of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid



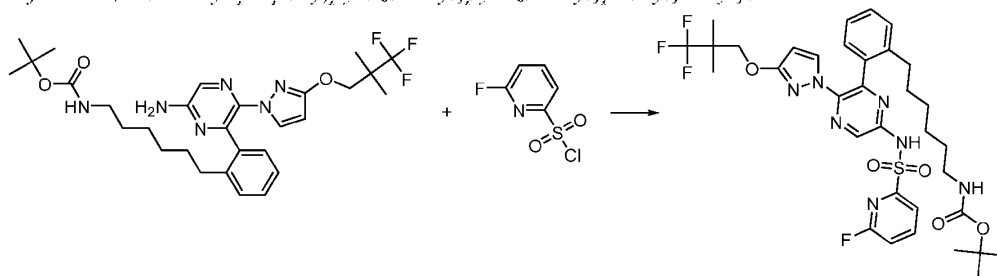
Step 1. Synthesis of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate



[520] To a solution of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (**Intermediate A7**, 7000 mg, 20.9 mmol) in THF (100 mL) and water (20 mL) were added tert-butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate (**Intermediate 1A**, 8411 mg, 20.9 mmol), [2'-(amino- κ N)[1,1'-biphenyl]-2-yl- κ C][butylbis(tricyclo[3.3.1.1.3,7]dec-1-yl)phosphine](methanesulfonato- κ O) Palladium (II) (**CAS#**: 1651823-59-4, 1521 mg, 2.09 mmol), and potassium phosphate (**CAS#**: 007778-53-2, 13278 mg, 62.6 mmol). The reaction was stirred at 80 °C overnight under N₂. After cooled to room temperature, the reaction mixture was filtered and the solid was washed with EA (100 mL). The combined filtrates were concentrated under reduced pressure. The crude was then purified by flash column chromatography on silica gel (eluting with 0-50% EtOAc in PE) to obtain tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (11000 mg, 19.1 mmol, 91.5 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 2.11 min. MS (ESI) m/z 577.0 [M+H]⁺.

Step 2. Synthesis of tert-butyl N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate

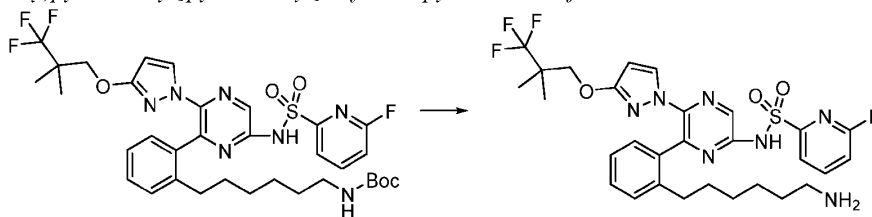


[521] To a suspension of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (2500 mg, 4.34 mmol) and 4A molecular sieves in pyridine (5 mL) was added 6-fluoropyridine-2-sulfonyl chloride (1018 mg, 5.20 mmol). The reaction was stirred at rt for 2 h, then concentrated under reduced pressure.

The residue was purified by column chromatography on silica gel (eluting with 0-75% EA in PE) to give tert-butyl N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (2000 mg, 2.72 mmol, 62.7 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.71 min. MS (ESI) m/z 736.3 $[M+H]^+$.

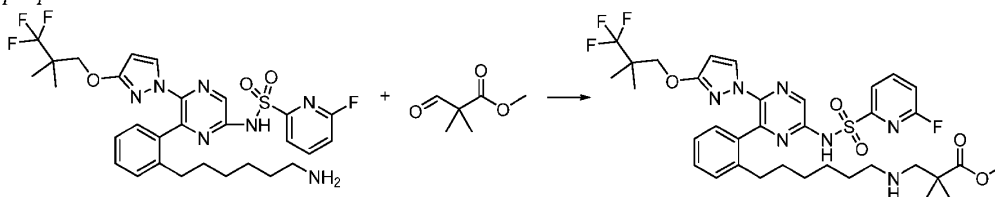
Step 3. Synthesis of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide



[522] To a solution of tert-butyl N-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (1300 mg, 1.77 mmol) in DCM (10 mL) was added trifluoroacetic acid (2.0 mL, 26.0 mmol). The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure to give N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (1123 mg, 1.77 mmol, 100 % yield) as a yellow oil which was used directly in the next step.

LCMS (Method 4): LC retention time = 1.87 min. MS (ESI) m/z 636.3 $[M+H]^+$.

Step 4. Synthesis of methyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate

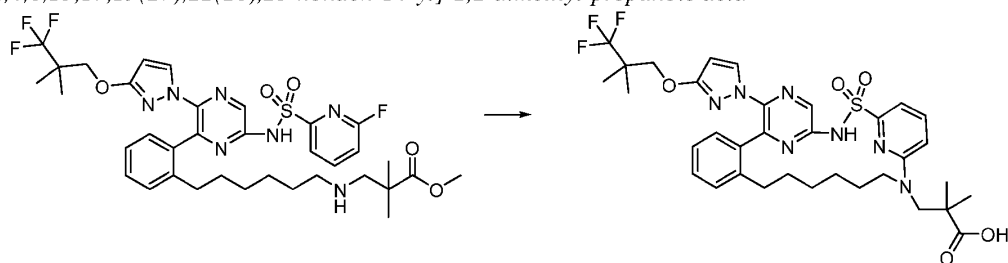


[523] To a solution of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (1125 mg, 1.77 mmol) in DCE (15mL) were added methyl 2,2-dimethyl-3-oxo-propanoate (**Intermediate D-2**, 299 mg, 2.30 mmol) and acetic acid (4 drops). The reaction mixture was stirred at rt for 5 h. Sodium triacetoxyborohydride (1876 mg, 8.85 mmol) was then added to the reaction mixture, and

stirring was continued at rt for 12 h. The reaction mixture was poured into water (50 mL) and extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with 5% MeOH in DCM, to give methyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (1.20 g, 1.60 mmol, 90.4 % yield) as a white solid.

LCMS (Method 4): LC retention time = 2.06 min. MS (ESI) m/z 750.2 [M+H]⁺

Step 5. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosal(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid



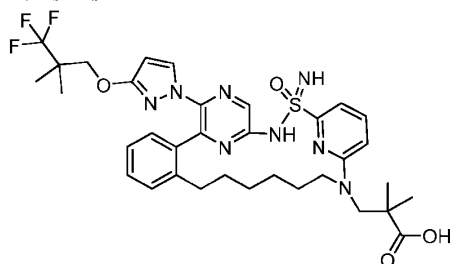
[524]

To a solution of methyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (1.20 g, 1.60 mmol) in DMSO (25 mL) and water (2 mL) was added cesium fluoride (4862 mg, 32.0 mmol). The reaction mixture was stirred at 100 °C for 3 days under N₂. The reaction mixture was poured into water (50 mL), the pH adjusted to 6-7 with aqueous citric acid, and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by reversed phase flash chromatography to give 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosal(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid (305 mg, 0.426 mmol, 26.6 % yield) as a white solid.

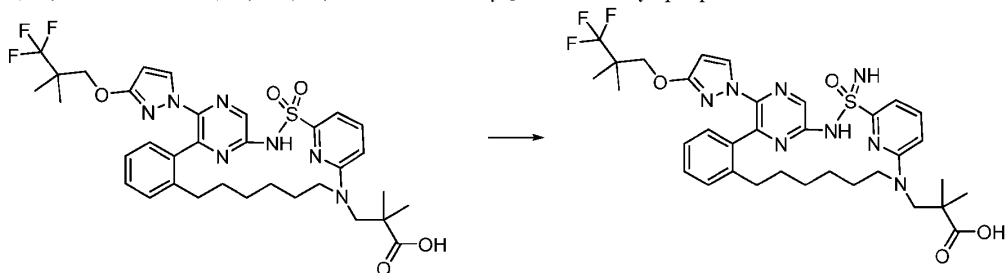
LCMS (Method 4): LC retention time = 1.61 min. MS (ESI) m/z 716.3 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.78 (s, 1H), 7.90 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 8.7, 7.3 Hz, 1H), 7.30-7.13 (m, 4H), 7.09 (d, J = 6.9 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.81 (d, J = 2.7 Hz, 1H), 3.89 – 3.37 (m, 6H), 2.57 – 2.04 (m, 2H), 1.49-1.26 (m, 4H), 1.18-1.02 (m, 14H), 0.81 (s, 2H).

EXAMPLE 24. Preparation of 3-[20-imino-20-oxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid



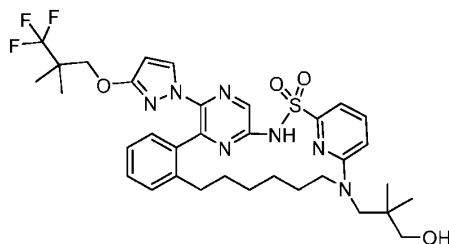
Step 1. Synthesis of 3-[20-imino-20-oxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid



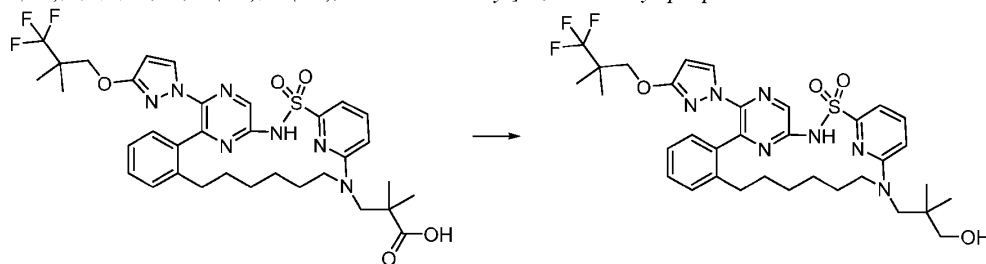
[525] To a solution of triphenylphosphine (235 mg, 0.894 mmol) and 1,1,1,2,2,2-hexachloroethane (212 mg, 0.894 mmol) was added 80 mg (0.11 mmol) of **EXAMPLE 23** in dry DCM (2 mL). The mixture was stirred at 0 °C for 2 h. To this mixture was added triethylamine (0.047 mL, 0.335 mmol) dropwise and the solution was stirred at 0 °C for 30 min. The resulting mixture was treated dropwise with NH₃-THF (0.2 mL of 1M solution in THF) and stirring at rt was continued for 4 h. Reaction progress was monitored by LCMS. Upon reaction completion, water (100 mL) was added at 0 °C and the mixture was extracted with DCM (100 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by reverse-phase flash chromatography (C18, 0.1% NH₄HCO₃ in water, 10-100% MeCN) to give 3-[20-imino-20-oxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid (15 mg, 0.0208 mmol, 18.7 % yield) as a white solid. LCMS (Method 4): LC retention time = 1.94 min. MS (ESI) *m/z* 715.0 [M+H]⁺.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.58 (s, 1H), 8.64 (s, 1H), 8.05 (d, $J = 2.6$ Hz, 1H), 7.75-7.54 (m, 1H), 7.26 (t, $J = 7.4$ Hz, 1H), 7.21-7.10 (m, 5H), 7.07 (d, $J = 8.7$ Hz, 1H), 6.96 (s, 1H), 5.93 (d, $J = 2.6$ Hz, 1H), 3.65-3.36 (m, 6H), 2.40-2.23 (m, 1H), 2.18-1.92 (m, 1H), 1.40-1.16 (m, 4H), 1.10-0.90 (m, 14H), 0.83-0.47 (m, 2H).

EXAMPLE 25. Preparation of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol



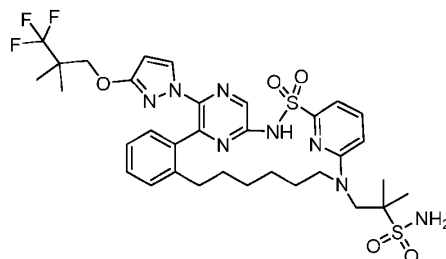
Step 1. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol



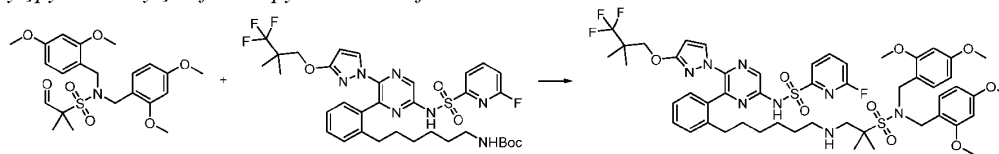
[526] To a solution of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid (**EXAMPLE 23**, 140 mg, 0.196 mmol) in THF (5 mL) was added borane tetrahydrofuran complex (4.0 mL, 4.00 mmol). The reaction mixture was stirred at rt for 2 h, methanol (5 mL) was added and stirring continued for another 2 h. The reaction was concentrated in vacuo. The residue was purified by reverse phase flash chromatography to give 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol (113 mg, 0.161 mmol, 82.3 % yield) as a white solid. LCMS (Method 4): LC retention time = 2.04 min. MS (ESI) m/z 702.2 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 7.93 (s, 1H), 7.63 (dd, $J = 8.7, 7.3$ Hz, 1H), 7.29-7.18 (m, 3H), 7.13 (t, $J = 7.3$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 1H), 5.81 (d, $J = 2.7$ Hz, 1H), 3.92-3.38 (m, 6H), 3.14 (s, 2H), 2.47-2.07 (m, 2H), 1.66-1.26 (m, 4H), 1.18-0.99 (m, 8H), 0.96-0.75 (m, 8H).

EXAMPLE 26. Preparation of 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,26-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-2-sulfonamide



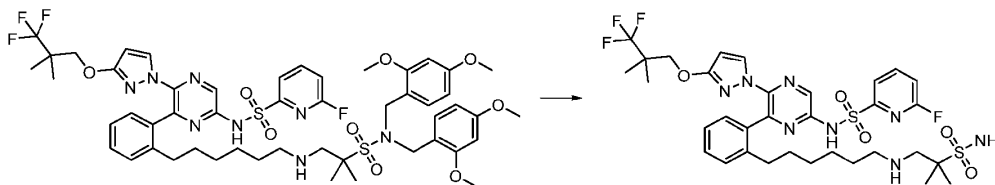
Step 1. Synthesis of N-[6-[2-[6-[2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propyl]amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide



[527] To a solution of tert-butyl N-[6-[2-[6-[2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propyl]amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate from Step 2 of **EXAMPLE 23**, 163 mg, 0.221 mmol) in DCM (5 mL) were added sodium triacetoxyborohydride (47 mg, 0.221 mmol) and N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-1-oxo-propane-2-sulfonamide (**Intermediate D-4**, 100 mg, 0.221 mmol). The reaction was stirred at 25 °C for 3 h, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column, eluting with 30% ethyl acetate in petroleum ether) to yield N-[6-[2-[6-[2-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-methyl-propyl]amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (90 mg, 0.0840 mmol, 37.9 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.94 min. MS (ESI) m/z 1071.3 $[M+H]^+$.

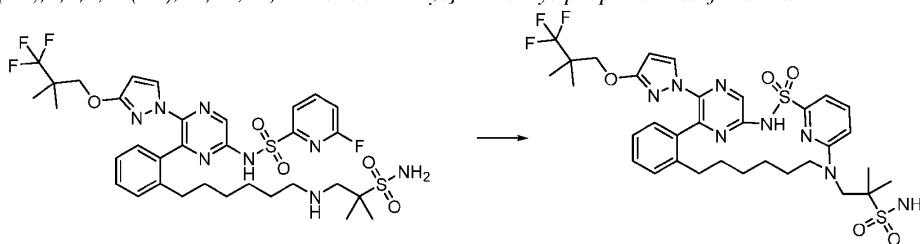
Step 2. Synthesis of 6-fluoro-N-[6-[2-[6-[(2-methyl-2-sulfamoyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide



[528] To a solution of N-[6-[2-[6-[(2-methyl-2-sulfamoyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (80 mg, 0.0747 mmol) in DCM (5 mL) was added trifluoroacetic acid (1.0 mL, 13.0 mmol). The reaction was stirred at 25 °C for 3 h. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column, eluting with 80% ethyl acetate in petroleum ether) to afford 6-fluoro-N-[6-[2-[6-[(2-methyl-2-sulfamoyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (50 mg, 0.0649 mmol, 86.9 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.70 min. MS (ESI) m/z 771.3 $[M+H]^+$.

Step 3. Synthesis of 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosal(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-2-sulfonamide



[529] To a solution of 6-fluoro-N-[6-[2-[6-[(2-methyl-2-sulfamoyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (150 mg, 0.195 mmol) in DMSO (10 mL) was added cesium fluoride (591 mg, 3.89 mmol). The reaction mixture was stirred at 100 °C for 48 h under

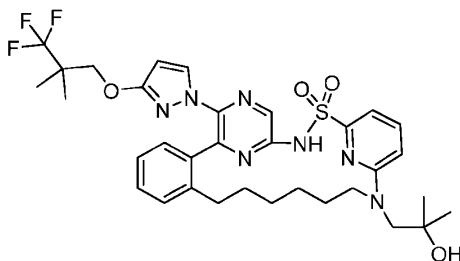
nitrogen. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-

pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-2-sulfonamide (2.6 mg, 0.00346 mmol, 1.8 % yield) as a white solid.

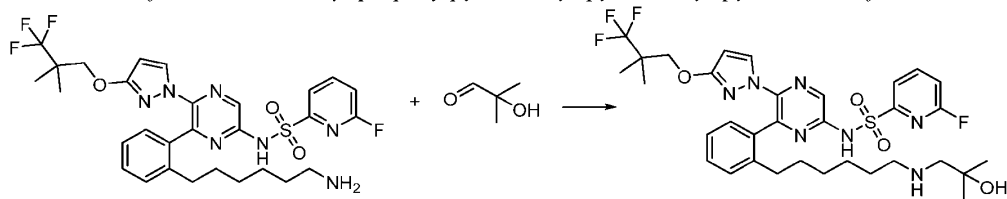
LCMS (Method 1): LC retention time = 1.76 min. MS (ESI) m/z 751.2 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.86 (s, 1H), 7.86 (d, J = 2.7 Hz, 1H), 7.66 (dd, J = 8.6, 7.4 Hz, 1H), 7.29-7.11 (m, 4H), 7.05 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.80 (d, J = 2.7 Hz, 1H), 4.06 (s, 1H), 3.80-3.43 (m, 5H), 2.46-2.04 (m, 2H), 1.65-1.26 (m, 10H), 1.22-0.99 (m, 8H), 0.96-0.63 (m, 2H).

EXAMPLE 27. Preparation of 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propan-2-ol



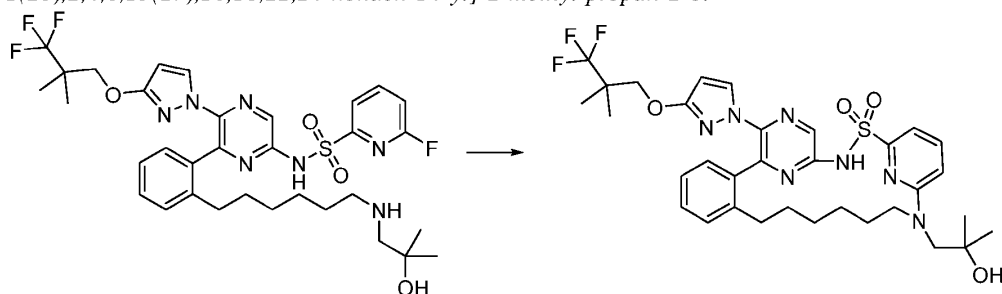
Step 1. Synthesis of 6-fluoro-N-[6-[2-[6-[(2-hydroxy-2-methyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide



[530] To a solution of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate of **Example 23**, step 3, 200 mg, 0.315 mmol) in DCM (5 mL), was added 2-hydroxy-2-methyl-propanal (**Intermediate D-5**, 28 mg, 0.315 mmol). The reaction mixture was stirred at rt for

10 min. To the mixture was added sodium triacetoxyborohydride (267 mg, 1.26 mmol) and the reaction was stirred at rt for 30 min. The reaction was quenched with saturated aqueous NaHCO₃ (100 mL) and the two phases were separated. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 10% MeOH in DCM to give 6-fluoro-N-[6-[2-[6-[(2-hydroxy-2-methyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (110 mg, 0.140 mmol, 44.5 % yield) as a white solid. LCMS (Method 1): LC retention time = 1.75 min. MS (ESI) m/z 708.2 [M+H]⁺.

Step 2. Synthesis of 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propan-2-ol

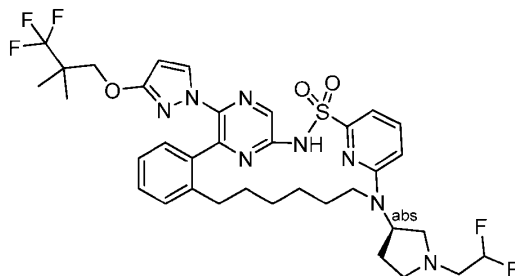


[531] To a solution of 6-fluoro-N-[6-[2-[6-[(2-hydroxy-2-methyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (110 mg, 0.134 mmol) in DMSO (4 mL) was added cesium fluoride (406 mg, 2.67 mmol). The reaction mixture was stirred at 100 °C for 32 h. The mixture was poured into water (30 mL) and extracted with EA (50 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (formic acid). After concentration of the product-containing fractions under reduced pressure, the residue was freeze-dried to get 1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propan-2-ol (9.5 mg, 0.0138 mmol, 10.3 % yield) as a white solid. LCMS (Method 1): LC retention time = 2.33 min. MS (ESI) m/z 688.2 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.79 (s, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.62 (dd, J = 8.8, 7.3 Hz, 1H), 7.30-7.12 (m, 4H), 7.08 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.81 (d, J =

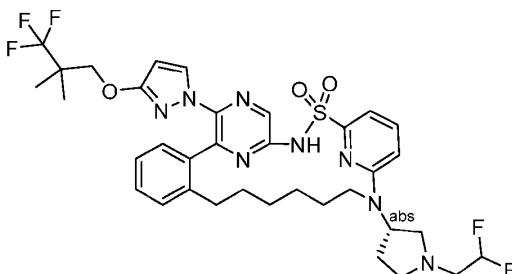
2.7 Hz, 1H), 3.73-3.51 (m, 4H), 3.45-3.34 (m, 1H), 3.26-3.04 (m, 1H), 2.53-2.07 (m, 2H), 1.56-1.31 (m, 4H), 1.21-1.01 (m, 14H), 0.97-0.71 (m, 2H).

EXAMPLE 28 (P1 and P2). Preparation of 14-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

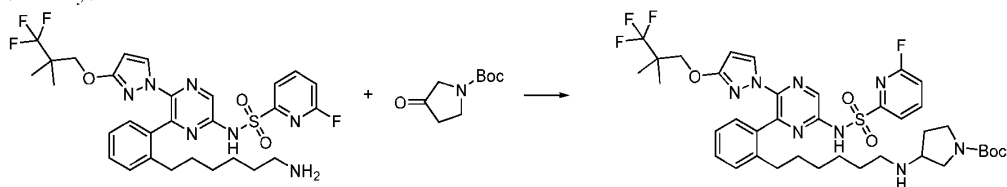


and

14-[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



Step 1. Synthesis of tert-butyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]pyrrolidine-1-carboxylate

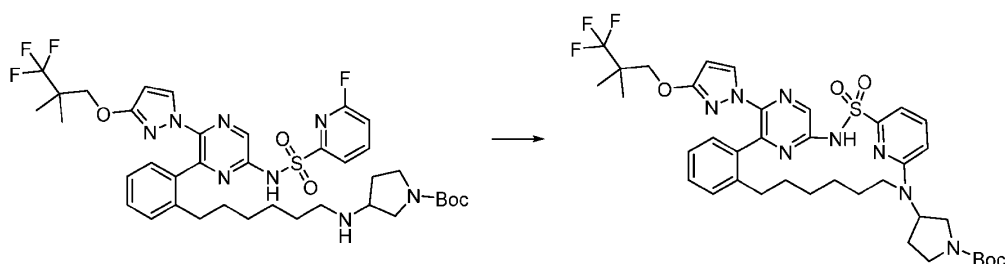


[532] To a solution of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate from **EXAMPLE 23**, step 3, 200 mg, 0.315 mmol) in DCM (5 mL) was added tert-butyl 3-oxopyrrolidine-1-carboxylate (76 mg, 0.409 mmol). The reaction mixture was stirred at rt for 1 h. To this reaction mixture was added sodium triacetoxyborohydride (167 mg, 0.787 mmol) and stirring was continued at rt for 16 h. The reaction was quenched with water (30 mL) and extracted with EA (30 mL $\times$ 3). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 0-10% MeOH in DCM) to give tert-butyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]pyrrolidine-1-carboxylate (125 mg, 0.154 mmol, 48.9 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.79 min. MS (ESI) m/z 805.3 [M+H]⁺.

Step 2. Synthesis of tert-butyl 3-{20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-

pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]pyrrolidine-1-carboxylate

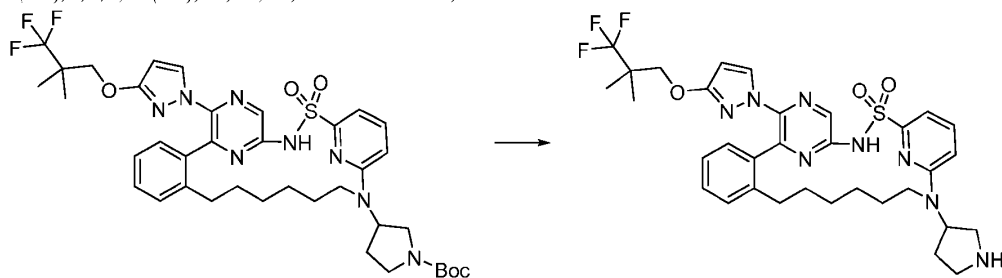


[533] To a solution of tert-butyl 3-[6-[2-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]pyrrolidine-1-carboxylate (150 mg, 0.186 mmol) in DMSO (10 mL) was added cesium fluoride (566 mg, 3.73 mmol). The mixture was stirred at 100 °C for 14 days. Water (20 mL) was added and the mixture was extracted with EA (20 mL $\times$ 3). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (TFA) to give tert-butyl 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-

pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]pyrrolidine-1-carboxylate (35 mg, 0.0441 mmol, 23.7 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.07 min. MS (ESI) m/z 785.3 [M+H]⁺.

Step 3. Synthesis of 14-pyrrolidin-3-yl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

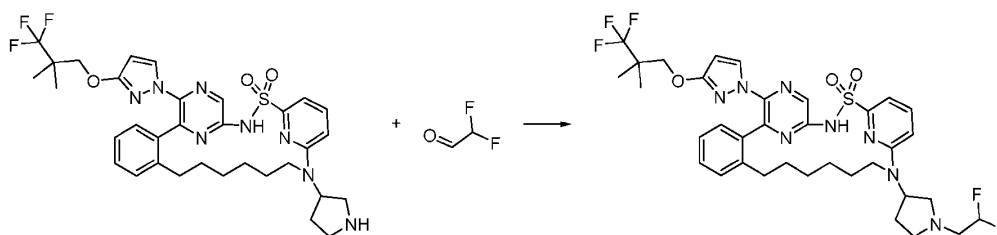


[534] A solution of tert-butyl 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]pyrrolidine-1-carboxylate (30 mg, 0.0382 mmol) in DCM (2 mL) was treated with trifluoroacetic acid (1.0 mL, 13.0 mmol) at rt for 1 h. The reaction mixture was concentrated in vacuo and the residue was purified by prep-HPLC (NH₄HCO₃) to give 14-pyrrolidin-3-yl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (4.5 mg, 0.00651 mmol, 17.0 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.91 min. MS (ESI) m/z 685.3 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ: 8.14 (m, 1H), 7.67-7.52 (m, 1H), 7.42 (m, 1H), 7.33-7.00 (m, 5H), 6.96-6.81 (m, 1H), 5.66 (d, J = 2.4 Hz, 1H), 4.31-4.12 (m, 1H), 4.04-3.38 (m, 5H), 3.24-3.77 (m, 3H), 2.41-1.99 (m, 2H), 1.97-1.68 (m, 2H), 1.61-1.35 (m, 4H), 1.23-0.98 (m, 9H), 0.97-0.67 (m, 1H).

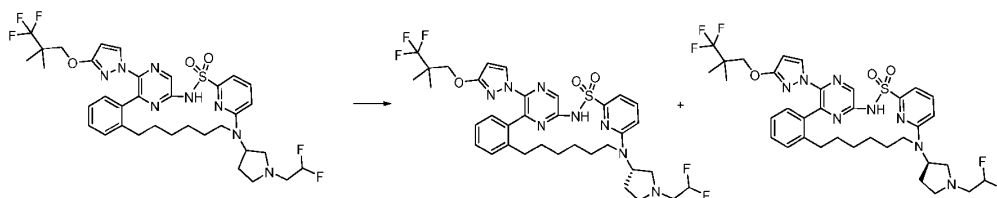
Step 4. Synthesis of 14-[1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



[535] To a solution of 14-pyrrolidin-3-yl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (30 mg, 0.0438 mmol) in DCM (1 mL) was added 2,2-difluoroacetaldehyde (105 mg, 0.131 mmol). The reaction mixture was stirred at rt for 1 h. To this mixture was added sodium triacetoxyborohydride (28 mg, 0.131 mmol), the mixture was stirred at rt for 16 h, and diluted with water (5 mL). The resulting suspension was extracted with DCM (5 mL × 3). The combined organic layers extracts were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (Condition: A: water (10 mmol/L NH₄CO₃); B: ACN). The product thus obtained was further purified by prep-TLC, followed by reverse phase combi-flash chromatography (eluent: A: water (10 mmol/L NH₄CO₃); B: ACN) to give 14-[1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (10 mg, 0.0132 mmol, 30.2 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.96 min. MS (ESI) m/z 749.3 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ: 8.48 (s, 1H), 7.64 (dd, J = 8.7, 7.4 Hz, 2H), 7.34-7.08 (m, 5H), 7.00 (d, J = 7.8 Hz, 1H), 6.53 (brs, 1H), 5.74 (d, J = 2.5 Hz, 1H), 4.34 (s, 1H), 3.90-3.36 (m, 6H), 3.24-2.74 (m, 4H), 2.42-1.75 (m, 4H), 1.61-1.21 (m, 4H), 1.18-1.05 (m, 8H), 1.03-0.63 (m, 2H).



The two enantiomers in the product mixture were separated by SFC. The separation details are as follows:

SFC conditions:

Instrument: SFC-150 (Waters)

Column: IC 25*250 mm, 10 μ m

Column temperature: Room temperature

Mobile phase: CO₂/ [MeOH(0.5%NH₃(7M in MeOH))] = 60/40

Flow rate: 100 ml/min

Back pressure: 100 bar

Detection wavelength: 214 nm

Cycle time: 6 min

Sample solution: 80 mg dissolved in 15 ml Methanol and Dichloromethane

Injection volume: 1 ml

P1:LCMS (Method 1): LC retention time = 1.74 min. MS (ESI) m/z 749.1 [M+H]⁺.

Chiral HPLC: purity: 100%, RT = 1.98 min.

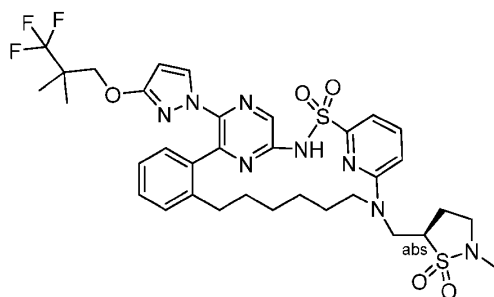
¹H NMR (400 MHz, CD₃OD) δ 8.48 (s, 1H), 7.70-7.60 (m, 2H), 7.32-7.13 (m, 5H), 7.00 (d, J = 8.0 Hz, 1H), 6.82-6.03 (m, 1H), 5.74 (d, J = 2.6 Hz, 1H), 4.40-4.31 (m, 1H), 3.90-3.37 (m, 6H), 3.24-2.65 (m, 4H), 2.44-1.83 (m, 4H), 1.52-1.32 (m, 4H), 1.16-1.06 (m, 8H), 1.00-0.68 (m, 2H).

P2:LCMS (Method 1): LC retention time = 1.74 min. MS (ESI) m/z 749.1 [M+H]⁺.

Chiral HPLC: purity: 99.64%, RT = 2.38 min.

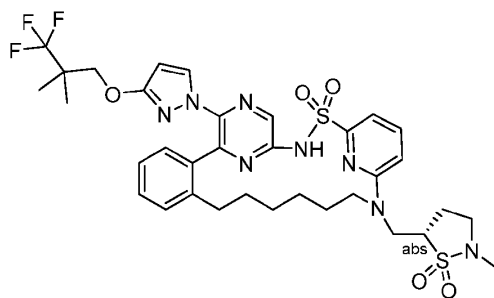
¹H NMR (400 MHz, CD₃OD) δ 8.48 (s, 1H), 7.70-7.60 (m, 2H), 7.32-7.13 (m, 5H), 7.00 (d, J = 8.0 Hz, 1H), 6.82-6.03 (m, 1H), 5.74 (d, J = 2.6 Hz, 1H), 4.40-4.31 (m, 1H), 3.90-3.37 (m, 6H), 3.24-2.65 (m, 4H), 2.44-1.83 (m, 4H), 1.52-1.32 (m, 4H), 1.16-1.06 (m, 8H), 1.00-0.68 (m, 2H).

EXAMPLE 29 (P1 and P2). Preparation of 14-[[[(5R)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

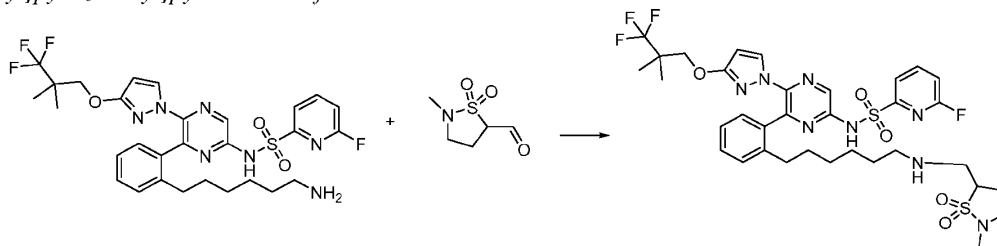


and

14-[[[(5S)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,26-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



Step 1. Synthesis of 6-fluoro-N-[6-[2-[6-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methylamino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide

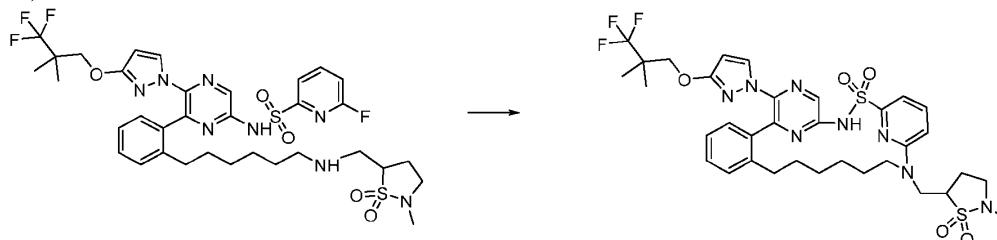


[536] To a solution of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate from **EXAMPLE 23**, step 3, 195 mg, 0.306 mmol) and 2-methyl-1,1-dioxo-1,2-thiazolidine-5-carbaldehyde (**Intermediate D-6**, 50 mg, 0.306 mmol) in DCM (4 mL) was added AcOH (catalytic amount). The mixture was stirred at rt for 30 min. To this mixture was added sodium

triacetoxyborohydride (195 mg, 0.919 mmol) at rt in three portions. The reaction mixture was stirred at rt for 4 h, then concentrated to dryness, and the residue was purified by reverse-phase flash chromatography (C18, eluting with 0.1% NH_4HCO_3 in water, 10-100% MeCN) to give 6-fluoro-N-[6-[2-[6-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methylamino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (100 mg, 0.128 mmol, 41.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.77 min. MS (ESI) m/z 783.2 $[\text{M}+\text{H}]^+$.

Step 2. Synthesis of 14-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



[537] To a solution of 6-fluoro-N-[6-[2-[6-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methylamino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (90 mg, 0.115 mmol) in DMSO (8 mL) was added cesium fluoride (349 mg, 2.30 mmol). The reaction mixture was stirred at 100 °C for 7 days under nitrogen. The reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL x 3), dried over anhydrate sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to yield 14-[(2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl)methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (8.5 mg, 0.0111 mmol, 9.7 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.92min. MS (ESI) m/z 763.2 $[\text{M}+\text{H}]^+$.

The constituent enantiomers of the product mixture were separated by SFC as follows.

SFC conditions:

Instrument: SFC-150 (Waters)

Column: (R,R) WHELK-O1 25*250 mm, 10 μ m (Regis)

Column temperature: Room temperature

Mobile phase: CO₂/ [MeOH(0.2% NH₃ (7M in MeOH))] = 55/45

Flow rate: 120 ml/min

Back pressure: 100 bar

Detection wavelength: 214 nm

Cycle time: 6.65 min

Sample solution: 50 mg dissolved in 25 ml methanol and dichloromethane

Injection: 4.8 ml

P1:

LCMS (Method 4): LC retention time = 1.87 min. MS (ESI) m/z 763.2 [M+H]⁺.

¹H NMR: (400 MHz, CD₃OD) δ 8.77 (s, 1H), 7.93 (d, J = 2.3 Hz, 1H), 7.74-7.64 (m, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.28-7.18 (m, 2H), 7.01 (m, 3H), 5.81 (d, J = 2.2 Hz, 1H), 3.85-3.38 (m, 7H), 3.18 (m, 2H), 2.62 (s, 3H), 2.43 (m, 2H), 2.19 (s, 1H), 1.88 (s, 1H), 1.40 (t, J = 9.6 Hz, 4H), 1.15-1.02 (m, 8H), 0.89 (m, 2H).

Chiral HPLC: RT = 1.495 min, chiral purity: 100%

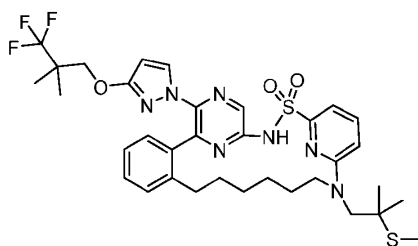
P2:

LCMS (Method 4): LC retention time = 1.87 min. MS (ESI) m/z 763.2 [M+H]⁺.

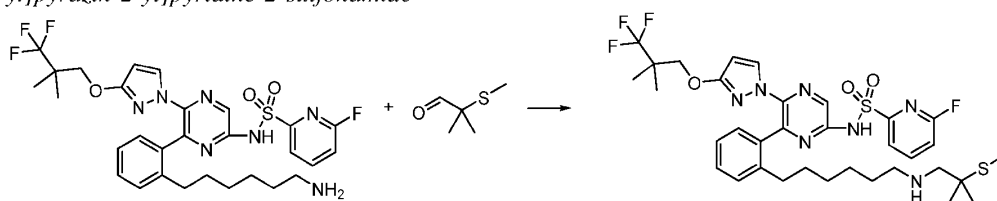
¹H NMR (400 MHz, CD₃OD) δ 8.76 (s, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.28-7.18 (m, 2H), 7.01 (m, 3H), 5.81 (d, J = 2.0 Hz, 1H), 3.92-3.40 (m, 7H), 3.24-3.04 (m, 2H), 2.60 (s, 3H), 2.56-2.21 (m, 2H), 2.19 (s, 1H), 1.88 (s, 1H), 1.56-1.32 (m, 4H), 1.07 (m, 8H), 0.95-0.77 (m, 2H).

Chiral HPLC: RT = 2.038 min, chiral purity: 99.6%

EXAMPLE 30. Preparation of 14-(2-methyl-2-methylsulfanyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20¹⁶-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



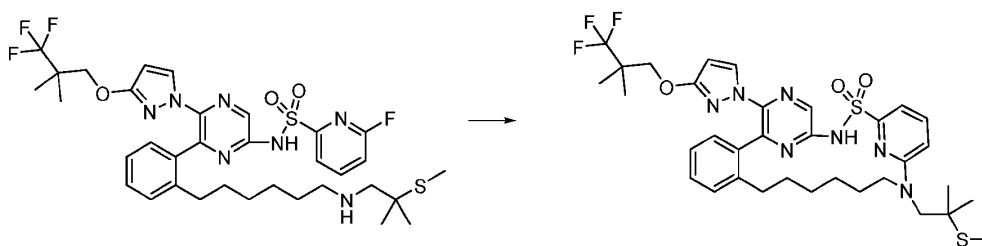
Step 1. Synthesis of 6-fluoro-N-[6-[2-[6-[(2-methyl-2-methylsulfanyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide



[538] To a mixture of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate from **EXAMPLE 23**, Step 3, 800 mg, 1.26 mmol) in DCM (10 mL) was added 2-methyl-2-methylsulfanyl-propanal (**CAS #** 16042-21-0, 149 mg, 1.26 mmol). The reaction mixture was stirred at rt for 0.5 h, then cooled to 0 °C, and sodium triacetoxyborohydride (1334 mg, 6.29 mmol) added. The mixture was stirred at rt for 2 h. The reaction mixture was poured into water (10 mL) and extracted with EA (50 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (NH₄HCO₃). The product-containing fractions were concentrated and freeze-dried to obtain 6-fluoro-N-[6-[2-[6-[(2-methyl-2-methylsulfanyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (300 mg, 0.407 mmol, 32.3 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.90 min. MS (ESI) *m/z* 738.0 [M+H]⁺.

Step 2. Synthesis of 14-(2-methyl-2-methylsulfanyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

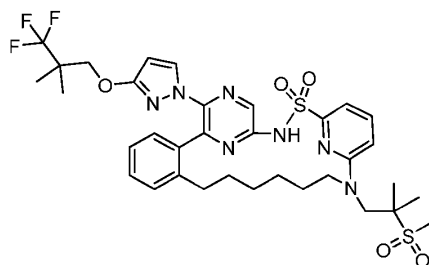


[539] To a solution of 6-fluoro-N-[6-[2-[6-[(2-methyl-2-methylsulfanyl-propyl)amino]hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (300 mg, 0.407 mmol) in DMSO (15 mL), was added cesium fluoride (618 mg, 4.07 mmol), and the mixture heated at 120 °C for 240 h. The reaction mixture was filtered, and the solids were washed with EA (30 mL). The combined filtrate was poured into water (20 mL) and extracted with EA (80 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (NH₄HCO₃). The product-containing fractions were concentrated and freeze-dried to obtain 14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (40 mg, 0.0557 mmol, 13.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.97 min. MS (ESI) m/z 718.0 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.80 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 8.6, 7.3 Hz, 1H), 7.30-7.11 (m, 4H), 7.06 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 5.81 (d, J = 2.7 Hz, 1H), 3.88-3.33 (m, 6H), 2.53-2.12 (m, 2H), 2.03 (s, 3H), 1.66-1.33 (m, 4H), 1.21 (s, 6H), 1.08 (s, 8H), 0.93-0.72 (m, 2H).

EXAMPLE 31. Preparation of 14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



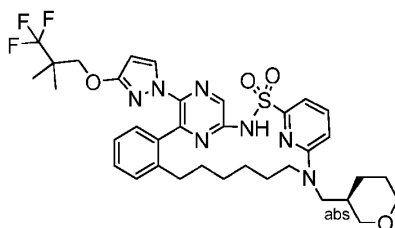
Step 1. Synthesis of 14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

[540] To a solution of 14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (**EXAMPLE 30**, 40 mg, 0.0557 mmol) in DCM (10 mL) was added 3-chloroperoxybenzoic acid (19 mg, 0.111 mmol) and the mixture was stirred at rt for 0.5 h. The reaction was poured into water (20 mL) and extracted with DCM (50 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude was purified by prep-HPLC (The product-containing fractions were concentrated and freeze-dried to get 14-(2-methyl-2-methylsulfonyl-propyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (20 mg, 0.0268 mmol, 48.1 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.77 min. MS (ESI) *m/z* 750.0 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.81 (s, 1H), 7.92 (d, *J* = 2.6 Hz, 1H), 7.69 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.28-7.17 (m, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 2H), 5.81 (d, *J* = 2.7 Hz, 1H), 4.28-3.39 (m, 6H), 2.95 (s, 3H), 2.46-2.01 (m, 2H), 1.62-1.30 (m, 10H), 1.22-1.00 (m, 8H), 1.00-0.52 (m, 2H).

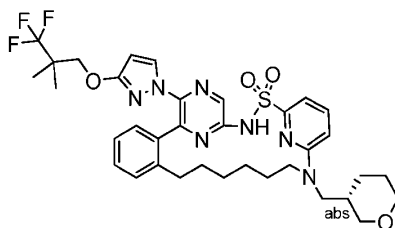
EXAMPLE 32 (P1 and P2). Preparation of 14-[[[(3R)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (P1)



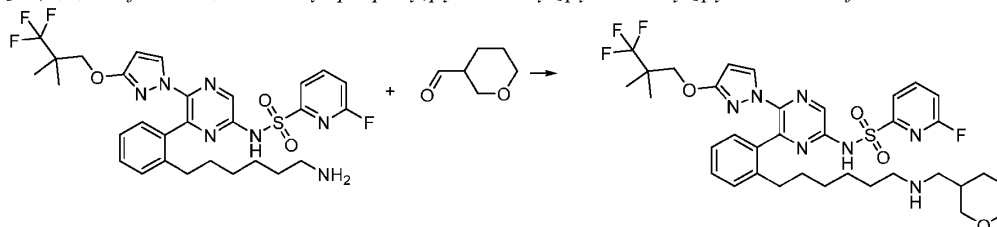
and

14-[[[(3S)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-

pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene
20,20-dioxide (P2)



Step 1. Synthesis of 6-fluoro-N-[6-[2-[6-(tetrahydropyran-3-ylmethylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide

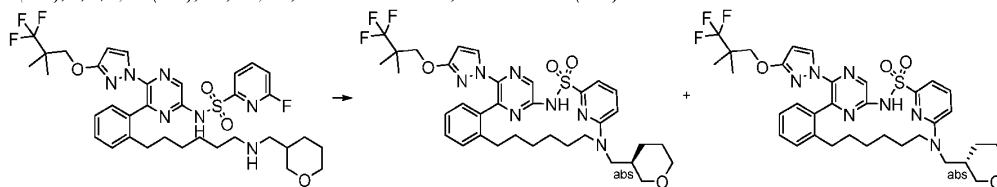


[541] To a solution of N-[6-[2-(6-aminoethyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-6-fluoro-pyridine-2-sulfonamide (Intermediate from **EXAMPLE 23**, Step 3, 500 mg, 0.787 mmol) in DCM (10 mL) were added tetrahydropyran-3-carbaldehyde (CAS#: 77342-93-9, 90 mg, 0.787 mmol) and AcOH (catalytic amount). The mixture was stirred at rt for 30 min, and sodium borohydride (89 mg, 2.36 mmol) was added at RT in three portions. The mixture was stirred at rt for 4 h, the solvent was evaporated and the residue was purified by reverse-phase flash chromatography (C18, eluting with 0.1% NH_4HCO_3 in water, 10-100% MeCN) to give 6-fluoro-N-[6-[2-[6-(tetrahydropyran-3-ylmethylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (540 mg, 0.736 mmol, 93.6 % yield) as a white solid. LCMS (Method 1): LC retention time = 1.90 min. MS (ESI) m/z 734.2 $[\text{M}+\text{H}]^+$.

Step 2. Synthesis of 14-[[[(3R)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (P1)

and

14-[[[(3*S*)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (**P2**)



[542] To a solution of 6-fluoro-N-[6-[2-[6-(tetrahydropyran-3-yl)methylamino)hexyl]phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]pyridine-2-sulfonamide (1.00 eq, 150 mg, 0.204 mmol) in DMSO (10 mL) was added cesium fluoride (621 mg, 4.09 mmol). The reaction was stirred at 100 °C for 7 days under nitrogen. The reaction mixture was cooled to rt and poured into water (50 mL). The aqueous suspension was extracted with ethyl acetate (50 mL x 3), the combined organic layers were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by HPLC to give 14-(tetrahydropyran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (410 mg, 0.574 mmol, 78.1 % yield). This sample was separated by chiral HPLC to give product **P1**, whose configuration was arbitrarily assigned as 14-[(3*R*)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (77 mg, 0.108 mmol, 53.0 % yield) and product **P2**, whose configuration was correspondingly assigned as 14-[[[(3*S*)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (79 mg, 0.111 mmol, 54.1 % yield). Both **P1** and **P2** appear as white solids.

SFC conditions:

Instrument: SFC-150 (Waters)

Column: AD 50*250 mm, 10 μm (Daicel)

Column temperature: Room temperature

Mobile phase: CO₂/MeOH[0.2%NH₃(7M in MeOH)]=70/30

Flow rate: 100 ml/min

Back pressure: 100 bar

Detection wavelength: 214 nm

Cycle time: 14.7 min

Sample solution: 410 mg dissolved in 40 ml Ethanol and Dichloromethane

Injection volume: 2.5 ml

P1:

LCMS (Method 1): LC retention time = 1.88 min. MS (ESI) m/z 714.2 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.74 (s, 1H), 7.88 (d, J = 2.7 Hz, 1H), 7.64 (dd, J = 8.7, 7.3 Hz, 1H), 7.28-7.18 (m, 3H), 7.15 (td, J = 7.5, 1.3 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 5.81 (d, J = 2.7 Hz, 1H), 3.81-3.68 (m, 2H), 3.62 (s, 2H), 3.55-3.39 (m, 3H), 3.28-3.03 (m, 3H), 2.58-2.10 (m, 2H), 2.06-1.90 (m, 1H), 1.84-1.72 (m, 1H), 1.66-1.49 (m, 2H), 1.42-1.31 (m, 4H), 1.18-1.04 (m, 8H), 0.94-0.78 (m, 2H).

Chiral HPLC: RT = 1.856 min, chiral purity: 100%.

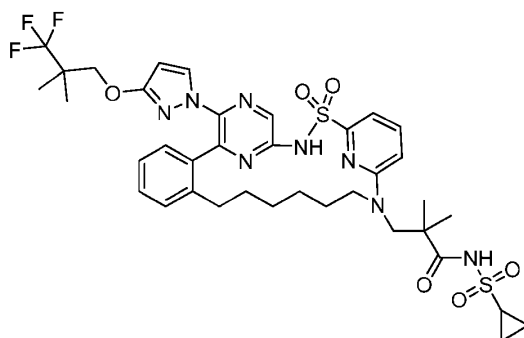
P2:

LCMS (Method 1): LC retention time = 1.88 min. MS (ESI) m/z 714.2 [M+H]⁺.

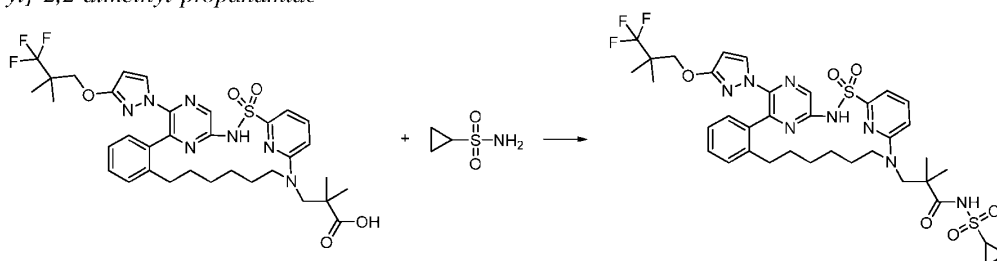
¹H NMR (400 MHz, CD₃OD) δ 8.74 (s, 1H), 7.88 (d, J = 2.7 Hz, 1H), 7.64 (dd, J = 8.7, 7.3 Hz, 1H), 7.28-7.18 (m, 3H), 7.15 (td, J = 7.5, 1.3 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 5.81 (d, J = 2.7 Hz, 1H), 3.81-3.68 (m, 2H), 3.62 (s, 2H), 3.55-3.39 (m, 3H), 3.28-3.03 (m, 3H), 2.58-2.10 (m, 2H), 2.06-1.90 (m, 1H), 1.84-1.72 (m, 1H), 1.66-1.49 (m, 2H), 1.42-1.31 (m, 4H), 1.18-1.04 (m, 8H), 0.94-0.78 (m, 2H).

Chiral HPLC: RT = 3.659 min, chiral purity: 99.6%.

EXAMPLE 33. Preparation of N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanamide



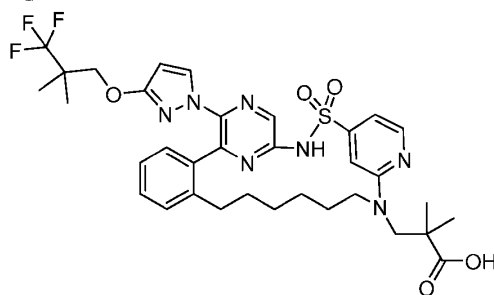
Step 1. Synthesis of N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanamide



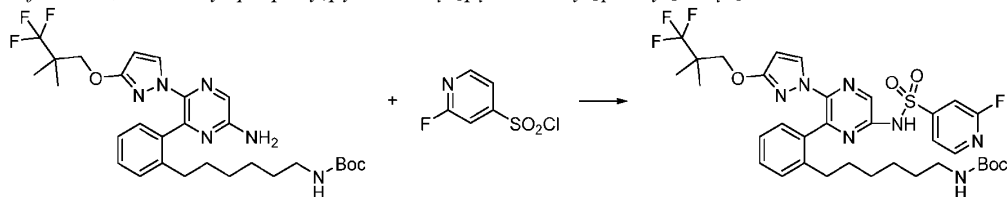
[543] To a solution of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid (**EXAMPLE 23**, 358 mg, 0.500 mmol) in DCM (5 mL) was added 4-dimethylaminopyridine (61 mg, 0.500 mmol), cyclopropane sulfonamide (121 mg, 1.00 mmol), N,N-diisopropylethylamine (0.26 mL, 1.50 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144 mg, 0.750 mmol). The reaction mixture was stirred at rt for 18 h, poured into water (50 mL), and extracted with DCM (30 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by reverse phase flash chromatography to give N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanamide (106 mg, 0.129 mmol, 25.9 % yield) as a white solid. LCMS (Method 1): LC retention time = 2.28 min. MS (ESI) m/z 819.1 [M+H]⁺.

^1H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.64 (dd, J = 8.6, 7.3 Hz, 1H), 7.30-7.10 (m, 4H), 7.05 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 5.81 (d, J = 2.7 Hz, 1H), 3.94-3.39 (m, 6H), 3.02-2.93 (m, 1H), 2.51-2.04 (m, 2H), 1.57-1.28 (m, 4H), 1.22-0.98 (m, 18H), 0.84 (s, 2H).

EXAMPLE 34. Preparation of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid

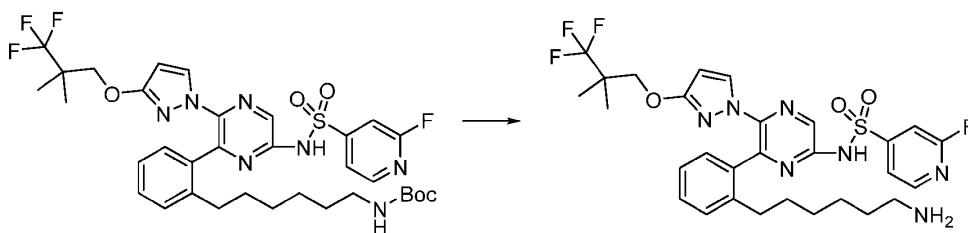


Step 1. Synthesis of tert-butyl N-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate



[544] To a solution of tert-butyl N-[6-[2-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (Intermediate from **EXAMPLE 23**, Step 2, 1300 mg, 2.25 mmol) in pyridine (1 mL) was added 2-fluoropyridine-4-sulfonyl chloride (441 mg, 2.25 mmol). The reaction mixture was stirred at rt for 12 h. The mixture was concentrated and the residue was purified by flash column chromatography on silica gel (eluting with EtOAc in PE: 0-50% for 30 min) to obtain tert-butyl N-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (1500 mg, 2.04 mmol, 90.4 % yield) as a yellow oil. LCMS (Method 1): LC retention time = 2.39 min. MS (ESI) m/z 736.0 $[\text{M}+\text{H}]^+$.

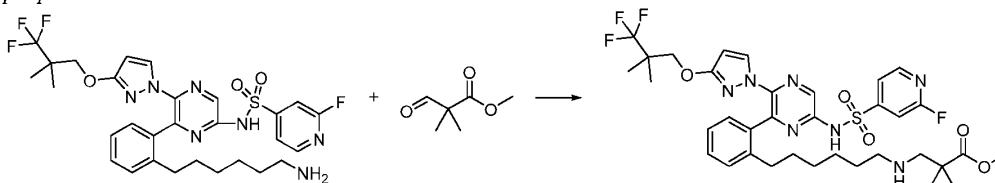
Step 2. Synthesis of N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-fluoro-pyridine-4-sulfonamide



[545] To a solution of tert-butyl N-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexyl]carbamate (1000 mg, 1.36 mmol) in DCM (4 mL) was added trifluoroacetic acid (1.0 mL, 13.0 mmol). The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure to get N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-fluoro-pyridine-4-sulfonamide (800 mg, 1.26 mmol, 92.6 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.74 min. MS (ESI) m/z 636.0 $[M+H]^+$.

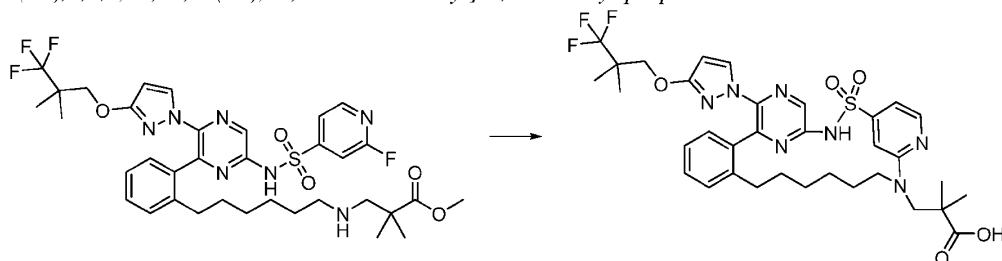
Step 3. Synthesis of methyl 3-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate



[546] To a solution of methyl 2,2-dimethyl-3-oxo-propanoate (**Intermediate D-2**, 123 mg, 0.944 mmol) in DCM (10 mL) was added N-[6-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-fluoro-pyridine-4-sulfonamide (600 mg, 0.944 mmol). The reaction mixture was stirred at rt for 0.5 h, cooled to 0 °C, and sodium triacetoxyborohydride (1000 mg, 4.72 mmol) was added portion wise at 0 °C. The reaction mixture was stirred at rt for 2 h, poured into water (50 mL) and extracted with EA (200 mL $\times$ 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with MeOH in DCM: 0-15%) to afford methyl 3-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (600 mg, 0.800 mmol, 84.8 % yield) as a yellow oil.

LCMS (Method 1): LC retention time = 1.76 min. MS (ESI) m/z 750.0 $[M+H]^+$.

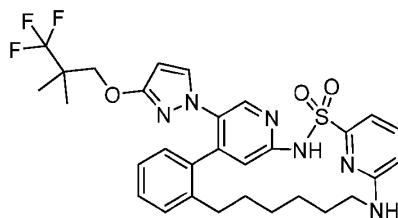
Step 4. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid



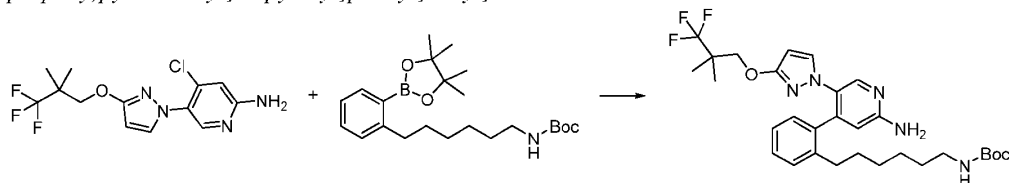
[547] To a mixture of methyl 3-[6-[2-[6-[(2-fluoro-4-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (1.00 eq, 400 mg, 0.533 mmol) in DMSO (10 mL) and water (1 mL) was added cesium fluoride (810 mg, 5.33 mmol). The mixture was stirred at 100 °C for 120 h and cooled to rt. The reaction was filtered and the solids were washed with EA (30 mL). The combined filtrate was poured into water (30 mL) and extracted with EA (80 mL × 3). The organic extracts were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by pre-HPLC (formic acid), and the product-containing fractions were concentrated and freeze-dried to get 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid (129 mg, 0.180 mmol, 33.7 % yield) as an off white solid. LCMS (Method 1): LC retention time = 2.16 min. MS (ESI) *m/z* 716.0 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.40 (s, 1H), 8.29-8.13 (m, 1H), 7.87 (d, *J* = 2.7 Hz, 1H), 7.36-7.08 (m, 4H), 7.03 (d, *J* = 3.9 Hz, 2H), 5.80 (d, *J* = 2.7 Hz, 1H), 3.79 (m, 2H), 3.58 (s, 2H), 3.43 (m, 2H), 2.11 (m, 2H), 1.32 (m, 2H), 1.05 (m, 18H).

EXAMPLE 35. Preparation of 25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



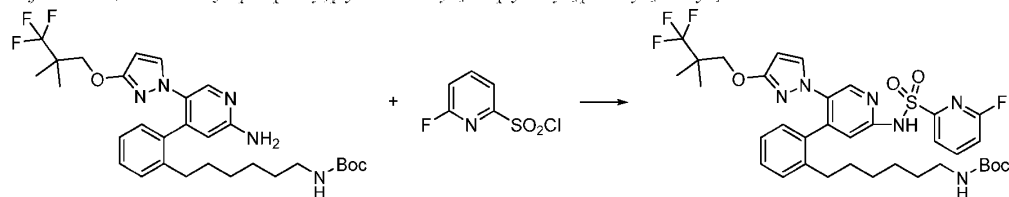
Step 1. Synthesis of tert-butyl N-[6-[2-[2-amino-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate



[548] To a solution of 4-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyridin-2-amine (**Intermediate A-8**, 800 mg, 2.39 mmol) in THF (10 mL) and water (2 mL) was added [2'-(amino-κN)[1,1'-biphenyl]-2-yl-κC][butylbis(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phosphine](methanesulfonato-κO) palladium (CAS#: **1651823-59-4**, 349 mg, 0.478 mmol), tert-butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate (**Intermediate 1A**, 964 mg, 2.39 mmol), and potassium phosphate (CAS#: **007778-53-2**, 1522 mg, 7.17 mmol). The reaction was stirred at 80 °C overnight under N₂. After cooling to room temperature, the reaction mixture was filtered and the solids were washed with EA (30 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with EtOAc in PE, 0-100%) to get tert-butyl N-[6-[2-[2-amino-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate (600 mg, 1.04 mmol, 43.6 % yield) as a yellow oil.

LCMS (Method 4): LC retention time = 2.32 min. MS (ESI) *m/z* 576.0 [M+H]⁺.

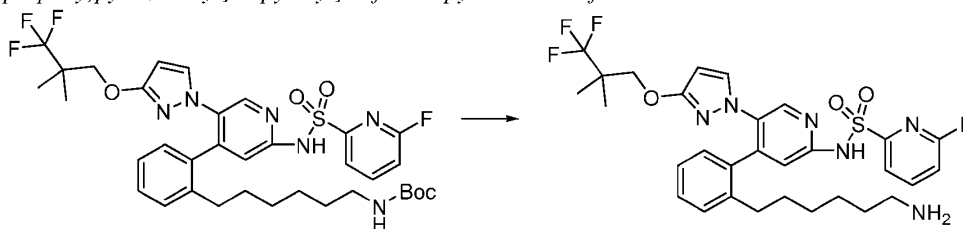
Step 2. Synthesis of tert-butyl N-[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate



[549] To a solution of tert-butyl N-[6-[2-[2-amino-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate (500 mg, 0.869 mmol) in pyridine (2 mL) was added 6-fluoropyridine-2-sulfonyl chloride (170 mg, 0.869 mmol). The reaction mixture was stirred at rt for 12 h, concentrated, and the residue was purified by flash column chromatography on silica gel (eluting with EtOAc in PE: 0-100%) to get tert-butyl N-[6-[2-[2-

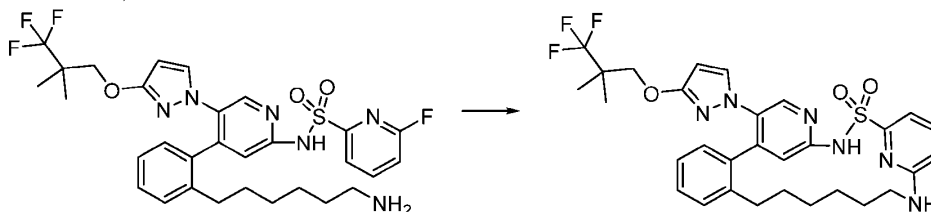
[(6-fluoro-2-pyridyl)sulfonylamino]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate (500 mg, 0.680 mmol, 78.3 % yield) as a yellow oil.
LCMS (Method 4): LC retention time = 1.90 min. MS (ESI) m/z 735.0 [M+H]⁺.

Step 3. Synthesis of N-[4-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide



[550] A solution of tert-butyl N-[6-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-4-pyridyl]phenyl]hexyl]carbamate (500 mg, 0.680 mmol) in DCM (4 mL) was treated with trifluoroacetic acid (1.0 mL, 13.0 mmol) at rt for 1 h. The reaction solution was concentrated under reduced pressure to obtain N-[4-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (350 mg, 0.551 mmol, 81.0 % yield) as a yellow oil.
LCMS (Method 1): LC retention time = 1.50 min. MS (ESI) m/z 635.0 [M+H]⁺.

Step 4. Synthesis of 25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20,6-thia-14,21,23,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide



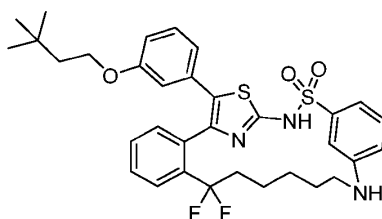
[551] To a solution of N-[4-[2-(6-aminohexyl)phenyl]-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-pyridyl]-6-fluoro-pyridine-2-sulfonamide (100 mg, 0.158 mmol) in DMSO (10 mL) was added cesium fluoride (239 mg, 1.58 mmol), and the mixture was stirred at 100 °C for 24 h. The reaction was filtered, and the solids were washed with EA (20 mL). The combined filtrates were poured into water (20 mL), and extracted with EA (30 mL × 3). The extracts were combined, washed with brine, dried over Na₂SO₄, filtered and

concentrated. The crude was purified by prep-HPLC and the product isolated by freeze-drying to get 25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide (11 mg, 0.0176 mmol, 11.2 % yield) as a white solid.

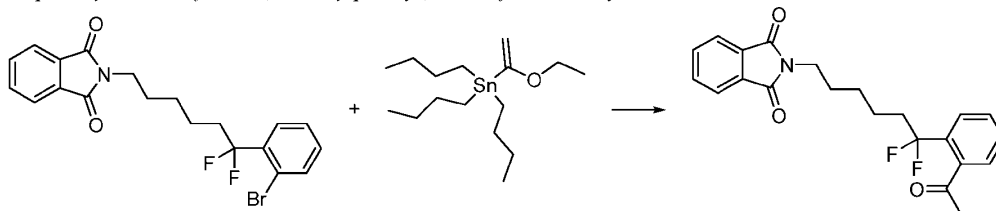
LCMS (Method 1): LC retention time = 1.95 min. MS (ESI) m/z 615.3 $[M+H]^+$.

^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.49 (dd, J = 8.4, 7.3 Hz, 1H), 7.30 (td, J = 7.5, 1.3 Hz, 1H), 7.25-7.17 (m, 3H), 7.15-7.08 (m, 2H), 6.91 (d, J = 2.6 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 5.64 (d, J = 2.6 Hz, 1H), 4.03-3.92 (m, 2H), 3.52-3.38 (m, 1H), 3.07-2.91 (m, 1H), 2.39-2.28 (m, 1H), 2.23-2.08 (m, 1H), 1.43-1.25 (m, 4H), 1.23-1.04 (m, 10H).

EXAMPLE 36. Preparation of 6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octacene 2,2-dioxide



Step 1. Synthesis of 2-[6-(2-acetylphenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione

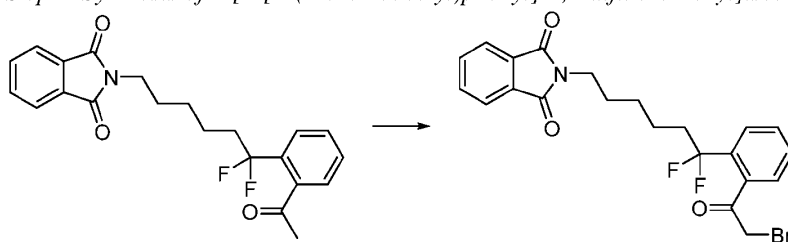


[552] To a solution of 2-[6-(2-bromophenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione (**Intermediate 2**, 1800 mg, 2.39 mmol) in toluene (20 mL) was added 1-ethoxyvinyltri-n-butyltin (1.1 mL, 3.10 mmol) and bis(triphenylphosphine)palladium(II) chloride (168 mg, 0.239 mmol). The mixture was stirred at 90 °C for 4 h under N_2 , cooled to rt and concentrated in vacuo. The residue was dissolved in THF (20 mL). To this solution was added HCl (2N in water, 5 mL). The mixture was stirred at rt for 1 h, poured into water (50 mL), and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 15% EtOAc in petroleum

ether to give 2-[6-(2-acetylphenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione (700 mg, 1.82 mmol, 76.1 % yield) as a yellow solid.

LCMS (Method 2): LC retention time = 2.41 min. MS (ESI) m/z 386.0 $[M+H]^+$.

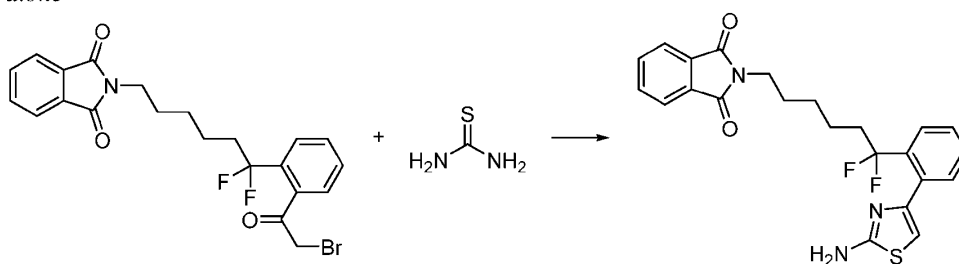
Step 2. Synthesis of 2-[6-[2-(2-bromoacetyl)phenyl]-6,6-difluoro-hexyl]isoindoline-1,3-dione



[553] To a solution of 2-[6-(2-acetylphenyl)-6,6-difluoro-hexyl]isoindoline-1,3-dione (850 mg, 1.39 mmol) in MeCN (20 mL) was added pyridine hydrobromide perbromide (667 mg, 2.08 mmol). The mixture was stirred at rt for 12 h. The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 2-[6-[2-(2-bromoacetyl)phenyl]-6,6-difluoro-hexyl]isoindoline-1,3-dione (1.50 g, 3.23 mmol) as a yellow oil. The crude product was used directly in the next step without purification.

LCMS (Method 1): LC retention time = 2.00 min. MS (ESI) m/z 464, 466 $[M+H]^+$.

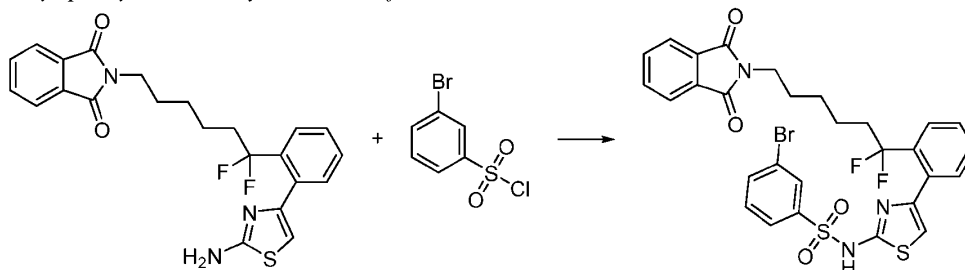
Step 3. Synthesis of 2-[6-[2-(2-aminothiazol-4-yl)phenyl]-6,6-difluoro-hexyl]isoindoline-1,3-dione



[554] To a solution of 2-[6-[2-(2-bromoacetyl)phenyl]-6,6-difluoro-hexyl]isoindoline-1,3-dione (1500 mg, 3.23 mmol) in ethanol (100 mL) was added thiourea (492 mg, 6.46 mmol). The mixture was stirred at 80 °C for 12 h, cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 15% EtOAc in petroleum ether to give 2-[6-[2-(2-aminothiazol-4-yl)phenyl]-6,6-difluoro-hexyl]isoindoline-1,3-dione (760 mg, 1.72 mmol, 53.3 % yield) as a white solid.

LCMS (Method 2): LC retention time = 1.62 min. MS (ESI) m/z 442.0 $[M+H]^+$.

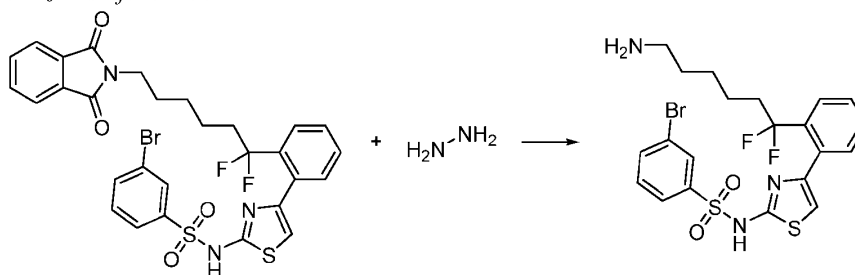
Step 4. Synthesis of 3-bromo-N-[4-[2-[6-(1,3-dioxoisindolin-2-yl)-1,1-difluoro-hexyl]phenyl]thiazol-2-yl]benzenesulfonamide



[555] To a solution of 2-[6-[2-(2-aminothiazol-4-yl)phenyl]-6,6-difluoro-hexyl]isindoline-1,3-dione (440 mg, 0.997 mmol) in pyridine (10 mL) was added 3-bromobenzenesulfonyl chloride (331 mg, 1.30 mmol). The reaction mixture was stirred at rt for 12 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting 20% EtOAc in petroleum ether to give 3-bromo-N-[4-[2-[6-(1,3-dioxoisindolin-2-yl)-1,1-difluoro-hexyl]phenyl]thiazol-2-yl]benzenesulfonamide (640 mg, 0.969 mmol, 97.2 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.01 min. MS (ESI) m/z 660.0, 662.0 $[M+H]^+$.

Step 5. Synthesis of N-[4-[2-(6-amino-1,1-difluoro-hexyl)phenyl]thiazol-2-yl]-3-bromobenzenesulfonamide

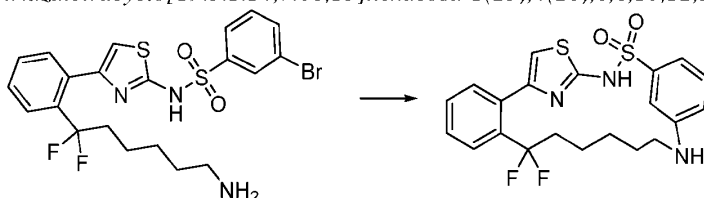


[556] A solution of 3-bromo-N-[4-[2-[6-(1,3-dioxoisindolin-2-yl)-1,1-difluoro-hexyl]phenyl]thiazol-2-yl]benzenesulfonamide (640 mg, 0.969 mmol) in ethanol (10 mL) was treated with hydrazine (0.15 mL, 4.84 mmol) at 70 °C for 3 h. The mixture was filtered, and the filtrate was concentrated. The crude was purified by reverse phase flash chromatography

to give N-[4-[2-(6-amino-1,1-difluoro-hexyl)phenyl]thiazol-2-yl]-3-bromo-benzenesulfonamide (500 mg, 0.943 mmol, 97.3 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.51 min. MS (ESI) m/z 530 and 532 $[M+H]^+$.

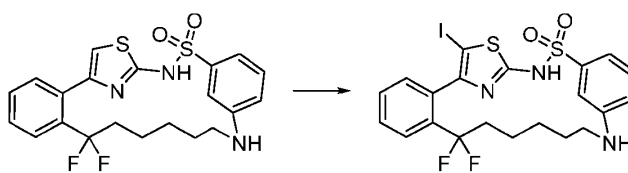
Step 6. Synthesis of 14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide



[557] To a solution of N-[4-[2-(6-amino-1,1-difluoro-hexyl)phenyl]thiazol-2-yl]-3-bromo-benzenesulfonamide (330 mg, 0.622 mmol) in 1,4-dioxane (10 mL) were added BrettPhos Pd G3 (CAS#: 470372-59-8, 56 mg, 0.0622 mmol) and cesium carbonate (608 mg, 1.87 mmol). The reaction mixture was stirred at 95 °C for 3 h under N₂, cooled to rt, poured into water (50 mL), and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting 50% EtOAc in petroleum ether to give 14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (110 mg, 0.245 mmol, 39.3 % yield) as a white solid.

LCMS (Method 2): LC retention time = 1.92 min. MS (ESI) m/z 450.0 $[M+H]^+$.

Step 7. Synthesis of 14,14-difluoro-6-iodo-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

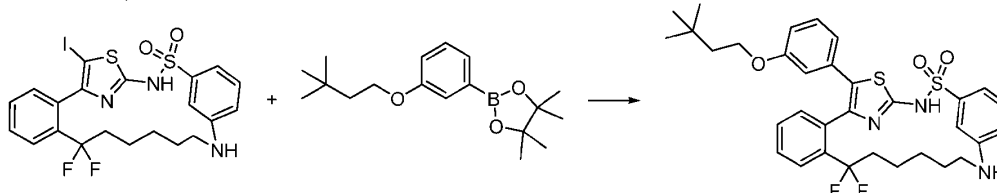


[558] To a solution of 14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (110 mg, 0.245 mmol) in THF (5 mL) was added n-iodosuccinimide (61 mg, 0.269 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo and the residue was purified by reverse phase flash chromatography to give 14,14-difluoro-6-iodo-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-

1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (100 mg, 0.174 mmol, 71.0 % yield) as a white solid.

LCMS (Method 2): LC retention time = 2.03 min. MS (ESI) m/z 576.0 [M+H]⁺.

Step 8. Synthesis of 6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

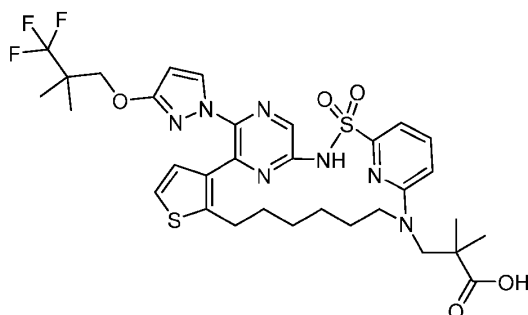


[559] To a solution of 14,14-difluoro-6-iodo-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (100 mg, 0.174 mmol) in 1,4-dioxane (5 mL) and water (0.25 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (CAS#: **651823-59-4**, 13 mg, 0.0174 mmol), 2-[3-(3,3-dimethylbutoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**Intermediate B-2**, 79 mg, 0.261 mmol) and potassium carbonate (72 mg, 0.521 mmol). The reaction mixture was stirred at 95 °C for 3 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by reverse phase flash chromatography to give 6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide (32 mg, 0.0508 mmol, 29.2 % yield) as a white solid.

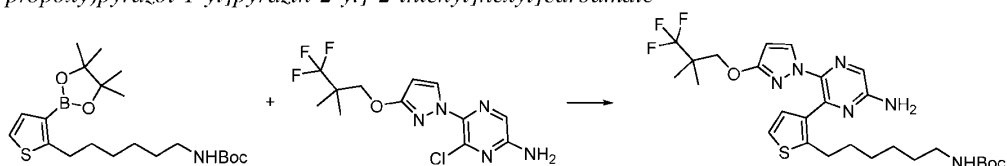
LCMS (Method 1): LC retention time = 2.12 min. MS (ESI) m/z 626.4 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 7.74-7.67 (m, 1H), 7.65-7.56 (m, 2H), 7.54-7.47 (m, 1H), 7.23-7.10 (m, 3H), 7.05-7.00 (m, 1H), 6.83-6.71 (m, 3H), 6.51-6.43 (m, 1H), 3.62 (t, J = 7.2 Hz, 2H), 3.21 (t, J = 6.2 Hz, 2H), 1.99-1.78 (m, 2H), 1.65-1.36 (m, 8H), 0.92 (s, 9H).

EXAMPLE 37. Preparation of 3-[19,19-dioxo-24-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-5,19λ6-dithia-13,20,23,25,26-pentazatetracyclo[19.3.1.114,18.02,6]hexacos-1(25),2(6),3,14(26),15,17,21,23-octaen-13-yl]-2,2-dimethyl-propanoic acid



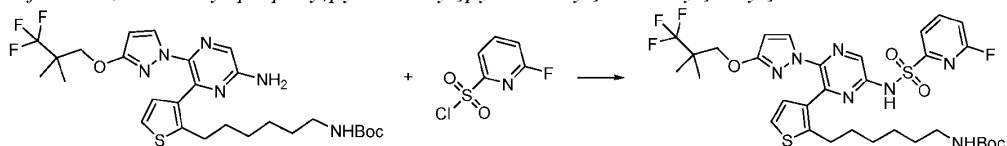
Step 1. synthesis of tert-butyl N-[6-[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexyl]carbamate



[560] To a solution of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (**Intermediate A-7**, 172 mg, 0.513 mmol) and tert-butyl N-[6-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]hexyl]carbamate (**Intermediate 8A**, 210 mg, 0.513 mmol) in THF (5 mL) and water (1 mL) were added potassium phosphate (**CAS#**: **007778-53-2**, 327 mg, 1.54 mmol), [2'-(amino-κN)[1,1'-biphenyl]-2-yl-κC][butylbis(tricyclo[3.3.1.1.3,7]dec-1-yl)phosphine](methanesulfonato-κO)-palladium (CataCXium A Pd G3, **CAS#**: **1651823-59-4** (33 mg, 0.0447 mmol). The reaction was stirred at 80 °C for 16 h under nitrogen. The reaction mixture was cooled to rt, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40g silica gel column eluting with 40% ethyl acetate in petroleum ether) to give tert-butyl N-[6-[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexyl]carbamate (200 mg, 0.343 mmol, 66.9 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.28 min. MS (ESI) m/z 583.2 [M+H]⁺.

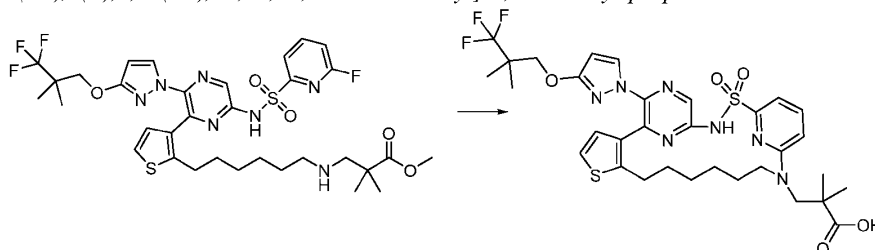
Step 2. synthesis of tert-butyl N-[6-[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexyl]carbamate



[561] To a solution of 6-fluoropyridine-2-sulfonyl chloride (8.1 mg, 0.0412 mmol) in pyridine (2 mL) was added tert-butyl N-[6-[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexyl]carbamate (20 mg, 0.0343 mmol). The reaction was stirred at 25 °C for 3 h. The reaction was quenched with water (50 mL), and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (40 g silica gel column eluting with 30% ethyl acetate in petroleum ether @ 50mL/min for 20 min) to yield tert-butyl N-[6-[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexyl]carbamate (10 mg, 0.0135 mmol, 39.3 % yield) as a yellow solid. LCMS (Method 1): LC retention time = 1.76 min. MS (ESI) m/z 742.2 [M+H]⁺.

[562] Step 3 and 4 were carried out by following Steps 2 and 3 of **EXAMPLE 34**, to obtain the cyclization precursor methyl 3-[6-[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexylamino]-2,2-dimethyl-propanoate for the next step.

Step 5. synthesis of 3-[19,19-dioxo-24-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-5,19,6-dithia-13,20,23,25,26-pentazatetracyclo[19.3.1.114,18.02,6]hexacosal(25),2(6),3,14(26),15,17,21,23-octaen-13-yl]-2,2-dimethyl-propanoic acid



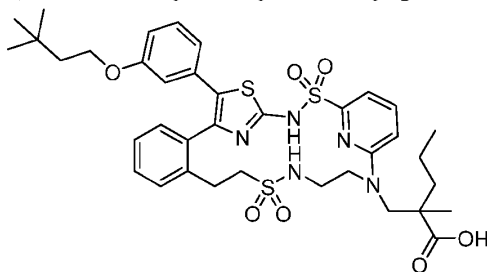
[563] To a solution of methyl 3-[6-[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexylamino]-2,2-dimethyl-propanoate (80 mg, 0.106 mmol) in DMSO (5 mL) and water (0.5 mL) was added cesium fluoride (322 mg, 2.12 mmol). The reaction mixture was stirred at 100 °C for 3 days. The reaction was quenched with water (2 mL) and its pH was adjusted 4 with 2N aqueous HCl (1 mL) at 0 °C. After concentration, the crude product was purified by reverse-phase chromatography (C18, eluting with 0.1% FA in water, 10-100% ACN) to give 3-[19,19-dioxo-24-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-5,19,6-dithia-13,20,23,25,26-

pentazatetracyclo[19.3.1.114,18.02,6]hexacosa-1(25),2(6),3,14(26),15,17,21,23-octaen-13-yl]-2,2-dimethyl-propanoic acid (14 mg, 0.0187 mmol, 17.7 % yield) as a white solid.

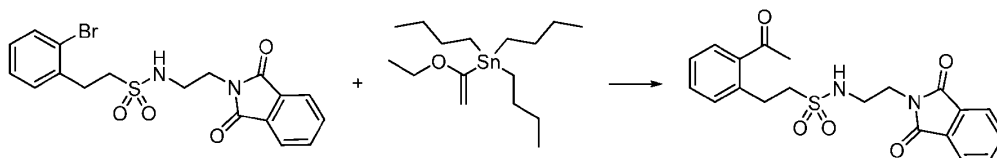
LCMS (Method 4): LC retention time = 1.60 min. MS (ESI) m/z 722.3 [M+H]⁺.

¹H NMR (500 MHz, CD₃OD) δ 8.72 (s, 1H), 7.87 (s, 1H), 7.61 (dd, J = 8.6, 7.4 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 5.3 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 5.1 Hz, 1H), 5.89 (d, J = 2.6 Hz, 1H), 3.88 (s, 2H), 3.54 – 3.33 (m, 4H), 2.70 (s, 2H), 1.59 – 1.50 (m, 2H), 1.39 – 1.30 (m, 2H), 1.25 – 1.18 (m, 2H), 1.16 (s, 6H), 1.02 (s, 6H), 0.92 – 0.80 (m, 2H).

EXAMPLE 38. Preparation of 2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,16,16-tetraoxo-2 λ 6,5,16 λ 6-trithia-3,17,20,25,26-pentazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid



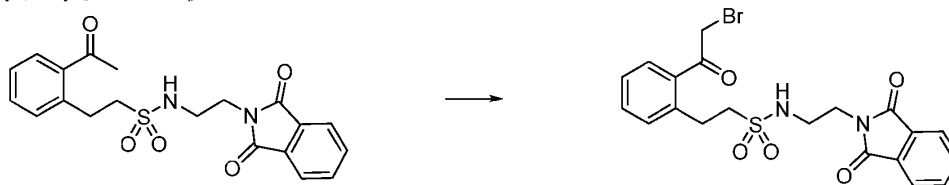
Step 1. Synthesis of 2-(2-(2-acetylphenyl)-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide



[564] The title compound was synthesized (in 63.9% yield) by following the procedures of Step 1, **EXAMPLE 36** starting from **Intermediate 7**.

LCMS (Method 1): LC retention time = 1.80 min. MS (ESI) m/z 401.2 [M+H]⁺.

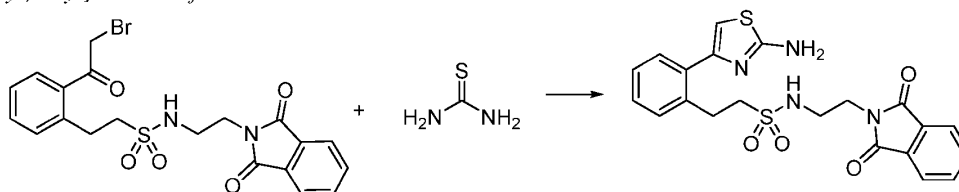
Step 2. Synthesis of 2-[2-(2-bromoacetyl)phenyl]-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide



[565] 2-[2-(2-bromoacetyl)phenyl]-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide was synthesized by following the procedures of Step 2, **EXAMPLE 36**.

LCMS (Method 1): LC retention time = 1.90 min. MS (ESI) m/z 479 and 481 $[M+H]^+$.

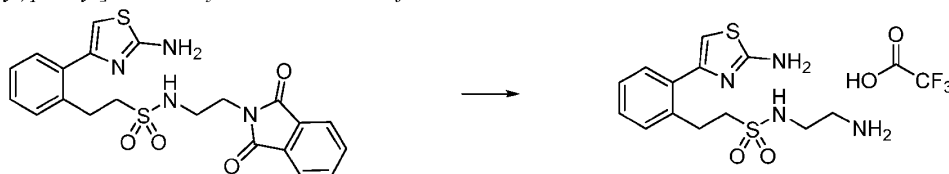
Step 3. Synthesis of 2-[2-(2-aminothiazol-4-yl)phenyl]-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide



[566] 2-[2-(2-aminothiazol-4-yl)phenyl]-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide was synthesized by following procedures of Step 3, **EXAMPLE 36**.

LCMS (Method 1): LC retention time = 1.57 min. MS (ESI) m/z 457.2 $[M+H]^+$.

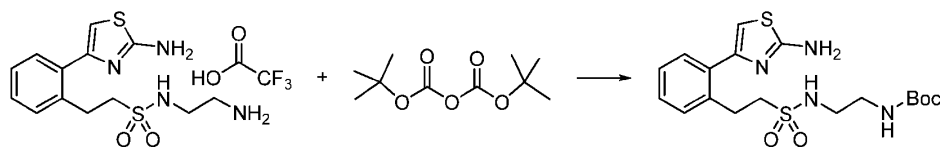
Step 4. Synthesis of N-(2-aminoethyl)-2-[2-(2-aminothiazol-4-yl)phenyl]ethanesulfonamide; 2,2,2-trifluoroacetic acid



[567] A solution of 2-[2-(2-aminothiazol-4-yl)phenyl]-N-[2-(1,3-dioxoisindolin-2-yl)ethyl]ethanesulfonamide (3.30 g, 7.23 mmol) in methanol (15mL) was treated with hydrazine hydrate (3.5 mL, 72.3 mmol) ($N_2H_4 \cdot H_2O$) at 80 °C for 4 h. The mixture was concentrated and purified by reverse-phase flash chromatography (C18, 0.1% TFA in water, 10-100% MeCN) to give N-(2-aminoethyl)-2-[2-(2-aminothiazol-4-yl)phenyl]ethanesulfonamide 2,2,2-trifluoroacetic acid (2.50 g, 5.68 mmol, 78.5 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.40 min. MS (ESI) m/z 327.0 $[M+H]^+$.

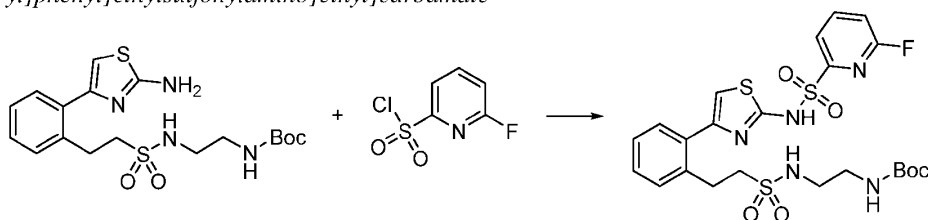
Step 5. Synthesis of tert-butyl N-[2-[2-[2-(2-aminothiazol-4-yl)phenyl]ethylsulfonylamino]ethyl]carbamate



[568] To a solution of N-(2-aminoethyl)-2-[2-(2-aminothiazol-4-yl)phenyl]ethanesulfonamide 2,2,2-trifluoroacetic acid salt (3.37 g, 7.66 mmol) and triethylamine (1.1 mL, 7.66 mmol) in DCM (5 mL) was added di-tert-butyl dicarbonate (1.8 mL, 7.66 mmol) portion wise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse-phase flash chromatography (C18, 0.1% NH_4HCO_3 in water, 10-100% MeCN) to give tert-butyl N-[2-[2-[2-(2-aminothiazol-4-yl)phenyl]ethylsulfonylamino]ethyl]carbamate (1.70 g, 3.99 mmol, 52.0 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.60 min. MS (ESI) m/z 427.2 $[\text{M}+\text{H}]^+$.

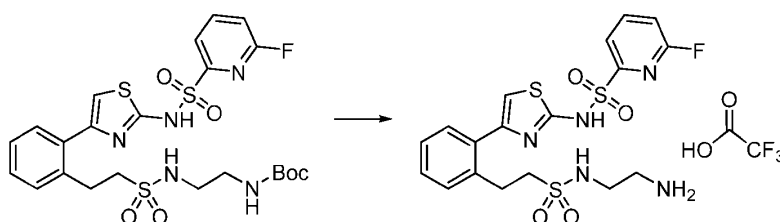
Step 6. Synthesis of tert-butyl N-[2-[2-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]ethylsulfonylamino]ethyl]carbamate



[569] To a solution of tert-butyl N-[2-[2-[2-(2-aminothiazol-4-yl)phenyl]ethylsulfonylamino]ethyl]carbamate (1.50 g, 3.52 mmol) in pyridine (5 mL) was added 6-fluoropyridine-2-sulfonyl chloride (688 mg, 3.52 mmol). The reaction mixture was stirred at rt for 2 h, concentrated, and purified by flash column chromatography on silica gel (eluting with PE : EA = 1:8) to give tert-butyl N-[2-[2-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]ethylsulfonylamino]ethyl]carbamate (1.80 g, 3.07 mmol, 87.4 % yield) as a white solid.

LCMS (Method 1): LC retention time = 1.53 min. MS (ESI) m/z 585.6 $[\text{M}+\text{H}]^+$.

Step 6. Synthesis of N-[4-[2-[2-(2-aminoethylsulfamoyl)ethyl]phenyl]thiazol-2-yl]-6-fluoropyridine-2-sulfonamide; 2,2,2-trifluoroacetic acid



[570] A solution of tert-butyl N-[2-[2-[2-[2-[(6-fluoro-2-pyridyl)sulfonylamino]thiazol-4-yl]phenyl]ethylsulfonylamino]ethyl]carbamate (1.20 g, 2.05 mmol) in DCM (10 mL) was treated with trifluoroacetic acid (0.16 mL, 2.05 mmol) for 1 h at rt. The mixture was concentrated and purified by reverse phase flash chromatography (C18, 0.1%TFA in water, 10-100% MeCN) to give N-[4-[2-[2-(2-aminoethylsulfamoyl)ethyl]phenyl]thiazol-2-yl]-6-fluoro-pyridine-2-sulfonamide;2,2,2-trifluoroacetic acid (1.30 g, 2.17 mmol, 105.8 % yield) as a white solid.

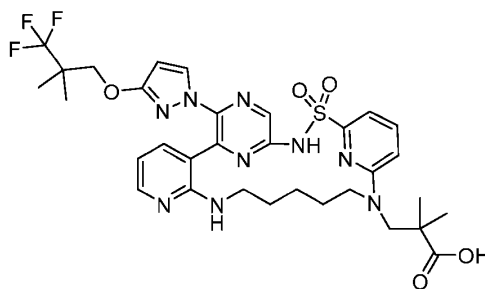
LCMS (Method 4): LC retention time = 1.48 min. MS (ESI) m/z 486.0 [M+H-Boc]⁺.

[571] The rest of the steps (Step 7-10) were analogues to Step 3-6, **EXAMPLE 6**. The title compound was obtained in 56.1 % yield as a white solid.

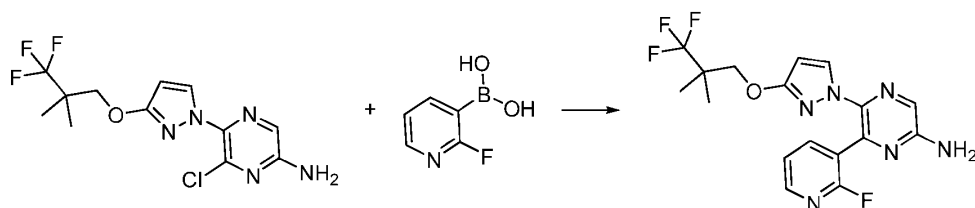
LCMS (Method 1): LC retention time = 1.67 min. MS (ESI) m/z 770.0 [M+H]⁺

¹H NMR (400 MHz, CD₃OD) δ 7.63 (dd, J = 8.7, 7.4 Hz, 1H), 7.54 – 7.36 (m, 4H), 7.26 (d, J = 7.2 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.85 – 6.73 (m, 2H), 6.52 – 6.49 (m, 1H), 4.08 – 3.45 (m, 6H), 3.27 – 3.21 (m, 1H), 3.20 – 3.10 (m, 1H), 3.07 – 3.01 (m, 2H), 2.84 – 2.76 (m, 2H), 1.81 – 1.69 (m, 1H), 1.56 (t, J = 7.2 Hz, 2H), 1.43 – 1.36 (m, 2H), 1.31 – 1.09 (m, 4H), 0.98 – 0.83 (m, 12H).

EXAMPLE 39. Preparation of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-6,8,14,21,24,26,27-heptazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2(7),3,5,15(27),16,18,22,24-nonacn-14-yl]-2,2-dimethyl-propanoic acid



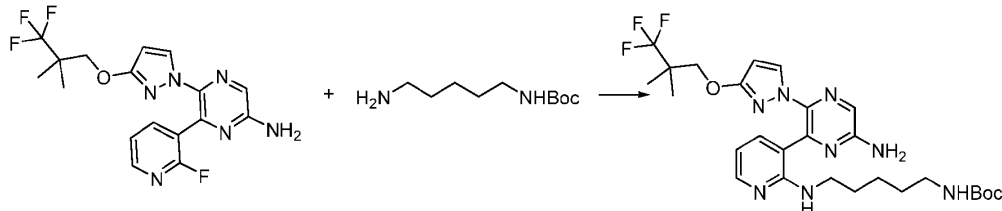
Step 1. Synthesis of 6-(2-fluoro-3-pyridyl)-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine



[572] To a solution of 6-chloro-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (34 mg, 0.101 mmol) in THF (1 mL) and water (0.2 mL) was added (2-fluoro-3-pyridyl)boronic acid (19 mg, 0.132 mmol), [2'-(amino- κ N)[1,1'-biphenyl]-2-yl- κ C][butylbis(tricyclo[3.3.1.1.3,7]dec-1-yl)phosphine](methanesulfonato- κ O)-palladium (CataCXium A Pd G3, CAS#: 1651823-59-4, 7.4 mg, 0.0101 mmol) and potassium phosphate (43 mg, 0.203 mmol). The reaction mixture was stirred at 80 °C for 2 h under N₂. The reaction mixture was cooled to rt, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (50 mL x 3), dried over anhydrate sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (40 g silica gel column eluting with 40% ethyl acetate in petroleum ether) to give 6-(2-fluoro-3-pyridyl)-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (600 mg, 1.51 mmol, 75.9 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 1.98 min. MS (ESI) m/z 397.2 [M+H]⁺.

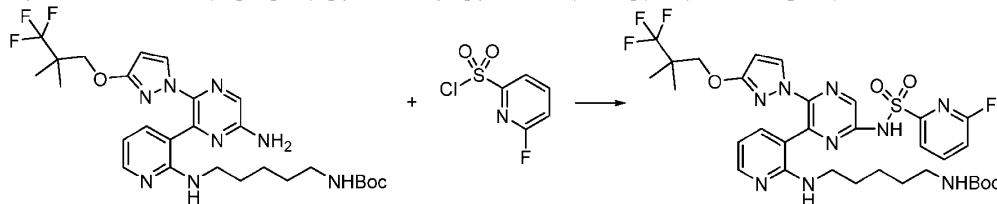
Step 2. Synthesis of tert-butyl N-[5-[[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentyl]carbamate



[573] To a solution of 6-(2-fluoro-3-pyridyl)-5-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-amine (300 mg, 0.757 mmol) was added tert-butyl N-(5-aminopentyl)carbamate (1.53 g, 7.57 mmol). The reaction mixture was stirred at 100 °C for 1 h, concentrated, and purified by reverse-phase flash chromatography (C18, 0.1% NH₄HCO₃ in water, 10-100% MeCN) to give tert-butyl N-[5-[[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentyl]carbamate (450 mg, 0.778 mmol, 102.8 % yield) as a yellow solid.

LCMS (Method 4): LC retention time = 1.96 min. MS (ESI) m/z 579.3 [M+H]⁺.

Step 3. Synthesis of tert-butyl N-[5-[[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentyl]carbamate

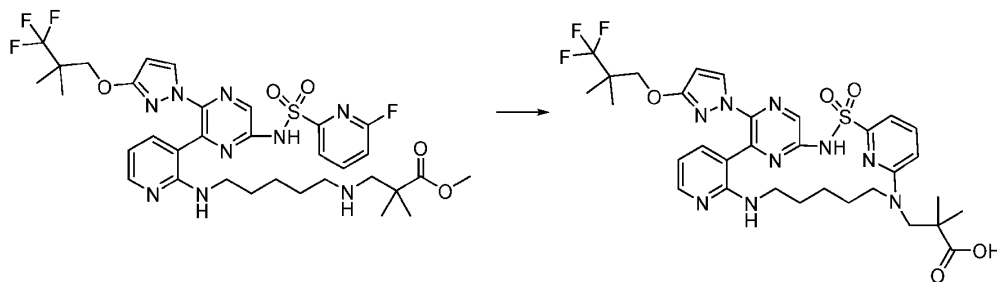


[574] To a solution of tert-butyl N-[5-[[3-[6-amino-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentyl]carbamate (450 mg, 0.778 mmol) in pyridine (1 mL) was added 6-fluoropyridine-2-sulfonyl chloride (183 mg, 0.933 mmol). The reaction mixture was stirred at rt for 16 h. The reaction was monitored by LCMS. Upon reaction completion, the reaction mixture was concentrated and purified by reverse-phase chromatography (C18, 0.1% NH_4HCO_3 in water, 10-100% ACN) to give tert-butyl N-[5-[[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentyl]carbamate (400 mg, 0.542 mmol, 69.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.57 min. MS (ESI) m/z 738.1 $[\text{M}+\text{H}]^+$.

[575] Step 4 and 5 were carried out by following Steps 2 and 3 of **EXAMPLE 34**, to obtain the cyclization precursor methyl 3-[6-[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-thienyl]hexylamino]-2,2-dimethyl-propanoate for the next step.

Step 4. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-6,8,14,21,24,26,27-heptazatetracyclo[20.3.1.115,19.02,7]heptacosal(26),2(7),3,5,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid



[576] To a solution of methyl 3-[5-[[3-[6-[(6-fluoro-2-pyridyl)sulfonylamino]-3-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]pyrazin-2-yl]-2-pyridyl]amino]pentylamino]-2,2-dimethyl-propanoate (50 mg, 0.0665 mmol) in DMSO (2.5 mL) and water (0.3 mL) was

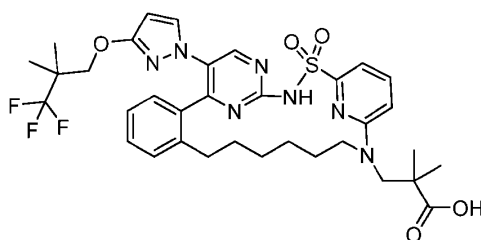
added cesium fluoride (101 mg, 0.665 mmol). The reaction mixture was stirred at 100 °C for 3 days. The reaction was monitored by LCMS. Upon reaction completion, the reaction mixture was concentrated and purified by reverse-phase chromatography (C18, 0.1% NH₄HCO₃ in water, 10-100% ACN) to give 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-6,8,14,21,24,26,27-

heptazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2(7),3,5,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid (11 mg, 0.0150 mmol, 22.6 % yield) as a white solid.

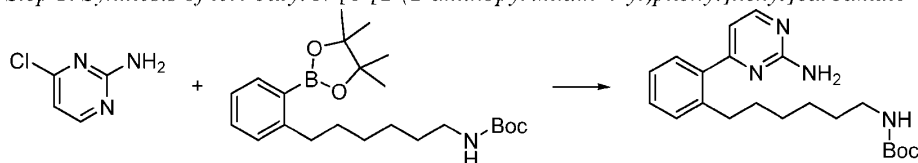
LCMS (Method 4): LC retention time = 1.48 min. MS (ESI) *m/z* 718.3 [M+H]⁺.

¹H NMR (400 MHz, CD₃OD) δ 8.71 (s, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 7.95 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.62 (dd, *J* = 8.7, 7.3 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.51 (dd, *J* = 7.4, 5.2 Hz, 1H), 5.88 (d, *J* = 2.7 Hz, 1H), 3.74 (s, 2H), 3.64 – 3.35 (m, 4H), 3.29 – 3.21 (m, 2H), 1.67 – 1.37 (m, 4H), 1.29 – 1.18 (m, 2H), 1.12 (s, 6H), 0.91 (s, 6H).

EXAMPLE 40 Preparation of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid



Step 1. Synthesis of tert-butyl N-[6-[2-(2-aminopyrimidin-4-yl)phenyl]hexyl]carbamate

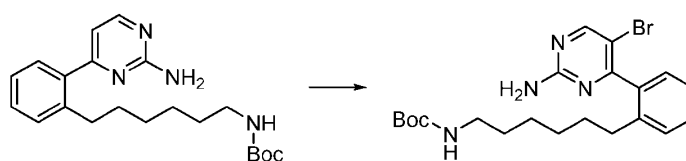


[577] To a solution of 4-chloropyrimidin-2-amine (130 mg, 1.00 mmol) in THF (5 mL) and water (1 mL) was added CataCXium A Pd G3 (CAS#: 1651823-59-4, 73 mg, 0.100 mmol), tert-butyl N-[6-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexyl]carbamate (405 mg, 1.00 mmol) and potassium phosphate (426 mg, 2.01 mmol). The mixture was stirred at 80 °C for 3 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with

ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting 35% EtOAc in petroleum ether to give tert-butyl N-[6-[2-(2-aminopyrimidin-4-yl)phenyl]hexyl]carbamate (300 mg, 0.810 mmol, 80.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.87 min. MS (ESI) m/z 371.3 [M+H]⁺.

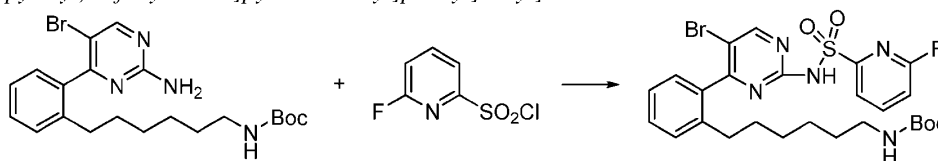
Step 2. Synthesis of tert-butyl N-[6-[2-(2-amino-5-bromo-pyrimidin-4-yl)phenyl]hexyl]carbamate



[578] To a mixture of tert-butyl N-[6-[2-(2-aminopyrimidin-4-yl)phenyl]hexyl]carbamate (300 mg, 0.810 mmol) in chloroform (0.5 mL) and MeCN (0.5 mL) was added N-bromosuccinimide (144 mg, 0.810 mmol). The mixture was stirred at rt for 3 h, then poured into water (50 mL). The aqueous suspension was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting 35% EtOAc in petroleum ether to give tert-butyl N-[6-[2-(2-amino-5-bromo-pyrimidin-4-yl)phenyl]hexyl]carbamate (300 mg, 0.668 mmol, 82.5 % yield) as a white solid.

LCMS (Method 1): LC retention time = 2.15 min. MS (ESI) m/z 449.1, 451.2 [M+H]⁺.

Step 3. Synthesis of tert-butyl N-[6-[2-[5-bromo-2-[(6-fluoro-2-pyridyl)sulfonylamino]pyrimidin-4-yl]phenyl]hexyl]carbamate



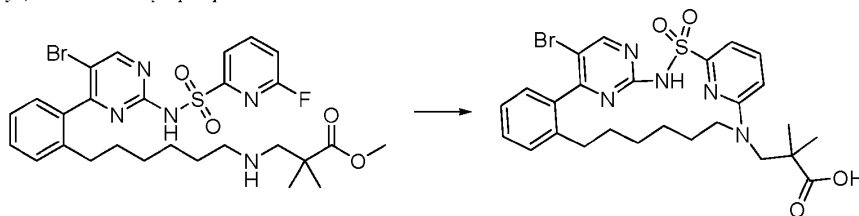
[579] To a solution of tert-butyl N-[6-[2-(2-amino-5-bromo-pyrimidin-4-yl)phenyl]hexyl]carbamate (1.00 eq, 300 mg, 0.668 mmol) in pyridine (1 mL) was added 6-fluoropyridine-2-sulfonyl chloride (261 mg, 1.34 mmol). The mixture was stirred at rt for 12 h under N₂. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 35% EtOAc in petroleum ether to give tert-

butyl N-[6-[2-[5-bromo-2-[(6-fluoro-2-pyridyl)sulfonylamino]pyrimidin-4-yl]phenyl]hexyl]carbamate (210 mg, 0.345 mmol, 51.7 % yield) as a white solid.

LCMS (Method 4): LC retention time = 1.62 min. MS (ESI) m/z 508.0, 510.0 [M+H-Boc]⁺.

[580] Steps 4 and 5 were carried out by following **EXAMPLE 34**, Step 2 and 3 to obtain the cyclization precursor methyl 3-[6-[2-[5-bromo-2-[(6-fluoro-2-pyridyl)sulfonylamino]pyrimidin-4-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate for the next step.

Step 6. Synthesis of 3-(25-bromo-20,20-dioxo-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl)-2,2-dimethyl-propanoic acid

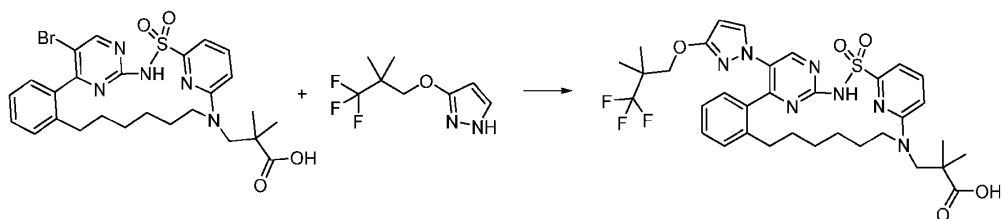


[581] To a solution of methyl 3-[6-[2-[5-bromo-2-[(6-fluoro-2-pyridyl)sulfonylamino]pyrimidin-4-yl]phenyl]hexylamino]-2,2-dimethyl-propanoate (165 mg, 0.265 mmol) in DMSO (5 mL) and water (0.5 mL) was added cesium fluoride (805 mg, 5.30 mmol). The mixture was stirred at 100 °C for 48 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by reverse phase flash chromatography to give 3-(25-bromo-20,20-dioxo-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl)-2,2-dimethyl-propanoic acid (80 mg, 0.136 mmol, 51.3 % yield) as a yellow solid.

LCMS (Method 1): LC retention time = 2.05 min. MS (ESI) m/z 588.0, 590.0 [M+H]⁺.

¹H NMR (500 MHz, CD₃OD) δ 8.51 (s, 1H), 7.62 (dd, J = 8.6, 7.4 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.28 – 7.23 (m, 3H), 7.21 – 7.17 (m, 1H), 6.96 (d, J = 8.7 Hz, 1H), 4.29 – 3.48 (m, 3H), 3.26 – 3.03 (m, 1H), 2.83 – 2.13 (m, 2H), 1.46 – 1.11 (m, 12H), 1.02 (s, 2H).

Step 7. Synthesis of 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid



[582] To a solution of 3-(25-bromo-20,20-dioxo-20 λ 6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl)-2,2-dimethyl-propanoic acid (60 mg, 0.102 mmol) in DMF (1 mL) was added 3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1H-pyrazole (2.50 eq, 53 mg, 0.255 mmol), copper (I) iodide (9.7 mg, 0.0510 mmol), N,N'-dimethylethane-1,2-diamine (90 mg, 1.02 mmol) and potassium carbonate (85 mg, 0.612 mmol). The mixture was stirred at 120 °C for 48 h under N₂. The reaction mixture was poured into water (50 mL), the pH adjusted to 6-7 with aqueous citric acid, and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by reverse phase flash chromatography to give 3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20 λ 6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid (16 mg, 0.0224 mmol, 21.9 % yield) as a white solid.

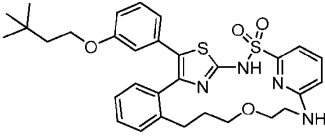
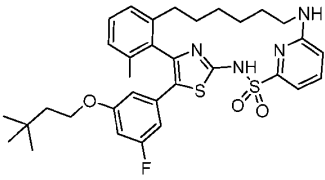
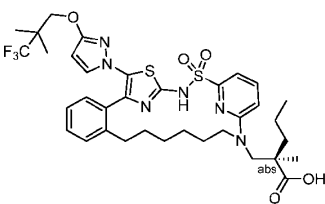
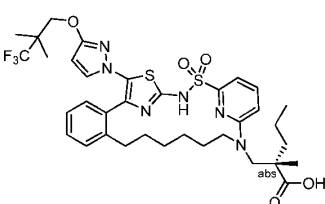
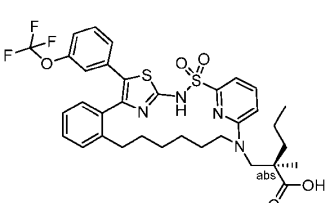
LCMS (Method 1): LC retention time = 2.21 min. MS (ESI) m/z 716.1 [M+H]⁺.

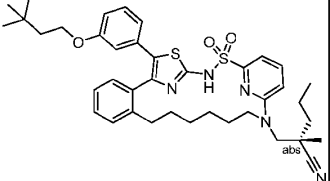
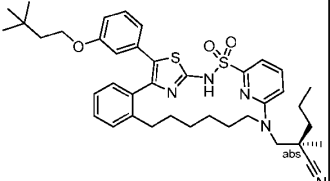
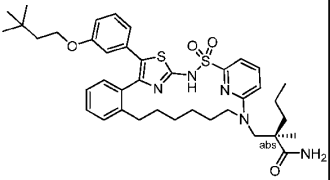
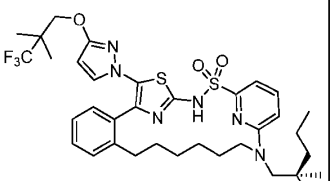
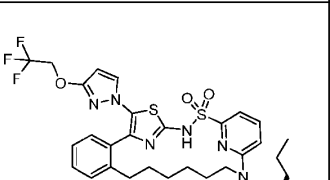
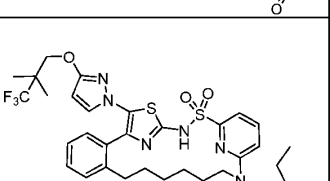
¹H NMR (400 MHz, CD₃OD) δ 8.56 (s, 1H), 7.61 (dd, J = 8.7, 7.3 Hz, 1H), 7.30 (dd, J = 11.7, 4.3 Hz, 2H), 7.16 (ddd, J = 9.0, 8.6, 4.4 Hz, 2H), 7.05 (dd, J = 7.6, 1.1 Hz, 1H), 6.97 – 6.90 (m, 2H), 5.67 (d, J = 2.6 Hz, 1H), 3.99 (s, 2H), 3.95 – 3.36 (m, 4H), 2.40 (s, 2H), 1.33 (s, 2H), 1.25 – 1.15 (m, 16H), 1.08 (s, 2H).

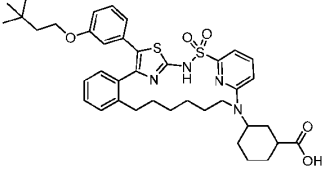
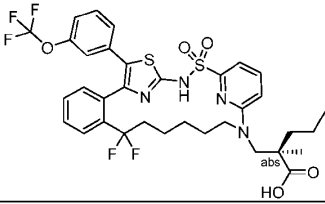
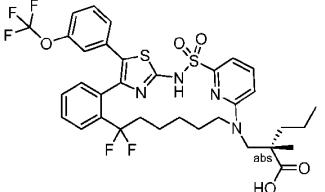
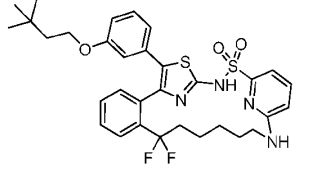
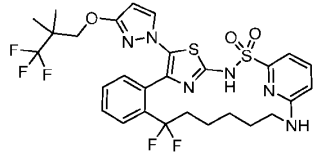
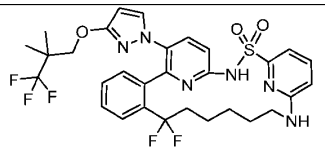
EXAMPLES 41-216.

[583] By following the **General Scheme 1 (Scheme 1, Scheme 1A, and Scheme 1B)** through **Scheme 3**, the following compounds were synthesized analogously to **EXAMPLE 1-40**.

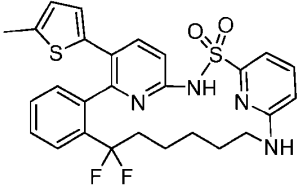
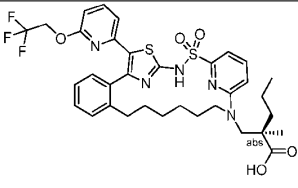
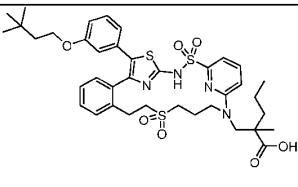
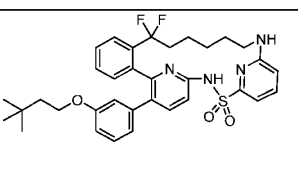
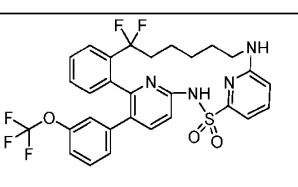
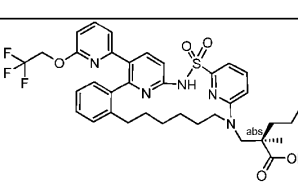
EX. No.	Structure	MW	LCMS*	¹ H-NMR
41		594.74	LCMS mtd 4; LC RT=2.03; MS (ESI) m/z 595.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.51 – 7.42 (m, 2H), 7.24 (dd, J = 7.6, 1.6 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.78 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.60 – 6.56 (m, 1H), 4.18 – 4.10 (m, 2H), 3.83 – 3.76 (m, 2H), 3.71 (t, J = 7.2 Hz, 2H), 3.63 (t, J = 4.8 Hz, 2H), 3.29 –

				3.26 (m, 2H), 1.59 (t, $J = 7.2$ Hz, 2H), 0.94 (s, 9H).
42		592.77	LCMS mtd 1; LC RT=2.15; MS (ESI) m/z 593.2 $[M+H]^+$	1H NMR (500 MHz, DMSO- d_6) δ 12.94 (s, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.44-7.41 (m, 2H), 7.39 – 7.31 (m, 2H), 7.22 (t, $J = 8.0$ Hz, 1H), 7.10 (t, $J = 5.5$ Hz, 1H), 6.97 (d, $J = 7.0$ Hz, 1H), 6.79 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 6.44 (s, 1H), 3.89-3.82 (m, 1H), 3.71 – 3.57 (m, 2H), 3.41 (q, $J = 7.5$ Hz, 1H), 3.38-3.35 (m, 1H), 3.23-3.18 (m, 1H), 3.11-3.07 (m, 1H), 3.02-2.96 (m, 1H), 2.58-2.583 (m, 1H), 2.27-2.22 (m, 1H), 1.60-1.47 (m, 4H), 0.88 (s, 9H).
43		622.82	LCMS mtd 1; LC RT=2.32; MS (ESI) m/z 623.3 $[M+H]^+$	1H NMR (400 MHz, CD_3OD) δ 7.45 (dd, $J = 8.4, 7.2$ Hz, 1H), 7.34 (t, $J = 7.6$ Hz, 1H), 7.24 (d, $J = 7.6$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.07 (d, $J = 7.2$ Hz, 1H), 6.59 – 6.46 (m, 3H), 6.34 (s, 1H), 3.85 – 3.75 (m, 1H), 3.72 – 3.57 (m, 2H), 3.02 – 2.92 (m, 1H), 2.50 – 2.38 (m, 1H), 2.32 – 2.19 (m, 4H), 1.62 – 1.16 (m, 10H), 0.93 (s, 9H).
44-P1		748.88	LCMS mtd 1; LC RT=2.69; MS (ESI) m/z 749.3 $[M+H]^+$	1H NMR (400 MHz, CD_3OD) δ 7.57 (dd, $J = 8.6, 7.4$ Hz, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.29 (m, 2H), 7.13 (d, $J = 7.2$ Hz, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 5.77 (d, $J = 2.6$ Hz, 1H), 4.16 (s, 2H), 3.79 – 3.61 (m, 2H), 3.29 – 3.17 (m, 2H), 2.46 – 2.27 (m, 2H), 1.74 – 1.33 (m, 6H), 1.28 – 1.05 (m, 15H), 0.90 (t, $J = 7.0$ Hz, 3H).
44-P2		748.88	LCMS mtd 4; LC RT=1.5; MS (ESI) m/z 749.4 $[M+H]^+$	1H NMR (400 MHz, CD_3OD) δ 7.57 (dd, $J = 8.6, 7.4$ Hz, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.29 (m, 2H), 7.13 (d, $J = 7.2$ Hz, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 5.77 (d, $J = 2.6$ Hz, 1H), 4.16 (s, 2H), 3.79 – 3.61 (m, 2H), 3.29 – 3.17 (m, 2H), 2.46 – 2.27 (m, 2H), 1.74 – 1.33 (m, 6H), 1.28 – 1.05 (m, 15H), 0.90 (t, $J = 7.0$ Hz, 3H).
45		702.81	LCMS mtd 5; LC RT=1.84; MS (ESI) m/z 701.2 $[M-H]^-$	1H NMR (400 MHz, CD_3OD) δ 7.62 – 7.56 (m, 1H), 7.48 – 7.34 (m, 4H), 7.32 (d, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 7.19 – 7.12 (m, 2H), 6.93 (d, $J = 8.7$ Hz, 1H), 6.88 (s, 1H), 4.38 – 3.95 (m, 1H), 3.85 – 3.51 (m, 2H), 3.14 – 2.76 (m, 1H), 2.53 – 2.07 (m, 2H), 1.78 – 0.79 (m, 18H).

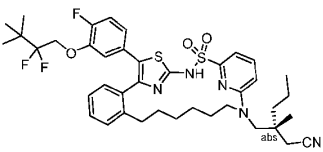
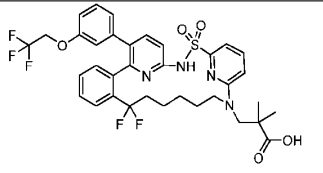
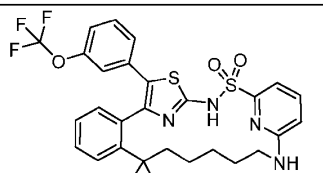
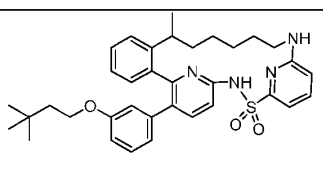
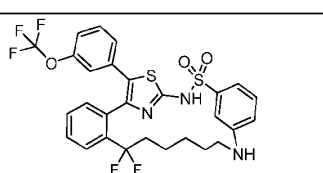
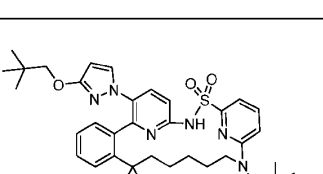
46-P1		699.97	LCMS mtd 5; LC RT=2.23; MS (ESI) m/z 698.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.46 – 7.30 (m, 4H), 7.25 – 7.17 (m, 2H), 7.01 (d, <i>J</i> = 8.7 Hz, 1H), 6.84 (d, <i>J</i> = 8.2 Hz, 1H), 6.79 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 6.54 – 6.50 (m, 1H), 4.30 – 3.79 (m, 2H), 3.74 – 3.38 (m, 4H), 2.57 – 2.13 (m, 2H), 1.81 – 1.42 (m, 9H), 1.36 – 1.07 (m, 8H), 0.97 – 0.85 (m, 12H).
46-P2		699.97	LCMS mtd 4; LC RT=1.87; MS (ESI) m/z 700.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.46 – 7.29 (m, 4H), 7.25 – 7.18 (m, 2H), 7.01 (d, <i>J</i> = 8.7 Hz, 1H), 6.84 (d, <i>J</i> = 8.1 Hz, 1H), 6.79 (dd, <i>J</i> = 8.3, 1.9 Hz, 1H), 6.57 – 6.48 (m, 1H), 4.35 – 3.79 (m, 2H), 3.76 – 3.40 (m, 4H), 2.57 – 2.14 (m, 2H), 1.84 – 1.39 (m, 9H), 1.38 – 1.02 (m, 8H), 0.99 – 0.81 (m, 12H).
47		717.99	LCMS mtd 5; LC RT=2.36; MS (ESI) m/z 716.4 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.58 (t, <i>J</i> = 7.9 Hz, 1H), 7.46 – 7.28 (m, 4H), 7.21 (t, <i>J</i> = 8.0 Hz, 1H), 7.13 (d, <i>J</i> = 7.1 Hz, 1H), 6.94 (d, <i>J</i> = 8.7 Hz, 1H), 6.85 – 6.75 (m, 2H), 6.51 (s, 1H), 4.34 – 3.92 (m, 1H), 3.77 – 3.47 (m, 4H), 3.18 – 2.87 (m, 1H), 2.59 – 2.09 (m, 2H), 1.73 – 1.43 (m, 6H), 1.36 – 1.10 (m, 10H), 0.98 – 0.77 (m, 13H).
48		729.88	LCMS mtd 5; LC RT=2.02; MS (ESI) m/z 728.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 7.61 (m, 1H), 7.45 – 7.38 (m, 2H), 7.33 (t, <i>J</i> = 7.3 Hz, 2H), 7.20 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (dd, <i>J</i> = 5.6, 3.0 Hz, 2H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 (s, 2H), 4.05 – 3.50 (m, 3H), 3.18 – 3.00 (m, 1H), 2.38 (s, 2H), 1.69 – 1.47 (m, 7H), 1.37 – 1.27 (m, 4H), 1.25 – 1.08 (m, 10H), 0.95 (t, <i>J</i> = 6.5 Hz, 3H).
49		706.8	LCMS mtd 5; LC RT=1.79; MS (ESI) m/z 705.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.46 – 7.29 (m, 4H), 7.13 (d, <i>J</i> = 7.2 Hz, 1H), 7.06 (d, <i>J</i> = 2.7 Hz, 1H), 6.93 (d, <i>J</i> = 8.8 Hz, 1H), 5.84 (d, <i>J</i> = 2.7 Hz, 1H), 4.69 (q, <i>J</i> = 8.6 Hz, 2H), 3.80 – 3.54 (m, 2H), 3.20 – 2.90 (m, 2H), 2.36 (s, 2H), 1.71 – 1.06 (m, 15H), 0.91 (t, <i>J</i> = 7.0 Hz, 3H).
50		788.91	LCMS mtd 5; LC RT=1.86; MS (ESI) m/z 787.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 – 7.55 (m, 1H), 7.44 – 7.37 (m, 2H), 7.32 (t, <i>J</i> = 8.3 Hz, 2H), 7.15 (d, <i>J</i> = 7.3 Hz, 1H), 6.99 (d, <i>J</i> = 2.6 Hz, 1H), 6.80 (d, <i>J</i> = 8.5 Hz, 1H), 5.76 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 (s, 2H), 3.97 – 3.53 (m, 3H), 3.24 – 3.17 (m, 1H), 2.37 (s, 2H), 1.83 – 1.70 (m, 1H), 1.63 – 1.47 (m, 2H), 1.36 – 1.13 (m, 18H), 0.91 (t, <i>J</i> = 6.9 Hz, 3H).

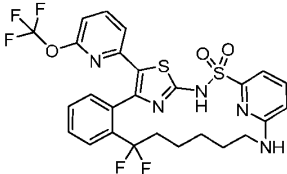
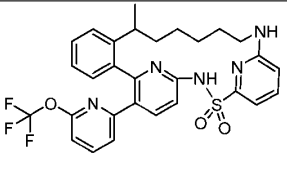
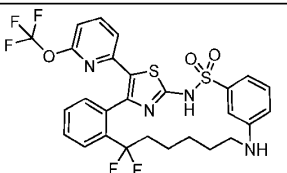
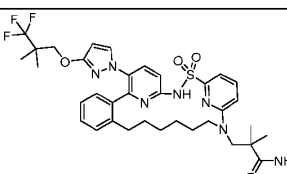
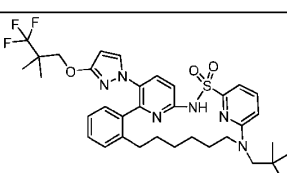
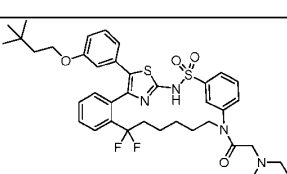
51		716.96	LCMS mtd 5; LC RT=1.98; MS (ESI) m/z 715.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 7.58 (m, 1H), 7.48 – 7.35 (m, 3H), 7.30 (d, <i>J</i> = 7.7 Hz, 1H), 7.21 (t, <i>J</i> = 8.0 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 6.88 (d, <i>J</i> = 8.8 Hz, 1H), 6.82 (d, <i>J</i> = 7.8 Hz, 1H), 6.79 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 6.56 – 6.50 (m, 1H), 4.16 – 3.93 (m, 1H), 3.87 – 3.52 (m, 3H), 3.03 (dd, <i>J</i> = 14.6, 7.3 Hz, 1H), 2.57 – 2.36 (m, 2H), 2.23 – 2.05 (m, 1H), 2.00 – 1.46 (m, 10H), 1.40 – 0.97 (m, 8H), 0.92 (s, 9H).
52-P1		738.79	LCMS mtd 1; LC RT=2.07; MS (ESI) m/z 739.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.75 – 7.69 (m, 1H), 7.68 – 7.49 (m, 4H), 7.37 (t, <i>J</i> = 8.1 Hz, 1H), 7.20 (dd, <i>J</i> = 7.4, 3.7 Hz, 2H), 7.12 (d, <i>J</i> = 8.3 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 6.86 (s, 1H), 4.20 – 3.11 (m, 4H), 2.04 – 1.78 (m, 2H), 1.76 – 1.17 (m, 10H), 1.11 (s, 3H), 0.97 – 0.82 (m, 3H).
52-P2		738.79	LCMS mtd 1; LC RT=2.07; MS (ESI) m/z 739.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.75 – 7.69 (m, 1H), 7.68 – 7.49 (m, 4H), 7.37 (t, <i>J</i> = 8.1 Hz, 1H), 7.20 (dd, <i>J</i> = 7.4, 3.7 Hz, 2H), 7.12 (d, <i>J</i> = 8.3 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 6.86 (s, 1H), 4.20 – 3.11 (m, 4H), 2.04 – 1.78 (m, 2H), 1.76 – 1.17 (m, 10H), 1.11 (s, 3H), 0.97 – 0.82 (m, 3H).
53		626.78	LCMS mtd 1; LC RT=2.71; MS (ESI) m/z 627.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.76 – 7.70 (m, 1H), 7.66 – 7.57 (m, 2H), 7.55 – 7.51 (m, 1H), 7.46 (dd, <i>J</i> = 8.4, 7.3 Hz, 1H), 7.16 (t, <i>J</i> = 8.0 Hz, 1H), 7.10 (d, <i>J</i> = 7.1 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.58 (d, <i>J</i> = 8.4 Hz, 1H), 6.48 (d, <i>J</i> = 1.9 Hz, 1H), 3.64 (t, <i>J</i> = 7.1 Hz, 2H), 3.61 – 3.51 (m, 1H), 3.13 – 3.02 (m, 1H), 2.13 – 1.76 (m, 2H), 1.61 – 1.32 (m, 8H), 0.93 (s, 9H).
54		656.69	LCMS mtd 1; LC RT=2.07; MS (ESI) m/z 657.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 – 7.67 (m, 1H), 7.66 – 7.52 (m, 3H), 7.46 (dd, <i>J</i> = 8.5, 7.2 Hz, 1H), 7.15 – 6.98 (m, 2H), 6.59 (d, <i>J</i> = 8.4 Hz, 1H), 5.74 (d, <i>J</i> = 2.7 Hz, 1H), 4.08 (s, 2H), 3.26 – 3.09 (m, 2H), 2.11 – 1.81 (m, 2H), 1.66 – 1.39 (m, 6H), 1.20 (s, 6H).
55		650.67	LCMS mtd 4; LC RT=2.16; MS (ESI) m/z 651.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.85 (d, <i>J</i> = 8.9 Hz, 1H), 7.54 – 7.41 (m, 4H), 7.36 (t, <i>J</i> = 7.4 Hz, 1H), 7.24 (d, <i>J</i> = 7.0 Hz, 1H), 7.07 (d, <i>J</i> = 7.7 Hz, 1H), 6.97 (d, <i>J</i> = 2.6 Hz, 1H), 6.58 (d, <i>J</i> = 8.4 Hz, 1H), 5.59 (d, <i>J</i> = 2.6 Hz, 1H), 4.00 – 3.96 (m, 2H), 3.82 – 3.74 (m, 1H), 3.01 – 2.90 (m, 1H), 2.40 – 2.14 (m, 1H), 2.07 – 1.81 (m, 1H), 1.61 – 1.31 (m, 6H), 1.18 (s, 6H).

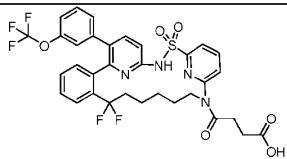
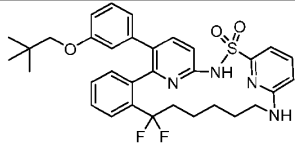
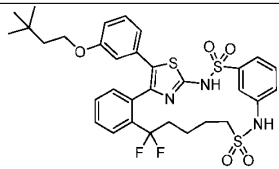
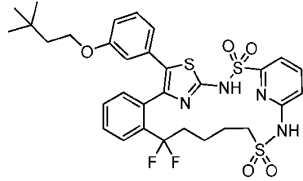
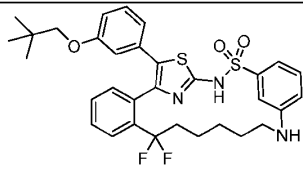
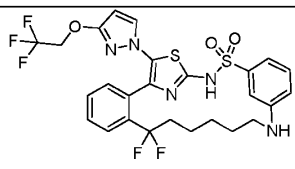
56		657.81	LCMS mtd 5; LC RT=2.11; MS (ESI) m/z 656.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.50 – 7.40 (m, 2H), 7.40 – 7.32 (m, 2H), 7.27 – 7.18 (m, 2H), 7.08 (t, <i>J</i> = 8.0 Hz, 1H), 7.00 (td, <i>J</i> = 8.0, 1.4 Hz, 1H), 6.87 – 6.78 (m, 2H), 6.53 (s, 1H), 4.08 – 3.72 (m, 2H), 3.45 – 3.37 (m, 1H), 3.22 – 3.06 (m, 1H), 2.60 – 2.21 (m, 1H), 1.53 – 1.41 (m, 2H), 1.36 – 1.12 (m, 5H), 1.04 (s, 9H), 0.94 – 0.84 (m, 1H), 0.75 (s, 3H).
57		604.83	LCMS mtd 5; LC RT=2.03; MS (ESI) m/z 603.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.51 – 7.31 (m, 5H), 7.23 (t, <i>J</i> = 7.9 Hz, 1H), 7.05 (d, <i>J</i> = 7.1 Hz, 1H), 6.85 – 6.76 (m, 2H), 6.58 – 6.49 (m, 2H), 3.90 – 3.52 (m, 3H), 3.03 – 2.91 (m, 1H), 2.88 – 2.74 (m, 1H), 1.56 (t, <i>J</i> = 7.1 Hz, 2H), 1.49 – 1.43 (m, 1H), 1.35 – 0.94 (m, 7H), 0.91 (s, 9H), 0.58 (d, <i>J</i> = 6.1 Hz, 3H).
58-P1		660.89	LCMS mtd 5; LC RT=2.04; MS (ESI) m/z 659.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 (d, <i>J</i> = 9.1 Hz, 1H), 7.78 (d, <i>J</i> = 8.8 Hz, 1H), 7.59 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.35 (td, <i>J</i> = 7.4, 1.7 Hz, 1H), 7.29 – 7.14 (m, 4H), 6.88 (d, <i>J</i> = 8.7 Hz, 1H), 6.55 – 6.48 (m, 2H), 3.65 – 3.38 (m, 3H), 3.23 – 3.09 (m, 1H), 2.32 (s, 3H), 2.29 – 2.18 (m, 4H), 1.72 – 1.45 (m, 3H), 1.37 – 1.18 (m, 6H), 1.15 – 1.05 (m, 2H), 0.99 – 0.74 (m, 9H).
58-P2		660.89	LCMS mtd 5; LC RT=2.03; MS (ESI) m/z 659.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 (d, <i>J</i> = 9.1 Hz, 1H), 7.78 (d, <i>J</i> = 8.8 Hz, 1H), 7.59 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.35 (td, <i>J</i> = 7.4, 1.7 Hz, 1H), 7.29 – 7.14 (m, 4H), 6.88 (d, <i>J</i> = 8.7 Hz, 1H), 6.55 – 6.48 (m, 2H), 3.65 – 3.38 (m, 3H), 3.23 – 3.09 (m, 1H), 2.32 (s, 3H), 2.29 – 2.18 (m, 4H), 1.72 – 1.45 (m, 3H), 1.37 – 1.18 (m, 6H), 1.15 – 1.05 (m, 2H), 0.99 – 0.74 (m, 9H).
59-P1		618.81	LCMS mtd 5; LC RT=1.94; MS (ESI) m/z 617.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 (d, <i>J</i> = 9.1 Hz, 1H), 7.74 (s, 1H), 7.60 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.17 (m, 5H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 6.85 (dd, <i>J</i> = 5.1, 3.7 Hz, 1H), 6.77 (s, 1H), 3.88 – 3.39 (m, 4H), 2.31 – 2.22 (m, 2H), 1.72 – 1.61 (m, 1H), 1.52 – 1.04 (m, 12H), 0.97 – 0.77 (m, 5H).
59-P2		618.81	LCMS mtd 5; LC RT=1.94; MS (ESI) m/z 617.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 (d, <i>J</i> = 9.1 Hz, 1H), 7.74 (s, 1H), 7.60 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.17 (m, 5H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 6.85 (dd, <i>J</i> = 5.1, 3.7 Hz, 1H), 6.77 (s, 1H), 3.88 – 3.39 (m, 4H), 2.31 – 2.22 (m, 2H), 1.72 – 1.61 (m, 1H), 1.52 – 1.04 (m, 12H), 0.97 – 0.77 (m, 5H).

60		540.65	LCMS mtd 1; LC RT=2.1; MS (ESI) m/z 541.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.81 (d, <i>J</i> = 8.9 Hz, 1H), 7.57 – 7.30 (m, 5H), 7.22 (d, <i>J</i> = 7.2 Hz, 1H), 7.13 – 7.00 (m, 1H), 6.58 (d, <i>J</i> = 8.4 Hz, 1H), 6.46 (s, 2H), 3.90 – 3.66 (m, 1H), 3.02 – 2.86 (m, 1H), 2.29 (s, 3H), 2.21 – 1.82 (m, 2H), 1.59 – 1.32 (m, 6H).
61		717.82	LCMS mtd 4; LC RT=1.56; MS (ESI) m/z 718.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ: 7.62 – 7.52 (m, 2H), 7.50 – 7.45 (m, 1H), 7.44 – 7.35 (m, 3H), 7.15 (d, <i>J</i> = 7.2 Hz, 1H), 6.93 (dd, <i>J</i> = 8.0, 4.5 Hz, 1H), 6.73 (d, <i>J</i> = 8.2 Hz, 1H), 6.68 – 6.62 (m, 1H), 4.69 – 4.51 (m, 2H), 4.35 – 4.03 (m, 1H), 3.78 – 3.50 (m, 2H), 3.11 – 2.84 (m, 1H), 2.62 – 2.50 (m, 1H), 2.44 – 2.32 (m, 1H), 1.73 – 1.49 (m, 4H), 1.42 – 1.06 (m, 10H), 0.95 – 0.84 (m, 4H).
62		769	LCMS mtd 4; LC RT=1.74; MS (ESI) m/z 769.2 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 7.59 – 7.51 (m, 1H), 7.35 – 7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 7.08 (t, <i>J</i> = 8.0 Hz, 1H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 6.73 (d, <i>J</i> = 7.7 Hz, 1H), 6.63 (dd, <i>J</i> = 8.2, 1.9 Hz, 1H), 6.42 (s, 1H), 4.19 – 4.08 (m, 1H), 3.80 – 3.50 (m, 5H), 3.22 – 3.04 (m, 2H), 3.01 – 2.81 (m, 4H), 2.03 – 1.82 (m, 2H), 1.70 – 1.62 (m, 1H), 1.54 (t, <i>J</i> = 7.2 Hz, 2H), 1.43 – 1.20 (m, 3H), 1.06 (s, 3H), 0.95 – 0.86 (m, 12H).
63		620.76	LCMS mtd 1; LC RT=2.3; MS (ESI) m/z 621.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.40 (d, <i>J</i> = 8.6 Hz, 1H), 7.32 (t, <i>J</i> = 7.3 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.09 (t, <i>J</i> = 7.9 Hz, 1H), 6.86 (s, 1H), 6.79 (d, <i>J</i> = 7.8 Hz, 1H), 6.62 (dd, <i>J</i> = 8.2, 1.8 Hz, 1H), 6.59 – 6.54 (m, 2H), 3.86 – 3.77 (m, 1H), 3.76 – 3.67 (m, 1H), 3.58 – 3.44 (m, 1H), 3.06 – 2.95 (m, 1H), 2.66 – 2.37 (m, 1H), 2.23 – 2.05 (m, 1H), 1.67 – 1.42 (m, 8H), 0.92 (s, 9H).
64		604.6	LCMS mtd 1; LC RT=2.15; MS (ESI) m/z 605.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> = 8.6 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.34 (t, <i>J</i> = 7.7 Hz, 1H), 7.30 – 7.20 (m, 3H), 7.16 (d, <i>J</i> = 7.8 Hz, 1H), 7.04 – 6.86 (m, 3H), 6.58 (d, <i>J</i> = 8.5 Hz, 1H), 3.88 – 3.74 (m, 1H), 3.05 – 2.91 (m, 1H), 2.50 – 1.84 (m, 2H), 1.64 – 1.38 (m, 6H).
65-P1		711.8	LCMS mtd 5; LC RT=2.02; MS (ESI) m/z 710.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 8.16 (d, <i>J</i> = 8.9 Hz, 1H), 7.81 (t, <i>J</i> = 11.7 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.33 – 7.14 (m, 5H), 6.98 – 6.87 (m, 2H), 6.68 (d, <i>J</i> = 8.1 Hz, 1H), 4.39 – 4.08 (m, 2H), 3.83 – 3.38 (m, 4H), 2.23 (s, 2H), 1.74 – 1.60 (m, 1H), 1.49 – 1.05 (m, 12H), 0.96 – 0.75 (m, 5H).

65-P2		711.8	LCMS mtd 5; LC RT=2.02; MS (ESI) m/z 710.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 8.16 (d, <i>J</i> = 8.9 Hz, 1H), 7.81 (t, <i>J</i> = 11.7 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.33 – 7.14 (m, 5H), 6.98 – 6.87 (m, 2H), 6.68 (d, <i>J</i> = 8.1 Hz, 1H), 4.39 – 4.08 (m, 2H), 3.83 – 3.38 (m, 4H), 2.23 (s, 2H), 1.74 – 1.60 (m, 1H), 1.49 – 1.05 (m, 12H), 0.96 – 0.75 (m, 5H).
66		668.73	LCMS mtd 4; LC RT=1.87; MS (ESI) m/z 669.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 (d, <i>J</i> = 8.9 Hz, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.61 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.35 – 7.16 (m, 6H), 7.12 (d, <i>J</i> = 7.6 Hz, 1H), 7.08 (d, <i>J</i> = 8.3 Hz, 1H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 6.88 (s, 1H), 3.84 – 3.45 (m, 4H), 2.19 (s, 2H), 1.54 – 1.23 (m, 4H), 1.17 (s, 6H), 1.13 – 0.73 (m, 4H).
67		672.72	LCMS mtd 1; LC RT=2.5; MS (ESI) m/z 673.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.94 (d, <i>J</i> = 8.9 Hz, 1H), 7.70 (d, <i>J</i> = 8.9 Hz, 1H), 7.61 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.34 – 7.13 (m, 5H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 6.90 (d, <i>J</i> = 2.6 Hz, 1H), 5.69 (d, <i>J</i> = 2.6 Hz, 1H), 4.56 (q, <i>J</i> = 8.6 Hz, 2H), 3.87 – 3.40 (m, 4H), 2.23 (s, 2H), 1.48 – 1.22 (m, 4H), 1.17 (s, 6H), 1.12 – 0.77 (m, 4H).
68		724.76	LCMS mtd 1; LC RT=1.99; MS (ESI) m/z 725.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.76 – 7.69 (m, 1H), 7.67 – 7.52 (m, 4H), 7.25 – 7.17 (m, 2H), 6.97 (d, <i>J</i> = 8.7 Hz, 1H), 6.88 (dd, <i>J</i> = 8.0, 2.1 Hz, 1H), 6.84 (d, <i>J</i> = 7.8 Hz, 1H), 6.66 – 6.62 (m, 1H), 4.35 – 4.14 (m, 2H), 4.02 – 3.55 (m, 3H), 3.41 – 3.33 (m, 1H), 2.00 – 1.80 (m, 2H), 1.73 – 1.12 (m, 12H).
69		626.78	LCMS mtd 5; LC RT=1.71; MS (ESI) m/z 625.2 [M-H] ⁻	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.34 (s, 1H), 8.12 (d, <i>J</i> = 5.1 Hz, 1H), 7.70 – 7.55 (m, 4H), 7.19 (t, <i>J</i> = 8.0 Hz, 1H), 6.99 (s, 1H), 6.83 (dd, <i>J</i> = 5.1, 1.3 Hz, 1H), 6.81 – 6.73 (m, 3H), 6.41 (s, 1H), 3.60 (t, <i>J</i> = 7.2 Hz, 2H), 3.27 – 3.15 (m, 2H), 1.96 – 1.71 (m, 2H), 1.54 – 1.19 (m, 8H), 0.88 (s, 9H).
70-P1		767.97	LCMS mtd 1; LC RT=1.84; MS (ESI) m/z 768.4 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 (t, <i>J</i> = 7.8 Hz, 1H), 7.52 – 7.28 (m, 5H), 7.10 (dd, <i>J</i> = 10.6, 8.7 Hz, 1H), 6.99 (d, <i>J</i> = 8.1 Hz, 1H), 6.92 (bs, 1H), 6.69 (d, <i>J</i> = 7.8 Hz, 1H), 4.22 – 3.71 (m, 3H), 3.15 – 2.88 (m, 3H), 2.52 – 2.15 (m, 3H), 1.73 – 1.53 (m, 2H), 1.47 – 1.11 (m, 11H), 1.09 – 0.98 (m, 12H), 0.90 – 0.81 (m, 3H).

70-P2		767.97	LCMS mtd 1; LC RT=1.84; MS (ESI) m/z 768.4 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 (t, <i>J</i> = 7.8 Hz, 1H), 7.52 – 7.28 (m, 5H), 7.10 (dd, <i>J</i> = 10.6, 8.7 Hz, 1H), 6.99 (d, <i>J</i> = 8.1 Hz, 1H), 6.92 (bs, 1H), 6.69 (d, <i>J</i> = 7.8 Hz, 1H), 4.22 – 3.71 (m, 3H), 3.15 – 2.88 (m, 3H), 2.52 – 2.15 (m, 3H), 1.73 – 1.53 (m, 2H), 1.47 – 1.11 (m, 11H), 1.09 – 0.98 (m, 12H), 0.90 – 0.81 (m, 3H).
71		718.74	LCMS mtd 4; LC RT=1.7; MS (ESI) m/z 719 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 (d, <i>J</i> = 8.6 Hz, 1H), 7.62 (t, <i>J</i> = 7.9 Hz, 1H), 7.49 (d, <i>J</i> = 7.8 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.24 (t, <i>J</i> = 7.2 Hz, 1H), 7.11 (t, <i>J</i> = 7.9 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.85 (d, <i>J</i> = 7.6 Hz, 1H), 6.79 – 6.72 (m, 2H), 4.31 – 4.06 (m, 3H), 3.82 – 3.61 (m, 2H), 3.15 – 3.06 (m, 1H), 2.45 – 2.25 (m, 1H), 2.15 – 1.88 (m, 1H), 1.79 – 1.66 (m, 1H), 1.53 – 1.17 (m, 11H).
72		610.62	LCMS mtd 4; LC RT=1.62; MS (ESI) m/z 611.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.76 – 7.69 (m, 1H), 7.67 – 7.56 (m, 2H), 7.53 – 7.49 (m, 1H), 7.46 (dd, <i>J</i> = 8.4, 7.2 Hz, 1H), 7.35 (t, <i>J</i> = 8.1 Hz, 1H), 7.19 (d, <i>J</i> = 8.0 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.82 (s, 1H), 6.57 (d, <i>J</i> = 8.5 Hz, 1H), 3.65 – 3.45 (s, 1H), 3.12 – 3.02 (m, 1H), 2.00 – 1.80 (m, 2H), 1.57 – 1.30 (m, 6H).
73		598.81	LCMS mtd 6; LC RT=2.56; MS (ESI) m/z 599.4 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.04 – 7.59 (m, 2H), 7.56 – 7.28 (m, 4H), 7.24 – 7.06 (m, 3H), 6.79 (d, <i>J</i> = 7.5 Hz, 1H), 6.71 (d, <i>J</i> = 7.4 Hz, 1H), 6.53 (d, <i>J</i> = 8.3 Hz, 1H), 6.48 (s, 1H), 3.80 – 3.66 (m, 1H), 3.55 – 3.43 (m, 1H), 3.24 – 2.84 (m, 2H), 2.40 (s, 1H), 1.63 – 1.41 (m, 3H), 1.38 – 1.14 (m, 3H), 1.08 – 0.98 (m, 1H), 0.95 – 0.69 (m, 12H), 0.32 (d, <i>J</i> = 6.7 Hz, 3H).
74		609.63	LCMS mtd 5; LC RT=1.65; MS (ESI) m/z 608.1 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 – 7.66 (m, 1H), 7.65 – 7.57 (m, 2H), 7.55 – 7.47 (m, 1H), 7.35 (t, <i>J</i> = 8.1 Hz, 1H), 7.23 – 7.07 (m, 4H), 7.06 – 6.99 (m, 1H), 6.86 – 6.76 (m, 2H), 3.21 (t, <i>J</i> = 6.3 Hz, 2H), 1.99 – 1.76 (m, 2H), 1.66 – 1.24 (m, 6H).
75		696.81	LCMS mtd 1; LC RT=2.2; MS (ESI) m/z 697.4 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.85 (d, <i>J</i> = 8.9 Hz, 1H), 7.62 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.53 (d, <i>J</i> = 7.8 Hz, 1H), 7.47 – 7.35 (m, 3H), 7.31 (d, <i>J</i> = 7.2 Hz, 1H), 7.08 (d, <i>J</i> = 7.6 Hz, 1H), 6.99 (d, <i>J</i> = 8.8 Hz, 1H), 6.93 (d, <i>J</i> = 2.6 Hz, 1H), 5.57 (d, <i>J</i> = 2.6 Hz, 1H), 4.17 – 4.02 (m, 1H), 3.78 – 3.62 (m, 4H), 3.16 – 3.04 (m, 1H), 2.31 – 1.81 (m, 2H), 1.71 – 1.53 (m, 1H), 1.47 – 1.25 (m, 5H), 1.20 (d, <i>J</i> = 8.7 Hz, 6H), 0.97 (s, 9H).

76		611.61	LCMS mtd 5; LC RT=1.61; MS (ESI) m/z 610.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.80 – 7.74 (m, 1H), 7.71 – 7.57 (m, 3H), 7.55 – 7.51 (m, 1H), 7.46 (dd, <i>J</i> = 8.4, 7.3 Hz, 1H), 7.12 (d, <i>J</i> = 7.2 Hz, 1H), 6.86 (d, <i>J</i> = 8.1 Hz, 1H), 6.61 – 6.51 (m, 2H), 3.56 – 3.46 (m, 1H), 3.15 – 3.05 (m, 1H), 2.01 – 1.85 (m, 2H), 1.56 – 1.22 (m, 6H).
77		583.63	LCMS mtd 4; LC RT=2.25; MS (ESI) m/z 584.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.05 (s, 1H), 7.87 – 7.32 (m, 6H), 7.24 – 7.08 (m, 2H), 6.95 (d, <i>J</i> = 7.9 Hz, 1H), 6.79 (d, <i>J</i> = 7.7 Hz, 1H), 6.55 (d, <i>J</i> = 8.3 Hz, 1H), 3.26 – 2.91 (m, 2H), 2.42 (s, 1H), 1.52 – 1.12 (m, 4H), 1.11 – 0.62 (m, 4H), 0.35 (d, <i>J</i> = 6.5 Hz, 3H).
78		610.62	LCMS mtd 5; LC RT=1.6; MS (ESI) m/z 609.1 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.80 – 7.74 (m, 1H), 7.73 – 7.64 (m, 2H), 7.60 (t, <i>J</i> = 8.0 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.25 – 7.13 (m, 2H), 7.03 (d, <i>J</i> = 1.9 Hz, 1H), 6.88 (d, <i>J</i> = 8.1 Hz, 1H), 6.79 (ddd, <i>J</i> = 7.9, 2.2, 1.4 Hz, 1H), 6.52 (d, <i>J</i> = 7.8 Hz, 1H), 3.18 (t, <i>J</i> = 6.2 Hz, 2H), 1.97 – 1.73 (m, 2H), 1.66 – 1.23 (m, 6H).
79		713.82	LCMS mtd 4; LC RT=2.21; MS (ESI) m/z 714.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.93 (d, <i>J</i> = 8.9 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.60 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.34 – 7.09 (m, 5H), 6.94 (d, <i>J</i> = 8.7 Hz, 1H), 6.87 (d, <i>J</i> = 2.6 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.02 (s, 2H), 3.74 – 3.46 (m, 4H), 2.23 (s, 2H), 1.46 – 1.23 (m, 4H), 1.19 (s, 6H), 1.17 (s, 6H), 1.12 – 1.04 (m, 2H), 0.90 (s, 2H).
80		695.81	LCMS mtd 4; LC RT=2.35; MS (ESI) m/z 696.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.95 (d, <i>J</i> = 8.9 Hz, 1H), 7.75 – 7.61 (m, 2H), 7.32 – 7.24 (m, 2H), 7.23 – 7.11 (m, 3H), 7.01 (d, <i>J</i> = 8.7 Hz, 1H), 6.88 (d, <i>J</i> = 2.6 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.02 (s, 2H), 3.71 (s, 4H), 2.19 (s, 2H), 1.47 (s, 2H), 1.39 – 1.26 (m, 8H), 1.19 (s, 6H), 1.14 – 1.05 (m, 2H), 0.92 (s, 2H).
81		752.94	LCMS mtd 1; LC RT=2.03; MS (ESI) m/z 753.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.98 (d, <i>J</i> = 7.9 Hz, 1H), 7.94 (s, 1H), 7.76 – 7.58 (m, 4H), 7.55 – 7.47 (m, 2H), 7.14 (t, <i>J</i> = 8.0 Hz, 1H), 6.77 (d, <i>J</i> = 8.2 Hz, 1H), 6.73 (dd, <i>J</i> = 8.3, 2.1 Hz, 1H), 6.47 (s, 1H), 3.96 – 3.52 (m, 8H), 2.99 (s, 2H), 2.43 (s, 4H), 1.99 – 1.70 (m, 2H), 1.55 (t, <i>J</i> = 7.2 Hz, 2H), 1.51 – 1.37 (m, 4H), 1.34 – 1.24 (m, 2H), 0.91 (s, 9H).

82		704.67	LCMS mtd 4; LC RT=1.6; MS (ESI) m/z 705.0 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.08 (t, <i>J</i> = 7.8 Hz, 1H), 8.00 (d, <i>J</i> = 7.4 Hz, 1H), 7.81 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (d, <i>J</i> = 7.9 Hz, 1H), 7.62 (d, <i>J</i> = 8.6 Hz, 1H), 7.46 (d, <i>J</i> = 7.9 Hz, 1H), 7.35 (t, <i>J</i> = 7.6 Hz, 1H), 7.28 (t, <i>J</i> = 8.0 Hz, 1H), 7.23 (t, <i>J</i> = 7.6 Hz, 1H), 7.18 (d, <i>J</i> = 7.8 Hz, 1H), 7.02 (d, <i>J</i> = 8.2 Hz, 1H), 6.97 (s, 1H), 6.93 (d, <i>J</i> = 7.4 Hz, 1H), 4.25 – 4.12 (m, 1H), 3.71 – 3.56 (m, 1H), 2.83 – 2.71 (m, 1H), 2.67 – 2.28 (m, 4H), 1.97 – 1.66 (m, 2H), 1.52 – 1.39 (m, 1H), 1.37 – 1.17 (m, 4H).
83		606.73	LCMS mtd 1; LC RT=2.96; MS (ESI) m/z 607.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 (d, <i>J</i> = 8.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.40 (d, <i>J</i> = 8.6 Hz, 1H), 7.32 (t, <i>J</i> = 7.4 Hz, 1H), 7.27 – 7.16 (m, 2H), 7.06 (t, <i>J</i> = 7.9 Hz, 1H), 6.86 (s, 1H), 6.76 (d, <i>J</i> = 7.7 Hz, 1H), 6.64 (dd, <i>J</i> = 8.1, 1.9 Hz, 1H), 6.61 – 6.54 (m, 2H), 3.81 (s, 1H), 3.31 (s, 1H), 3.13 (d, <i>J</i> = 8.7 Hz, 1H), 3.07 – 2.92 (m, 1H), 2.62 – 2.29 (m, 1H), 2.18 – 1.95 (m, 1H), 1.64 – 1.40 (m, 6H), 0.92 (s, 9H).
84		675.82	LCMS mtd 5; LC RT=1.78; MS (ESI) m/z 674.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 (t, <i>J</i> = 1.8 Hz, 1H), 7.70 – 7.55 (m, 5H), 7.50 (t, <i>J</i> = 7.9 Hz, 1H), 7.40 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.16 (t, <i>J</i> = 8.0 Hz, 1H), 6.81 (d, <i>J</i> = 7.7 Hz, 1H), 6.76 (dd, <i>J</i> = 8.3, 1.9 Hz, 1H), 6.54 (d, <i>J</i> = 1.9 Hz, 1H), 3.66 (dd, <i>J</i> = 15.7, 7.6 Hz, 2H), 3.07 (dd, <i>J</i> = 15.4, 7.1 Hz, 2H), 1.91 – 1.37 (m, 8H), 0.93 (s, 9H).
85		676.81	LCMS mtd 5; LC RT=1.66; MS (ESI) m/z 675.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.93 (t, <i>J</i> = 7.9 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.69 – 7.55 (m, 3H), 7.23 – 7.12 (m, 2H), 6.84 (d, <i>J</i> = 7.8 Hz, 1H), 6.77 (dd, <i>J</i> = 8.3, 2.2 Hz, 1H), 6.56 (s, 1H), 3.66 (t, <i>J</i> = 6.6 Hz, 2H), 3.45 – 3.35 (m, 1H), 3.27 – 3.14 (m, 1H), 2.00 – 1.75 (m, 4H), 1.70 – 1.61 (m, 2H), 1.57 (t, <i>J</i> = 7.1 Hz, 2H), 0.93 (s, 9H).
86		611.77	LCMS mtd 1; LC RT=2.7; MS (ESI) m/z 612.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 7.68 (m, 1H), 7.66 – 7.57 (m, 2H), 7.54 – 7.49 (m, 1H), 7.19 (t, <i>J</i> = 7.8 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.03 (t, <i>J</i> = 1.9 Hz, 1H), 6.82 – 6.72 (m, 3H), 6.52 – 6.46 (m, 1H), 3.24 – 3.16 (m, 4H), 1.98 – 1.78 (m, 2H), 1.64 – 1.27 (m, 6H), 0.93 (s, 9H).
87		613.62	LCMS mtd 1; LC RT=2.36; MS (ESI) m/z 614.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 – 7.49 (m, 4H), 7.19 (t, <i>J</i> = 7.9 Hz, 1H), 7.11 (d, <i>J</i> = 7.8 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.80 (ddd, <i>J</i> = 8.2, 2.3, 0.9 Hz, 1H), 5.78 (d, <i>J</i> = 2.7 Hz, 1H), 4.62 (q, <i>J</i> = 8.6 Hz, 2H), 3.22 (t, <i>J</i> = 6.2 Hz, 2H), 1.90 (tt, <i>J</i> = 19.3, 6.9 Hz, 2H), 1.60 – 1.46 (m, 4H), 1.45 – 1.35 (m, 2H).

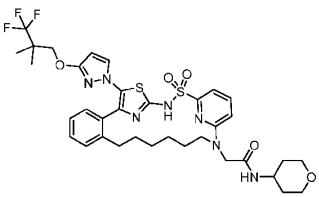
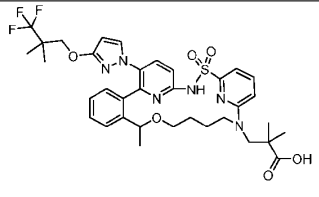
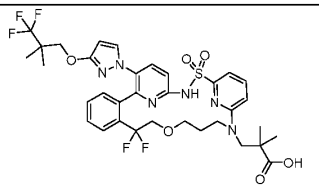
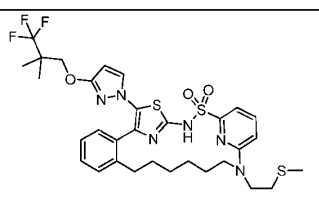
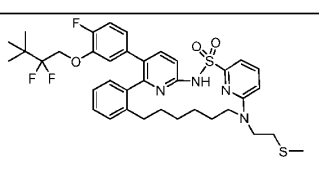
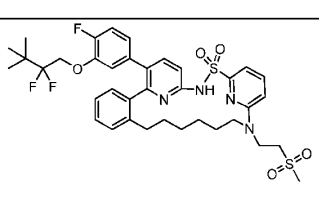
88		679.77	LCMS mtd 4; LC RT=1.68; MS (ESI) m/z 678.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 – 7.67 (m, 1H), 7.65 – 7.56 (m, 2H), 7.53 – 7.49 (m, 1H), 7.23 – 7.10 (m, 3H), 7.05 – 7.00 (m, 1H), 6.83 – 6.72 (m, 3H), 6.51 – 6.45 (m, 1H), 3.72 (t, <i>J</i> = 6.9 Hz, 2H), 3.21 (t, <i>J</i> = 6.2 Hz, 2H), 1.99 – 1.78 (m, 4H), 1.65 – 1.31 (m, 6H), 1.12 (s, 6H).
89		680.75	LCMS mtd 4; LC RT=1.63; MS (ESI) m/z 679.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.77 – 7.68 (m, 1H), 7.66 – 7.56 (m, 2H), 7.54 – 7.49 (m, 1H), 7.46 (dd, <i>J</i> = 8.5, 7.2 Hz, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 1H), 7.10 (d, <i>J</i> = 7.0 Hz, 1H), 6.84 – 6.74 (m, 2H), 6.58 (d, <i>J</i> = 8.1 Hz, 1H), 6.53 – 6.47 (m, 1H), 3.74 (t, <i>J</i> = 6.8 Hz, 2H), 3.61 – 3.50 (m, 1H), 3.16 – 3.02 (m, 1H), 2.11 – 1.69 (m, 4H), 1.59 – 1.31 (m, 6H), 1.13 (s, 6H).
90		608.59	LCMS mtd 5; LC RT=1.86; MS (ESI) m/z 607.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 (d, <i>J</i> = 8.9 Hz, 1H), 7.54 – 7.42 (m, 4H), 7.37 (t, <i>J</i> = 7.2 Hz, 1H), 7.24 (d, <i>J</i> = 7.1 Hz, 1H), 7.08 (d, <i>J</i> = 7.6 Hz, 1H), 7.00 (d, <i>J</i> = 2.6 Hz, 1H), 6.58 (d, <i>J</i> = 8.4 Hz, 1H), 5.65 (d, <i>J</i> = 2.6 Hz, 1H), 4.50 (q, <i>J</i> = 8.6 Hz, 2H), 3.86 – 3.72 (m, 1H), 3.02 – 2.89 (m, 1H), 2.29 – 2.10 (m, 1H), 2.02 – 1.83 (m, 1H), 1.56 – 1.33 (m, 6H).
91		797.94	LCMS mtd 4; LC RT=2.29; MS (ESI) m/z 798.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.92 (d, <i>J</i> = 8.9 Hz, 1H), 7.75 – 7.53 (m, 2H), 7.32 – 7.12 (m, 5H), 6.91 (d, <i>J</i> = 8.7 Hz, 1H), 6.86 (d, <i>J</i> = 2.5 Hz, 1H), 5.63 (d, <i>J</i> = 2.5 Hz, 1H), 4.02 (s, 2H), 3.96 – 3.78 (m, 3H), 3.69 – 3.38 (m, 6H), 2.24 (s, 2H), 1.65 – 1.25 (m, 8H), 1.20 (s, 6H), 1.17 (s, 6H), 1.11 – 1.01 (m, 2H), 0.88 (s, 2H).
92		680.81	LCMS mtd 4; LC RT=2.28; MS (ESI) m/z 681.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> = 8.7 Hz, 1H), 7.62 (t, <i>J</i> = 8.2 Hz, 1H), 7.49 (d, <i>J</i> = 7.9 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.25 – 7.14 (m, 1H), 7.07 (t, <i>J</i> = 7.9 Hz, 1H), 7.01 – 6.80 (m, 2H), 6.77 (d, <i>J</i> = 7.5 Hz, 1H), 6.67 – 6.62 (m, 1H), 6.61 (s, 1H), 4.41 – 4.18 (m, 1H), 3.91 – 3.80 (m, 1H), 3.67 – 3.36 (m, 4H), 3.26 – 3.03 (m, 3H), 2.76 – 2.36 (m, 1H), 2.25 – 1.96 (m, 1H), 1.85 – 1.66 (m, 1H), 1.58 – 1.33 (m, 5H), 0.92 (s, 9H).
93		768.9	LCMS mtd 1; LC RT=1.82; MS (ESI) m/z 769.5 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.95 – 7.40 (m, 3H), 7.32 – 7.03 (m, 5H), 6.94 – 6.70 (m, 2H), 5.69 – 5.55 (m, 1H), 4.69 – 4.24 (m, 1H), 4.01 (d, <i>J</i> = 7.8 Hz, 2H), 3.91 – 3.42 (m, 7H), 3.21 – 3.04 (m, 1H), 2.38 – 1.99 (m, 2H), 1.44 – 1.16 (m, 16H), 1.12 – 0.98 (m, 2H), 0.96 – 0.76 (m, 2H).

94		685.81	LCMS mtd 4; LC RT=2.28; MS (ESI) m/z 686.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.80 (d, <i>J</i> = 8.9 Hz, 1H), 7.61 (t, <i>J</i> = 8.0 Hz, 1H), 7.44 (d, <i>J</i> = 8.7 Hz, 1H), 7.31 – 7.21 (m, 2H), 7.20 – 7.10 (m, 3H), 6.88 – 6.79 (m, 2H), 5.60 (d, <i>J</i> = 2.5 Hz, 1H), 3.99 (s, 2H), 3.55 (s, 4H), 2.75 (s, 2H), 2.52 (s, 6H), 2.13 (s, 2H), 1.47 (s, 2H), 1.35 (s, 2H), 1.19 (s, 6H), 1.16 – 1.07 (m, 2H), 1.06 – 0.92 (m, 2H).
95		672.72	LCMS mtd 4; LC RT=1.81; MS (ESI) m/z 673.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.89 (d, <i>J</i> = 8.9 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.56 (d, <i>J</i> = 8.9 Hz, 1H), 7.32 (d, <i>J</i> = 7.3 Hz, 1H), 7.27 (t, <i>J</i> = 7.4 Hz, 1H), 7.20 (d, <i>J</i> = 7.4 Hz, 1H), 7.15 (t, <i>J</i> = 7.4 Hz, 1H), 7.08 (d, <i>J</i> = 7.5 Hz, 1H), 6.87 (d, <i>J</i> = 2.4 Hz, 1H), 6.70 (d, <i>J</i> = 8.7 Hz, 1H), 5.63 (d, <i>J</i> = 2.5 Hz, 1H), 4.11 (s, 2H), 4.01 (s, 2H), 3.48 (bs, 2H), 2.40 (bs, 2H), 1.50 – 1.29 (m, 4H), 1.25 – 1.10 (m, 8H), 1.09 – 0.96 (m, 2H).
96		755.86	LCMS mtd 1; LC RT=2.59; MS (ESI) m/z 756.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.90 (d, <i>J</i> = 8.8 Hz, 1H), 7.66 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.62 – 7.50 (m, 1H), 7.38 – 7.09 (m, 5H), 6.86 (d, <i>J</i> = 2.5 Hz, 1H), 6.76 (d, <i>J</i> = 8.3 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.11 – 3.82 (m, 7H), 3.79 – 3.38 (m, 4H), 2.26 (bs, 2H), 1.82 – 1.69 (m, 2H), 1.60 – 1.26 (m, 6H), 1.22 – 1.08 (m, 8H), 1.06 – 0.91 (m, 2H).
97		711.85	LCMS mtd 4; LC RT=2.21; MS (ESI) m/z 712.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> = 8.5 Hz, 1H), 7.57 (s, 1H), 7.41 – 7.05 (m, 6H), 6.88 (d, <i>J</i> = 8.7 Hz, 1H), 6.78 (d, <i>J</i> = 1.8 Hz, 1H), 5.57 (d, <i>J</i> = 2.5 Hz, 1H), 3.98 (s, 2H), 3.88 – 3.35 (m, 6H), 3.00 – 2.73 (m, 4H), 2.20 – 1.26 (m, 10H), 1.23 – 0.91 (m, 10H).
98		614.69	LCMS mtd 1; LC RT=2.72; MS (ESI) m/z 615.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.88 (d, <i>J</i> = 8.9 Hz, 1H), 7.57 (d, <i>J</i> = 8.6 Hz, 1H), 7.48 (dd, <i>J</i> = 8.4, 7.3 Hz, 1H), 7.31 – 7.10 (m, 5H), 6.85 (d, <i>J</i> = 2.6 Hz, 1H), 6.56 (d, <i>J</i> = 8.5 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.02 (s, 2H), 3.32 – 3.16 (m, 2H), 2.35 (bs, 2H), 1.43 – 1.23 (m, 4H), 1.19 (s, 6H), 1.09 (s, 4H).
99		650.67	LCMS mtd 4; LC RT=1.92; MS (ESI) m/z 651.2 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.42 (s, 1H), 8.05 (d, <i>J</i> = 5.3 Hz, 1H), 7.94 (d, <i>J</i> = 8.8 Hz, 1H), 7.57 (d, <i>J</i> = 8.8 Hz, 1H), 7.47 (d, <i>J</i> = 7.8 Hz, 1H), 7.43 (t, <i>J</i> = 7.6 Hz, 1H), 7.36 (t, <i>J</i> = 7.4 Hz, 1H), 7.05 (d, <i>J</i> = 7.6 Hz, 1H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.94 (s, 1H), 6.90 (d, <i>J</i> = 5.3 Hz, 1H), 5.61 (d, <i>J</i> = 2.6 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.41 – 3.33 (m, 2H), 2.09 – 1.93 (m, 1H), 1.88 – 1.76 (m, 1H), 1.66 – 1.47 (m, 2H), 1.43 – 1.32 (m, 4H), 1.18 (s, 6H).

100		631.73	LCMS mtd 1; LC RT=2.31; MS (ESI) m/z 632.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.26 (d, <i>J</i> = 8.9 Hz, 1H), 8.07 (d, <i>J</i> = 5.3 Hz, 1H), 7.43 (d, <i>J</i> = 9.0 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.32 – 7.24 (m, 2H), 7.19 (d, <i>J</i> = 7.6 Hz, 1H), 7.00 (d, <i>J</i> = 4.0 Hz, 1H), 6.76 (s, 1H), 6.07 (s, 1H), 4.19 (s, 2H), 3.44 – 3.35 (m, 1H), 3.21 – 3.10 (m, 1H), 2.34 – 2.12 (m, 2H), 1.50 – 1.36 (m, 2H), 1.31 – 1.05 (m, 12H).
101		584.78	LCMS mtd 5; LC RT=2.24; MS (ESI) m/z 583.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 8.04 – 7.55 (m, 2H), 7.48 (dd, <i>J</i> = 8.4, 7.3 Hz, 1H), 7.40 – 7.07 (m, 6H), 6.80 (d, <i>J</i> = 7.7 Hz, 1H), 6.69 (d, <i>J</i> = 7.9 Hz, 1H), 6.55 (d, <i>J</i> = 8.5 Hz, 1H), 6.43 (s, 1H), 3.59 (bs, 2H), 3.30 – 3.06 (m, 2H), 2.27 (bs, 2H), 1.55 (t, <i>J</i> = 7.2 Hz, 2H), 1.45 – 1.19 (m, 4H), 1.11 (s, 4H), 0.92 (s, 9H).
102		575.63	LCMS mtd 4; LC RT=1.61; MS (ESI) m/z 576.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 (t, <i>J</i> = 8.0 Hz, 1H), 7.54 – 7.37 (m, 5H), 7.06 (d, <i>J</i> = 7.1 Hz, 1H), 6.92 (d, <i>J</i> = 8.1 Hz, 1H), 6.72 (d, <i>J</i> = 7.8 Hz, 1H), 6.54 (d, <i>J</i> = 8.4 Hz, 1H), 3.78 (bs, 1H), 2.92 (bs, 1H), 2.60 – 2.31 (m, 2H), 1.59 – 1.33 (m, 3H), 1.28 – 0.98 (m, 5H).
103		620.71	LCMS mtd 1; LC RT=2.07; MS (ESI) m/z 621.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.48 – 7.38 (m, 3H), 7.36 – 7.28 (m, 2H), 7.10 – 6.99 (m, 2H), 6.55 (d, <i>J</i> = 8.4 Hz, 1H), 5.76 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 (s, 2H), 3.62 – 3.32 (m, 2H), 2.40 (t, <i>J</i> = 7.3 Hz, 2H), 1.44 (s, 4H), 1.32 – 1.15 (m, 10H).
104		596.7	LCMS mtd 1; LC RT=2.75; MS (ESI) m/z 597.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.84 (d, <i>J</i> = 8.9 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.36 (t, <i>J</i> = 7.5 Hz, 1H), 7.24 (d, <i>J</i> = 7.2 Hz, 1H), 7.06 (d, <i>J</i> = 7.6 Hz, 1H), 6.90 (d, <i>J</i> = 2.6 Hz, 1H), 6.58 (d, <i>J</i> = 8.5 Hz, 1H), 5.56 (d, <i>J</i> = 2.6 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.67 (d, <i>J</i> = 1.3 Hz, 2H), 3.02 – 2.87 (m, 1H), 2.39 – 2.16 (m, 1H), 2.07 – 1.85 (m, 1H), 1.57 – 1.33 (m, 6H), 0.96 (s, 9H).
105		807.9	LCMS mtd 1; LC RT=1.97; MS (ESI) m/z 808.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 (t, <i>J</i> = 7.8 Hz, 1H), 7.92 (d, <i>J</i> = 7.2 Hz, 1H), 7.71 (d, <i>J</i> = 7.4 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.50 (d, <i>J</i> = 7.0 Hz, 1H), 7.17 (t, <i>J</i> = 8.0 Hz, 1H), 6.82 – 6.73 (m, 2H), 6.50 (t, <i>J</i> = 2.0 Hz, 1H), 4.29 – 4.09 (m, 1H), 3.75 (t, <i>J</i> = 6.8 Hz, 2H), 3.69 – 3.61 (m, 1H), 3.56 – 3.46 (m, 1H), 3.44 – 3.33 (m, 5H), 2.36 (s, 4H), 2.08 – 1.75 (m, 4H), 1.62 – 1.38 (m, 4H), 1.32 – 1.18 (m, 2H), 1.14 (s, 6H).

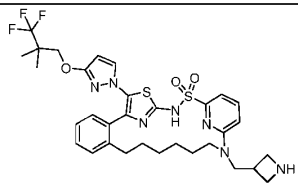
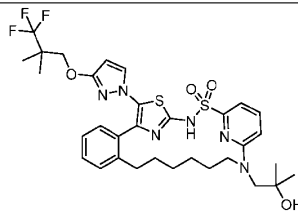
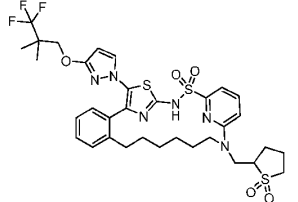
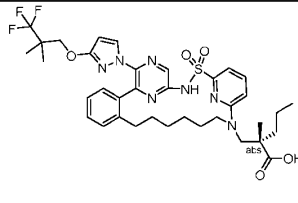
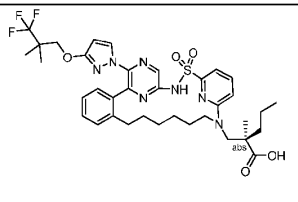
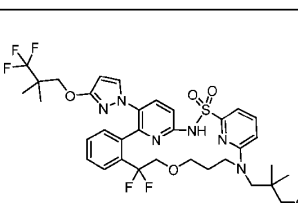
106		616.66	LCMS mtd 4; LC RT=2.12; MS (ESI) m/z 617.2 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 7.88 (d, <i>J</i> = 8.9 Hz, 1H), 7.57 – 7.45 (m, 2H), 7.28 (t, <i>J</i> = 7.6 Hz, 1H), 7.23 – 7.09 (m, 4H), 6.90 (d, <i>J</i> = 1.9 Hz, 1H), 6.60 (d, <i>J</i> = 8.5 Hz, 1H), 5.62 (d, <i>J</i> = 2.2 Hz, 1H), 3.99 (s, 2H), 3.38 (s, 4H), 3.24 (t, <i>J</i> = 6.2 Hz, 2H), 2.32 (s, 2H), 1.60 – 1.45 (m, 2H), 1.18 (s, 6H).
107		574.64	LCMS mtd 1; LC RT=2.05; MS (ESI) m/z 575.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.49 – 7.30 (m, 6H), 7.26 (d, <i>J</i> = 8.4 Hz, 1H), 7.15 (d, <i>J</i> = 8.6 Hz, 1H), 7.09 – 7.03 (m, 1H), 6.90 (s, 1H), 6.55 (dd, <i>J</i> = 8.5, 0.4 Hz, 1H), 3.78 (s, 1H), 2.93 (s, 1H), 2.33 (s, 2H), 1.67 – 1.03 (m, 8H).
108		620.71	LCMS mtd 1; LC RT=2.24; MS (ESI) m/z 621.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.07 (d, <i>J</i> = 4.8 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.37 – 7.27 (m, 2H), 7.00 (d, <i>J</i> = 2.6 Hz, 1H), 6.95 (d, <i>J</i> = 5.1 Hz, 1H), 6.92 (s, 1H), 5.75 (d, <i>J</i> = 2.6 Hz, 1H), 4.14 (s, 2H), 3.46 – 3.31 (m, 2H), 2.41 – 2.23 (m, 2H), 1.61 – 1.46 (m, 2H), 1.42 – 1.16 (m, 12H).
109		656.69	LCMS mtd 4; LC RT=1.79; MS (ESI) m/z 657.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 (s, 1H), 7.74 – 7.40 (m, 4H), 7.15 – 6.75 (m, 3H), 5.71 (d, <i>J</i> = 2.4 Hz, 1H), 4.08 (s, 2H), 3.44 – 3.33 (m, 2H), 2.02 – 1.79 (m, 2H), 1.62 – 1.46 (m, 4H), 1.46 – 1.32 (m, 2H), 1.21 (s, 6H).
110		700.82	LCMS mtd 4; LC RT=2.38; MS (ESI) m/z 701.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.75 (d, <i>J</i> = 7.3 Hz, 1H), 7.60 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.32 – 7.08 (m, 5H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 6.87 (d, <i>J</i> = 2.5 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.03 (s, 2H), 3.79 – 3.36 (m, 3H), 3.24 – 3.04 (m, 3H), 2.29 – 2.10 (m, 2H), 1.42 (s, 1H), 1.34 – 1.24 (m, 2H), 1.20 (s, 6H), 1.15 – 0.76 (m, 11H).
111		638.75	LCMS mtd 4; LC RT=2.43; MS (ESI) m/z 639.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.83 (s, 1H), 7.60 (s, 1H), 7.48 (dd, <i>J</i> = 8.4, 7.3 Hz, 1H), 7.37 – 7.08 (m, 6H), 6.81 (d, <i>J</i> = 7.7 Hz, 1H), 6.71 (d, <i>J</i> = 7.0 Hz, 1H), 6.55 (d, <i>J</i> = 8.4 Hz, 1H), 6.45 (s, 1H), 3.67 (s, 2H), 3.31 – 3.15 (m, 2H), 2.24 (s, 2H), 1.84 (t, <i>J</i> = 6.9 Hz, 2H), 1.48 – 1.22 (m, 4H), 1.17 – 1.03 (m, 10H).

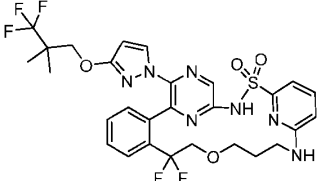
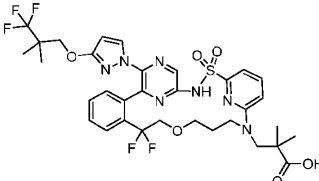
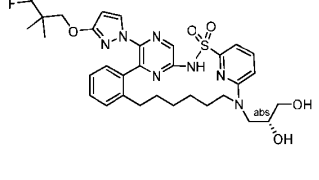
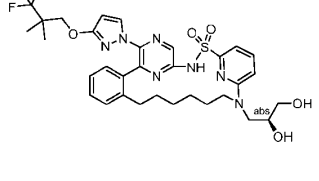
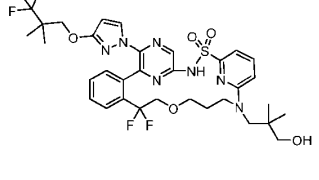
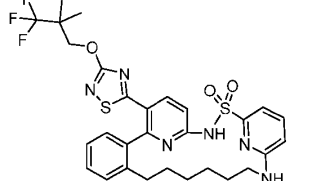
112		674.73	LCMS mtd 1; LC RT=2.82; MS (ESI) m/z 675.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> = 8.6 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.40 (d, <i>J</i> = 8.6 Hz, 1H), 7.32 (t, <i>J</i> = 7.1 Hz, 1H), 7.26 – 7.16 (m, 2H), 7.10 (t, <i>J</i> = 7.9 Hz, 1H), 6.87 (s, 1H), 6.81 (d, <i>J</i> = 7.7 Hz, 1H), 6.64 (d, <i>J</i> = 8.3 Hz, 1H), 6.61 – 6.55 (m, 2H), 3.89 – 3.74 (m, 2H), 3.67 – 3.57 (m, 1H), 3.06 – 2.94 (m, 1H), 2.56 – 2.36 (m, 1H), 2.18 – 1.98 (m, 1H), 1.83 (t, <i>J</i> = 6.9 Hz, 2H), 1.65 – 1.38 (m, 6H), 1.12 (s, 6H).
113		684.9	LCMS mtd 4; LC RT=2.02; MS (ESI) m/z 685.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 7.88 (d, <i>J</i> = 8.9 Hz, 1H), 7.77 (d, <i>J</i> = 8.7 Hz, 1H), 7.61 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.10 (m, 2H), 6.92 (d, <i>J</i> = 8.7 Hz, 1H), 6.79 (d, <i>J</i> = 7.8 Hz, 1H), 6.70 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 6.45 (t, <i>J</i> = 1.9 Hz, 1H), 3.82 – 3.46 (m, 6H), 2.31 – 2.15 (m, 2H), 1.56 (t, <i>J</i> = 7.1 Hz, 2H), 1.46 (s, 1H), 1.37 – 1.23 (m, 3H), 1.18 (s, 6H), 1.13 – 1.06 (m, 2H), 1.02 – 0.89 (m, 10H), 0.83 (s, 1H).
114		644.77	LCMS mtd 5; LC RT=1.97; MS (ESI) m/z 643.0 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.47 – 7.39 (m, 3H), 7.38 – 7.28 (m, 2H), 7.22 (t, <i>J</i> = 8.0 Hz, 1H), 7.05 (d, <i>J</i> = 7.1 Hz, 1H), 6.85 (d, <i>J</i> = 7.9 Hz, 1H), 6.80 (dd, <i>J</i> = 8.2, 2.3 Hz, 1H), 6.57 – 6.51 (m, 2H), 3.74 (s, 3H), 2.93 (s, 1H), 2.56 – 2.11 (m, 2H), 1.85 (t, <i>J</i> = 6.9 Hz, 2H), 1.63 – 1.34 (m, 3H), 1.26 – 1.08 (m, 11H).
115		699.84	LCMS mtd 4; LC RT=2.26; MS (ESI) m/z 700.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.76 (d, <i>J</i> = 8.5 Hz, 1H), 7.64 – 7.40 (m, 2H), 7.31 – 7.08 (m, 5H), 6.91 (d, <i>J</i> = 8.4 Hz, 1H), 6.82 (d, <i>J</i> = 2.5 Hz, 1H), 5.57 (d, <i>J</i> = 2.5 Hz, 1H), 4.09 – 3.74 (m, 3H), 3.27 – 3.11 (m, 2H), 2.86 – 2.44 (m, 3H), 2.22 – 1.83 (m, 2H), 1.59 – 0.91 (m, 20H).
116		750.79	LCMS mtd 2; LC RT=1.3; MS (ESI) m/z 751.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 (d, <i>J</i> = 8.9 Hz, 1H), 7.61 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.52 (d, <i>J</i> = 7.9 Hz, 1H), 7.47 – 7.35 (m, 3H), 7.29 (d, <i>J</i> = 7.2 Hz, 1H), 7.09 (d, <i>J</i> = 7.2 Hz, 1H), 7.04 – 6.96 (m, 2H), 5.59 (d, <i>J</i> = 2.6 Hz, 1H), 4.18 – 4.04 (m, 1H), 4.02 – 3.93 (m, 2H), 3.74 – 3.59 (m, 2H), 3.18 – 3.07 (m, 1H), 2.28 – 2.10 (m, 1H), 1.98 – 1.75 (m, 1H), 1.72 – 1.57 (m, 1H), 1.48 – 1.12 (m, 17H).
117		732.84	LCMS mtd 1; LC RT=2.14; MS (ESI) m/z 733.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.97 (dd, <i>J</i> = 5.9, 3.2 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.60 (dd, <i>J</i> = 8.5, 7.5 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.21 (d, <i>J</i> = 7.2 Hz, 1H), 6.97 (d, <i>J</i> = 7.3 Hz, 1H), 6.91 (d, <i>J</i> = 8.7 Hz, 1H), 4.33 (s, 2H), 3.97 – 3.79 (m, 1H), 3.71 – 3.42 (m, 3H), 2.44 – 2.23 (m, 2H), 1.56 – 1.46 (m, 1H), 1.41 – 1.07 (m, 17H), 1.02 – 0.90 (m, 1H), 0.85 – 0.75 (m, 1H).

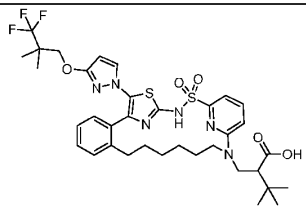
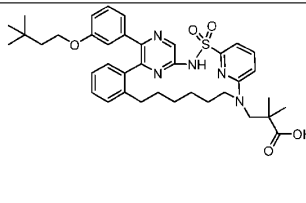
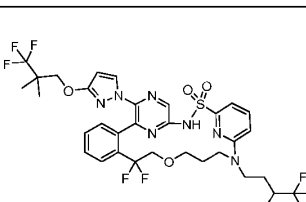
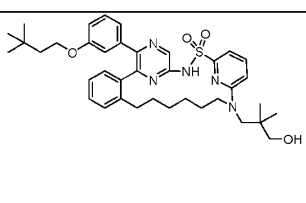
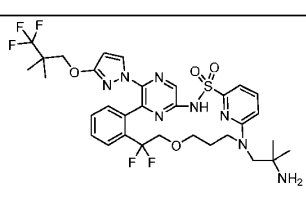
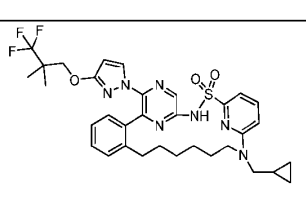
118		761.88	LCMS mtd 4; LC RT=1.86; MS (ESI) m/z 762.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.38 – 7.29 (m, 2H), 7.21 (d, <i>J</i> = 7.3 Hz, 1H), 7.02 (d, <i>J</i> = 2.7 Hz, 1H), 6.60 (d, <i>J</i> = 8.6 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.24 – 3.81 (m, 8H), 3.54 – 3.38 (m, 3H), 2.46 – 2.32 (m, 2H), 1.82 – 1.68 (m, 2H), 1.60 – 1.38 (m, 6H), 1.27 – 1.14 (m, 10H).
119		730.8	LCMS mtd 4; LC RT=1.86; MS (ESI) m/z 731.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.14 – 6.69 (m, 10H), 5.71 (s, 1H), 4.27 – 4.12 (m, 1H), 4.06 – 3.43 (m, 5H), 3.25 – 2.60 (m, 3H), 2.10 – 0.72 (m, 19H).
120		752.76	LCMS mtd 4; LC RT=1.79; MS (ESI) m/z 753.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.85 (d, <i>J</i> = 8.9 Hz, 1H), 7.62 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.53 (d, <i>J</i> = 7.7 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.29 (m, 2H), 7.03 – 6.93 (m, 3H), 5.60 (d, <i>J</i> = 2.6 Hz, 1H), 4.40 – 4.19 (m, 1H), 4.13 – 4.04 (m, 1H), 3.99 (s, 2H), 3.87 – 3.45 (m, 5H), 3.26 – 3.18 (m, 1H), 1.99–1.88 (m, 1H), 1.76 – 1.61 (m, 1H), 1.27 – 1.09 (m, 12H).
121		694.85	LCMS mtd 4; LC RT=1.82; MS (ESI) m/z 695.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.60 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.37 – 7.27 (m, 2H), 7.11 (d, <i>J</i> = 7.2 Hz, 1H), 7.01 (d, <i>J</i> = 2.6 Hz, 1H), 6.74 (d, <i>J</i> = 8.7 Hz, 1H), 5.75 (d, <i>J</i> = 2.6 Hz, 1H), 4.15 (s, 2H), 3.63 – 3.50 (m, 2H), 3.34 – 3.30 (m, 2H), 2.68 (t, <i>J</i> = 7.4 Hz, 2H), 2.36 (s, 2H), 2.14 (s, 3H), 1.65 – 1.32 (m, 4H), 1.24 – 1.05 (m, 10H).
122		712.89	LCMS mtd 4; LC RT=2.2; MS (ESI) m/z 713.3 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (s, 1H), 8.00 – 7.57 (m, 2H), 7.51 – 6.99 (m, 7H), 6.96 – 6.59 (m, 3H), 4.24 – 3.61 (m, 3H), 3.60 – 3.35 (m, 3H), 2.76 – 2.54 (m, 3H), 2.26 – 1.95 (m, 4H), 1.37 – 0.86 (m, 17H).
123		744.89	LCMS mtd 4; LC RT=2.05; MS (ESI) m/z 745.3 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 7.98 – 7.68 (m, 2H), 7.48 – 7.03 (m, 7H), 6.98 – 6.84 (m, 1H), 6.81 – 6.67 (m, 2H), 4.18 – 3.84 (m, 2H), 3.80 – 3.57 (m, 3H), 3.50 – 3.36 (m, 3H), 3.01 (s, 3H), 2.44 – 2.27 (m, 1H), 2.13 – 1.96 (m, 1H), 1.41 – 1.19 (m, 4H), 1.12 – 0.96 (m, 11H), 0.93 – 0.81 (m, 2H).

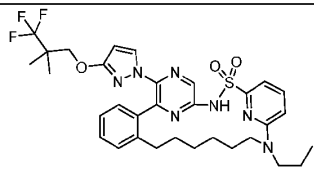
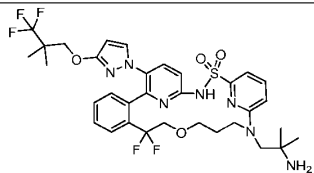
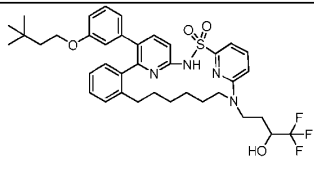
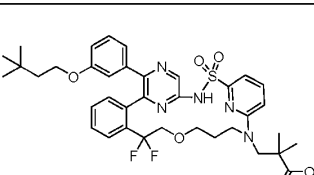
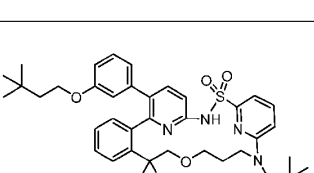
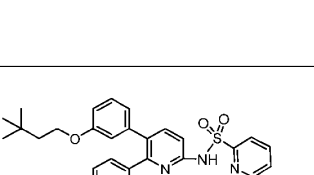
124		703.84	LCMS mtd 4; LC RT=1.8; MS (ESI) m/z 704.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.32 – 7.12 (m, 5H), 6.98 – 6.88 (m, 2H), 5.65 (d, <i>J</i> = 2.5 Hz, 1H), 4.06 (s, 2H), 4.02 – 3.69 (m, 3H), 3.66 – 3.38 (m, 4H), 2.38 – 2.09 (m, 3H), 2.07 – 1.96 (m, 1H), 1.92 – 1.79 (m, 1H), 1.76 – 1.53 (m, 3H), 1.50 – 1.38 (m, 2H), 1.28 – 1.03 (m, 10H).
125		756.81	LCMS mtd 4; LC RT=1.69; MS (ESI) m/z 757.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.19 (d, <i>J</i> = 5.1 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.60 – 7.51 (m, 2H), 7.51 – 7.46 (m, 1H), 7.04 – 6.97 (m, 2H), 6.93 (d, <i>J</i> = 2.6 Hz, 1H), 5.66 (d, <i>J</i> = 2.5 Hz, 1H), 4.06 (s, 2H), 3.95 (s, 2H), 3.44 (t, <i>J</i> = 6.9 Hz, 2H), 2.07 – 1.84 (m, 2H), 1.58 – 1.46 (m, 4H), 1.42 – 1.26 (m, 2H), 1.19 (s, 6H), 1.17 (s, 6H).
126 -P1		704.83	LCMS mtd 1; LC RT=9.61; MS (ESI) m/z 705.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 7.15 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 2.6 Hz, 1H), 6.71 (d, <i>J</i> = 8.6 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.17 (s, 2H), 3.81 – 3.69 (m, 1H), 3.42 – 3.33 (m, 2H), 2.59 – 2.49 (m, 2H), 2.38 (s, 2H), 2.22 – 2.11 (m, 2H), 1.55 – 1.46 (m, 2H), 1.42 – 1.29 (m, 5H), 1.26 – 1.13 (m, 10H).
126 -P2		704.83	LCMS mtd 1; LC RT=9.81; MS (ESI) m/z 705.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.36 – 7.28 (m, 2H), 7.16 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 2.7 Hz, 1H), 6.65 (d, <i>J</i> = 8.6 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.43 – 4.30 (m, 1H), 4.17 (s, 2H), 3.44 – 3.32 (m, 2H), 2.55 – 2.42 (m, 2H), 2.37 (s, 2H), 2.18 – 2.08 (m, 2H), 1.54 – 1.42 (m, 2H), 1.38 – 1.28 (m, 5H), 1.26 – 1.12 (m, 10H).
127		756.81	LCMS mtd 4; LC RT=1.69; MS (ESI) m/z 757.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 – 7.66 (m, 1H), 7.64 – 7.51 (m, 4H), 7.18 (d, <i>J</i> = 7.2 Hz, 1H), 7.00 (d, <i>J</i> = 2.7 Hz, 1H), 6.96 (d, <i>J</i> = 8.7 Hz, 1H), 5.72 (d, <i>J</i> = 2.6 Hz, 1H), 4.09 (s, 2H), 3.84 – 3.59 (m, 3H), 3.44 – 3.34 (m, 1H), 2.06 – 1.86 (m, 2H), 1.62 – 1.24 (m, 6H), 1.21 (s, 6H), 1.19 (s, 6H).
128		726.85	LCMS mtd 4; LC RT=1.88; MS (ESI) m/z 727.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.69 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.36 – 7.29 (m, 2H), 7.21 (d, <i>J</i> = 7.3 Hz, 1H), 7.03 (d, <i>J</i> = 2.6 Hz, 1H), 6.87 (d, <i>J</i> = 8.7 Hz, 1H), 5.76 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 (s, 2H), 3.91 (t, <i>J</i> = 6.7 Hz, 2H), 3.51 – 3.35 (m, 3H), 3.10 – 2.75 (m, 4H), 2.39 (t, <i>J</i> = 6.9 Hz, 2H), 1.62 – 1.43 (m, 4H), 1.30 – 1.13 (m, 10H).

129		694.79	LCMS mtd 1; LC RT=1.93; MS (ESI) m/z 695.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 7.53 (m, 1H), 7.43 – 7.35 (m, 2H), 7.34 – 7.26 (m, 2H), 7.12 (d, <i>J</i> = 7.2 Hz, 1H), 7.00 (d, <i>J</i> = 2.5 Hz, 1H), 6.87 (d, <i>J</i> = 8.7 Hz, 1H), 5.75 (d, <i>J</i> = 2.5 Hz, 1H), 4.16 (s, 2H), 4.07 – 3.43 (m, 6H), 3.41 – 3.34 (m, 1H), 2.39 (t, <i>J</i> = 6.9 Hz, 2H), 1.57 – 1.39 (m, 4H), 1.30 – 1.11 (m, 10H).
130		613.7	LCMS mtd 1; LC RT=2.17; MS (ESI) m/z 614.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.87 (d, <i>J</i> = 8.9 Hz, 1H), 7.44 (d, <i>J</i> = 8.8 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.22 – 7.10 (m, 5H), 6.97 (s, 1H), 6.83 (d, <i>J</i> = 2.6 Hz, 1H), 6.81 – 6.75 (m, 1H), 5.61 (d, <i>J</i> = 2.6 Hz, 1H), 4.01 (s, 2H), 3.18 – 3.09 (m, 2H), 2.38 – 2.09 (m, 2H), 1.44 – 1.32 (m, 2H), 1.23 – 1.07 (m, 12H).
131		718.81	LCMS mtd 4; LC RT=1.66; MS (ESI) m/z 719.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 7.57 (m, 1H), 7.44 – 7.38 (m, 2H), 7.36 – 7.29 (m, 2H), 7.13 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 2.5 Hz, 1H), 6.84 (d, <i>J</i> = 8.7 Hz, 1H), 5.77 (d, <i>J</i> = 2.5 Hz, 1H), 4.16 (s, 2H), 3.71 – 3.34 (m, 4H), 2.39 (t, <i>J</i> = 6.6 Hz, 2H), 1.63 – 1.40 (m, 6H), 1.26 – 1.06 (m, 11H), 0.91 – 0.83 (m, 1H).
132		746.79	LCMS mtd 4; LC RT=1.98; MS (ESI) m/z 747.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.30 (m, 2H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 2.7 Hz, 1H), 6.83 (d, <i>J</i> = 8.7 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.43 – 3.75 (m, 4H), 3.58 (t, <i>J</i> = 7.2 Hz, 2H), 3.20 – 2.76 (m, 1H), 2.39 (s, 2H), 2.10 – 1.89 (m, 1H), 1.86 – 1.70 (m, 1H), 1.63 – 1.37 (m, 4H), 1.30 – 1.07 (m, 10H).
133		744.86	LCMS mtd 4; LC RT=1.68; MS (ESI) m/z 745.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.51 – 7.37 (m, 3H), 7.37 – 7.26 (m, 2H), 7.10 (d, <i>J</i> = 7.2 Hz, 1H), 6.98 (d, <i>J</i> = 2.6 Hz, 1H), 6.49 (d, <i>J</i> = 8.7 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.17 (s, 2H), 3.72 (s, 2H), 3.29 – 3.21 (m, 2H), 2.33 (s, 2H), 1.60 – 1.44 (m, 8H), 1.31 – 0.91 (m, 12H).
134		664.76	LCMS mtd 4; LC RT=1.87; MS (ESI) m/z 665.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.39 – 7.29 (m, 2H), 7.12 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 2.6 Hz, 1H), 6.82 (d, <i>J</i> = 8.7 Hz, 1H), 5.77 (d, <i>J</i> = 2.6 Hz, 1H), 4.56 – 3.90 (m, 3H), 3.70 (t, <i>J</i> = 6.1 Hz, 2H), 3.51 (t, <i>J</i> = 5.7 Hz, 2H), 3.17 – 2.83 (m, 1H), 2.38 (s, 2H), 1.65 – 1.34 (m, 4H), 1.27 – 1.07 (m, 10H).

135		689.82	LCMS mtd 4; LC RT=1.96; MS (ESI) m/z 690.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.49 (s, 3H), 7.63 – 7.54 (m, 1H), 7.34 – 7.23 (m, 3H), 7.21 – 7.16 (m, 2H), 6.95 (d, <i>J</i> = 2.5 Hz, 1H), 6.80 (d, <i>J</i> = 8.6 Hz, 1H), 5.69 (d, <i>J</i> = 2.6 Hz, 1H), 4.13 – 3.98 (m, 6H), 3.80 – 3.56 (m, 4H), 3.26 – 3.16 (m, 1H), 2.45 – 2.33 (m, 2H), 1.58 – 1.41 (m, 4H), 1.27 – 1.05 (m, 10H).
136		692.82	LCMS mtd 4; LC RT=1.78; MS (ESI) m/z 693.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.55 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.33 – 7.27 (m, 2H), 7.10 (d, <i>J</i> = 7.2 Hz, 1H), 6.98 (d, <i>J</i> = 2.6 Hz, 1H), 6.93 (d, <i>J</i> = 8.9 Hz, 1H), 5.74 (d, <i>J</i> = 2.5 Hz, 1H), 4.16 (s, 2H), 3.43 (s, 2H), 3.29 – 3.20 (m, 2H), 2.45 – 2.34 (m, 2H), 1.57 – 1.40 (m, 3H), 1.25 – 1.11 (m, 17H).
137		752.89	LCMS mtd 4; LC RT=1.72; MS (ESI) m/z 753.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.32 – 7.23 (m, 2H), 7.18 (d, <i>J</i> = 7.3 Hz, 1H), 7.01 (d, <i>J</i> = 2.6 Hz, 1H), 6.85 (d, <i>J</i> = 8.7 Hz, 1H), 5.74 (d, <i>J</i> = 2.6 Hz, 1H), 4.15 (s, 2H), 3.94 – 3.45 (m, 5H), 3.20 – 3.11 (m, 1H), 3.07 – 2.96 (m, 1H), 2.47 – 2.32 (m, 3H), 2.24 – 2.02 (m, 2H), 1.86 – 1.75 (m, 1H), 1.63 – 1.41 (m, 4H), 1.29 – 1.07 (m, 10H).
138 -P1		743.85	LCMS mtd 4; LC RT=1.86; MS (ESI) m/z 744.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.79 (s, 1H), 7.90 (d, <i>J</i> = 2.4 Hz, 1H), 7.69 – 7.54 (m, 1H), 7.29 – 7.12 (m, 4H), 7.07 (bs, 1H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.6 Hz, 1H), 3.79 – 3.51 (m, 4H), 3.43 – 3.34 (m, 2H), 2.61 – 2.09 (m, 2H), 1.63 – 1.26 (m, 6H), 1.21 – 0.95 (m, 13H), 0.94 – 0.74 (m, 5H).
138 -P2		743.85	LCMS mtd 4; LC RT=1.86; MS (ESI) m/z 744.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.79 (s, 1H), 7.90 (d, <i>J</i> = 2.4 Hz, 1H), 7.69 – 7.54 (m, 1H), 7.29 – 7.12 (m, 4H), 7.07 (bs, 1H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.6 Hz, 1H), 3.79 – 3.51 (m, 4H), 3.43 – 3.34 (m, 2H), 2.61 – 2.09 (m, 2H), 1.63 – 1.26 (m, 6H), 1.21 – 0.95 (m, 13H), 0.94 – 0.74 (m, 5H).
139		738.78	LCMS mtd 4; LC RT=2.13; MS (ESI) m/z 739.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.88 (d, <i>J</i> = 8.8 Hz, 1H), 7.60 (dd, <i>J</i> = 8.7, 7.2 Hz, 1H), 7.56 – 7.41 (m, 3H), 7.36 (t, <i>J</i> = 7.4 Hz, 1H), 7.27 (d, <i>J</i> = 7.0 Hz, 1H), 7.10 – 6.93 (m, 3H), 5.61 (d, <i>J</i> = 2.6 Hz, 1H), 4.38 – 3.93 (m, 4H), 3.83 – 3.36 (m, 5H), 3.25 – 3.18 (m, 3H), 2.03 – 1.62 (m, 2H), 1.18 (s, 6H), 0.90 (d, <i>J</i> = 5.5 Hz, 6H).

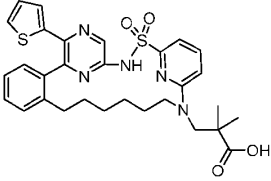
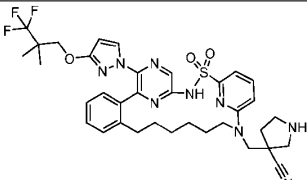
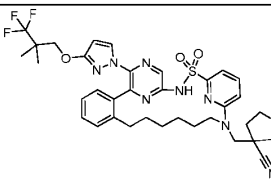
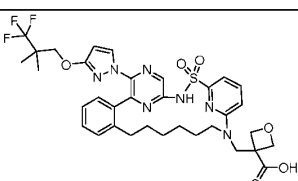
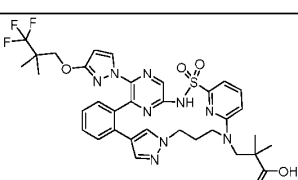
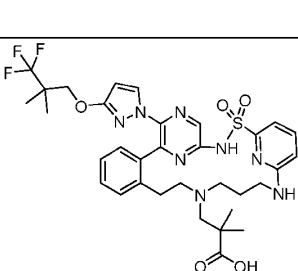
140		653.63	LCMS mtd 4; LC RT=1.84; MS (ESI) m/z 654.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 (s, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.54 – 7.37 (m, 4H), 7.31 (d, J = 7.1 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 5.75 (d, J = 2.7 Hz, 1H), 4.25 – 4.07 (m, 1H), 3.85 – 3.64 (m, 3H), 3.62 – 3.54 (m, 2H), 3.52 – 3.43 (m, 1H), 3.20 – 3.06 (m, 1H), 1.84 – 1.72 (m, 2H), 1.06 (d, J = 1.6 Hz, 6H).
141		753.75	LCMS mtd 4; LC RT=1.65; MS (ESI) m/z 754.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.52 (s, 1H), 8.00 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 8.7, 7.3 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.48 – 7.38 (m, 2H), 7.27 (d, J = 7.2 Hz, 1H), 7.15 – 7.06 (m, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.77 (d, J = 2.7 Hz, 1H), 4.03 – 3.89 (m, 1H), 3.88 – 3.34 (m, 9H), 1.91 – 1.68 (m, 2H), 1.15 (d, J = 13.2 Hz, 6H), 1.06 (d, J = 1.6 Hz, 6H).
142 -P1		689.76	LCMS mtd 4; LC RT=1.84; MS (ESI) m/z 690.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.69 (s, 1H), 7.81 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 8.7, 7.3 Hz, 1H), 7.28 – 7.21 (m, 2H), 7.20 – 7.09 (m, 3H), 6.91 (d, J = 8.7 Hz, 1H), 5.79 (d, J = 2.7 Hz, 1H), 3.90 – 3.80 (m, 1H), 3.64 (s, 2H), 3.61 – 3.42 (m, 6H), 2.65 – 1.97 (m, 2H), 1.45 – 1.30 (m, 4H), 1.18 – 1.01 (m, 8H), 0.93 – 0.77 (m, 2H).
142 -P2		689.76	LCMS mtd 4; LC RT=1.84; MS (ESI) m/z 690.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.69 (s, 1H), 7.81 (d, J = 2.5 Hz, 1H), 7.63 (dd, J = 8.7, 7.3 Hz, 1H), 7.28 – 7.21 (m, 2H), 7.20 – 7.09 (m, 3H), 6.91 (d, J = 8.7 Hz, 1H), 5.79 (d, J = 2.7 Hz, 1H), 3.90 – 3.80 (m, 1H), 3.64 (s, 2H), 3.61 – 3.42 (m, 6H), 2.65 – 1.97 (m, 2H), 1.45 – 1.30 (m, 4H), 1.18 – 1.01 (m, 8H), 0.93 – 0.77 (m, 2H).
143		739.76	LCMS mtd 4; LC RT=1.9; MS (ESI) m/z 740.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.58 (s, 1H), 8.02 (s, 1H), 7.61 (dd, J = 8.7, 7.3 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 7.23 (d, J = 7.1 Hz, 1H), 7.18 – 7.09 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), 5.77 (d, J = 2.7 Hz, 1H), 4.03 – 3.61 (m, 2H), 3.57 – 3.34 (m, 8H), 3.17 (s, 2H), 1.93 – 1.70 (m, 2H), 1.06 (s, 6H), 0.88 (d, J = 4.2 Hz, 6H).
144		632.72	LCMS mtd 4; LC RT=1.97; MS (ESI) m/z 633.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (d, J = 9.1 Hz, 1H), 7.72 – 7.60 (m, 1H), 7.57 – 7.45 (m, 2H), 7.39 (t, J = 6.3 Hz, 2H), 7.30 – 7.24 (m, 1H), 7.19 (d, J = 7.2 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.32 (s, 2H), 3.24 – 3.14 (m, 2H), 2.59 – 2.44 (m, 1H), 2.23 – 2.13 (m, 1H), 1.44 – 1.15 (m, 12H), 1.09 – 0.98 (m, 2H).

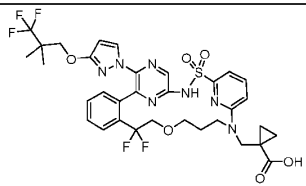
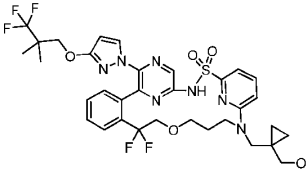
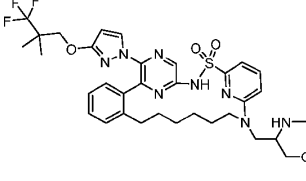
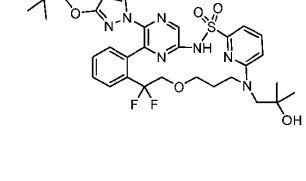
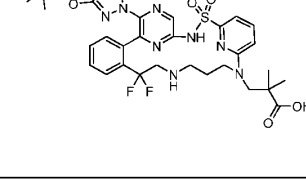
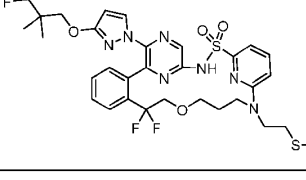
145		748.88	LCMS mtd 1; LC RT=2.19; MS (ESI) m/z 749.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 7.57 (m, 1H), 7.44 – 7.38 (m, 2H), 7.37 – 7.27 (m, 2H), 7.13 (d, <i>J</i> = 7.2 Hz, 1H), 7.01 (d, <i>J</i> = 2.7 Hz, 1H), 6.84 – 6.74 (m, 1H), 5.76 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 (s, 2H), 3.83 – 3.71 (m, 1H), 3.63 – 3.56 (m, 1H), 3.27 – 3.07 (m, 2H), 2.63 – 2.53 (m, 1H), 2.45 – 2.31 (m, 2H), 1.57 – 1.34 (m, 4H), 1.26 – 1.12 (m, 10H), 1.08 (s, 9H).
146		685.88	LCMS mtd 4; LC RT=1.88; MS (ESI) m/z 686.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.97 (s, 1H), 7.64 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.31 – 7.12 (m, 6H), 7.07 (d, <i>J</i> = 7.9 Hz, 1H), 6.96 (d, <i>J</i> = 8.8 Hz, 1H), 6.76 (dd, <i>J</i> = 8.2, 1.7 Hz, 1H), 6.74 – 6.68 (m, 1H), 3.93 – 3.44 (m, 6H), 2.44 – 2.12 (m, 2H), 1.58 (t, <i>J</i> = 7.1 Hz, 2H), 1.44 – 1.22 (m, 4H), 1.16 (s, 6H), 1.11 – 1.02 (m, 2H), 0.99 – 0.82 (m, 10H), 0.80 – 0.60 (m, 1H).
147		779.71	LCMS mtd 4; LC RT=1.89; MS (ESI) m/z 780.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.29 (s, 1H), 7.74 (s, 1H), 7.68 – 7.58 (m, 1H), 7.50 (d, <i>J</i> = 7.7 Hz, 1H), 7.46 – 7.26 (m, 3H), 7.02 (d, <i>J</i> = 7.4 Hz, 1H), 6.82 (d, <i>J</i> = 8.6 Hz, 1H), 5.70 (d, <i>J</i> = 2.6 Hz, 1H), 4.23 – 3.88 (m, 3H), 3.82 – 3.35 (m, 8H), 2.13 – 1.79 (m, 2H), 1.78 – 1.64 (m, 2H), 1.07 (s, 6H).
148		671.9	LCMS mtd 4; LC RT=2.17; MS (ESI) m/z 672.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 9.02 (s, 1H), 7.62 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.36 – 7.12 (m, 6H), 7.07 (d, <i>J</i> = 7.7 Hz, 1H), 6.98 (d, <i>J</i> = 8.7 Hz, 1H), 6.76 (dd, <i>J</i> = 8.0, 1.8 Hz, 1H), 6.71 (s, 1H), 3.78 – 3.36 (m, 6H), 3.21 – 3.12 (m, 2H), 2.31 – 2.15 (m, 2H), 1.58 (t, <i>J</i> = 7.1 Hz, 2H), 1.52 – 1.41 (m, 1H), 1.34 – 1.20 (m, 3H), 1.13 – 0.99 (m, 3H), 0.94 (s, 9H), 0.87 (s, 6H), 0.79 – 0.65 (m, 1H).
149		724.75	LCMS mtd 4; LC RT=1.93; MS (ESI) m/z 725.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.00 (s, 1H), 7.61 – 7.52 (m, 2H), 7.45 – 7.32 (m, 3H), 7.19 (d, <i>J</i> = 6.0 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 7.04 (d, <i>J</i> = 8.7 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.34 – 3.75 (m, 2H), 3.69 – 3.51 (m, 5H), 3.24 – 3.12 (m, 1H), 3.07 – 2.92 (m, 1H), 2.86 – 2.67 (m, 1H), 2.00 – 1.70 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 1.09 (s, 6H).
150		669.77	LCMS mtd 1; LC RT=2.41; MS (ESI) m/z 670.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.70 (s, 1H), 7.84 (d, <i>J</i> = 1.9 Hz, 1H), 7.64 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.28 – 7.12 (m, 4H), 7.09 (d, <i>J</i> = 7.7 Hz, 1H), 6.88 (d, <i>J</i> = 8.6 Hz, 1H), 5.80 (d, <i>J</i> = 2.7 Hz, 1H), 3.63 (s, 2H), 3.59 – 3.52 (m, 2H), 3.23 – 3.13 (m, 2H), 2.97 – 1.72 (m, 2H), 1.44 – 1.28 (m, 4H), 1.15 – 1.05 (m, 8H), 1.04 – 0.96 (m, 1H), 0.93 – 0.81 (m, 2H), 0.53 – 0.42 (m, 2H), 0.23 (q, <i>J</i> = 4.8 Hz, 2H).

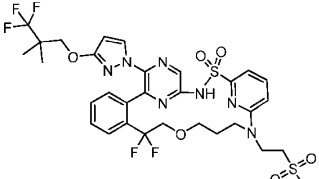
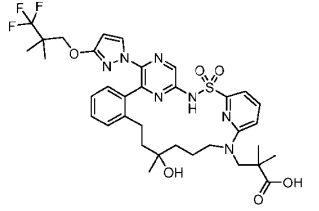
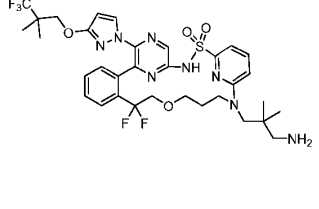
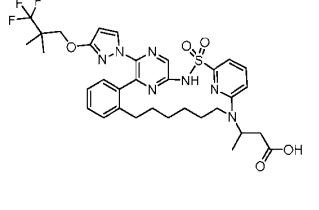
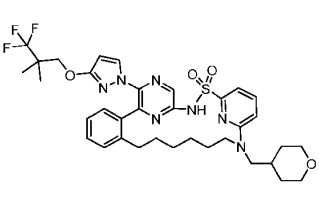
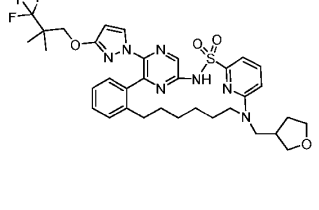
151		657.76	LCMS mtd 1; LC RT=2.43; MS (ESI) m/z 658.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.68 (s, 1H), 7.83 (d, <i>J</i> = 2.6 Hz, 1H), 7.64 (dd, <i>J</i> = 8.5, 7.5 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.09 (d, <i>J</i> = 7.6 Hz, 1H), 6.77 (d, <i>J</i> = 8.8 Hz, 1H), 5.80 (d, <i>J</i> = 2.7 Hz, 1H), 3.63 (s, 2H), 3.50 (t, <i>J</i> = 6.4 Hz, 2H), 3.27 – 3.19 (m, 2H), 2.89 – 1.91 (m, 2H), 1.62 – 1.52 (m, 2H), 1.43 – 1.25 (m, 4H), 1.16 – 1.02 (m, 8H), 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 0.85 (dt, <i>J</i> = 15.3, 7.6 Hz, 2H).
152		723.76	LCMS mtd 4; LC RT=1.97; MS (ESI) m/z 724.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (d, <i>J</i> = 8.7 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.46 – 7.27 (m, 3H), 7.19 – 6.99 (m, 4H), 6.93 (d, <i>J</i> = 2.5 Hz, 1H), 5.52 (d, <i>J</i> = 2.6 Hz, 1H), 4.18 – 3.34 (m, 9H), 3.06 – 2.75 (m, 1H), 2.07 – 1.88 (m, 1H), 1.81 – 1.67 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 1.17 (s, 6H).
153		710.86	LCMS mtd 1; LC RT=3.14; MS (ESI) m/z 711.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.07 – 7.57 (m, 3H), 7.41 – 7.07 (m, 6H), 6.88 – 6.77 (m, 2H), 6.70 (d, <i>J</i> = 8.1 Hz, 1H), 6.43 (s, 1H), 3.99 – 3.87 (m, 1H), 3.78 – 3.38 (m, 6H), 2.73 – 2.13 (m, 2H), 2.08 – 1.93 (m, 1H), 1.85 – 1.61 (m, 1H), 1.55 (t, <i>J</i> = 7.1 Hz, 2H), 1.50 – 1.30 (m, 4H), 1.21 – 1.10 (m, 2H), 1.07 – 0.97 (m, 2H), 0.92 (s, 9H).
154		723.84	LCMS mtd 4; LC RT=1.72; MS (ESI) m/z 724.2 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.49 (s, 1H), 11.88 (s, 1H), 8.57 (s, 1H), 7.68 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.56 (d, <i>J</i> = 7.7 Hz, 1H), 7.48 (t, <i>J</i> = 7.6 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.16 (t, <i>J</i> = 8.0 Hz, 1H), 7.10 (d, <i>J</i> = 8.8 Hz, 1H), 7.03 – 6.92 (m, 2H), 6.75 (dd, <i>J</i> = 8.2, 1.8 Hz, 1H), 6.68 (s, 1H), 4.36 (s, 1H), 4.15 – 4.04 (m, 1H), 3.99 – 3.80 (m, 1H), 3.78 – 3.41 (m, 6H), 3.14 – 2.94 (m, 1H), 1.97 – 1.82 (m, 1H), 1.64 – 1.43 (m, 3H), 1.11 (d, <i>J</i> = 20.3 Hz, 6H), 0.88 (s, 9H).
155		694.84	LCMS mtd 5; LC RT=2.23; MS (ESI) m/z 693.2 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 7.71 (d, <i>J</i> = 8.6 Hz, 1H), 7.59 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.50 (d, <i>J</i> = 7.9 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.18 (t, <i>J</i> = 7.5 Hz, 1H), 7.10 (t, <i>J</i> = 7.9 Hz, 1H), 7.01 (d, <i>J</i> = 8.8 Hz, 1H), 6.79 (d, <i>J</i> = 7.4 Hz, 2H), 6.63 (dd, <i>J</i> = 8.2, 2.1 Hz, 1H), 6.54 (s, 1H), 4.68 – 4.45 (m, 1H), 4.31 – 4.16 (m, 1H), 3.97 – 3.70 (m, 3H), 3.69 – 3.58 (m, 1H), 3.55 – 3.34 (m, 4H), 2.12 – 2.02 (m, 1H), 1.80 – 1.68 (m, 1H), 1.54 (t, <i>J</i> = 7.2 Hz, 2H), 1.22 (d, <i>J</i> = 13.1 Hz, 6H), 0.92 (s, 9H).
156		658.92	LCMS mtd 1; LC RT=3.35; MS (ESI) m/z 659.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.03 – 7.53 (m, 3H), 7.34 – 7.10 (m, 6H), 6.84 – 6.73 (m, 2H), 6.70 (d, <i>J</i> = 7.0 Hz, 1H), 6.43 (s, 1H), 3.80 – 3.42 (m, 6H), 2.67 (t, <i>J</i> = 7.4 Hz, 2H), 2.57 – 2.18 (m, 2H), 2.14 (s, 3H), 1.55 (t, <i>J</i> = 7.1 Hz, 2H), 1.50 – 1.29 (m, 4H), 1.20 – 1.11 (m, 2H), 1.05 – 0.98 (m, 2H), 0.92 (s, 9H).

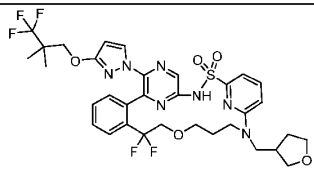
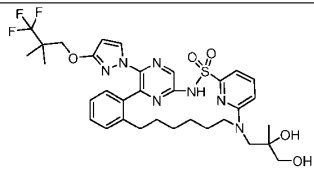
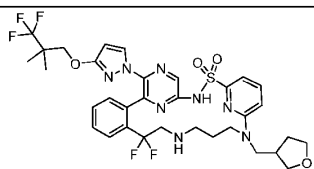
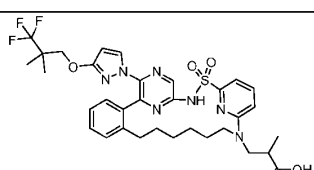
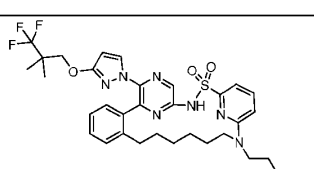
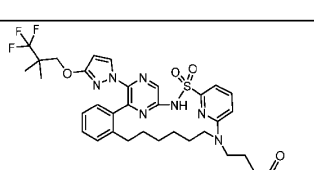
157		690.92	LCMS mtd 1; LC RT=2.86; MS (ESI) m/z 691.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 – 7.54 (m, 3H), 7.39 – 7.05 (m, 6H), 6.89 (d, <i>J</i> = 8.8 Hz, 1H), 6.77 (d, <i>J</i> = 7.4 Hz, 1H), 6.69 (d, <i>J</i> = 7.3 Hz, 1H), 6.43 (s, 1H), 4.03 – 3.35 (m, 8H), 2.92 (s, 3H), 2.16 (s, 2H), 1.60 – 1.31 (m, 6H), 1.20 – 1.10 (m, 2H), 1.05 – 0.86 (m, 11H).
158		674.92	LCMS mtd 1; LC RT=2.77; MS (ESI) m/z 675.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.01 – 7.53 (m, 3H), 7.36 – 7.06 (m, 6H), 6.91 (d, <i>J</i> = 8.5 Hz, 1H), 6.78 (d, <i>J</i> = 7.5 Hz, 1H), 6.69 (d, <i>J</i> = 7.9 Hz, 1H), 6.42 (s, 1H), 3.98 – 3.52 (m, 6H), 3.10 – 2.78 (m, 2H), 2.59 (s, 3H), 2.37 – 1.97 (m, 2H), 1.64 – 1.33 (m, 6H), 1.20 – 1.12 (m, 2H), 1.05 – 0.87 (m, 11H).
159		708.87	LCMS mtd 7; LC RT=2.07; MS (ESI) m/z 709.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 (d, <i>J</i> = 8.6 Hz, 1H), 7.60 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.50 (d, <i>J</i> = 7.5 Hz, 1H), 7.43 – 7.26 (m, 3H), 7.20 (t, <i>J</i> = 7.3 Hz, 1H), 7.10 (t, <i>J</i> = 7.9 Hz, 1H), 7.03 (d, <i>J</i> = 8.8 Hz, 1H), 6.87 – 6.75 (m, 2H), 6.63 (d, <i>J</i> = 8.4 Hz, 1H), 6.56 (s, 1H), 4.55 – 3.45 (m, 9H), 3.28 – 3.17 (m, 3H), 2.04 – 1.92 (m, 1H), 1.82 – 1.67 (m, 1H), 1.54 (t, <i>J</i> = 7.2 Hz, 2H), 0.98 – 0.85 (m, 15H).
160		746.84	LCMS mtd 1; LC RT=3.02; MS (ESI) m/z 747.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.71 (d, <i>J</i> = 8.5 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.49 (d, <i>J</i> = 7.6 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.24 – 7.15 (m, 1H), 7.09 (t, <i>J</i> = 7.9 Hz, 1H), 6.91 – 6.76 (m, 3H), 6.62 (d, <i>J</i> = 8.3 Hz, 1H), 6.56 (s, 1H), 4.42 – 4.14 (m, 1H), 4.03 – 3.87 (m, 1H), 3.77 – 3.67 (m, 1H), 3.65 – 3.44 (m, 3H), 3.18 – 3.00 (m, 1H), 2.81 – 2.46 (m, 1H), 2.26 – 1.87 (m, 2H), 1.85 – 1.65 (m, 2H), 1.62 – 1.25 (m, 7H), 0.92 (s, 9H).
161		714.81	LCMS mtd 7; LC RT=1.59; MS (ESI) m/z 715.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (s, 1H), 7.77 – 7.54 (m, 2H), 7.51 – 6.80 (m, 6H), 5.75 (s, 1H), 4.08 – 3.41 (m, 7H), 3.06 – 2.69 (m, 6H), 2.44 – 1.52 (m, 2H), 1.51 – 1.33 (m, 3H), 1.17 – 0.72 (m, 11H).
162		691.91	LCMS mtd 4; LC RT=1.92; MS (ESI) m/z 692.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.87 (s, 1H), 7.72 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.34 (d, <i>J</i> = 7.3 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.21 – 7.11 (m, 4H), 7.04 (d, <i>J</i> = 7.7 Hz, 1H), 6.94 (d, <i>J</i> = 8.7 Hz, 1H), 6.76 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 6.67 (s, 1H), 3.84 – 3.48 (m, 6H), 3.41 (t, <i>J</i> = 6.7 Hz, 2H), 2.93 (s, 3H), 2.42 – 2.05 (m, 2H), 1.57 (t, <i>J</i> = 7.1 Hz, 2H), 1.49 – 1.39 (m, 2H), 1.37 – 1.31 (m, 2H), 1.18 – 1.09 (m, 2H), 1.02 – 0.83 (m, 11H).

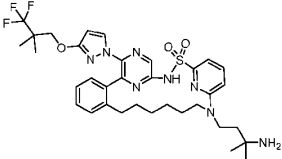
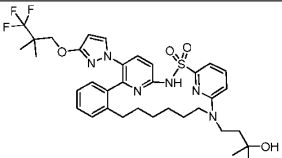
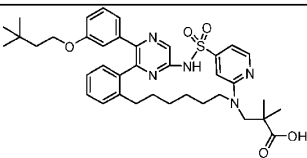
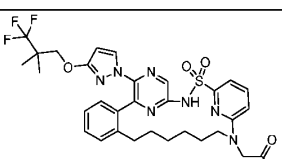
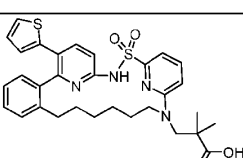
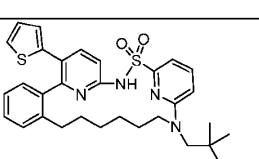
163		776.75	LCMS mtd 7; LC RT=1.95; MS (ESI) m/z 777.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.84 (d, <i>J</i> = 8.9 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.52 (d, <i>J</i> = 7.5 Hz, 1H), 7.46 – 7.30 (m, 4H), 7.04 (d, <i>J</i> = 7.2 Hz, 1H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.92 – 6.81 (m, 1H), 5.59 (d, <i>J</i> = 2.6 Hz, 1H), 4.36 – 4.15 (m, 1H), 4.03 – 3.88 (m, 3H), 3.68 – 3.51 (m, 2H), 3.11 – 3.00 (m, 1H), 2.51 – 2.29 (m, 1H), 2.09 – 1.85 (m, 2H), 1.80 – 1.55 (m, 2H), 1.54 – 1.31 (m, 5H), 1.18 (s, 6H).
164		713.78	LCMS mtd 4; LC RT=1.64; MS (ESI) m/z 714.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.71 (s, 1H), 7.86 (d, <i>J</i> = 2.7 Hz, 1H), 7.63 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.29 – 7.13 (m, 4H), 7.10 (d, <i>J</i> = 6.9 Hz, 1H), 6.91 (d, <i>J</i> = 8.7 Hz, 1H), 5.80 (d, <i>J</i> = 2.7 Hz, 1H), 3.75 – 3.50 (m, 6H), 2.56 – 2.01 (m, 2H), 1.43 – 1.26 (m, 4H), 1.18 – 1.02 (m, 10H), 0.94 (s, 2H), 0.81 (s, 2H).
165		792.89	LCMS mtd 7; LC RT=1.95; MS (ESI) m/z 793.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.78 (s, 1H), 7.91 (d, <i>J</i> = 2.6 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.28 – 7.12 (m, 4H), 7.07 (d, <i>J</i> = 7.8 Hz, 1H), 6.96 (d, <i>J</i> = 9.0 Hz, 1H), 5.81 (d, <i>J</i> = 2.7 Hz, 1H), 3.78 – 3.42 (m, 6H), 3.11 (s, 3H), 2.55 – 2.01 (m, 2H), 1.47 – 1.27 (m, 4H), 1.16 (s, 6H), 1.11 – 1.03 (m, 8H), 0.96 – 0.69 (m, 2H).
166		715.79	LCMS mtd 7; LC RT=1.9; MS (ESI) m/z 716.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.76 (s, 1H), 7.85 (s, 1H), 7.68 – 7.57 (m, 1H), 7.29 – 7.16 (m, 3H), 7.13 (t, <i>J</i> = 7.3 Hz, 1H), 7.04 (d, <i>J</i> = 7.6 Hz, 1H), 6.89 (d, <i>J</i> = 8.5 Hz, 1H), 5.79 (d, <i>J</i> = 2.6 Hz, 1H), 4.60 (s, 2H), 4.30 (d, <i>J</i> = 6.1 Hz, 2H), 3.72 (s, 2H), 3.67 – 3.43 (m, 6H), 2.52 – 2.07 (m, 2H), 1.60 – 1.28 (m, 4H), 1.18 – 1.03 (m, 8H), 1.00 – 0.72 (m, 2H).
167		742.82	LCMS mtd 8; LC RT=1.68; MS (ESI) m/z 743.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.77 (s, 1H), 7.92 (s, 1H), 7.71 – 7.60 (m, 1H), 7.32 – 7.12 (m, 4H), 7.06 (d, <i>J</i> = 7.5 Hz, 1H), 6.97 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.6 Hz, 1H), 4.15 – 3.98 (m, 1H), 3.93 – 3.42 (m, 9H), 2.50 – 2.08 (m, 3H), 2.05 – 1.88 (m, 1H), 1.58 – 1.25 (m, 4H), 1.16 – 0.98 (m, 8H), 0.91 – 0.67 (m, 2H).
168		743.8	LCMS mtd 8; LC RT=1.42; MS (ESI) m/z 744.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.76 (s, 1H), 8.32 (s, 1H), 7.89 (d, <i>J</i> = 2.4 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.32 – 7.12 (m, 4H), 7.07 (d, <i>J</i> = 7.6 Hz, 1H), 6.96 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.7 Hz, 1H), 4.04 – 3.89 (m, 2H), 3.87 – 3.40 (m, 8H), 2.51 – 2.06 (m, 3H), 1.95 – 1.83 (m, 1H), 1.55 – 1.24 (m, 4H), 1.16 – 1.01 (m, 8H), 0.83 (s, 2H).

169		591.74	LCMS mtd 8; LC RT=1.37; MS (ESI) m/z 592.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.91 (s, 1H), 7.69 – 7.54 (m, 1H), 7.43 – 7.19 (m, 6H), 6.94 (d, <i>J</i> = 8.8 Hz, 1H), 6.81 – 6.72 (m, 1H), 6.42 (d, <i>J</i> = 3.6 Hz, 1H), 3.88 – 3.64 (m, 1H), 3.60 – 3.38 (m, 3H), 2.40 – 2.15 (m, 2H), 1.53 – 1.38 (m, 1H), 1.37 – 1.10 (m, 9H), 1.10 – 0.97 (m, 2H), 0.90–0.80 (m, 1H), 0.71 – 0.58 (m, 1H).
170		723.82	LCMS mtd 8; LC RT=1.84; MS (ESI) m/z 724.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.39 (s, 1H), 7.69 – 7.56 (m, 2H), 7.33 – 7.01 (m, 5H), 6.96 (d, <i>J</i> = 8.7 Hz, 1H), 5.72 (d, <i>J</i> = 2.6 Hz, 1H), 4.16 – 3.36 (m, 9H), 3.22 – 3.01 (m, 1H), 2.47 – 1.87 (m, 4H), 1.85 – 1.30 (m, 4H), 1.20 – 1.01 (m, 9H), 0.97 – 0.81 (m, 1H).
171		724.8	LCMS mtd 8; LC RT=1.87; MS (ESI) m/z 725.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.81 (s, 1H), 8.47 (s, 1H), 7.92 (d, <i>J</i> = 2.5 Hz, 1H), 7.71 (t, <i>J</i> = 8.0 Hz, 1H), 7.31 (d, <i>J</i> = 7.3 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.13 (t, <i>J</i> = 7.1 Hz, 1H), 7.07 – 6.96 (m, 2H), 5.82 (d, <i>J</i> = 2.6 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.98 – 3.51 (m, 9H), 2.55 – 2.00 (m, 4H), 1.63 – 1.33 (m, 4H), 1.22 – 1.03 (m, 8H), 1.00 – 0.74 (m, 2H).
172		729.78	LCMS mtd 1; LC RT=2.1; MS (ESI) m/z 730.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.68 (s, 1H), 8.37 (s, 2H), 7.85 (s, 1H), 7.63 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 2H), 7.09 (d, <i>J</i> = 7.0 Hz, 1H), 6.94 (d, <i>J</i> = 8.7 Hz, 1H), 5.78 (d, <i>J</i> = 2.6 Hz, 1H), 4.76 (d, <i>J</i> = 5.7 Hz, 2H), 4.62 (s, 2H), 4.16 – 3.50 (m, 6H), 2.48 – 2.02 (m, 2H), 1.51 – 1.31 (m, 4H), 1.18 – 1.03 (m, 8H), 0.96 – 0.70 (m, 2H).
173		739.78	LCMS mtd 1; LC RT=2.03; MS (ESI) m/z 740.3 [M+H] ⁺	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12.46 (s, 1H), 11.82 (s, 1H), 8.11 (s, 1H), 7.87 (d, <i>J</i> = 2.5 Hz, 1H), 7.68 (t, <i>J</i> = 8.0 Hz, 1H), 7.59 – 7.26 (m, 4H), 7.24 – 7.17 (m, 2H), 7.09 (d, <i>J</i> = 7.7 Hz, 1H), 7.06 (d, <i>J</i> = 8.8 Hz, 1H), 5.83 (d, <i>J</i> = 2.6 Hz, 1H), 4.10 – 3.90 (m, 2H), 3.78 – 3.58 (m, 3H), 3.45 (d, <i>J</i> = 11.0 Hz, 1H), 3.41 – 3.35 (m, 1H), 3.24 – 3.08 (m, 1H), 2.03 – 1.93 (m, 1H), 1.81 (s, 1H), 1.07 (d, <i>J</i> = 2.5 Hz, 6H), 1.05 (s, 6H).
174		716.78	LCMS mtd 1; LC RT=1.71; MS (ESI) m/z 717.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.71 (s, 1H), 8.00 (d, <i>J</i> = 2.7 Hz, 1H), 7.55 (dd, <i>J</i> = 8.5, 7.3 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.32 (td, <i>J</i> = 7.5, 1.2 Hz, 1H), 7.25 (d, <i>J</i> = 7.0 Hz, 1H), 7.19 (td, <i>J</i> = 7.5, 1.3 Hz, 1H), 6.95 (d, <i>J</i> = 6.8 Hz, 1H), 6.64 (d, <i>J</i> = 8.4 Hz, 1H), 5.84 (d, <i>J</i> = 2.7 Hz, 1H), 3.52 (s, 2H), 3.30 – 3.23 (m, 8H), 3.23 – 2.85 (m, 2H), 1.69 – 1.55 (m, 2H), 1.18 (s, 6H), 1.07 (s, 6H).

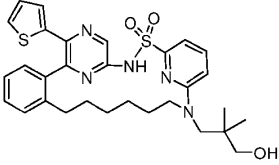
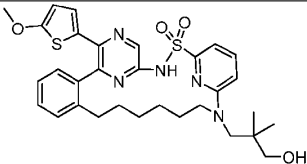
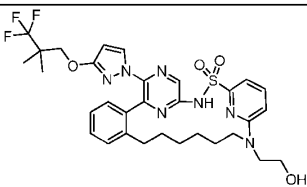
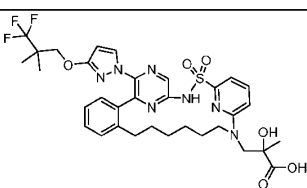
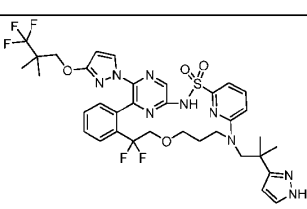
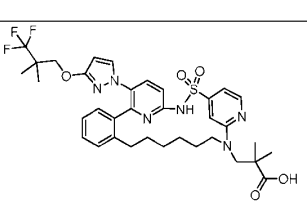
175		751.73	LCMS mtd 4; LC RT=1.54; MS (ESI) m/z 752.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 (s, 1H), 7.97 (d, <i>J</i> = 2.7 Hz, 1H), 7.63 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.51 (d, <i>J</i> = 7.1 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.32 (d, <i>J</i> = 7.2 Hz, 1H), 7.08 (d, <i>J</i> = 6.8 Hz, 1H), 6.95 (d, <i>J</i> = 8.8 Hz, 1H), 5.77 (d, <i>J</i> = 2.7 Hz, 1H), 4.15 – 4.03 (m, 1H), 4.01 – 3.35 (m, 9H), 1.97 – 1.81 (m, 1H), 1.81 – 1.68 (m, 1H), 1.25 – 1.16 (m, 2H), 1.05 (d, <i>J</i> = 1.6 Hz, 6H), 1.02 – 0.97 (m, 1H), 0.93 – 0.88 (m, 1H).
176		737.75	LCMS mtd 1; LC RT=2.09; MS (ESI) m/z 738.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 (s, 1H), 7.96 (d, <i>J</i> = 2.7 Hz, 1H), 7.63 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.52 (d, <i>J</i> = 7.3 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.32 (d, <i>J</i> = 7.2 Hz, 1H), 7.09 (d, <i>J</i> = 8.8 Hz, 1H), 7.06 (d, <i>J</i> = 7.2 Hz, 1H), 5.76 (d, <i>J</i> = 2.7 Hz, 1H), 4.21 – 3.91 (m, 2H), 3.78 – 3.26 (m, 10H), 1.97 – 1.84 (m, 1H), 1.82 – 1.69 (m, 1H), 1.05 (d, <i>J</i> = 2.1 Hz, 6H), 0.59 – 0.43 (m, 4H).
177		714.81	LCMS mtd 4; LC RT=1.97; MS (ESI) m/z 715.0 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.53 – 8.16 (m, 1H), 7.73 – 7.47 (m, 2H), 7.36 – 7.02 (m, 5H), 6.94 (d, <i>J</i> = 8.5 Hz, 1H), 5.70 (s, 1H), 4.01 – 3.49 (m, 9H), 3.43 – 3.36 (m, 1H), 3.29 – 3.20 (m, 2H), 3.13 – 3.00 (m, 1H), 2.16 – 1.77 (m, 2H), 1.67 – 1.29 (m, 4H), 1.19 – 0.97 (m, 9H), 0.91 – 0.71 (m, 1H).
178		725.74	LCMS mtd 7; LC RT=1.92; MS (ESI) m/z 726.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.46 (s, 1H), 7.94 (s, 1H), 7.59 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 7.26 (d, <i>J</i> = 7.1 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.97 (d, <i>J</i> = 8.8 Hz, 1H), 5.75 (d, <i>J</i> = 2.7 Hz, 1H), 4.11 – 3.97 (m, 1H), 3.96 – 3.74 (m, 1H), 3.71 – 3.38 (m, 8H), 1.96 – 1.67 (m, 2H), 1.18 (d, <i>J</i> = 11.5 Hz, 6H), 1.06 (s, 6H).
179		752.76	LCMS mtd 8; LC RT=1.26; MS (ESI) m/z 753.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.37 (s, 1H), 7.91 (d, <i>J</i> = 2.7 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.53 – 7.40 (m, 2H), 7.36 (d, <i>J</i> = 7.2 Hz, 1H), 7.08 (d, <i>J</i> = 7.1 Hz, 1H), 7.00 (d, <i>J</i> = 8.8 Hz, 1H), 5.75 (d, <i>J</i> = 2.7 Hz, 1H), 4.04 (s, 1H), 3.88 – 3.39 (m, 6H), 3.24 – 3.06 (m, 1H), 2.92 – 2.63 (m, 2H), 2.14 – 1.54 (m, 2H), 1.16 (s, 6H), 1.06 (s, 6H).
180		727.77	LCMS mtd 1; LC RT=2.17; MS (ESI) m/z 728.2 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.88 (s, 1H), 8.27 (s, 1H), 8.07 (s, 1H), 7.71 (s, 1H), 7.56 – 7.28 (m, 4H), 7.12 (d, <i>J</i> = 7.0 Hz, 1H), 6.88 (s, 1H), 5.88 (s, 1H), 4.33 – 3.96 (m, 2H), 3.86 – 3.39 (m, 7H), 3.25 – 3.11 (m, 1H), 2.72 – 2.56 (m, 2H), 2.13 (s, 3H), 1.93 – 1.80 (m, 1H), 1.70 – 1.59 (m, 1H), 0.99 (d, <i>J</i> = 3.3 Hz, 6H).

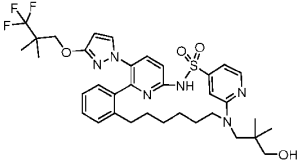
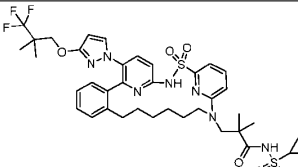
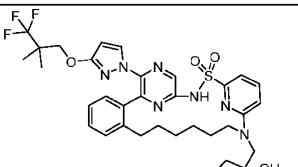
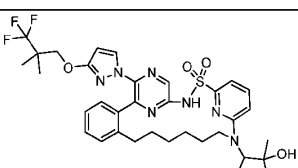
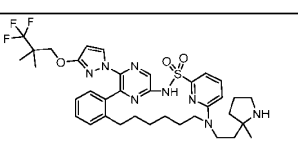
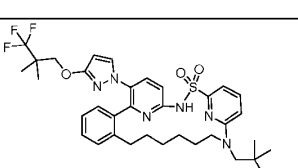
181		759.77	LCMS mtd 1; LC RT=2.05; MS (ESI) m/z 760.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.47 (s, 1H), 7.99 (d, <i>J</i> = 2.6 Hz, 1H), 7.67 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 7.31 (d, <i>J</i> = 7.2 Hz, 1H), 7.18 – 7.10 (m, 1H), 6.96 (d, <i>J</i> = 8.7 Hz, 1H), 5.77 (d, <i>J</i> = 2.7 Hz, 1H), 4.03 – 3.86 (m, 2H), 3.85 – 3.63 (m, 2H), 3.61 – 3.34 (m, 8H), 2.93 (s, 3H), 1.94 – 1.74 (m, 2H), 1.05 (d, <i>J</i> = 1.7 Hz, 6H).
182		745.82	LCMS mtd 4; LC RT=1.5; MS (ESI) m/z 746.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.62 (s, 1H), 7.90 (d, <i>J</i> = 2.7 Hz, 1H), 7.60 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.28 – 7.18 (m, 3H), 7.13 – 7.07 (m, 1H), 6.98 – 6.90 (m, 2H), 5.79 (d, <i>J</i> = 2.7 Hz, 1H), 3.71 – 3.48 (m, 6H), 2.39 (s, 2H), 1.66 – 1.46 (m, 2H), 1.35 (s, 2H), 1.18 – 1.10 (m, 8H), 1.08 (d, <i>J</i> = 5.1 Hz, 6H), 0.96 (s, 3H).
183		738.78	LCMS mtd 8; LC RT=1.84; MS (ESI) m/z 739.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.04 (s, 1H), 7.78 – 6.76 (m, 8H), 5.64 (d, <i>J</i> = 2.5 Hz, 1H), 4.28 – 3.87 (m, 2H), 3.74 – 3.36 (m, 6H), 3.01 – 2.72 (m, 2H), 2.51 (s, 2H), 2.00 – 1.67 (m, 2H), 1.17 – 0.90 (m, 12H).
184		701.77	LCMS mtd 4; LC RT=1.59; MS (ESI) m/z 702.0 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.66 (s, 1H), 7.83 (d, <i>J</i> = 2.7 Hz, 1H), 7.68 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.31 – 7.19 (m, 4H), 7.17 (d, <i>J</i> = 7.5 Hz, 1H), 7.05 (d, <i>J</i> = 8.8 Hz, 1H), 5.80 (d, <i>J</i> = 2.7 Hz, 1H), 4.61 – 4.49 (m, 1H), 3.65 (s, 2H), 3.41 – 3.34 (m, 2H), 2.62 (dd, <i>J</i> = 15.5, 7.6 Hz, 1H), 2.52 (dd, <i>J</i> = 15.5, 6.7 Hz, 1H), 2.43 – 2.08 (m, 2H), 1.46 – 1.15 (m, 7H), 1.09 (s, 6H), 1.07 – 0.98 (m, 2H), 0.77 (s, 2H).
185		713.82	LCMS mtd 8; LC RT=1.85; MS (ESI) m/z 714.3 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.61 (s, 1H), 8.56 (d, <i>J</i> = 24.7 Hz, 1H), 8.03 (s, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.26 (t, <i>J</i> = 7.4 Hz, 1H), 7.22 – 7.08 (m, 4H), 6.93 (d, <i>J</i> = 8.7 Hz, 1H), 5.92 (d, <i>J</i> = 2.5 Hz, 1H), 3.81 (dd, <i>J</i> = 11.1, 2.7 Hz, 2H), 3.55 (s, 2H), 3.42 (s, 2H), 3.27 – 3.01 (m, 4H), 2.48 – 2.35 (m, 1H), 2.21 – 1.97 (m, 1H), 1.94 – 1.78 (m, 1H), 1.57 – 1.41 (m, 2H), 1.33 – 1.13 (m, 6H), 1.11 – 0.93 (m, 8H), 0.73 (s, 2H).
186		699.79	LCMS mtd 4; LC RT=1.82; MS (ESI) m/z 700.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.75 (s, 1H), 7.88 (d, <i>J</i> = 2.6 Hz, 1H), 7.65 (dd, <i>J</i> = 8.7, 7.4 Hz, 1H), 7.29 – 7.18 (m, 3H), 7.14 (td, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.05 (d, <i>J</i> = 7.5 Hz, 1H), 6.88 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.7 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.75 – 3.67 (m, 2H), 3.65 – 3.45 (m, 5H), 3.29 – 3.10 (m, 2H), 2.74 – 2.62 (m, 1H), 2.59 – 2.09 (m, 2H), 2.06 – 1.92 (m, 1H), 1.67 – 1.54 (m, 1H), 1.47 – 1.32 (m, 4H), 1.17 – 1.02 (m, 8H), 0.94 – 0.78 (m, 2H).

187		737.75	LCMS mtd 4; LC RT=1.68; MS (ESI) m/z 738.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.46 (d, <i>J</i> = 1.9 Hz, 1H), 7.97 (s, 1H), 7.69 – 7.62 (m, 1H), 7.51 (d, <i>J</i> = 7.4 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.32 (d, <i>J</i> = 7.2 Hz, 1H), 7.08 (d, <i>J</i> = 7.2 Hz, 1H), 6.88 (d, <i>J</i> = 8.8 Hz, 1H), 5.76 (d, <i>J</i> = 2.7 Hz, 1H), 4.17 – 3.39 (m, 13H), 3.30 – 3.22 (m, 1H), 2.76 – 2.61 (m, 1H), 2.07 – 1.96 (m, 1H), 1.95 – 1.83 (m, 1H), 1.83 – 1.73 (m, 1H), 1.70 – 1.57 (m, 1H), 1.05 (d, <i>J</i> = 1.4 Hz, 6H).
188		703.78	LCMS mtd 1; LC RT=2.11; MS (ESI) m/z 704.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.76 (s, 1H), 7.91 (s, 1H), 7.63 (dd, <i>J</i> = 8.5, 7.5 Hz, 1H), 7.31 – 7.18 (m, 3H), 7.14 (t, <i>J</i> = 6.8 Hz, 1H), 7.09 – 6.94 (m, 2H), 5.81 (d, <i>J</i> = 2.6 Hz, 1H), 3.73 – 3.52 (m, 4H), 3.49 – 3.38 (m, 2H), 3.29 – 3.19 (m, 2H), 2.54 – 2.09 (m, 2H), 1.59 – 1.30 (m, 4H), 1.19 – 1.02 (m, 11H), 0.99 – 0.75 (m, 2H).
189		736.76	LCMS mtd 4; LC RT=1.62; MS (ESI) m/z 737.1 [M+H] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.25 (s, 1H), 7.99 (d, <i>J</i> = 2.4 Hz, 1H), 7.66 (dd, <i>J</i> = 8.5, 7.4 Hz, 1H), 7.51 – 7.36 (m, 3H), 7.29 (d, <i>J</i> = 7.2 Hz, 1H), 7.11 (d, <i>J</i> = 7.3 Hz, 1H), 6.87 (d, <i>J</i> = 8.7 Hz, 1H), 5.85 (d, <i>J</i> = 2.7 Hz, 1H), 4.07 – 3.43 (m, 10H), 3.30 – 2.86 (m, 4H), 2.70 – 2.52 (m, 1H), 2.04 – 1.86 (m, 1H), 1.82 – 1.45 (m, 3H), 0.99 (s, 6H).
190		701.77	LCMS mtd 5; LC RT=1.4; MS (ESI) m/z 700.1 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 8.69 (s, 1H), 8.43 (s, 2H), 7.84 (d, <i>J</i> = 2.4 Hz, 1H), 7.64 (dd, <i>J</i> = 8.5, 7.5 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.20 – 7.10 (m, 3H), 6.86 (d, <i>J</i> = 8.7 Hz, 1H), 5.79 (d, <i>J</i> = 2.6 Hz, 1H), 3.67 – 3.46 (m, 4H), 3.26 – 3.03 (m, 2H), 2.85 – 2.74 (m, 1H), 2.61 – 2.06 (m, 2H), 1.41 – 1.27 (m, 4H), 1.18 – 1.05 (m, 11H), 0.88 – 0.71 (m, 2H).
191		701.81	LCMS mtd 4; LC RT=1.8; MS (ESI) m/z 702.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.66 (s, 1H), 7.83 (d, <i>J</i> = 2.7 Hz, 1H), 7.70 – 7.57 (m, 1H), 7.29 – 7.18 (m, 3H), 7.16 (t, <i>J</i> = 7.4 Hz, 1H), 7.09 (d, <i>J</i> = 7.3 Hz, 1H), 6.80 (d, <i>J</i> = 8.7 Hz, 1H), 5.80 (d, <i>J</i> = 2.7 Hz, 1H), 3.63 (s, 2H), 3.50 (t, <i>J</i> = 6.3 Hz, 2H), 3.44 – 3.36 (m, 2H), 2.81 – 1.98 (m, 2H), 1.75 – 1.58 (m, 2H), 1.48 – 1.28 (m, 4H), 1.22 (s, 6H), 1.18 – 1.10 (m, 2H), 1.08 (s, 6H), 0.94 – 0.76 (m, 2H).
192		729.82	LCMS mtd 4; LC RT=1.72; MS (ESI) m/z 730.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.66 (s, 1H), 7.83 (d, <i>J</i> = 2.7 Hz, 1H), 7.65 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.30 – 7.13 (m, 4H), 7.10 (dd, <i>J</i> = 7.6, 1.0 Hz, 1H), 6.85 (d, <i>J</i> = 8.7 Hz, 1H), 5.79 (d, <i>J</i> = 2.7 Hz, 1H), 3.63 (s, 2H), 3.48 (t, <i>J</i> = 6.3 Hz, 2H), 3.38 – 3.30 (m, 2H), 2.35 (s, 2H), 1.85 – 1.69 (m, 2H), 1.44 – 1.26 (m, 4H), 1.21 (s, 6H), 1.16 – 1.04 (m, 8H), 0.91 – 0.78 (m, 2H).

193		700.83	LCMS mtd 1; LC RT=1.88; MS (ESI) m/z 701.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.51 (s, 1H), 7.67 (s, 1H), 7.60 (t, <i>J</i> = 7.9 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.22 – 7.06 (m, 3H), 6.82 (d, <i>J</i> = 8.7 Hz, 1H), 5.74 (d, <i>J</i> = 2.5 Hz, 1H), 3.78 – 3.36 (m, 6H), 2.10 (s, 2H), 1.82 (s, 2H), 1.61 – 1.22 (m, 10H), 1.14 (s, 2H), 1.08 (s, 6H), 0.95 (s, 2H).
194		700.82	LCMS mtd 1; LC RT=2.1; MS (ESI) m/z 701.4 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 7.88 (d, <i>J</i> = 8.9 Hz, 1H), 7.63 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.53 (d, <i>J</i> = 7.0 Hz, 1H), 7.32 – 7.07 (m, 5H), 6.86 (d, <i>J</i> = 2.5 Hz, 1H), 6.77 (d, <i>J</i> = 8.7 Hz, 1H), 5.63 (d, <i>J</i> = 2.6 Hz, 1H), 4.02 (s, 2H), 3.93 – 3.37 (m, 4H), 2.39 (s, 2H), 1.79 – 1.58 (m, 2H), 1.48 – 1.30 (m, 4H), 1.23 (s, 6H), 1.19 (s, 6H), 1.19 – 1.12 (m, 2H), 0.99 (s, 2H).
195		685.88	LCMS mtd 5; LC RT=1.62; MS (ESI) m/z 684.3 [M-H] ⁻	¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 (s, 1H), 8.41 (s, 1H), 8.21 (d, <i>J</i> = 5.2 Hz, 1H), 7.32 – 7.19 (m, 3H), 7.16 – 7.03 (m, 4H), 7.00 (d, <i>J</i> = 7.8 Hz, 1H), 6.74 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 6.68 – 6.61 (m, 1H), 3.94 – 3.75 (m, 1H), 3.71 – 3.52 (m, 3H), 3.50 – 3.37 (m, 2H), 2.38 – 2.23 (m, 1H), 2.16 – 2.05 (m, 1H), 1.56 (t, <i>J</i> = 7.2 Hz, 2H), 1.44 – 1.22 (m, 2H), 1.20 – 0.97 (m, 12H), 0.93 (s, 9H).
196		673.71	LCMS mtd 4; LC RT=1.4; MS (ESI) m/z 674.2 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.64 (s, 1H), 7.83 (d, <i>J</i> = 2.6 Hz, 1H), 7.65 (dd, <i>J</i> = 8.5, 7.5 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.20 (d, <i>J</i> = 7.2 Hz, 1H), 7.15 (t, <i>J</i> = 7.3 Hz, 1H), 7.09 (d, <i>J</i> = 7.3 Hz, 1H), 6.69 (d, <i>J</i> = 8.7 Hz, 1H), 5.79 (d, <i>J</i> = 2.7 Hz, 1H), 3.99 (s, 2H), 3.62 (s, 2H), 3.59 (s, 2H), 2.70 – 2.10 (m, 2H), 1.47 – 1.26 (m, 4H), 1.20 – 1.11 (m, 2H), 1.07 (s, 6H), 0.95 – 0.80 (m, 2H).
197		590.76	LCMS mtd 4; LC RT=1.46; MS (ESI) m/z 591.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.00 (d, <i>J</i> = 9.0 Hz, 1H), 7.74 (d, <i>J</i> = 8.9 Hz, 1H), 7.60 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.30 – 7.15 (m, 5H), 6.92 (d, <i>J</i> = 8.7 Hz, 1H), 6.85 (dd, <i>J</i> = 5.1, 3.7 Hz, 1H), 6.77 (dd, <i>J</i> = 3.6, 1.0 Hz, 1H), 3.86 – 3.71 (m, 1H), 3.61 – 3.43 (m, 3H), 2.24 (t, <i>J</i> = 7.8 Hz, 2H), 1.46 (s, 1H), 1.39 – 1.22 (m, 3H), 1.17 (s, 6H), 1.14 – 1.05 (m, 2H), 0.99 – 0.68 (m, 2H).
198		576.77	LCMS mtd 4; LC RT=2.02; MS (ESI) m/z 577.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.00 (s, 1H), 7.79 (s, 1H), 7.60 (dd, <i>J</i> = 8.7, 7.3 Hz, 1H), 7.42 – 7.10 (m, 6H), 6.94 (d, <i>J</i> = 8.7 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.74 (s, 1H), 3.82 – 3.37 (m, 3H), 3.25 – 3.03 (m, 3H), 2.19 (s, 2H), 1.54 (s, 1H), 1.42 – 1.20 (m, 3H), 1.09 (s, 2H), 1.03 – 0.70 (m, 8H).

199		729.82	LCMS mtd 1; LC RT=2.21; MS (ESI) m/z 730.3 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.74 (s, 1H), 7.88 (d, <i>J</i> = 2.4 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.28 – 7.22 (m, 2H), 7.22 – 7.04 (m, 3H), 6.86 (d, <i>J</i> = 8.7 Hz, 1H), 5.81 (d, <i>J</i> = 2.6 Hz, 1H), 3.69 – 3.55 (m, 3H), 3.50 – 3.35 (m, 3H), 2.86 – 2.76 (m, 1H), 2.56 – 2.05 (m, 2H), 1.63 – 1.26 (m, 8H), 1.18 – 1.04 (m, 8H), 0.94 (t, <i>J</i> = 7.1 Hz, 3H), 0.89 – 0.78 (m, 2H).
200		766.79	LCMS mtd 4; LC RT=1.58; MS (ESI) m/z 767.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.38 (s, 1H), 7.97 (d, <i>J</i> = 2.7 Hz, 1H), 7.65 (dd, <i>J</i> = 8.5, 7.6 Hz, 1H), 7.55 (d, <i>J</i> = 7.7 Hz, 1H), 7.45 (t, <i>J</i> = 7.5 Hz, 1H), 7.39 (t, <i>J</i> = 7.3 Hz, 1H), 7.32 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 (d, <i>J</i> = 7.5 Hz, 1H), 6.98 (d, <i>J</i> = 8.8 Hz, 1H), 5.76 (d, <i>J</i> = 2.7 Hz, 1H), 3.93 – 3.77 (m, 1H), 3.69 (d, <i>J</i> = 14.9 Hz, 1H), 3.63 – 3.40 (m, 3H), 3.26 – 3.09 (m, 2H), 3.04 – 2.80 (m, 1H), 2.50 (s, 3H), 2.47 – 2.26 (m, 2H), 1.74 – 1.58 (m, 1H), 1.54 – 1.42 (m, 1H), 1.18 (d, <i>J</i> = 11.1 Hz, 6H), 1.06 (s, 6H).
201		794.84	LCMS mtd 4; LC RT=1.66; MS (ESI) m/z 795.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.41 (s, 1H), 7.94 (d, <i>J</i> = 2.5 Hz, 1H), 7.62 (dd, <i>J</i> = 8.6, 7.4 Hz, 1H), 7.53 (d, <i>J</i> = 8.0 Hz, 1H), 7.44 (t, <i>J</i> = 7.6 Hz, 1H), 7.35 (t, <i>J</i> = 7.3 Hz, 1H), 7.28 (d, <i>J</i> = 7.2 Hz, 1H), 6.94 (d, <i>J</i> = 8.8 Hz, 1H), 6.90 (d, <i>J</i> = 7.7 Hz, 1H), 5.76 (d, <i>J</i> = 2.7 Hz, 1H), 3.76 – 3.55 (m, 3H), 3.52 – 3.37 (m, 2H), 3.27 – 3.03 (m, 4H), 2.55 – 2.28 (m, 2H), 1.46 (s, 2H), 1.18 (d, <i>J</i> = 15.1 Hz, 6H), 1.12 – 1.01 (m, 12H).
202		701.81	LCMS mtd 1; LC RT=2.34; MS (ESI) m/z 702.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.39 (s, 1H), 8.21 (d, <i>J</i> = 5.3 Hz, 1H), 7.86 (d, <i>J</i> = 2.4 Hz, 1H), 7.33 – 7.12 (m, 4H), 7.11 – 7.02 (m, 2H), 5.80 (d, <i>J</i> = 2.6 Hz, 1H), 3.59 (s, 2H), 3.52 – 3.34 (m, 3H), 3.27 – 3.18 (m, 1H), 3.09 (s, 2H), 2.23 (bs, 2H), 1.42 – 1.27 (m, 2H), 1.21 – 1.01 (m, 12H), 0.88 (s, 6H).
203		751.77	LCMS mtd 1; LC RT=2.28; MS (ESI) m/z 752.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.59 (s, 1H), 8.47 (s, 1H), 8.03 (d, <i>J</i> = 2.6 Hz, 1H), 7.61 (dd, <i>J</i> = 8.6, 7.3 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.47 – 7.42 (m, 2H), 7.25 (d, <i>J</i> = 7.2 Hz, 1H), 7.15 (dd, <i>J</i> = 5.1, 3.7 Hz, 1H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 5.78 (d, <i>J</i> = 2.7 Hz, 1H), 3.92 – 3.34 (m, 9H), 3.30 – 3.24 (m, 1H), 2.18 (s, 3H), 1.87 – 1.70 (m, 2H), 1.13 (s, 6H), 1.06 (s, 6H).
204		621.77	LCMS mtd 1; LC RT=2.17; MS (ESI) m/z 622.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.83 (s, 1H), 7.68 – 7.56 (m, 1H), 7.39 (t, <i>J</i> = 7.4 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.25 – 7.15 (m, 2H), 6.93 (d, <i>J</i> = 8.8 Hz, 1H), 5.98 (d, <i>J</i> = 4.2 Hz, 1H), 5.91 (d, <i>J</i> = 4.2 Hz, 1H), 3.82 (s, 3H), 3.81 – 3.74 (m, 1H), 3.58 – 3.39 (m, 3H), 2.40 – 2.17 (m, 2H), 1.52 – 1.40 (m, 1H), 1.38 – 1.12 (m, 9H), 1.12 – 0.98 (m, 2H), 0.93 – 0.79 (m, 1H), 0.74 – 0.59 (m, 1H).

205		577.76	LCMS mtd 1; LC RT=2.26; MS (ESI) m/z 578.1 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.98 (s, 1H), 7.69 – 7.58 (m, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 5.1 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 6.95 (d, J = 8.8 Hz, 1H), 6.83 – 6.68 (m, 1H), 6.42 (d, J = 3.6 Hz, 1H), 3.79 – 3.38 (m, 3H), 3.25 – 2.44 (m, 3H), 2.35 – 2.14 (m, 2H), 1.62 – 1.43 (m, 1H), 1.38 – 1.17 (m, 3H), 1.17 – 0.97 (m, 2H), 0.96 – 0.81 (m, 7H), 0.75 – 0.56 (m, 1H).
206		607.79	LCMS mtd 1; LC RT=2.25; MS (ESI) m/z 608.1 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.89 (s, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.24 – 7.15 (m, 2H), 6.94 (d, J = 8.8 Hz, 1H), 5.97 (d, J = 4.1 Hz, 1H), 5.90 (d, J = 4.2 Hz, 1H), 3.82 (s, 3H), 3.76 – 3.37 (m, 3H), 3.23 – 2.52 (m, 3H), 2.34 – 2.10 (m, 2H), 1.65 – 1.46 (m, 1H), 1.38 – 1.21 (m, 3H), 1.18 – 0.98 (m, 2H), 0.96 – 0.82 (m, 7H), 0.74 – 0.56 (m, 1H).
207		659.73	LCMS mtd 4; LC RT=1.68; MS (ESI) m/z 660.2 [M+H] ⁺	¹ H NMR (500 MHz, CD ₃ OD) δ 8.68 (s, 1H), 7.82 (d, J = 2.7 Hz, 1H), 7.64 (dd, J = 8.7, 7.3 Hz, 1H), 7.29 – 7.15 (m, 4H), 7.11 (d, J = 7.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.79 (d, J = 2.7 Hz, 1H), 3.67 (t, J = 6.0 Hz, 2H), 3.63 (s, 2H), 3.58 – 3.51 (m, 2H), 3.46 – 3.39 (m, 2H), 2.61 – 2.04 (m, 2H), 1.43 – 1.24 (m, 4H), 1.15 – 1.02 (m, 8H), 0.91 – 0.77 (m, 2H).
208		717.77	LCMS mtd 4; LC RT=1.59; MS (ESI) m/z 718.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.70 (s, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 8.6, 7.4 Hz, 1H), 7.31 – 7.14 (m, 5H), 7.10 (d, J = 8.8 Hz, 1H), 5.80 (d, J = 2.7 Hz, 1H), 3.80 – 3.39 (m, 6H), 2.50 – 2.12 (m, 2H), 1.43 – 1.25 (m, 7H), 1.13 – 0.96 (m, 8H), 0.77 (s, 2H).
209		775.8	LCMS mtd 1; LC RT=2.17; MS (ESI) m/z 776.1 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.50 (s, 1H), 7.98 (d, J = 2.6 Hz, 1H), 7.55 – 7.37 (m, 5H), 7.23 (d, J = 7.2 Hz, 1H), 7.16 – 7.02 (m, 1H), 6.63 (d, J = 8.7 Hz, 1H), 6.15 (d, J = 2.1 Hz, 1H), 5.76 (d, J = 2.7 Hz, 1H), 3.96 – 3.32 (m, 9H), 2.93 – 2.67 (m, 1H), 1.77 – 1.54 (m, 2H), 1.34 (d, J = 4.5 Hz, 6H), 1.05 (d, J = 1.2 Hz, 6H).
210		714.81	LCMS mtd 1; LC RT=1.63; MS (ESI) m/z 715.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.20 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.16 (d, J = 7.5 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.84 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.02 (s, 2H), 3.97 – 3.55 (m, 2H), 3.50 – 3.39 (m, 2H), 2.21 (s, 2H), 1.43 – 1.31 (m, 2H), 1.26 – 1.00 (m, 18H).

211		700.82	LCMS mtd 4; LC RT=1.87; MS (ESI) m/z 701.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.18 (d, J = 5.3 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.35 – 7.19 (m, 4H), 7.16 (d, J = 7.4 Hz, 1H), 7.09 (dd, J = 5.3, 1.2 Hz, 1H), 7.05 (s, 1H), 6.85 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.02 (s, 2H), 3.73 – 3.33 (m, 4H), 3.09 (s, 2H), 2.55 – 2.09 (m, 2H), 1.44 – 1.28 (m, 2H), 1.25 – 1.07 (m, 12H), 0.90 (s, 6H).
212		817.94	LCMS mtd 4; LC RT=1.80; MS (ESI) m/z 818.3 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD-d ₄) δ 7.95 (d, J = 8.9 Hz, 1H), 7.76 – 7.58 (m, 2H), 7.33 – 7.08 (m, 5H), 6.95 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.01 (s, 2H), 3.85 – 3.47 (m, 4H), 3.03 – 2.93 (m, 1H), 2.24 (s, 2H), 1.46 – 1.26 (m, 4H), 1.19 (s, 14H), 1.13 – 1.02 (m, 4H), 0.90 (s, 2H).
213		743.85	LCMS mtd 4; LC RT=1.83; MS (ESI) m/z 744.2 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ: 8.81 (s, 1H), 7.90 (s, 1H), 7.61 (dd, J = 8.7, 7.3 Hz, 1H), 7.34 – 7.17 (m, 3H), 7.14 (t, J = 7.3 Hz, 1H), 7.05 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 5.80 (s, 1H), 4.05 – 3.43 (m, 6H), 2.65 – 2.08 (m, 2H), 1.99 – 1.35 (m, 10H), 1.22 – 1.01 (m, 11H), 0.98 – 0.70 (m, 2H).
214		713.82	LCMS mtd 4; LC RT=1.86; MS (ESI) m/z 714.0 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 8.80 (s, 1H), 7.89 (s, 1H), 7.62 (dd, J = 8.8, 7.2 Hz, 1H), 7.42 – 6.85 (m, 6H), 5.81 (d, J = 2.8 Hz, 1H), 4.52 – 3.97 (m, 1H), 3.89 – 3.38 (m, 4H), 2.73 – 1.36 (m, 12H), 1.24 – 0.81 (m, 13H).
215		726.86	LCMS mtd 4; LC RT=2.05; MS (ESI) m/z 727.0 [M+H] ⁺	¹ H NMR (400 MHz, DMSO) δ 9.36 (d, J = 331.4 Hz, 1H), 8.18 (s, 1H), 7.67 (s, 1H), 7.58 – 7.39 (m, 1H), 7.11 (t, J = 15.6 Hz, 5H), 6.80 (d, J = 8.7 Hz, 1H), 5.72 (d, J = 2.4 Hz, 1H), 4.10 – 3.45 (m, 5H), 3.09 (d, J = 64.0 Hz, 3H), 2.25 – 1.31 (m, 11H), 1.24 – 0.84 (m, 13H), 0.62 (s, 1H).
216		686.8	LCMS mtd 4; LC RT=2.09; MS (ESI) m/z 687.0 [M+H] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ 7.94 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.7, 7.3 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.19 (m, 4H), 6.95 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 5.63 (d, J = 2.6 Hz, 1H), 4.03 (s, 2H), 3.63 (s, 2H), 3.46 (m, 2H), 2.24 (s, 2H), 1.54 – 1.24 (m, 4H), 1.19 (d, J = 4.8 Hz, 12H), 1.15 – 1.03 (m, 2H), 0.98 m, 2H).

*Note: “mtd” stands for LCMS “Method”; (ESI) m/z is [M+H]⁺ unless indicated otherwise.

Biological Assays

Methods for Compounds 1 - 19: TECC24 AUC fold over DMSO @ 3 μ M

[584] The effects of a test agent on CFTR-mediated transepithelial chloride transport were measured using TECC24 recording analysis. Test agents were solubilized in DMSO. Solubilized test agents were mixed with incubation medium containing DMEM/F12, Ultrosor G (2%; Crescent Chemical, catalog #67042), Hyclone Fetal Clone II (2%; GE Healthcare, catalog # SH30066.02), bovine brain extract (0.25%; Lonza, catalog #CC-4098), insulin (2.5 μ g/mL), IL-13 (10 ng/mL), hydrocortisone (20 nM), transferrin (2.5 μ g/mL), triiodothyronine (500 nM), ethanolamine (250 nM), epinephrine (1.5 μ M), phosphoethanolamine (250 nM), and retinoic acid (10 nM). Primary human bronchial epithelial cells from a Δ F508 homozygous CF donor (CF-HBE cells; from University of North Carolina Cystic Fibrosis Tissue Procurement Center), grown on Transwell HTS 24-well cell culture inserts (Costar, catalog #3378), were exposed to test agents or controls dissolved in incubation medium. The CF-HBE cells were cultured at 36.5°C for 48 h before TECC24 recordings were performed in the presence or absence of test agent, a positive control or vehicle (DMSO).

[585] Following incubation, the transwell cell culture inserts containing the test agent or control-treated CF-HBE cells were loaded onto a TECC24 apparatus (TECC v7 or MTECC v2; EP Design) to record the transepithelial voltage (VT) and resistance (TEER) using 4 AgCl electrodes per well configured in current-clamp mode. The apical and basolateral bath solutions both contained (in mM) 140 NaCl, 5 KCl, 2 CaCl₂, 1 MgCl₂, 10 Hepes, and 10 glucose (adjusted to pH 7.4 with NaOH) ppm. To inhibit basal Na⁺ absorption, the ENaC inhibitor benzamil (10 μ M) was added to the bath. Then, the adenylate cyclase activator, forskolin (10 μ M), was added to the bath to activate CFTR. The forskolin-stimulated Cl⁻ transport was halted by addition of CFTR inhibitor-172 (20 μ M) to the bath at the end of the experiment to confirm specificity. VT and TEER recordings were digitally acquired at routine intervals using TECC or MTECC software (EP Design). VT and TEER were transformed into equivalent transepithelial Cl⁻ current (IEQ), and the Area Under the Curve (AUC) of the IEQ time course between forskolin and CFTR inhibitor-172 addition is generated using Excel (Microsoft). Efficacy is expressed as the ratio of the test agent AUC divided by vehicle AUC. EC50s based on AUC are generated using the non-linear regression log(agonist) vs. response function in Prism software (Graphpad) with HillSlope fixed = 1.

[586] If a test agent increased the AUC of the forskolin-stimulated IEQ relative to vehicle in CF-HBE cells, and this increase was inhibited by CFTR inhibitor-172, then the test agent was considered a CFTR corrector.

[587] Biological data for Examples 1 - 19 are provided in Table 2 below.

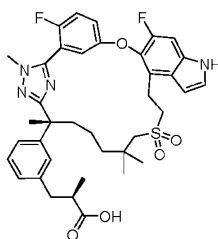
Table 2. Biological data for Example 1-19

Example No.	TECC AUC vs. DMSO @ 3 μ M *
1	B
2	B
3	B
4	A
5	C
6	A
7 (P1)	A
7 (P2)	A
8	A
9	A
10	A
11	C
12	C
13	A
14	A
15	B
16	C
17	C
18	B
19	C

* “A” refers to AUC > 20; “B” refers to AUC 20-10; “C” refers to AUC < 10. ND stands for “not determined”.

Methods for Compounds 20 - 216: TECC24 AUC fold over DMSO @ 100 nM.

[588] The effects of a test agent on CFTR-mediated transepithelial chloride transport were measured using TECC24 recording analysis. Test agents were solubilized in DMSO. Solubilized test agents were mixed with incubation medium containing DMEM/F12, Ultrosor G (2%; Crescent Chemical, catalog #67042), Hyclone Fetal Clone II (2%; GE Healthcare, catalog # SH30066.02), bovine brain extract (0.25%; Lonza, catalog #CC-4098), insulin (2.5 µg/mL), IL-13 (10 ng/mL), hydrocortisone (20 nM), transferrin (2.5 µg/mL), triiodothyronine (500 nM), ethanolamine (250 nM), epinephrine (1.5 µM), phosphoethanolamine (250 nM), and retinoic acid (10 nM). Primary human bronchial epithelial cells from a ΔF508 homozygous CF donor (CF-HBE cells; from University of North Carolina Cystic Fibrosis Tissue Procurement Center), grown on Transwell HTS 24-well cell culture inserts (Costar, catalog #3378), were exposed to test agents or controls dissolved in incubation medium. The CF-HBE cells were cultured at 36.5°C for 48 h before TECC24 recordings were performed in the presence or absence of test agent, a positive control or vehicle (DMSO). All test agents were co-incubated with 100 nM of Compound A:



A

[589] Positive control and vehicle were not co-incubated with Compound A. Compound A was prepared as shown in International Application No. PCT/US2023/073543, filed September 6, 2023 (published as WO2024/054840A1, see compound 6A).

[590] Following incubation, the transwell cell culture inserts containing the test agent or control-treated CF-HBE cells were loaded onto a TECC24 apparatus (TECC v7 or MTECC v2; EP Design) to record the transepithelial voltage (VT) and resistance (TEER) using 4 AgCl electrodes per well configured in current-clamp mode. The apical and basolateral bath solutions both contained (in mM) 140 NaCl, 5 KCl, 2 CaCl₂, 1 MgCl₂, 10 Hepes, and 10 glucose (adjusted to pH 7.4 with NaOH) ppm. To inhibit basal Na⁺ absorption, the ENaC inhibitor benzamil (10 µM) was added to the bath. Then, the adenylate cyclase activator, forskolin (10 µM), was added to the bath to activate CFTR. The forskolin-stimulated Cl⁻ transport was halted by addition of CFTR inhibitor-172 (20 µM) to the bath at the end of the

experiment to confirm specificity. VT and TEER recordings were digitally acquired at routine intervals using TECC or MTECC software (EP Design). VT and TEER were transformed into equivalent transepithelial Cl⁻ current (IEQ), and the Area Under the Curve (AUC) of the IEQ time course between forskolin and CFTR inhibitor-172 addition is generated using Excel (Microsoft). Efficacy is expressed as the ratio of the test agent AUC divided by vehicle AUC. EC50s based on AUC are generated using the non-linear regression log(agonist) vs. response function in Prism software (Graphpad) with HillSlope fixed = 1.

[591] If a test agent increased the AUC of the forskolin-stimulated IEQ relative to vehicle in CF-HBE cells, and this increase was inhibited by CFTR inhibitor-172, then the test agent was considered a CFTR corrector.

[592] Biological data for Examples 20 - 216 are provided in Table 3 below.

Table 3. Biological data for Examples 20 - 216

Example No.	TECC AUC vs. DMSO @ 0.1 μ M *
20-P1	B
20-P2	B
21-P1	B
21-P2	B
22	B
23	B
24	B
25	A
26	B
27	A
28 P1	ND
28 P2	ND
29-P1	ND
29-P2	ND
30	B
31	B
32-P1	B
32-P2	B
33	B
34	C
35	C
36	B
37	A
38	ND
39	C
40	C
41	B
42	C

43	ND
44-P1	B
44-P2	B
45	B
46-P1	B
46-P2	B
47	C
48	C
49	ND
50	B
51	B
52-P1	B
52-P2	A
53	C
54	B
55	B
56	C
57	C
58-P1	A
58-P2	B
59-P1	B
59-P2	B
60	B
61	B
62	C
63	B
64	B
65-P1	B
65-P2	B
66	A
67	A
68	B
69	B
70-P1	B
70-P2	B
71	A
72	C
73	C
74	C
75	B
76	B
77	B
78	B
79	B
80	B

81	B
82	B
83	C
84	B
85	B
86	C
87	C
88	C
89	C
90	B
91	B
92	B
93	A
94	B
95	B
96	A
97	B
98	C
99	A
100	B
101	B
102	B
103	B
104	B
105	B
106	B
107	B
108	B
109	B
110	A
111	B
112	B
113	A
114	A
115	A
116	A
117	A
118	C
119	B
120	B
121	C
122	B
123	B
124	C
125	C

126-P1	C
126-P2	C
127	B
128	B
129	B
130	B
131	C
132	B
133	C
134	C
135	C
136	B
137	B
138-P1	B
138-P2	B
139	B
140	C
141	B
142-P1	B
142-P2	B
143	B
144	B
145	B
146	A
147	A
148	A
149	A
150	A
151	A
152	B
153	B
154	B
155	B
156	A
157	A
158	B
159	A
160	A
161	B
162	B
163	B
164	A
165	A
166	A
167	A

168	A
169	A
170	A
171	A
172	B
173	B
174	C
175	B
176	B
177	B
178	B
179	C
180	B
181	B
182	C
183	B
184	B
185	B
186	B
187	B
188	A
189	B
190	B
191	B
192	B
193	B
194	B
195	B
196	B
197	A
198	A
199	B
200	A
201	A
202	B
203	B
204	B
205	B
206	B
207	B
208	B
209	A
210	A
211	A
212	B

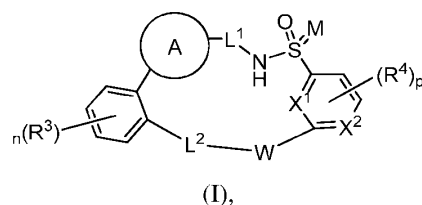
213	A
214	A
215	A
216	B

“A” refers to AUC > 20; “B” refers to AUC 10 and < 20; “C” refers to AUC < 10. “ND” stands for not determined.

CLAIMS

What is claimed:

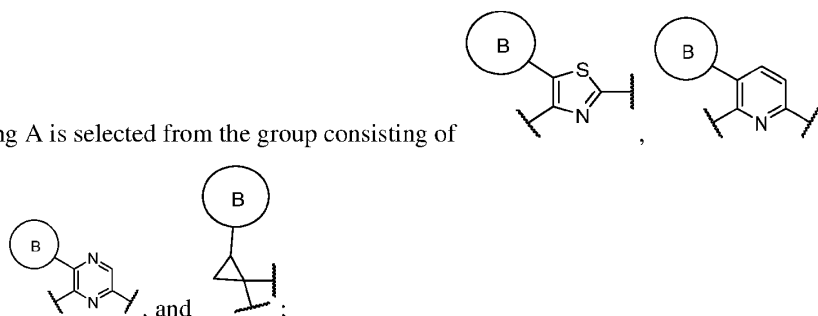
1. A compound of Formula (I):



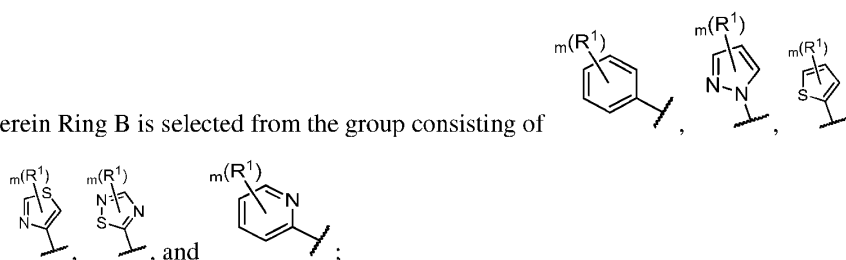
or a pharmaceutically acceptable salt thereof,

wherein

Ring A is selected from the group consisting of



wherein Ring B is selected from the group consisting of



X¹ is -C(H)=, -C(R⁴)=, or -N=;

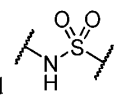
X² is -C(H)=, -C(R⁴)=, or -N=;

L¹ is a bond or -C(=O)-;

L² is an optionally substituted C₄₋₈ alkylene chain, wherein 1-3 methylene units are optionally replaced with -O- or -N(H)-, and wherein L² is optionally substituted with 1-4 instances of halogen;

M is =O or =N(H);

W is selected from the group consisting of -N(H)-, -N(R²)-, and



each R^1 is independently selected from the group consisting of H, halogen, optionally substituted C_{1-5} alkyl, and optionally substituted $-O-C_{1-8}$ alkyl, wherein $-O-C_{1-8}$ alkyl is optionally substituted with 1-3 instances of halogen;

R^2 is selected from the group consisting of optionally substituted C_{1-5} alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, wherein C_{1-5} alkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of optionally substituted halogen, C_{1-3} alkyl, optionally substituted 4-7 membered cycloalkyl, optionally substituted 4-7 membered heterocyclyl, and $-C(=O)OH$;

each R^3 is H, halogen, or optionally substituted C_{1-3} alkyl;

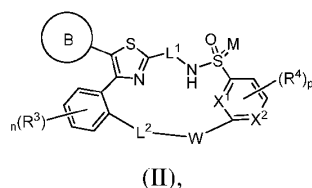
each R^4 is H, halogen, or optionally substituted C_{1-3} alkyl;

m is selected from the group consisting of 1, 2, 3, 4, and 5;

n is selected from the group consisting of 1, 2, 3, and 4; and

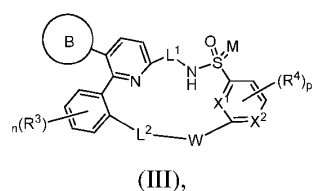
p is 1 or 2.

2. The compound of claim 1, wherein the compound is a compound of Formula (II):



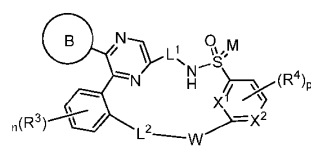
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is a compound of Formula (III):



or a pharmaceutically acceptable salt thereof.

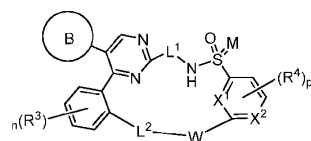
4. The compound of claim 1, wherein the compound is a compound of Formula (IV):



(IV),

or a pharmaceutically acceptable salt thereof.

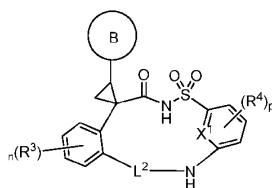
5. The compound of claim 1, wherein the compound is a compound of Formula (V):



(V),

or a pharmaceutically acceptable salt thereof.

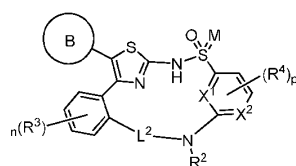
6. The compound of claim 1, wherein the compound is a compound of Formula (VI):



(VI),

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is a compound of Formula (VII):



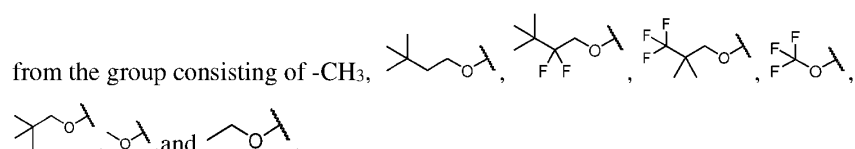
(VII),

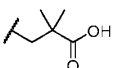
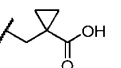
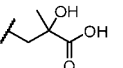
or a pharmaceutically acceptable salt thereof.

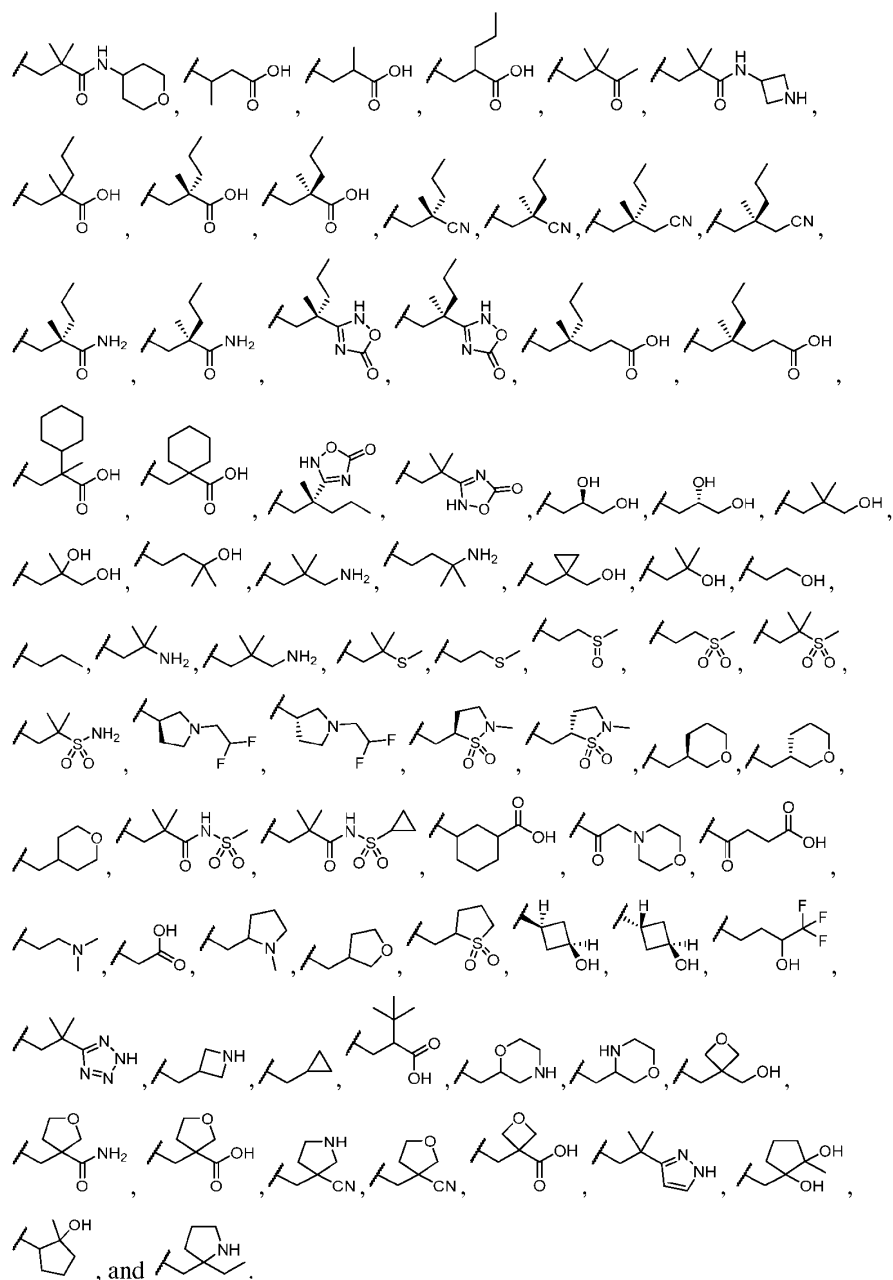
8. The compound of any one of claims 1-7, wherein X^1 is $-\text{N}=\text{}$.

9. The compound of any one of claims 1-7, wherein X^1 is $-\text{C}(\text{R}^4)=$.

10. The compound of claim 9, wherein X^1 is $-\text{CH}=\text{}$.
11. The compound of claim 9, wherein X^1 is $-\text{CF}=\text{}$.
12. The compound of any one of claims 1-11, wherein L^1 is a bond.
13. The compound of any one of claims 1-11, wherein L^1 is $-\text{C}(=\text{O})-$.
14. The compound of any one of claims 1-13, wherein L^2 is an optionally substituted C_5 -alkylene chain, wherein 1 methylene unit is optionally replaced with $-\text{O}-$ or $-\text{N}(\text{H})-$, and wherein L^2 is optionally substituted with 2 instances of halogen.
15. The compound of any one of claims 1-13, wherein each R^1 is independently $-\text{O}-\text{C}_1$ -alkyl, wherein $-\text{O}-\text{C}_1$ -alkyl is optionally substituted with 1-3 instances of halogen.
16. The compound of claim 15, wherein the halogen is fluoro.
17. The compound of any one of claims 1-13, wherein each R^1 is independently selected



18. The compound of any one of claims 1-17, wherein W is $-\text{NR}^2$, wherein R^2 is optionally substituted C_1 -alkyl, wherein R^2 is optionally substituted with 1-3 instances of a substituent independently selected from the group consisting of C_1 -alkyl, 4-7 membered cycloalkyl, 4-7 membered heterocyclyl, and $-\text{C}(=\text{O})\text{OH}$.
19. The compound of any one of claims 1-17, wherein W is $-\text{NR}^2$, and wherein R^2 is
- selected from the group consisting of $-\text{CH}_3$, , , , ,



20. The compound of claim 19, wherein R^2 is $-CH_3$.

21. The compound of any one of claims 1-20, wherein at least one R^3 is $-CH_3$.

22. The compound of any one of claims 1-21, wherein at least one R³ is halogen.

23. The compound of any one of claims 1-22, wherein at least one R⁴ is halogen.

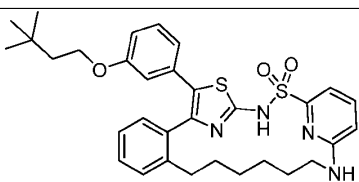
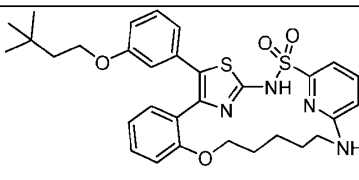
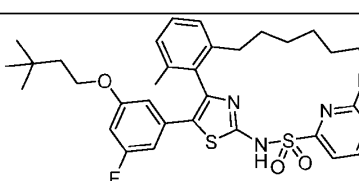
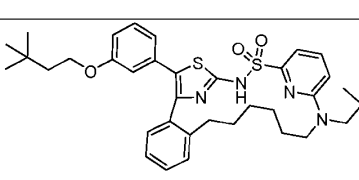
24. The compound of any one of claims 1-23, wherein m is 1 or 2.

25. The compound of any one of claims 1-24, wherein n is 1 or 2.

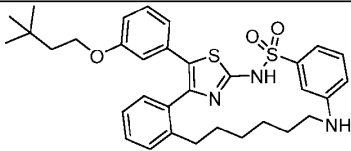
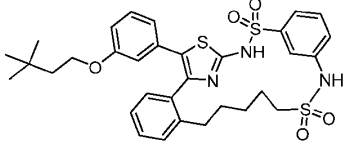
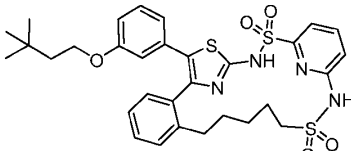
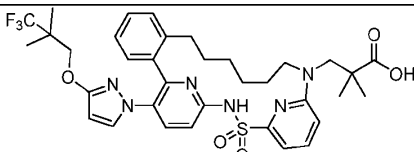
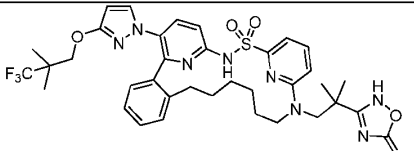
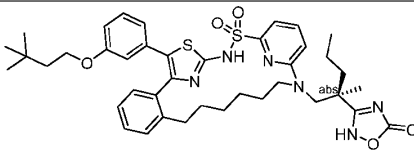
26. The compound of any one of claims 1-25, wherein p is 1.

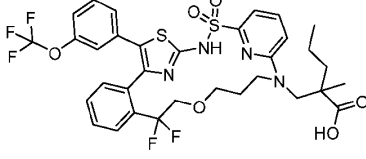
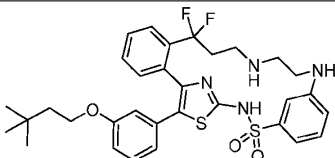
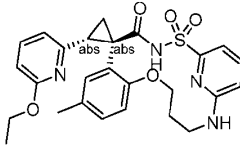
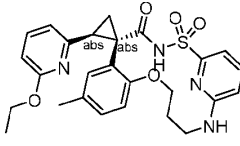
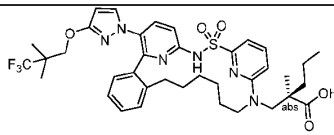
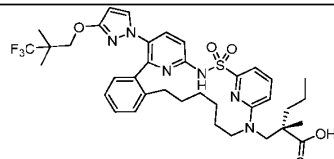
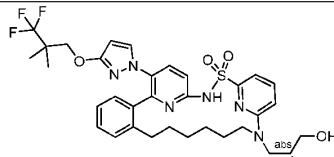
27. The compound of any one of claims 1-26, wherein M is =O.

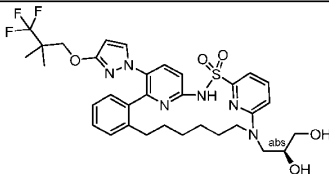
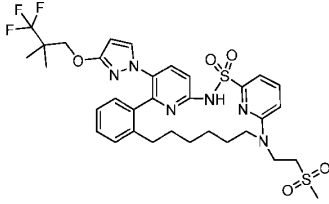
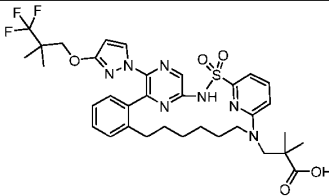
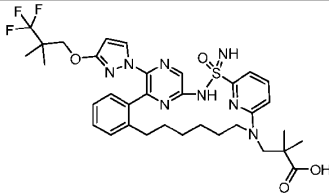
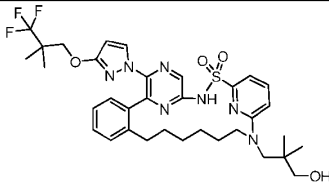
28. A compound selected from:

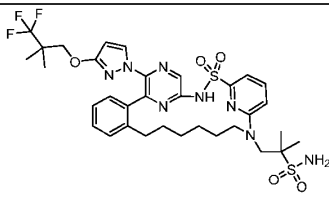
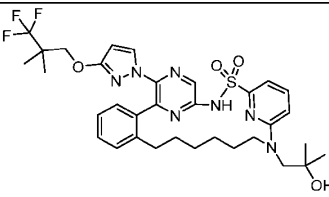
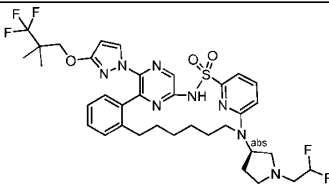
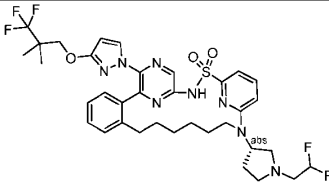
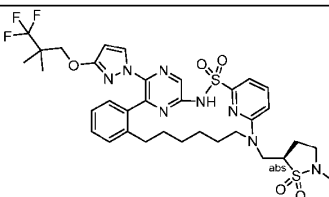
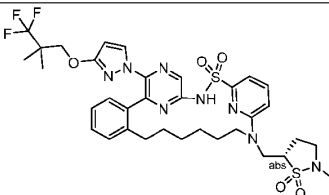
Compound No.	Structure	IUPAC name
1		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
2		6-[3-(3,3-dimethylbutoxy)phenyl]-14-oxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
3		6-[3-(3,3-dimethylbutoxy)-5-fluoro-phenyl]-9,20-dimethyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(24),4(26),6,8(13),9,11,21(25),22-octaene 2,2-dioxide
4		3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-

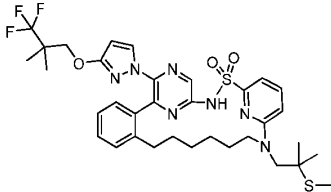
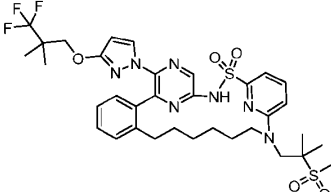
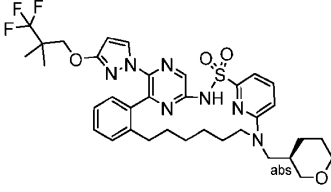
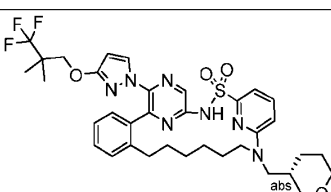
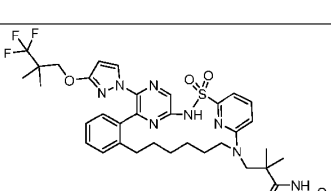
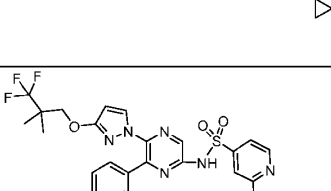
		octaen-20-yl]-2,2-dimethyl-propanoic acid
5		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethyl-propanoic acid
6		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
7(P1)		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
7(P2)		(2S)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
8		2-cyclohexyl-3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-methyl-propanoic acid
9		1-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-

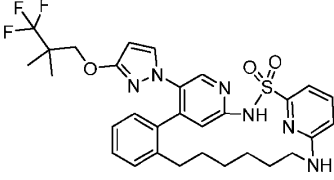
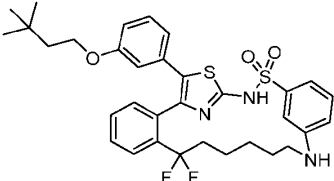
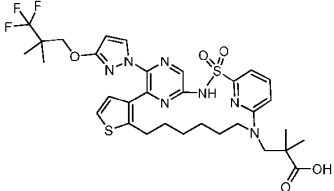
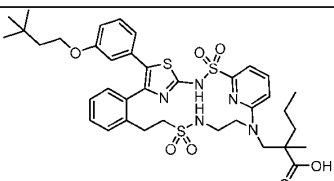
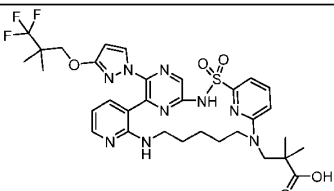
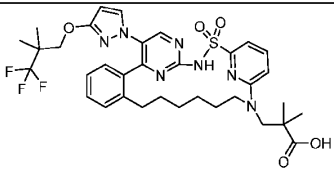
		yl]methyl]cyclohexanecarboxylic acid
10		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
11		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
12		6-[3-(3,3-dimethylbutoxy)phenyl]-2λ6,5,19λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
13		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
14		3-[2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-1,1-dimethylethyl]-2H-1,2,4-oxadiazol-5-one
15		3-[(1R)-1-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-1-methylbutyl]-2H-1,2,4-oxadiazol-5-one

16		2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-16-oxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
17		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,17,20,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
18		(2'R,5R)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicosa-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one
19		(2'S,5S)-2'-(6-ethoxy-2-pyridyl)-8-methyl-2,2-dioxo-spiro[12-oxa-2λ6-thia-3,16,21-triazatricyclo[15.3.1.06,11]henicosa-1(21),6,8,10,17,19-hexaene-5,1'-cyclopropane]-4-one
20-P1		(2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
20-P2		(2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
21-P1		(2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-

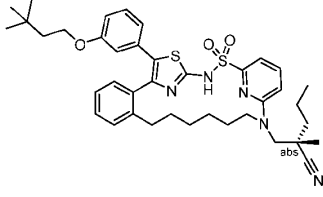
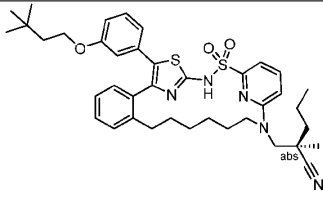
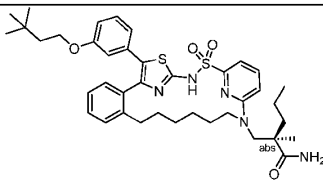
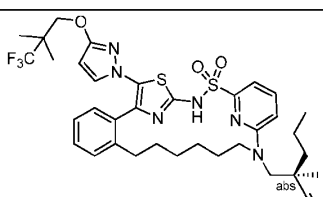
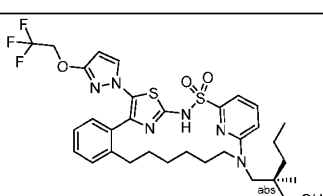
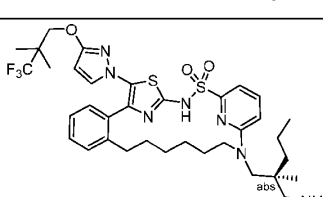
		nonaen-14-yl]propane-1,2-diol
21-P2		(2S)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
22		14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
23		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
24		3-[20-imino-20-oxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
25		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosan-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol

26		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-2-sulfonamide
27		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propan-2-ol
28-P1		14-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
28-P2		14-[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
29-P1		14-[[[(5R)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
29-P2		14-[[[(5S)-2-methyl-1,1-dioxo-1,2-thiazolidin-5-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-

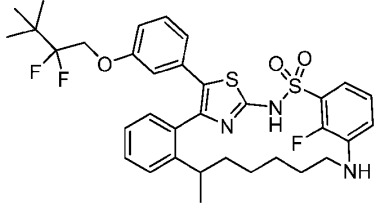
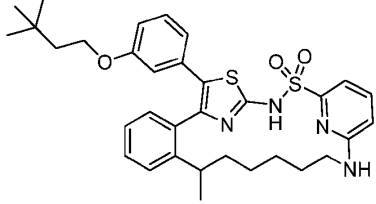
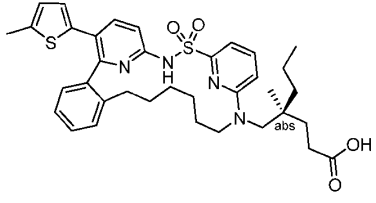
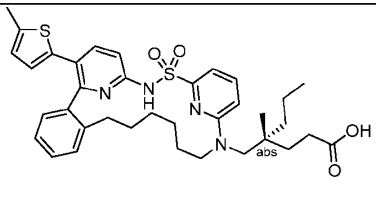
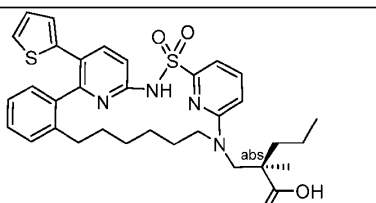
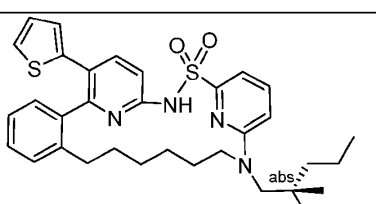
		1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
30		14-(2-methyl-2-methylsulfanylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
31		14-(2-methyl-2-methylsulfonamido-2-methyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
32-P1		14-[(3R)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
32-P2		14-[(3S)-tetrahydropyran-3-yl]methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
33		N-cyclopropylsulfonamide-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15(27),16,18,22,24-nonaene-14-yl]-2,2-dimethylpropanamide
34		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane 1(26),2,4,6,15,17,19(27),22,24-

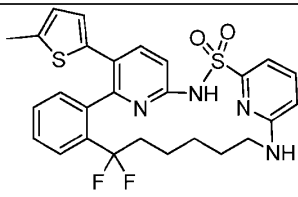
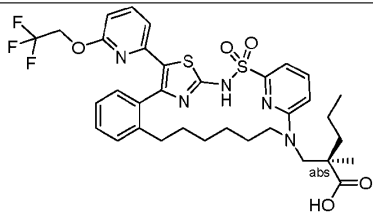
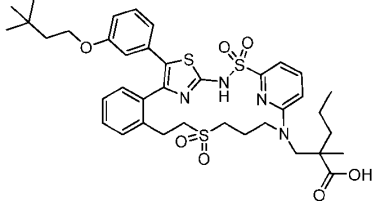
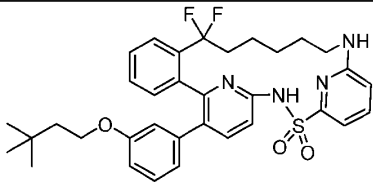
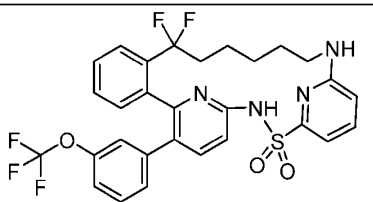
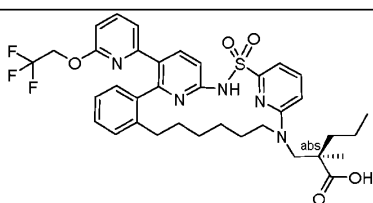
		nonaen-14-yl]-2,2-dimethyl-propanoic acid
35		25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
36		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
37		3-[19,19-dioxo-24-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-5,19λ6-dithia-13,20,23,25,26-pentazatetracyclo[19.3.1.114,18.02,6]hexacosa-1(25),2(6),3,14(26),15,17,21,23-octaen-13-yl]-2,2-dimethyl-propanoic acid
38		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,16,16-tetraoxo-2λ6,5,16λ6-trithia-3,17,20,25,26-pentazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methyl-pentanoic acid
39		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-6,8,14,21,24,26,27-heptazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2(7),3,5,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
40		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,23,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid

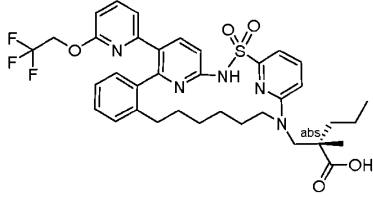
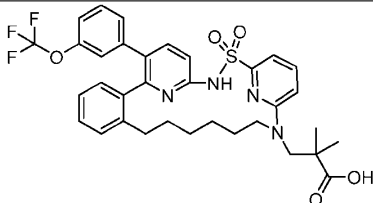
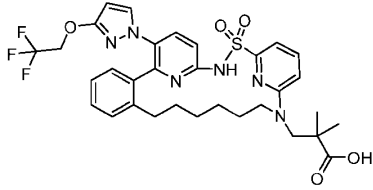
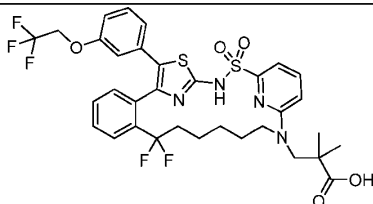
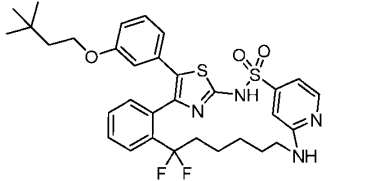
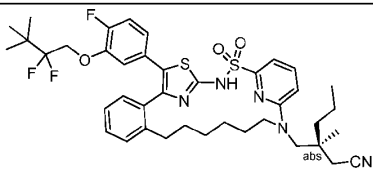
41		6-[3-(3,3-dimethylbutoxy)phenyl]-14,17-dioxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
42		6-[3-(3,3-dimethylbutoxy)phenyl]-17-oxa-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
43		6-[3-(3,3-dimethylbutoxy)-5-fluorophenyl]-9-methyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
44-P1		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid
44-P2		(2S)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid
45		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl)methyl]-2-methylpentanoic acid

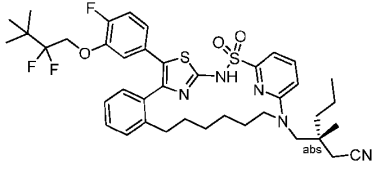
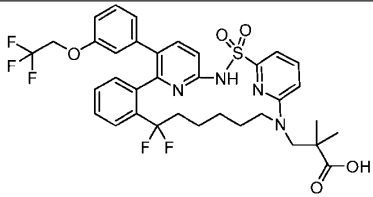
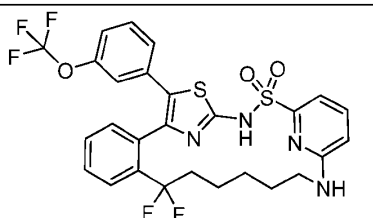
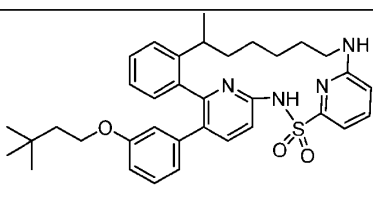
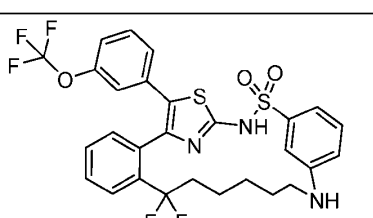
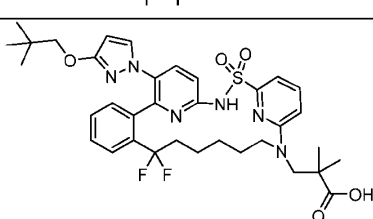
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46-P2		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanenitrile
47		(2R)-2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanamide
48		(2R)-2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanenitrile
49		(2R)-2-[[2,2-dioxo-6-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
50		3-[(1R)-1-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-1-methylbutyl]-2H-1,2,4-oxadiazol-5-one

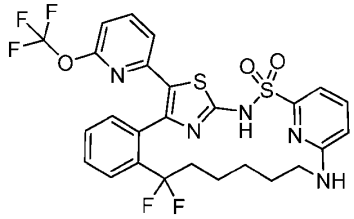
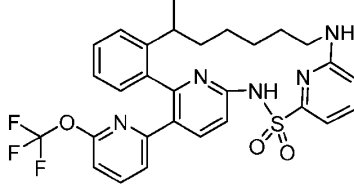
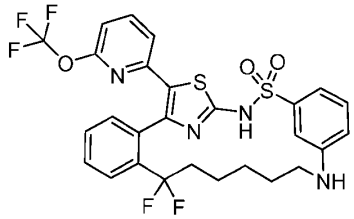
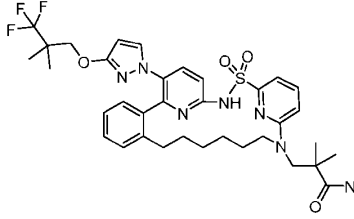
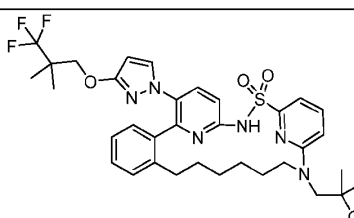
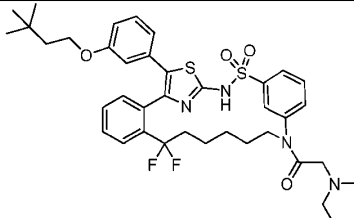
51		3-[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]cyclohexanecarboxylic acid
52-P1		(2R)-2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]methyl]-2-methylpentanoic acid
52-P1		(2S)-2-[[14,14-difluoro-2,2-dioxo-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]methyl]-2-methylpentanoic acid
53		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
54		14,14-difluoro-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14.7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
55		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115.19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

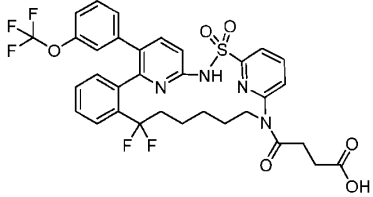
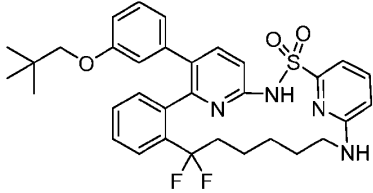
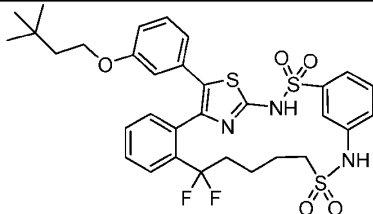
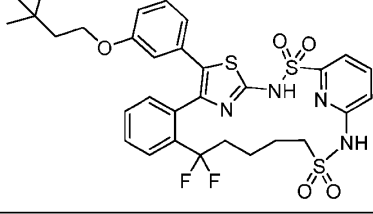
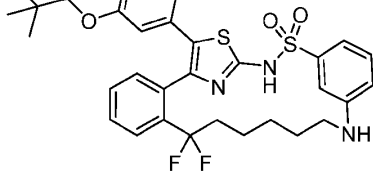
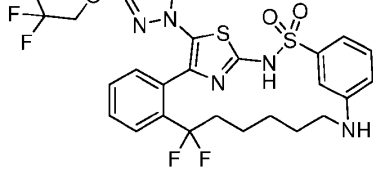
56		6-[3-(2,2-difluoro-3,3-dimethylbutoxy)phenyl]-25-fluoro-14-methyl-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
57		6-[3-(3,3-dimethylbutoxy)phenyl]-14-methyl-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
58-P1		(4S)-4-methyl-4-[[25-(5-methyl-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]heptanoic acid
58-P2		(4R)-4-methyl-4-[[25-(5-methyl-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]heptanoic acid
59-P1		(2R)-2-[[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid
59-P2		(2S)-2-[[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid

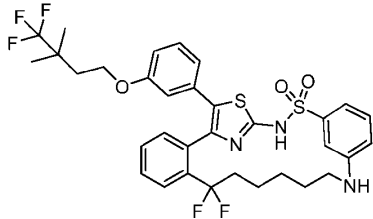
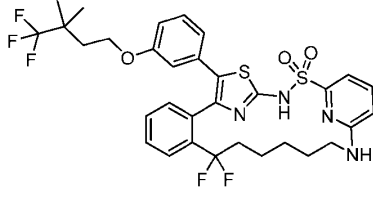
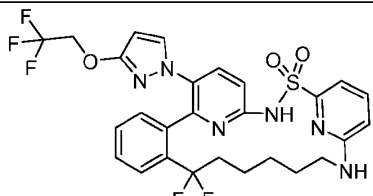
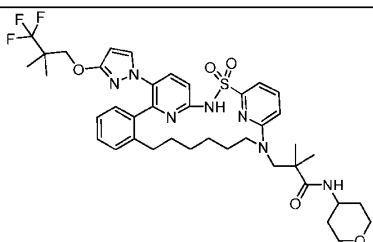
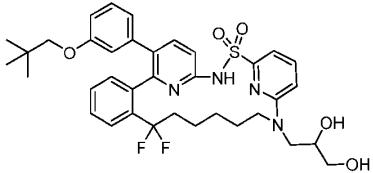
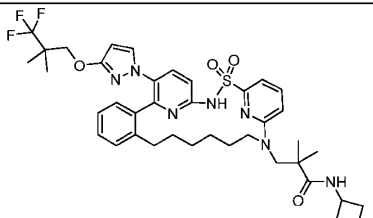
60		8,8-difluoro-25-(5-methyl-2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
61		(2R)-2-[[2,2-dioxo-6-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
62		2-[[6-[3-(3,3-dimethylbutoxy)phenyl]-2,2,16,16-tetraoxo-2λ6,5,16λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-2-methylpentanoic acid
63		25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
64		8,8-difluoro-25-[3-(trifluoromethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
65-P1		(2R)-2-[[20,20-dioxo-25-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methylpentanoic acid

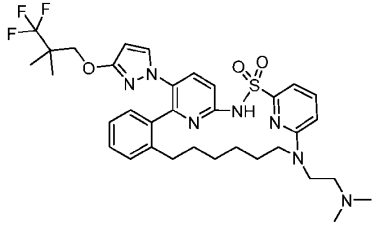
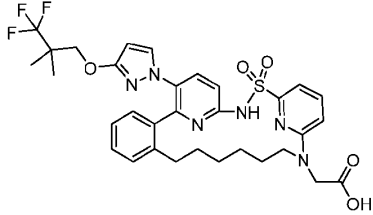
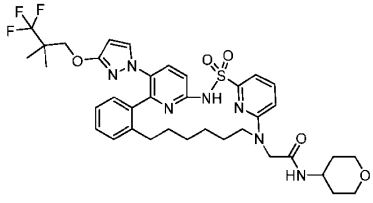
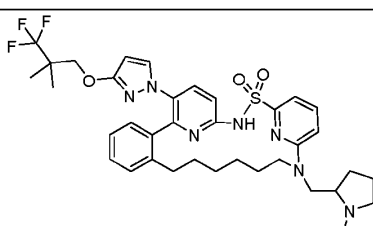
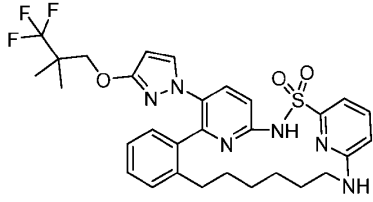
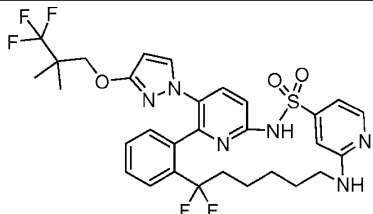
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66		3-[20,20-dioxo-25-[3-(trifluoromethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
67		3-[20,20-dioxo-25-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
68		3-[14,14-difluoro-2,2-dioxo-6-[3-(2,2,2-trifluoroethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid
69		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
70-P1		(3S)-3-[[6-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-3-methylhexanenitrile

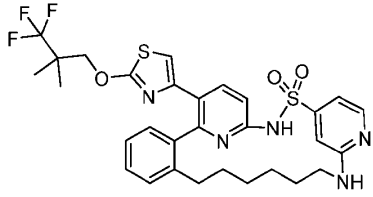
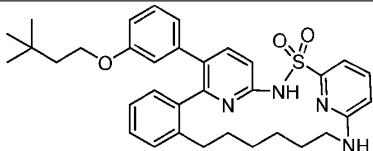
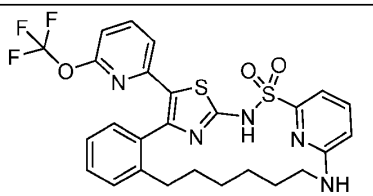
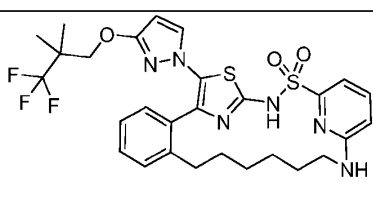
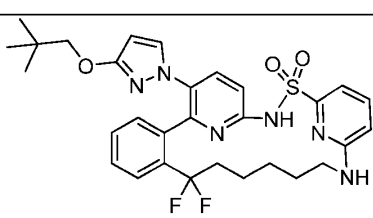
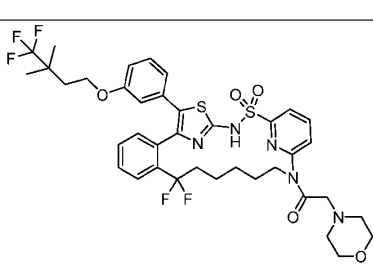
70-P2		(3R)-3-[[6-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-2,2-dioxo-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-3-methyl-hexanenitrile
71		3-[8,8-difluoro-20,20-dioxo-25-[3-(2,2,2-trifluoroethoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
72		14,14-difluoro-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
73		25-[3-(3,3-dimethylbutoxy)phenyl]-8-methyl-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
74		14,14-difluoro-6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
75		3-[25-[3-(2,2-dimethylpropoxy)pyrazol-1-yl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid

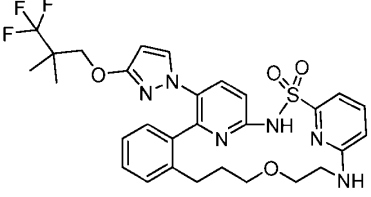
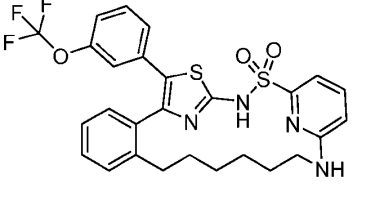
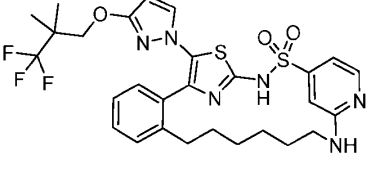
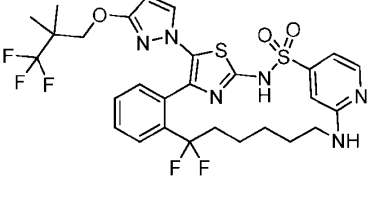
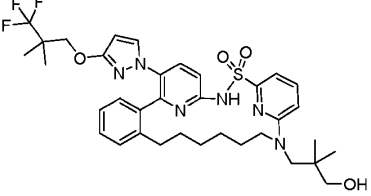
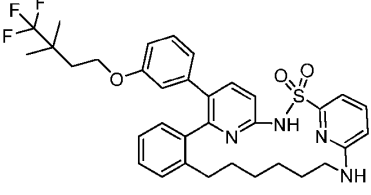
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77		8-methyl-25-[6-(trifluoromethoxy)-2-pyridyl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
78		14,14-difluoro-6-[6-(trifluoromethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
79		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanamide
80		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanenitrile
81		1-[6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2,2-dioxo-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-morpholinoethanone

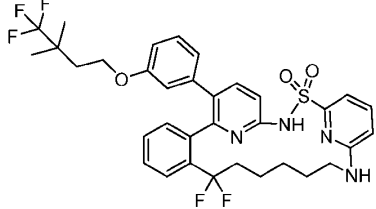
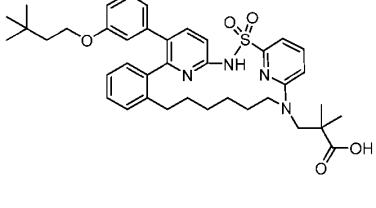
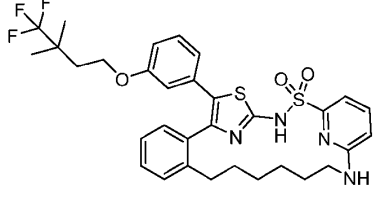
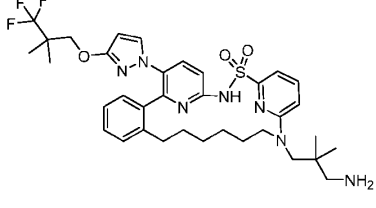
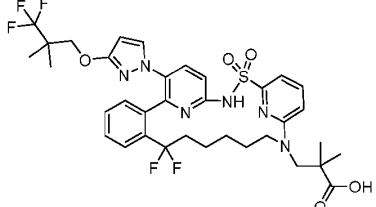
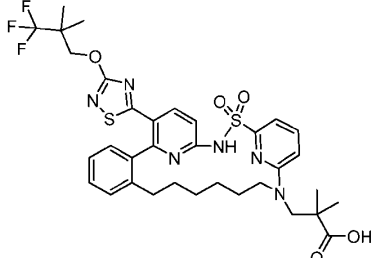
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83		25-[3-(2,2-dimethylpropoxy)phenyl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
84		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5,19λ6-trithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
85		6-[3-(3,3-dimethylbutoxy)phenyl]-14,14-difluoro-2λ6,5,19λ6-trithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2,19,19-tetraoxide
86		6-[3-(2,2-dimethylpropoxy)phenyl]-14,14-difluoro-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
87		14,14-difluoro-6-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,26-triazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

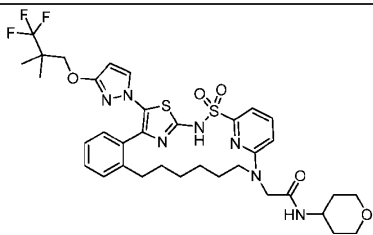
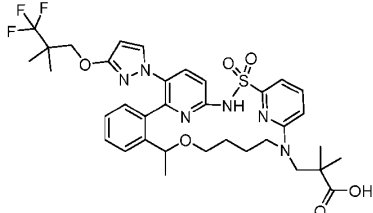
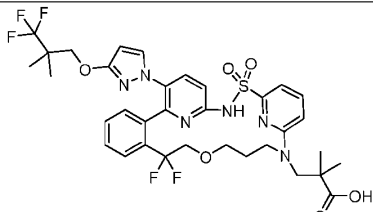
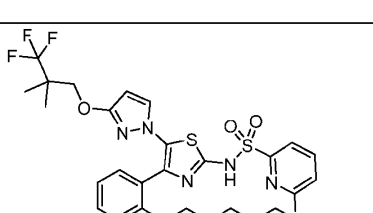
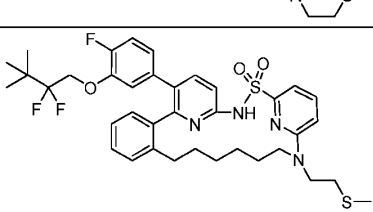
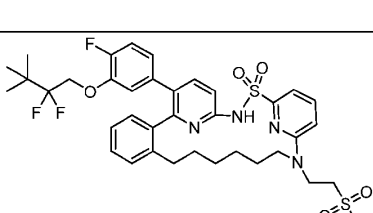
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89		14,14-difluoro-6-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
90		8,8-difluoro-25-[3-(2,2,2-trifluoroethoxy)pyrazol-1-yl]-20λ6,6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
91		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-N-tetrahydropyran-4-yl-propanamide
92		3-[25-[3-(2,2-dimethylpropoxy)phenyl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
93		N-(azetidin-3-yl)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide

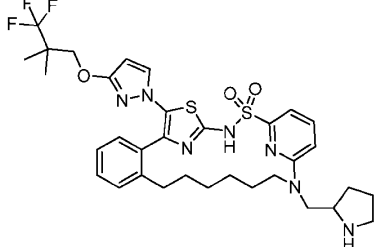
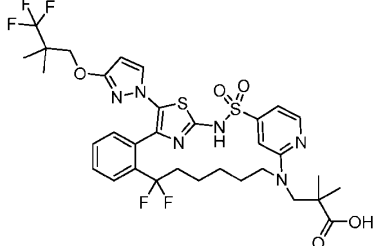
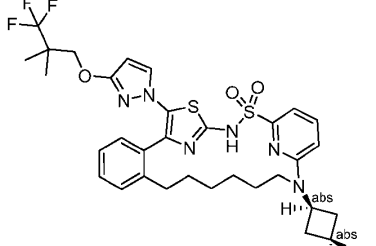
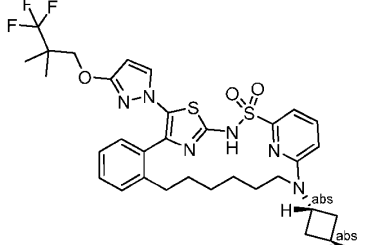
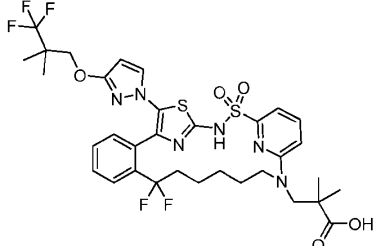
94		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-N,N-dimethylethanamine
95		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]acetic acid
96		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-N-tetrahydropyran-4-yl-acetamide
97		14-[(1-methylpyrrolidin-2-yl)methyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
98		25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
99		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

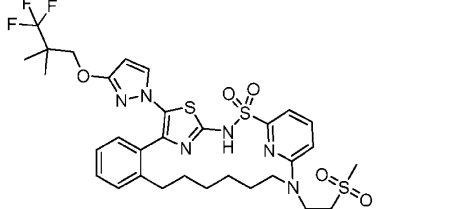
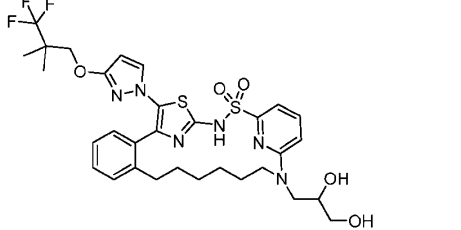
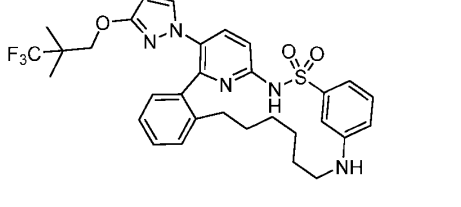
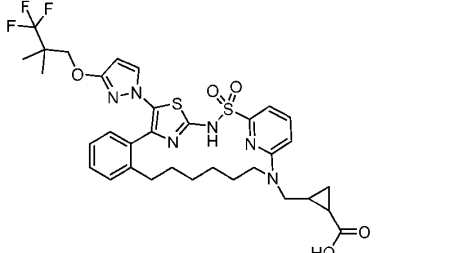
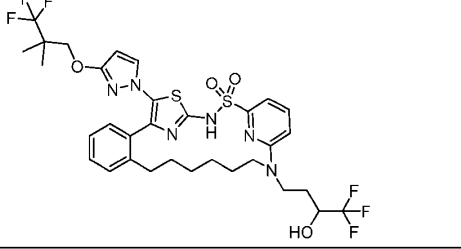
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101		25-[3-(3,3-dimethylbutoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
102		6-[6-(trifluoromethoxy)-2-pyridyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
103		6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
104		25-[3-(2,2-dimethylpropoxy)pyrazol-1-yl]-8,8-difluoro-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
105		1-[14,14-difluoro-2,2-dioxo-6-[3-(4,4,4-trifluoro-3,3-dimethylbutoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosane-1(25),4(26),6,8,10,12,21,23-octaene-20-yl]-2-morpholino-ethanone

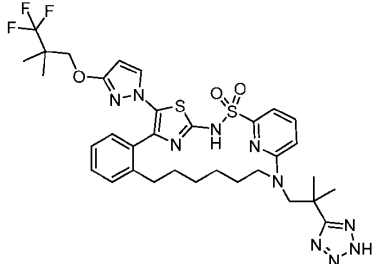
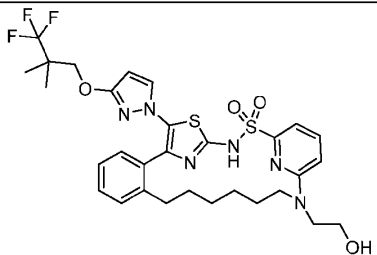
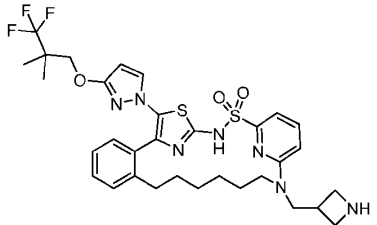
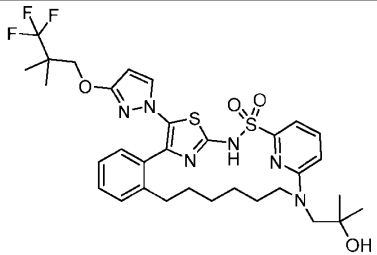
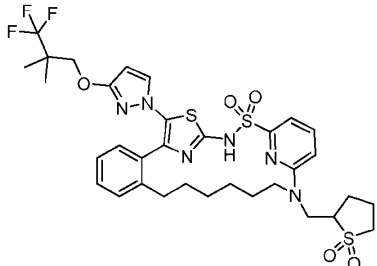
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107		6-[3-(trifluoromethoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
108		6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
109		14,14-difluoro-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]h exacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
110		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
111		25-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

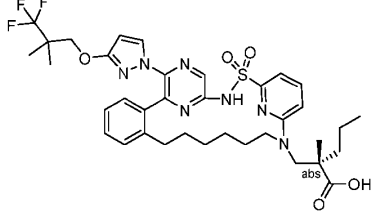
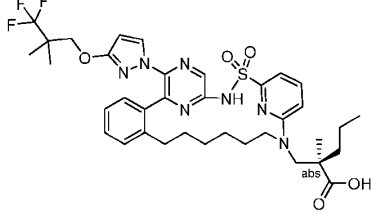
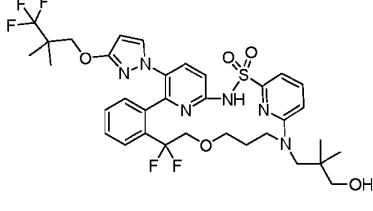
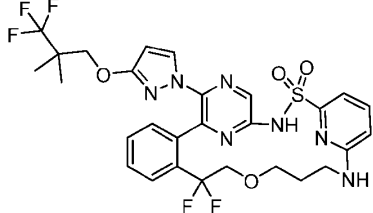
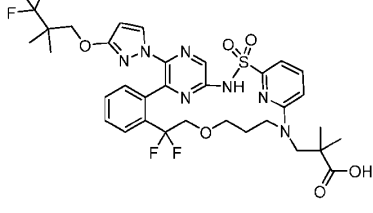
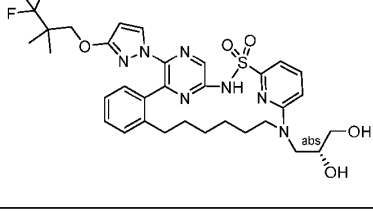
112		8,8-difluoro-25-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
113		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
114		6-[3-(4,4,4-trifluoro-3,3-dimethyl-butoxy)phenyl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
115		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-amine
116		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
117		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)-1,2,4-thiadiazol-5-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid

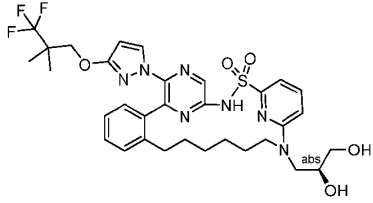
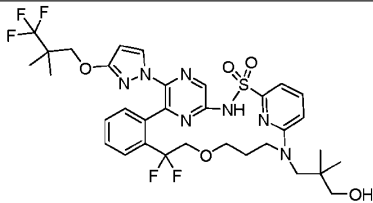
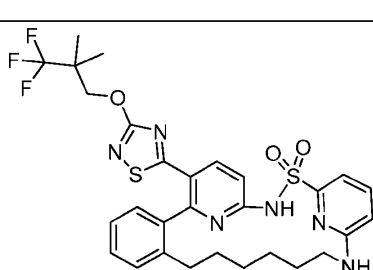
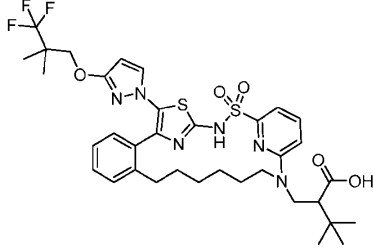
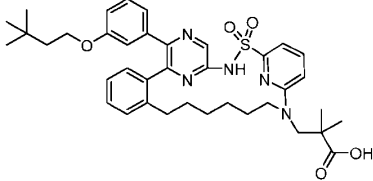
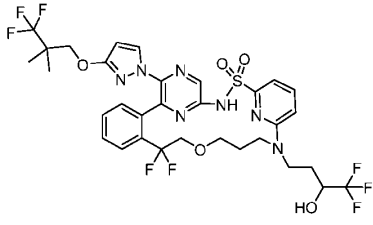
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119		2,2-dimethyl-3-[8-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-9-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propanoic acid
120		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
121		20-(2-methylsulfanylethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
122		25-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-14-(2-methylsulfanylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
123		25-[3-(2,2-difluoro-3,3-dimethyl-butoxy)-4-fluoro-phenyl]-14-(2-methylsulfanylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

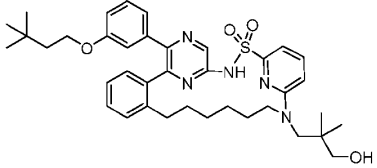
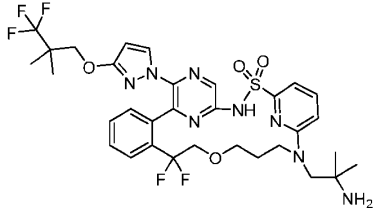
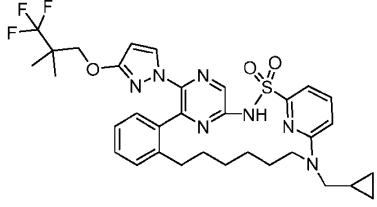
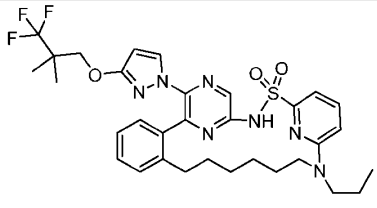
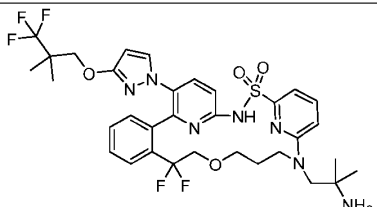
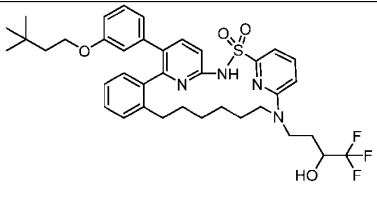
124		20-(pyrrolidin-2-ylmethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
125		3-[14,14-difluoro-2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,22,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid
126-P1		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1-methyl-cyclobutanol
126-P2		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1-methyl-cyclobutanol
127		3-[14,14-difluoro-2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2,2-dimethylpropanoic acid

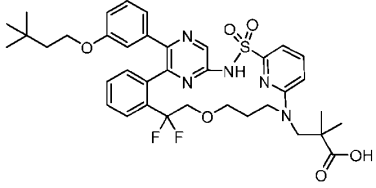
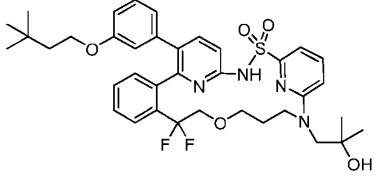
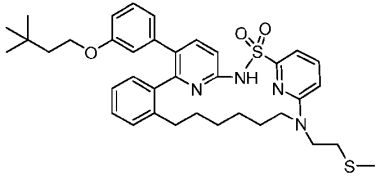
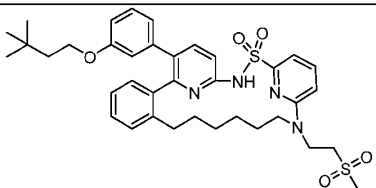
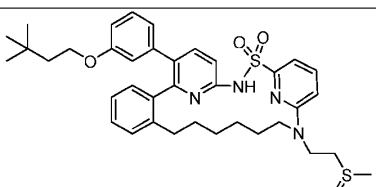
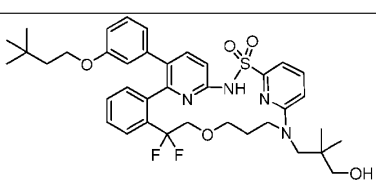
128		20-(2-methylsulfonyl-ethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
129		3-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]propane-1,2-diol
130		25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26-triazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
131		2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]cyclopropanecarboxylic acid
132		4-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-1,1,1-trifluoro-butan-2-ol

133		20-[2-methyl-2-(2H-tetrazol-5-yl)propyl]-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
134		2-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]ethanol
135		20-(azetidin-3-ylmethyl)-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide
136		1-[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]-2-methyl-propan-2-ol
137		20-[(1,1-dioxothiolan-2-yl)methyl]-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacosa-1(25),4(26),6,8,10,12,21,23-octaene 2,2-dioxide

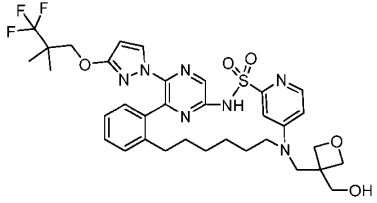
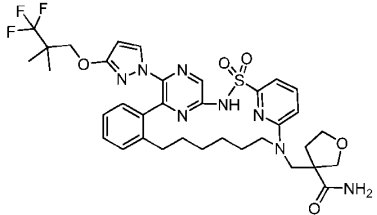
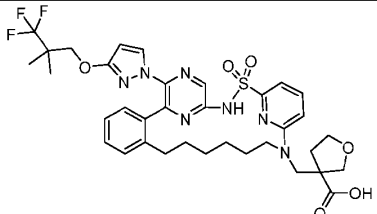
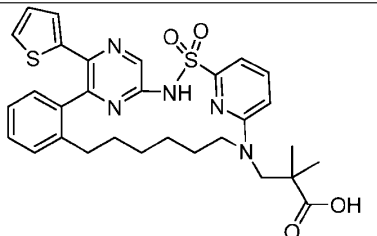
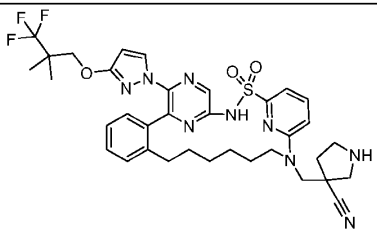
138-P1		(2S)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid
138-P2		(2R)-2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]-2-methyl-pentanoic acid
139		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
140		8,8-difluoro-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
141		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
142-P1		(2R)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol

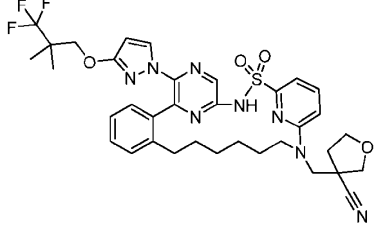
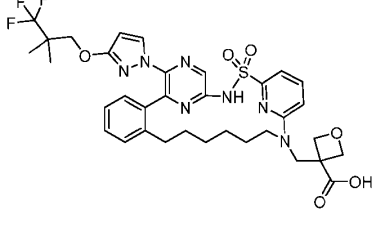
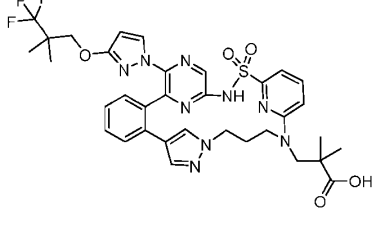
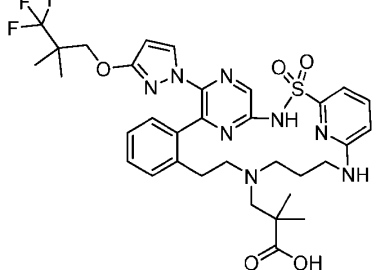
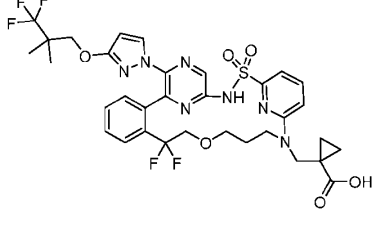
142-P2		(2S)-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]propane-1,2-diol
143		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol
144		25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,2,4-thiadiazol-5-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-20,20-dioxide
145		2-[[2,2-dioxo-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2λ6,5-dithia-3,20,25,26-tetrazatetracyclo[19.3.1.14,7.08,13]hexacos-1(25),4(26),6,8,10,12,21,23-octaen-20-yl]methyl]-3,3-dimethylbutanoic acid
146		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
147		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluorobutan-2-ol

148		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
149		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-amine
150		14-(cyclopropylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
151		14-propyl-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
152		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-amine
153		4-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol

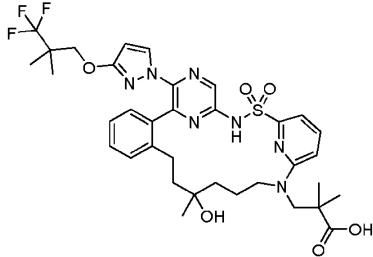
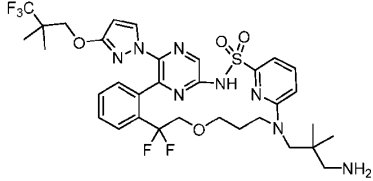
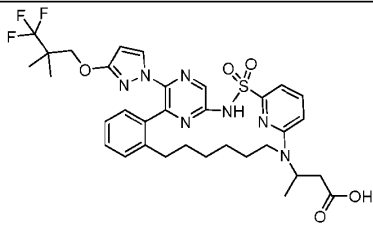
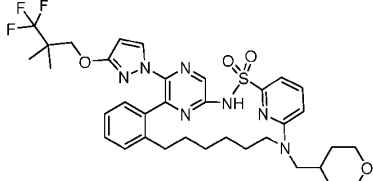
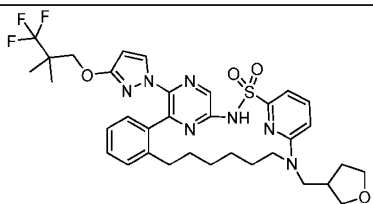
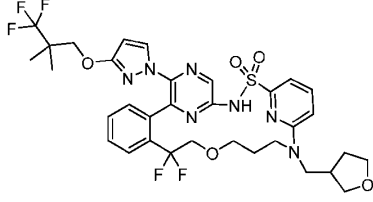
154		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
155		1-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methyl-propan-2-ol
156		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfanylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
157		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
158		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfinylethyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
159		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-10-oxa-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

160		4-[25-[3-(3,3-dimethylbutoxy)phenyl]-8,8-difluoro-20,20-dioxo-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol
161		14-(morpholin-2-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
162		25-[3-(3,3-dimethylbutoxy)phenyl]-14-(2-methylsulfonyl-ethyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
163		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-1,1,1-trifluoro-butan-2-ol
164		1-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropanecarboxylic acid
165		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-N-methylsulfonyl-propanamide

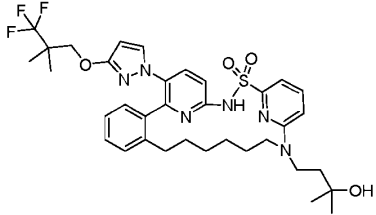
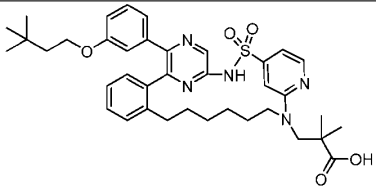
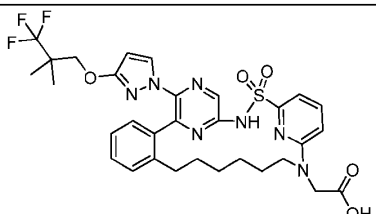
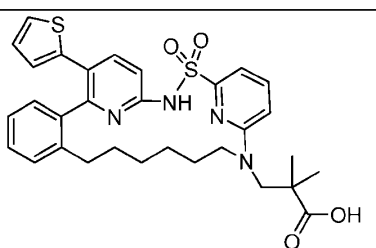
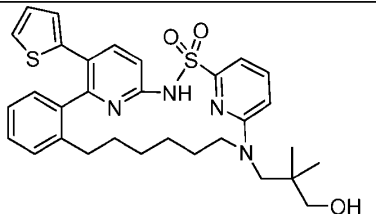
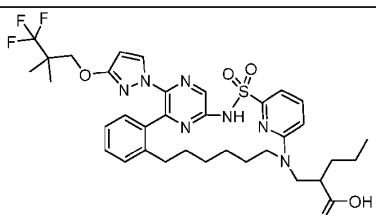
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167		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carboxamide
168		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carboxylic acid
169		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
170		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]pyrrolidine-3-carbonitrile

171		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]tetrahydrofuran-3-carbonitrile
172		3-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]oxetane-3-carboxylic acid
173		3-[21,21-dioxo-26-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-21λ6-thia-10,11,15,22,25,27,28-heptazapentacyclo[21.3.1.18,11.116,20.02,7]nonacosa-1(26),2,4,6,8(29),9,16,18,20(28),23(27),24-undecaen-15-yl]-2,2-dimethyl-propanoic acid
174		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-10-yl]-2,2-dimethyl-propanoic acid
175		1-[[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropanecarboxylic acid

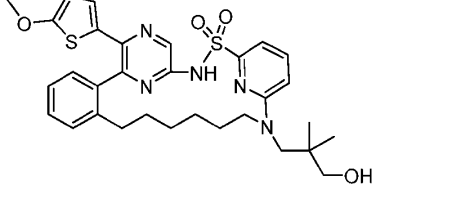
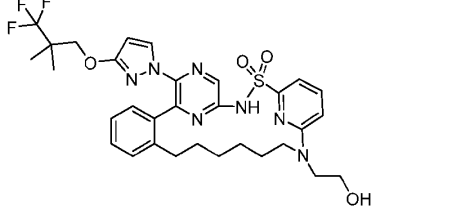
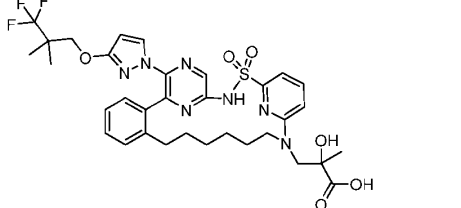
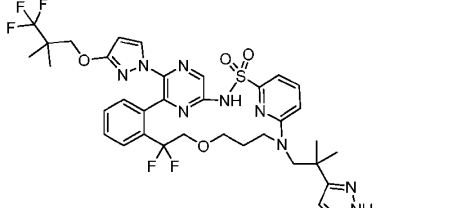
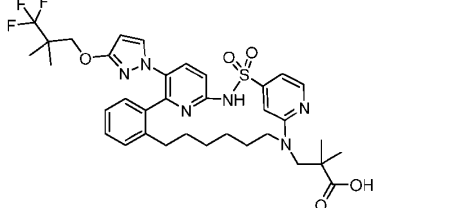
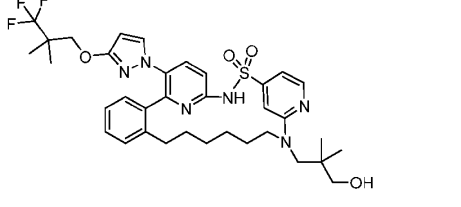
176		[1-[[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]methyl]cyclopropyl]methanol
177		14-(morpholin-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
178		1-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2-methylpropan-2-ol
179		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
180		8,8-difluoro-14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
181		8,8-difluoro-14-(2-methylsulfonyl-ethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide

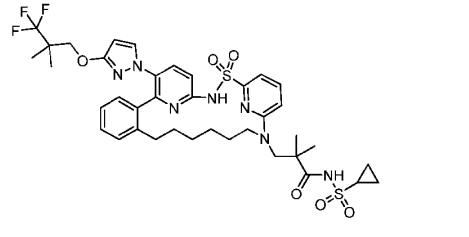
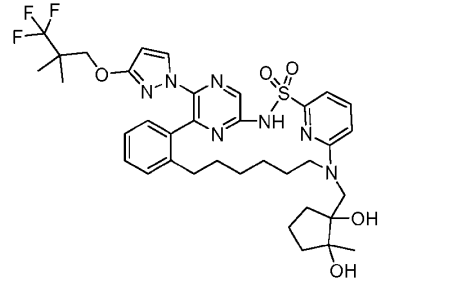
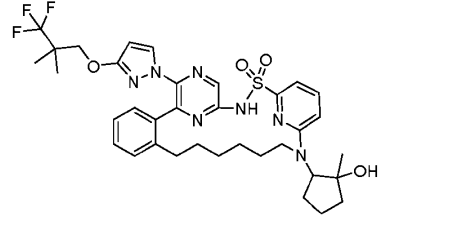
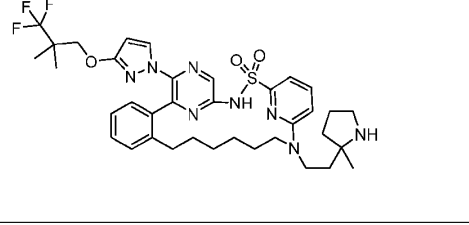
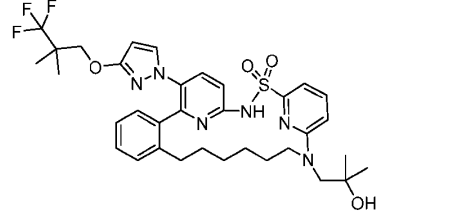
182		3-[10-hydroxy-10-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
183		3-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-amine
184		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]butanoic acid
185		14-(tetrahydropyran-4-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15,17,19(27),22(26),23-nonaene 20,20-dioxide
186		14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
187		8,8-difluoro-14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide

188		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propane-1,2-diol
189		8,8-difluoro-14-(tetrahydrofuran-3-ylmethyl)-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
190		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-propanoic acid
191		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-butan-2-ol
192		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-butanoic acid
193		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-methyl-butan-2-amine

194		4-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2-methyl-butan-2-ol
195		3-[25-[3-(3,3-dimethylbutoxy)phenyl]-20,20-dioxo-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethylpropanoic acid
196		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]acetic acid
197		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropanoic acid
198		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacos-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethylpropan-1-ol
199		2-[[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacos-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]methyl]pentanoic acid

200		3-[8,8-difluoro-10-methyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
201		3-[8,8-difluoro-10-isopropyl-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-10,14,21,24,26,27-hexazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
202		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,24,26-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15,17,19(27),22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
203		4-[8,8-difluoro-20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-3,3-dimethyl-butan-2-one
204		3-[25-(5-methoxy-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propanoic acid
205		3-[20,20-dioxo-25-(2-thienyl)-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

206		3-[25-(5-methoxy-2-thienyl)-20,20-dioxo-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2,2-dimethyl-propan-1-ol
207		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]ethanol
208		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-2-hydroxy-2-methyl-propanoic acid
209		8,8-difluoro-14-[2-methyl-2-(1H-pyrazol-3-yl)propyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-10-oxa-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
210		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propanoic acid
211		3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,16,21,26-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosane-1(25),2,4,6,15,17,19(27),22(26),23-nonaen-14-yl]-2,2-dimethyl-propan-1-ol

212		N-cyclopropylsulfonyl-3-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2,2-dimethyl-propanamide
213		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]methyl]-2-methyl-cyclopentane-1,2-diol
214		2-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaen-14-yl]-1-methyl-cyclopentanol
215		14-[2-(2-methylpyrrolidin-2-yl)ethyl]-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,24,26,27-pentazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(26),2,4,6,15(27),16,18,22,24-nonaene 20,20-dioxide
216		1-[20,20-dioxo-25-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-20λ6-thia-14,21,26,27-tetrazatetracyclo[20.3.1.115,19.02,7]heptacosa-1(25),2,4,6,15(27),16,18,22(26),23-nonaen-14-yl]-2-methyl-propan-2-ol

or a pharmaceutically acceptable salt thereof.

29. The compound of any one of claims 1-28, wherein the compound is a CFTR corrector.

30. A pharmaceutical composition comprising a compound of any one of the preceding claims, and one or more pharmaceutically acceptable carriers or excipients.

31. The pharmaceutical composition of claim 30, further comprising one or more CFTR therapeutic agents.
32. A method of treating deficient CFTR activity in a cell, comprising contacting the cell with a compound of any one of claims 1–29, or the pharmaceutical composition of claim 30 or 31.
33. The method of claim 32, wherein contacting the cell occurs in a subject in need thereof, thereby treating a CFTR-mediated condition and/or disease.
34. The method of claim 33, 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, 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, myeloperoxidase 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, spinocerebellar 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.

35. The method of claim 33 or 34, 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, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.
36. The method of any one of claims 33-35, wherein the disease or condition is cystic fibrosis.
37. A method of treating cystic fibrosis in a subject, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-29, or the pharmaceutical composition of claim 30 or 31.
38. The method of claim 37, wherein the subject is human.
39. The method according to claim 37 or 38, wherein said subject is at risk of developing cystic fibrosis, and wherein said administering step is carried out prior to the onset of symptoms of cystic fibrosis in said subject.